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UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Human Development and Health

**IS GRIP STRENGTH ASSOCIATED WITH LUNG FUNCTION
IN OLDER HOSPITALISED PATIENTS?**

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Thesis for the Degree of Master of Philosophy

June 2014

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ABSTRACT

Is grip strength associated with lung function in older hospitalised patients?

Introduction

Changes in airway compliance contribute to the declining ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) with ageing. This leads to increased airflow obstruction during forced expiration. Consequently, many older people meet the spirometric criteria for obstructive airways disease. Older people may be unable to generate and sustain sufficient expiratory pressure to reach and hold maximum flow as lung volume falls. This study used grip strength to reflect expiratory muscle strength in investigating the relationship between expiratory muscle strength and lung function.

Methods

Patients on acute Medicine for Older People wards were recruited who met the inclusion criteria: age above 70 years; never smoked; no history, symptoms or signs of respiratory disease; Mini Mental State Examination (MMSE) ≥ 24 ; willing and able to consent to participate; able to perform hand grip and forced spirometry. Outcome measure was lung function (FEV1, FVC, FEV1/FVC, peak expiratory flow rate (PEFR) and slow vital capacity (SVC)), covariates were grip strength, age, weight and height. Unadjusted and adjusted (for age, height, weight) linear regressions were used for analysis.

Results

50 patients (men=20, women=30) were recruited. Significant relationships were found in men between grip strength and FEV1 (unadjusted $\beta=0.032$, 95%CI=(0.001,0.063), $p=0.047$) although attenuated after adjustment; in women between grip strength and PEFR (unadjusted $\beta=6.881$, 95%CI=(1.537,12.226), $p=0.013$); (adjusted $\beta=6.938$, 95%CI=(1.268,12.607), $p=0.018$), and in women between grip strength and SVC (unadjusted $\beta=0.052$, 95%CI=(0.006,0.099), $p=0.028$); (adjusted $\beta=0.050$, 95%CI=(0.0005,0.100), $p=0.048$). No other significant relationship was found.

Conclusions

The relationship of grip strength with PEFR and SVC in women might reflect stronger patients generating higher intra-thoracic pressure at the start of spirometry and pushing harder against thoracic cage recoil at end-expiration. No significant relationship was found with FEV1/FVC and grip strength in this small study. Further research is needed to evaluate the relationship between lung function and grip strength in older people.

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DECLARATION OF AUTHORSHIP

I, Sarah Holmes

declare that the thesis entitled:-

“Is grip strength associated with lung function in older hospitalised patients?”

and the works presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- an abstract of this work is shortly to be published in Age and Ageing 2014 online.

Signed:

Date:.....

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Definitions and Abbreviations

ADP	Adenosine diphosphate
Akt	Protein kinase b
ARTP	Association for Respiratory Technology and Physiology
ATP	Adenosine triphosphate
ATS	American Thoracic Society
BIA	Bioelectrical impedance analysis
BMI	Body mass index
Ca ²⁺	Calcium ion
CLOX	Executive clock drawing task
CNTF	Ciliary neurotrophic factor
COPD	Chronic obstructive pulmonary disease
CRF	Corticotrophin releasing factor
CRP	C Reactive Protein
CrP	Creatinine Phosphate
CT	Computed tomography
DEXA	Dual energy x-ray absorptiometry
DHEA	Dehydroepiandrosterone
ECAT	European Community and American Thoracic Society
ECHRS	European Community Health and Respiratory Survey
EMS	Expiratory muscle strength
EPR	Electron paramagnetic resonance
ERS	European Respiratory Society

ERV	Expiratory reserve volume
FEV1	Forced expiratory volume in 1 second
FEV1/FVC	Ratio of forced expiratory volume in 1 second to forced vital capacity
FEV0.25	Forced expiratory volume in 0.25 seconds
FEV0.5	Forced expiratory volume in 0.5 seconds
FRC	Functional residual capacity
FVC	Forced vital capacity
GH	Growth hormone
GLI	Global lung function initiative
GOLD	Global initiative for chronic obstructive lung disease
H ₂ O ₂	Hydrogen peroxide
HRQoL	Health related quality of life
IGF-1	Insulin-like growth factor
IL-1	Interleukin-1
IL-6	Interleukin-6
IOV	Intra- and Inter-observer variability
IRV	Inspiratory reserve volume
Kg	Kilograms
K ⁺	Potassium ion
MMSE	Mini-mental state examination
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging

Mstn	Myostatin
mtDNA	Mitochondrial DNA
MURF-1	Murine Ring Finger-1
MAFBx	Muscle Associated F-box
MUST	Malnutrition Universal Screening Tool
mTOR	Mammalian Target of Rapamycin
M	Metres
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-Kb	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	Nerve growth factor
oxLDL	Oxidised low-density lipoprotein
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PE _{max}	Maximal static expiratory pressure
PI3K	Phosphatidylinositol-3-phosphate kinase
PI _{max}	Maximal static inspiratory pressure
P _o	Specific force
ROS	Reactive Oxygen Species
RV	Residual volume
SF-36	Short form-36 health survey questionnaire
SPPB	Short physical performance battery
SVC	Slow vital capacity
tdi	Diaphragm thickness

TLC	Total lung capacity
TNF- α	Tumour necrosis factor-alpha
VC	Vital capacity
V_o	Shortening velocity

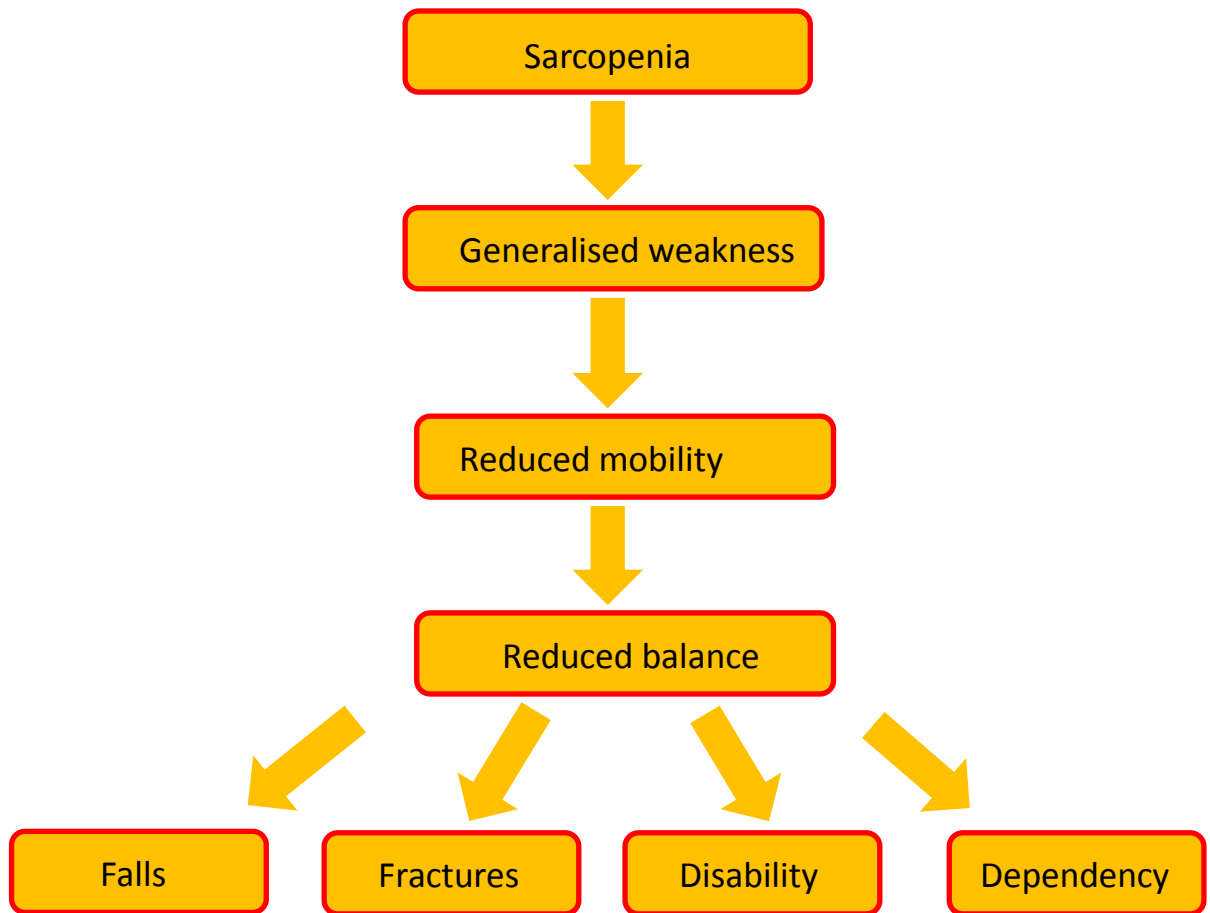
1. Introduction

1.1 Sarcopenia

Ageing is associated with a decrease in muscle mass, strength and function. These qualities define the condition sarcopenia (1;2). It has been further categorised into primary sarcopenia associated with an age-related aetiology or secondary sarcopenia associated with sedentary behaviour, malnutrition and disease-related. The term was first described by Irwin Rosenberg in 1989 from the Greek “sarx” meaning flesh and “penia” meaning loss, to define the age related changes in muscle (3;4). Sarcopenia has been recognised in healthy, active adults 50 years and over (1). Muscle mass is estimated to decline between 30 to 50% between 40 to 80 years old. After the age of 50 functional capacity has been reported to decline by 1-2% and by as much as 3% after the age of 60 (5) The prevalence of sarcopenia in community dwelling adults in the UK was reported to be between 4-8% in the Hertfordshire Cohort Study with a mean age of 67 years (5). The prevalence of sarcopenia worldwide varies between 3 and 30% depending on the operational definition of sarcopenia used (5-6).

Sarcopenia is associated with a reduced quality of life (including physical frailty, falls, and disability) and increased social and health care needs which have a significant economic impact for the individual as well as society (1;7;8). See Figure 1.

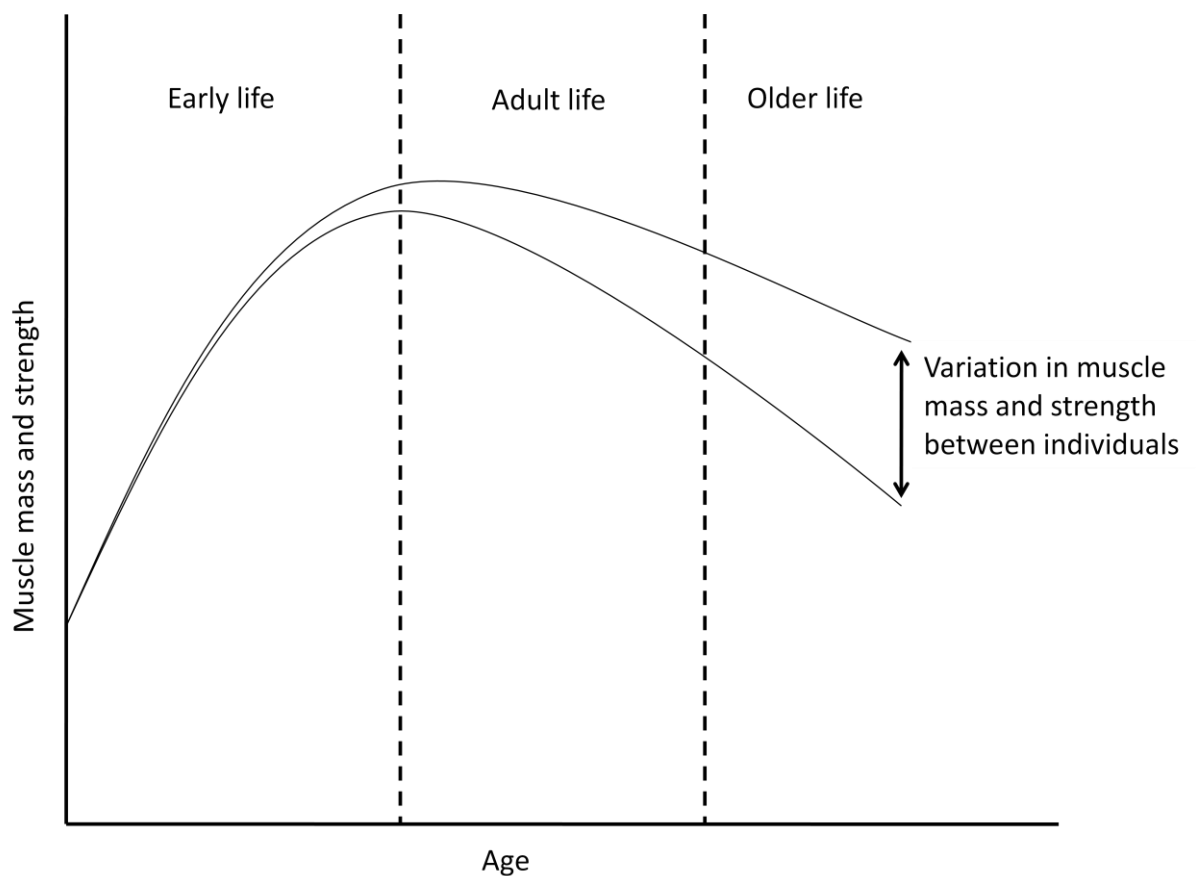
Figure 1: Consequences of Sarcopenia



Muscle mass and strength increase through childhood, peak in adulthood and decreases after 35 years of age. From person to person, the rate of ageing varies, this is known as biological ageing. The variation in muscle mass and strength between individuals of a similar chronological age may reflect differences in the rate of decline of mass and strength with ageing as well as the difference in peak attained muscle mass and strength at a younger age (9;10). Sarcopenia is not solely due to decreased levels of physical activity in older people. Some loss of muscle mass and strength have been demonstrated

even in elite athletes maintaining high levels of exercise into later life (11). See Figure 2. Kirkwood's disposable soma theory defined ageing as the outcome of incorrect somatic maintenance and repair. Many factors are likely to contribute to somatic damage throughout the life course. The variable response to these factors in repair and maintenance is likely to contribute to the differing rates of ageing amongst individuals (12). Age, gender, size, level of physical activity, ethnicity and genetics appear to be significant life determinants of muscle mass and strength (14).

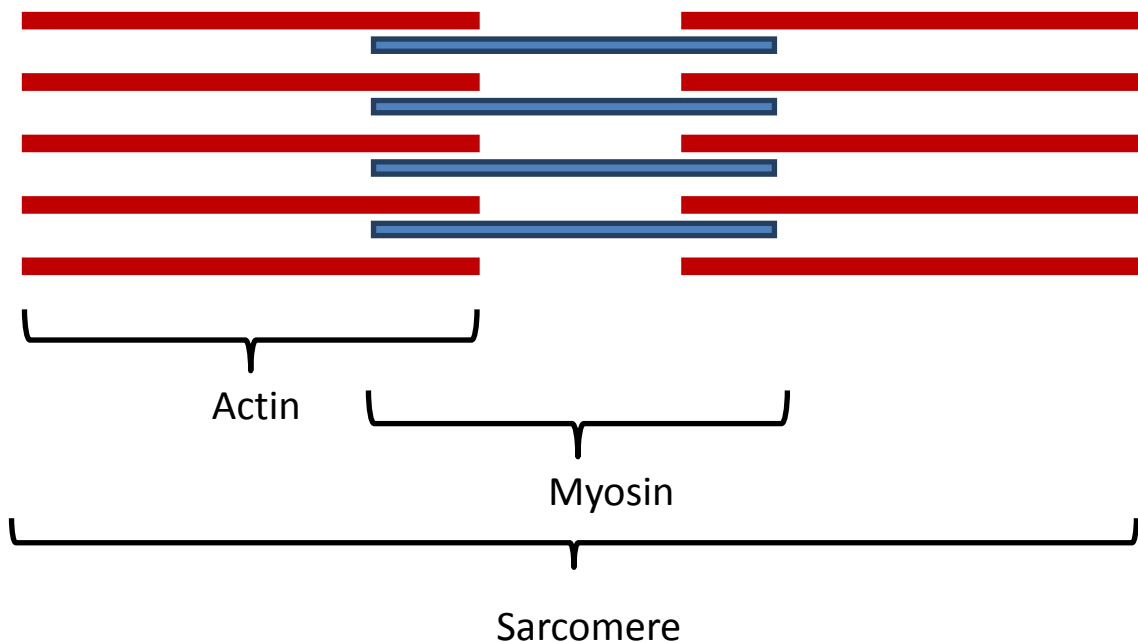
Figure 2: A life course model of sarcopenia (13)



1.2 Muscle structure and contractility

The myofibril is the basic contractile unit of muscle which is made up of a linear array of sarcomeres. Each sarcomere consists of interdigitating thick and thin filaments. Myosin molecules are the main components of the thick filament and aggregated via their “tail” regions into a bipolar filament (15). The “head” region of myosin contains the catalytic domain with sites for adenosine triphosphate (ATP) hydrolysis and interaction with actin. Its light chain domain contains the essential and regulatory light chains. The thin filaments contain the helical polymer of globular actin monomers with specific sites of interaction with myosin (16). See Figure 3.

Figure 3: Adapted diagram illustrating the myofibril (17)



The myosin “head” interacts with actin in the presence of ATP causing sliding of the thin filaments past thick filaments toward the centre of the sarcomere causing contraction. During ATP hydrolysis when there is an interaction between actin and myosin, there is a sequence of structural transitions in both proteins. Without ATP or Adenosine diphosphate (ADP), the myosin “head” forms a strong, well-ordered complex with actin. ATP binds to myosin causing a weaker complex where the catalytic domain and light chain domain of myosin are disordered. Myosin releases phosphate causing a structural transition in the catalytic and light chain binding domains, producing force and initiating a new cycle. Muscle force can decrease if the system spends too long in the weak-binding states or the strong binding states are weakened. Velocity can decrease if the system spends too long in the strong binding states. Hence age-related changes in actin and myosin that affect the actomyosin ATPase activity by affecting the weak-to-strong actomyosin transition are likely to alter muscle function (16).

1.3 Mechanisms proposed in sarcopenia

There has been much research and several theories proposed as to the underlying molecular mechanisms accounting for sarcopenia. Sarcopenia is associated with a reduced muscle mass, muscle fibre atrophy, loss of muscle fibre numbers, decline in neurone numbers and conduction velocity. There is a loss of motor neurones, reduced excitation-contraction coupling, increased fat content in muscle, oxidative damage and reduced satellite cell activation and

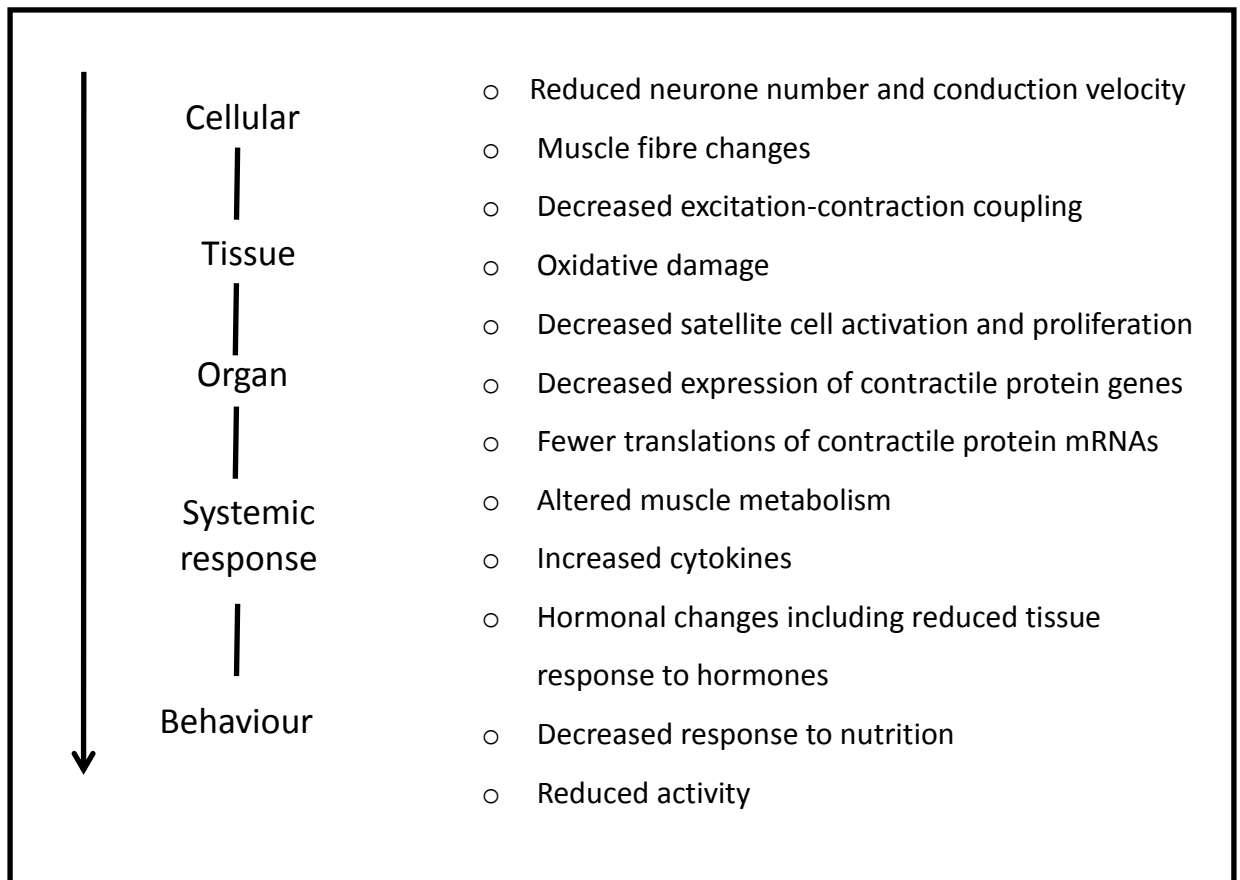
proliferation. At a cellular level there is decreased expression of contractile protein genes, reduced translation of contractile protein mRNAs, altered protein synthesis and proteolysis, altered muscle metabolism, increased cytokines, reduced hormonal levels and response to hormones (18-20). See Figure 4.

The age-related decline of muscle contractility involves numerous factors associated with changes in the process of muscle excitation, regulation and molecular interactions. There are changes in structural composition, innervations, contractility, capillary density, fatigability and glucose metabolism (20;21). These factors are likely to contribute to asthenia, mobility, reduced balance and increased risk of hip fractures (22).

1.3.1 Hormonal changes with ageing

Several hormones appear to have altered production with ageing particularly growth hormone (GH), insulin-like growth factor (IGF-1), glucocorticoids, androgens (testosterone and dehydroepiandrosterone (DHEA)), oestrogens and insulin. These may affect both the anabolic and catabolic states for optimal muscle protein turnover and consequently contribute to the loss of muscle mass and strength (23).

Figure 4: Proposed mechanisms of sarcopenia adapted from (18)



Levels of free testosterone and DHEA decrease with age and are associated with a decrease in lean muscle mass and reduced strength. Growth hormone and IGF-1 decrease with age and are associated with a decrease in muscle mass and increase in adipose tissue (24). Glucocorticoids appear to interfere with insulin and IGF-1 and are associated with muscle atrophy with increasing ageing. Decreased insulin action in older age may be secondary to reduced lean body mass and impaired ability of the muscle to respond to insulin (25). Insulin resistance may alter the rate of protein synthesis in skeletal muscle with

increased ageing. Raised levels of angiotensin 2 have also been associated with muscle wasting.

The regenerative potential of skeletal muscle and overall muscle mass decreases with ageing. This may be influenced by autocrine growth factors intrinsic to muscle itself. There may be extrinsic host factors that affect muscle regeneration including hormones, growth factors secreted in a paracrine manner by accessory cells, innervations and antioxidant mechanisms. There may be a decreased sensitivity to several hormones and growth factors in muscle with increased ageing. Another theory is that there may be a defect in signal transduction that could be associated with the ubiquitin system in ageing muscle cells (22).

1.3.2 Inflammation

Cytokines appear to have a role in muscle wasting. Tumour necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) may modulate removal and repair processes in skeletal muscle after injury and contribute to the sustained viability of muscle cells. Nerve Growth Factor (NGF), Ciliary Neurotrophic factor (CNTF), angiogenesis and connective tissue matrix formation influence successful muscle and neuronal repair processes. Successful muscle ageing will depend on successful muscle and neuronal repair mechanisms. Cumulative repeated episodes of incomplete repair of muscle may contribute to the age-related loss of muscle mass or function.

Reduction in muscle mass or function may be secondary to cumulative repeated episodes of incomplete muscle repair. This may be contributed to by an abnormal production or sensitivity to cytokines by the ageing cells contributing to the loss in muscle mass and function. Inflammatory cytokines may interfere with IGF-1 signalling in skeletal muscle contributing to sarcopenia. Interleukins and possibly other cytokines appear to stimulate both corticotrophin releasing factor (CRF) and prostaglandin E_{1α} production contributing to the reduced food intake associated with ageing (22).

Higher levels of reactive oxygen species (ROS) have been noticed in ageing skeletal muscle and linked to the occurrence of chronic inflammation. Myostatin (Mstn), a pro-oxidant, signals the generation of ROS in muscle cells and plays an important role in increasing protein degradation. Mstn induces oxidative stress by producing ROS in skeletal muscle cells through tumour necrosis factor-alpha (TNF-α) signalling via NF-κB and Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. TNF-α and hydrogen peroxide (H₂O₂) are potent inducers of Mstn and require NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) signalling for Mstn induction (26).

Several inflammatory mechanisms exist which down regulate myofibre number through inflammatory proteins including IL-6 and TNF-α via apoptotic pathways or through initiation of E3 ubiquitin ligases Murine Ring Finger-1 (MuRF-1) and Muscle Associated F-box (MAFBx/Atrogin-1) which breaks down protein (26).

1.3.3 Impaired nutritional intake and response to protein metabolism

With increased age, there appear to be multiple factors that contribute to a decline in food intake. These include: early satiety, partly due to reduced gastric fundus relaxation; increased cholecystokinin secretion in response to fat; increased leptin production by adipose tissue particularly in men; poor taste and smell; inflammatory cytokines associated with disease states; depression; medications and chronic conditions. A low calorific intake and low protein intake may result in a negative nitrogen balance and muscle breakdown and decrease in muscle mass (27).

1.3.4 Impaired protein synthesis with ageing

The synthesis of mixed muscle protein appears to be reduced by about one third with age and in studies that have looked at skeletal muscle breakdown rates appear to either not have changed or decreased with age. This imbalance between muscle protein synthesis and breakdown rates may contribute to the reduced muscle mass and quality of muscle seen with increasing age (24).

1.3.5 Reduced mitochondrial activity with ageing

It has been suggested that a decrease in the mitochondrial number or activity may account for muscle fatigability, decreased endurance capacity and muscle strength. Mitochondria generate ATP and are essential for the generation of contractile force. Hence ATP production is necessary to maintain repeated

contractile activity. Rodent studies have also demonstrated an associated decrease in glycogenolytic and glycolytic enzyme activities as well as creatinine phosphate (CrP), a rapidly mobilisable high energy phosphate. There is a decrease in actomyosin ATPase activity with ageing resulting in decreased contractility of muscle (16). There is a decrease in the sliding speed of actin on myosin from aged muscle and also a decrease in the fraction of myosin heads in the strong-binding, force-generating structural state. There is also a reduced oxidative capacity in older age, with a decrease in citrate, CrP and ATP in older human skeletal muscles compared to younger ones. The reduction in the mitochondrial functioning with ageing is thought to be secondary to the accumulation of somatic, detrimental mutations of mitochondrial DNA (mtDNA) (deletions, base substitutions, duplications and accumulated 8-hydroxy deoxyguanosine, a measure of oxidative damage to DNA) with increased ageing, also known as the “mitochondrial theory of ageing”.

1.3.6 Age related changes of the whole muscle and muscle fibre

Muscle is made up of two types of muscle fibres: type I, slow-twitch, which use aerobic respiration via oxidative phosphorylation and type II, fast-twitch, which use anaerobic metabolism via glycolysis (28). Muscle atrophy is the result of individual fibre atrophy, a loss of muscle fibre number, in particular loss of type II (with myosin heavy chain type II isoform) muscle fibres and possibly myofibre area (1). This may be secondary to increased apoptosis associated with mitochondrial DNA and capsase activity (9;29). There is limited evidence to suggest that there may be a link between fewer type IIa myofibres, increased

type IIa myofibre width and increased type I myofibre width in patients with lower birth weight. Muscle fibre number, influenced by genetic factors, appears to be a critical determinant of muscle mass and strength (9;29-31). Animal studies have revealed a decrease of about 20% in force generation for muscle cross-sectional area with ageing. Additionally there is increased denervation of motor units with ageing. These are replaced by slower motor units leading to muscle fatigability. Satellite cells also become fewer in number with ageing. These cells normally have an important role in muscle regeneration (9;32-33).

1.3.7 Altered ion channel and molecular signalling

There is a decrease in dihydropyridine and ryanodine receptors that translate membrane depolarisation into intracellular Calcium ion (Ca^{2+}) release and a reduction in functional dihydropyridine receptors leading to excitation-contraction uncoupling in old skeletal muscle. Specific force (P_o) and unloaded shortening velocity (V_o), two significant contractile parameters of muscle fibre decrease with increased age (16). Electron paramagnetic resonance (EPR) is a high resolution spectroscopic method which has been used to look at contractile proteins of muscle. EPR studies have shown age-related loss of specific force associated with a reduction in the fraction of myosin heads in the strong binding, force generating structural states. There are age-related molecular changes in myosin and actin which appear to be secondary to oxidative modifications (1).

It has been postulated that ion channels and their ability to respond to growth factors such as IGF-1 could be important in the underlying skeletal muscle impairment mechanisms with ageing. In ageing mice, a reduction in L-type Ca^{2+} channel expression leads to decreased peak cytosolic Ca^{2+} with subsequent reduced skeletal muscle force. K^{+} channels are important to both induce myogenesis and proliferation of muscle cells, and are modified by IGF-1. The over-expression of human IGF-1 in skeletal muscle increases the number and prevents age-related decline in sarcoplasmic reticulum dihydropyridine-sensitive voltage-gated L-type Ca^{2+} channels. Ion channels appear to have an important role in the age-related decline in muscle strength (22).

Several possible intracellular signalling mechanisms (phosphatidylinositol-3-phosphate kinase (PI3K), protein kinase b (Akt) and mammalian target of rapamycin (mTOR)) exist through which an up regulation of myofibres can occur. These molecular signalling molecules are up regulated by ligands including IGF-1, which regulates myoblast proliferation *in utero* and muscle protein synthesis and hypertrophy through increased protein transcription (22).

1.4 Influences of early life

Previous epidemiological studies, systematic reviews and meta-analyses have shown that there is a strong association between birth weight and skeletal muscle mass and strength throughout life but particularly in middle as well as

older age (34-37). This was particularly demonstrated in the Hertfordshire Ageing study. This birth cohort study followed the life course of men and women born in Hertfordshire in the UK between 1920 and 1930 into their later years. Birth weights were recorded by health visitors at birth and 1 year and obtained through the National Health Service Central Registry in Southport. 717 patients from this group were recruited and interviewed at home and agreed to attend local clinic for measurements of markers of ageing including hand grip strength. Those with lower birth weight and lower weight at 1 year had a significantly weaker hand grip in later life independent of adult size (38;39). Following this a larger Hertfordshire Cohort study (HCS) was established to examine the effects of genetic and early environmental influences and adult nutrition and lifestyle on health, ageing and disease in people born between 1931 and 1939 (40). A positive relationship was found between birth weight and adult body mass which may reflect pre-natal and maternal influences on fat-free mass in older people. Early dietary exposure can have a life-long influence on food choice. Variations in dietary intake of community-dwelling older women may be linked to differences in physical performance. Participants in the HCS with sarcopenia were reported to be shorter, weighed less and had worse physical performance and self-reported poorer general health.

The retrospective cohort studies such as the Hertfordshire Cohort Study enabled the study of influences operating over a long period but did not have sufficient detailed early data to identify specific early nutritional influences. The Southampton Women's Survey addressed this and examined the early

nutritional influences on birth weight, fat and lean muscle mass. This study recruited 12,500 women in their 20's and 30's living in Southampton and conducted interviews to assess health, body composition, lifestyle and diet. Data from 448 mother-offspring pairs were looked at to examine parental influences on neonatal body composition. Women that were taller, had higher parity and had offspring with higher birth weight, fat mass and lean mass. It also showed that maternal walking speed was negatively associated with birth weight. Fat mass was positively predictive of neonatal total and proportionate fat and negatively associated with lean mass (41;42).

The Health, Aging and Body Composition study reviewed body composition and knee extension strength over 7 years follow-up of 2307 men and women between 70 and 79 years of age. It found that higher fat mass measured using dual energy X-ray absorptiometry was associated with an accelerated decline in lean muscle mass not explained by higher levels of adipocytokines and insulin resistance. There was no association between fat mass and knee extension muscle strength (43).

1.5 **Research tools for measuring sarcopenia**

Sarcopenia has been studied in terms of the triad that make up the syndrome (loss of muscle mass, strength or performance). It requires periodic review of the same measurements accurately over time to recognise a change in the

same individuals. See Table 1. Cost, availability of equipment and ease of use determine whether tools used to measure sarcopenia are better suited to research or clinical practice.

Muscle mass has been measured using various techniques in research (CT, MRI, DEXA, bioimpedance analysis, urinary excretion of creatinine and total or partial body potassium per fat-free soft tissue) and in clinical practice (with bioimpedance, DEXA and anthropometry) (44;45). DEXA, anthropometry and bioelectrical impedance analysis (BIA) are the most commonly used low cost and accessible techniques for measuring skeletal muscle mass in research (44). The most specific gold standard methods of assessing muscle mass or cross sectional area of muscle are MRI, CT and creatinine excretion.

Skeletal muscle strength has been measured using dynamometers to measure hand grip and quadriceps strength and peak expiratory flow, to indirectly measure skeletal muscle strength involved in breathing. The use of simple dynamometers to measure hand grip strength has been found to be a good surrogate measure for other more complex muscle groups and has strongly correlated with lower extremity muscle power (44).

Skeletal muscle performance has been measured using gait speed, timed get-up-and-go, standing balance, 4 metre walk test, 6 minute walk test and stair

climb power test. These tend to be the most commonly and validated measures of physical performance (44;46). The European Working Party in Sarcopenia for Older People recommended grip strength for the measurement of muscle strength and function as a good simple tool for use in clinical practice (47-51).

Table 1: Measurements of sarcopenia in research and practice (47)

Variable	Research	Clinical practice
Muscle mass	Computed tomography (CT) Magnetic resonance imaging (MRI) Dual energy x-ray absorptiometry (DEXA) Bioimpedance analysis (BIA) Total or partial body potassium per fat-free soft tissue	BIA DEXA Anthropometry
Muscle strength	Grip strength Knee flexion/extension Peak expiratory flow	Grip strength
Physical performance	Short Physical Performance Battery (SPPB) Timed get-up-and-go Stair climb power test	SPPB Usual gait speed Get-up-and-go

Pro-inflammatory cytokines (TNF- α , IL-1, IL-6) have been shown to have independent associations with lower muscle strength, reduced physical function

and higher risk of disability in older people (52;53). Oxidised low-density lipoprotein (oxLDL), an oxidative damage biomarker has also been found to be an independent predictor of reduced mobility (54). Reduced grip strength has been associated with protein carbonyls, markers of lipoprotein peroxidation. Other biological markers associated with sarcopenia include: C Reactive protein (CRP) has been associated with weak grip strength; anaemia associated with lower muscle strength; reduced albumin associated with weak hand grip (55); low plasma selenium levels with reduced hand grip (56); high plasma uric acid levels with stronger hand grip and quadriceps strength (56); higher magnesium levels with better muscle performance and strength; low serum 25-hydroxyvitamin D levels with reduced muscle mass measured using DEXA and reduced grip strength. However, several of these markers are associated with several other conditions and have limited specificity for sarcopenia, therefore their use is limited (44).

1.5.1 Feasibility of measuring grip strength in older people

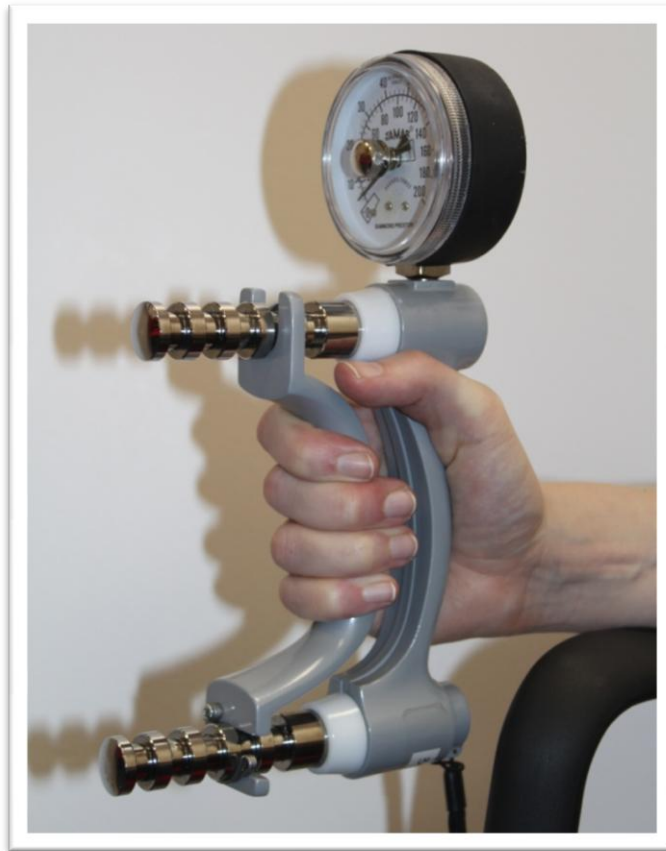
Measurements of grip strength can be done in a timely manner and are easily reproducible. Previously grip strength has been shown to be an acceptable measure in hospitalised older medical patients in international studies (49). Additionally the measurement of grip strength in older hospitalised patients who may have cognitive impairment or physical frailty has been previously been found to be acceptable and reproducible (58).

A study in the UK compared older people's views on having grip strength measured in four different health care settings: out-patient clinic, rehabilitation ward, physiotherapy referrals and care home. Patients found this was an easy test to perform and felt it may be useful to have it measured to see if there was any change in strength over time (49). Patients excluded from the study had moderate to severe dementia precluding informed consent and included those with injury, arthritis and stroke. Patients in nursing homes that were recruited found it easy to do and were generally in agreement to have the test repeated in the future. A minority found grip to be painful and tiring to do (59). Some patients complained of minor discomfort and fatigue but these were not reported as significant. It was concluded that grip strength was attainable even in the acute setting and frailer individuals. Consent caused more reluctance than the test itself. Most studies exclude the most severely ill or cognitively impaired because of their inability to be able to obtain consent. However this is a common limitation found in studies in older people (58).

1.5.2 Practical benefit of using hand grip

Hand grip has been used as a marker of physical strength. See Figure 5. Patients with weaker grip have been shown to have longer length of hospital stay and higher all-cause mortality (49; 60-62).

Figure 5: Hand grip being performed using a Jamar dynamometer



Data from the Hertfordshire Cohort Study showed that a 1 kg increment in male grip strength was associated with a reduction by 0.07 seconds in the six minute timed get-up-and-go test and 0.02 second decrease in the 3 minute walk time plus a 1% decrease in stand time with $p < 0.001$. In women a 1kg increment in grip strength was associated with a 0.13 second reduction in the six minute timed get-up-and-go test and a 0.03 second decrease in the 3 minute walk and a 1% decrease in stand time with $p < 0.001$ (57).

1.5.3 Differing dynamometers: how grip strength is measured

Grip is widely used to quantify skeletal muscle strength and reflects muscle function. Several dynamometer models are available; however the Jamar tends to be the most widely used. This has been shown to have good intra- and inter-rater reliability and reproducibility. Other models include the Dexter, Baseline and Rolyan dynamometers. Dynamometers can be subdivided into hydraulic, pneumatic, mechanical and strain type. Each type of dynamometer has its own advantages and disadvantages including ease of use and units measured (49). See Table 2.

Table 2: Comparison of hand dynamometers adapted from (49)

Instrument Type	Hydraulic	Pneumatic	Mechanical	Strain
Example	Jamar	Martin Vigorimeter	Harpenden	Isometric Strength Testing Unit
Grip Measures	strength	pressure	strength	strength
Unit of measure	Kilogram or pound of force	Milimeters of mercury or pounds per square inch	Kilograms or pounds of force	Newtons of force
Advantages	Portable, Economical, Large amount of normative data	Gentler on weak or painful joints	None shown	Not subject to leaks which can compromise accuracy
Disadvantages	Can cause stress on weak joints. Can develop slow leaks and hysteresis	Hand size can influence measurement	Difficulties in replicating grip position and in calibration	Can be expensive and heavy

1.5.4 Protocols for establishing grip strength

Across different countries and regions, a variety of dynamometers and protocols are used. Not all studies give detailed protocols consequently it is difficult to compare study results. Additionally the lack of a standardised technique in measuring grip strength and use of dynamometers makes it difficult to compare study outcomes (49).

Several studies have shown that grip strength is greater in men than women. A UK study showed that men had grip strength twice as strong as women in the over 65 year olds which was significantly related to demispan and body mass index (63). After four years follow-up, there was a decline in grip strength of 12% in men and 19% in women.

Several studies have looked at grip strength in men and women of different ethnicities with age but few have compared the influence of ethnicity alone for its impact on strength and sarcopenia.

1.6 Associations with grip strength

Strong hand grip, a reflection of increased skeletal muscle strength, has been associated with male gender, Caucasians, higher body mass index (BMI), increased weight, higher mini-mental state examination (MMSE) scores, higher Barthel indices, discharge to own home and younger age. Weaker hand grip, a

reflection of weak skeletal muscle strength, has been associated with female gender, Asian origin, lower BMI and older age. These relationships may reflect the influence of muscle mass and strength on physical function.

1.7 Muscle strength and rehabilitation

Grip strength has been used as a research tool to identify patients' length of stay. A prospective study that recruited 100 participants found that particularly male in-patients with stronger grip strength were associated with shorter stays on a rehabilitation ward. Potential confounding factors to the study included availability of health and social care and personal choice to undergo rehabilitation. However, this study replicated results found in the acute medical, oncology and surgical setting. Conversely patients with weak grip had longer stays and increased complications (50).

A further study recruited 110 patients admitted for rehabilitation to a community hospital. Those with increased grip strength particularly male patients were associated with a reduced length of stay and an increased chance of being discharged back to their pre-hospital residence (58).

1.8 **Sarcopenia: an association with falls and immobility**

Sarcopenia is associated with an increased risk of falls, fractures and reduced mobility (64;65). A cross sectional survey in the United States involving 4504 participants over 18 years and older looked at the prevalence of sarcopenia with increasing age. Muscle mass was measured using bioimpedance. Participants were defined as having class I sarcopenia in those who had a skeletal muscle mass index within one to two standard deviations of younger adults and class II sarcopenia with skeletal muscle mass indexes below two standard deviations of young adults. Sarcopenia was shown to be more significantly prevalent in participants over 60 year of age for both class I (59% compared to 45%), and class II (10% compared to 7%) compared to younger participants ($p < 0.001$). Functional impairment and disability was two times greater in older men and three times greater in older women with sarcopenia class II than those with normal skeletal muscle mass indexes of the same age group (66).

A further study looked at the relationship between sarcopenia and falls risk. 260 patients from the Sirente region in Italy with sarcopenia had a three-fold increased risk of falls over a two year follow-up irrespective of age, gender and other confounding factors (67).

Similarly, the Hertfordshire study, which collected data from 2148 participants showed an inverse relationship between falls and adult grip strength, height and walking speed in men and women (34).

1.9 **Sarcopenia: association with longer hospital admission**

Several studies have reviewed the impact of sarcopenia on recovery from acute medical admissions, rehabilitation and discharge to pre-admission destinations. Patients with normal cognition or mild cognitive impairment fare better than those with severe cognitive impairment (68-70). Patients with sarcopenia were more likely to have prolonged hospital stay and increased risk of re-admission than those that did not have sarcopenia (71).

A prospective study identified patients admitted to acute wards for older people in hospital with sarcopenia using DEXA and appendicular skeletal muscle mass expressed. Those diagnosed with sarcopenia had twice the risk of developing a hospital-acquired infection and an increased risk of reduced mobility (72).

1.10 **Sarcopenia: association with increased mortality**

Additional research has looked at whether there may be increased mortality associated with the reduced functional performance of muscle with age.

A study across eight regions of the UK followed up participants of 65 years and over with baseline grip strength during 1973 and 1974 and monitored mortality over a 24 year period. Grip strength was used as a measure of sarcopenia. Male participants with weaker grip strength had greater all-cause mortality, cardiovascular disease and cancer than those with stronger grip strength;

however similar results were not demonstrated in women (73). Another study also demonstrated increased mortality and poorer hospital outcomes in patients with weaker grip strength (74).

A study looked at mortality in 82 older women admitted to acute medical wards. This study also used grip strength as a measure of sarcopenia. Those who died had significantly weaker grip strength ($p < 0.01$) and arm muscle circumference ($p < 0.05$). Maximum grip strength of 5 kg was shown to be the most sensitive and specific determinants separating those who survived and those who died (75).

A further study recruited 2292 patients between 70 and 79 years old. It looked at grip strength and muscle mass as measures of sarcopenia in relation to mortality. Measurements of grip strength (using knee extension and hand grip) and muscle mass (using CT of thigh muscle area and DEXA of arm and leg areas) were recorded. 286 participants died over a 4.9 year period. Grip and knee strength were highly associated with an increased mortality whereas muscle mass was not shown to be significantly associated with mortality (70).

In a study following 8006 Japanese-American men over a 27 year period, participants that died prematurely to follow-up at 27 years had a significantly

weaker baseline grip strength (mid life grip strength) compared to those that survived to follow-up (76).

1.11 Sarcopenia and surgical recovery

Patients with colorectal carcinoma and pancreatic adenocarcinoma pre-resection demonstrated to have sarcopenia have increased post-operative infections, lengths of stay, post-operative rehabilitation times and mortality (77;78).

There is increasing interest in identifying pre-operative markers that will indicate post-operative outcomes including risk of complication, length of stay and mortality in older patients (80-82).

Sarcopenia is being considered as a significant prognostic marker for post-operative pancreatic adenocarcinoma resection. A follow-up study of mortality in pancreatic adenocarcinoma resection showed that patients demonstrated to have sarcopenia based on pre-operative muscle mass imaging had a 63% increased mortality at 3 years (78).

Conversely, post-operative resistance training in patients requiring elective hip replacement surgery has been shown to increase muscle mass, strength and function, and reduced length of hospital stay (83).

In patients undergoing radical cystectomy for urothelial cancer, sarcopenia, measured by psoas muscle area on CT was associated with longer hospital stays and higher 90 day complication rates (47).

1.12 **Sarcopenia and disability**

Previous studies have reported an association between sarcopenia measured using several tools including grip strength and disability (79;80). One such cohort study carried out over a 25 year period measured grip strength, walking speed, ability to rise from a chair, self-reported upper extremity strength, mobility and self-care disability and mortality in healthy Japanese-American men between the ages of 45 and 69. It showed that hand grip in middle age was predictive of future disability (79).

Another study looked at hand grip in 140 older healthy men between 71 and 91 years old. Weaker grip strength adjusting for confounders was found to be a predictor for disability (84).

Another study investigated the association of sarcopenia with reported disability. This epidemiological study carried out in New Mexico included 883 elderly Hispanic and non-Hispanic white men and women with sarcopenia being defined by a reduced appendicular skeletal muscle mass less than two standard deviations below the mean of a young reference group. It showed that the prevalence of sarcopenia increased from 13 to 24% in the under 70 year old age group to over 50% in the over 80 year olds. Self-reported disability was slightly increased in those with sarcopenia irrespective of other factors including age, ethnicity, obesity, income, morbidity and health behaviour (85).

A further Mexican cohort study over a 7 year period also looked at grip strength as a predictor for disability in older men and women over 65 years old. 2493 community dwelling subjects were recruited and maximal hand grip strength, body mass index, cognitive function, activities of daily living and co-morbidities were recorded. It showed there was a linear relationship between grip strength and activities of daily living independent of other factors (80).

1.13 **Sarcopenia and institutionalisation**

Several studies have reported increased prevalence of sarcopenia in older people in institutionalised care using measures of grip strength, muscle mass and physical performance (81).

An Italian study of 140 nursing home residents with sarcopenia based upon their reduced muscle mass, strength and performance measurements were monitored for mortality. It found that about one third of residents had sarcopenia and was associated with an increased risk of all-cause mortality (81).

1.14 **Management of sarcopenia**

Despite there being a consensus in the definition of sarcopenia, there is a lack of consensus in the diagnostic criteria of sarcopenia and management of it. Optimising diet throughout life of an adequate quality and quantity, sufficient in protein, vitamin D and anti-oxidants are felt to be beneficial in prevention of sarcopenia. Evidence for this is mainly observational of older patients lacking in these nutritional requirements (27). Further research is being undertaken to better understand the mechanisms causing sarcopenia to try and prevent or manage sarcopenia. Currently resistance training is thought to be beneficial in limiting the effects of sarcopenia as well as physical activity. An alternative strategy may be through medical intervention. There is research looking at the use of ACE inhibitors in improving muscle exercise capacity in older patients with reduced muscle function. This may occur through angiogenesis, limiting inflammatory processes and increasing neuro-hormonal processes (86).

1.15 Sarcopenia and respiratory muscle strength

With increasing age the changes that occur to muscle are thought to be generic affecting all muscle groups including respiratory muscles. Grip strength and lung function have been demonstrated to decrease with increasing age. There is already a considerable interest in measuring respiratory muscle strength through measuring spirometry, diaphragmatic thickness and inspiratory and expiratory pressures in the context of critical care, surgical outcomes, COPD and malnutrition but less so with ageing.

1.16 Lung structure and function

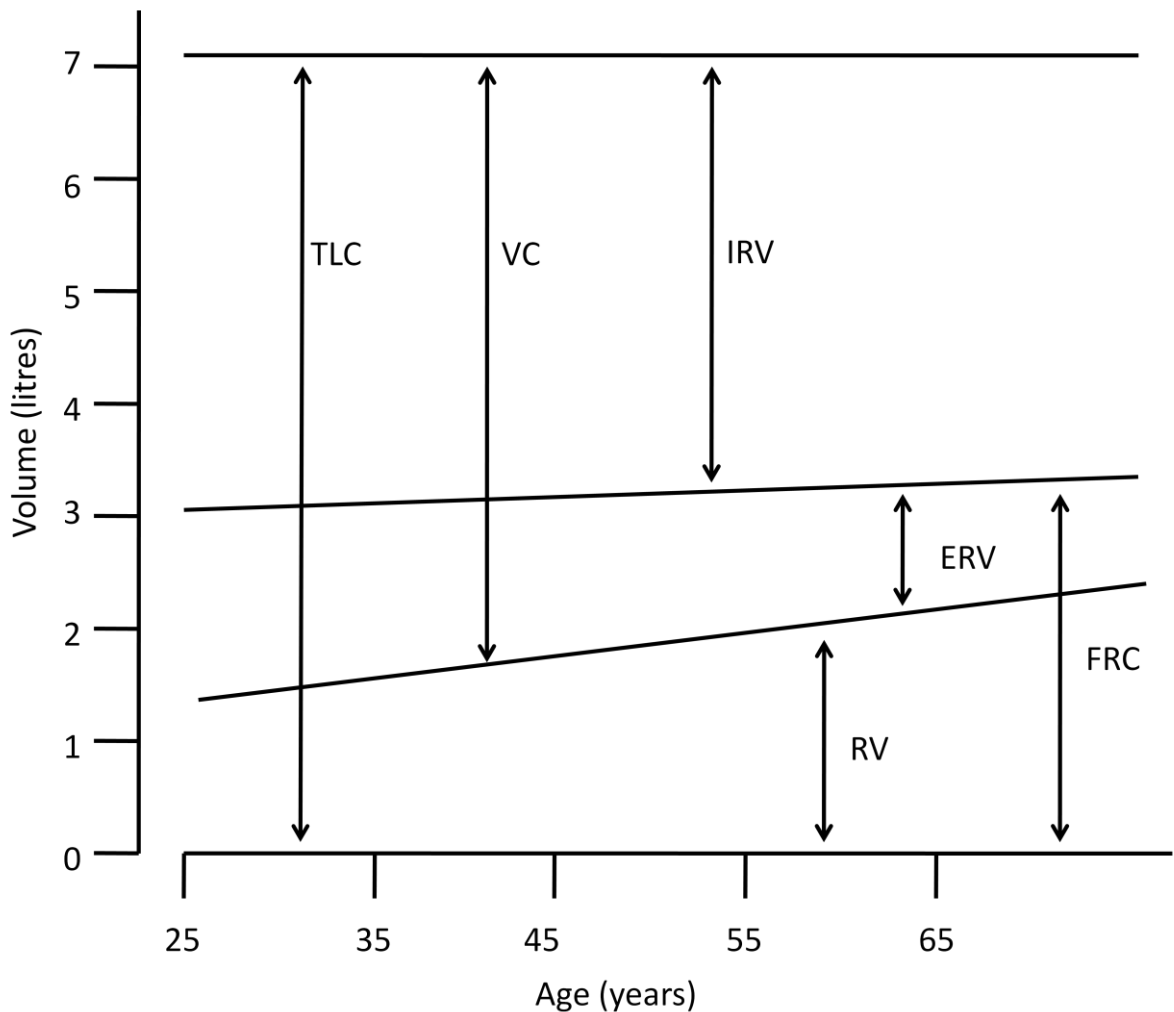
Increased lung volume in puberty is related to increased thoracic length. In girls the growth spurt has occurred between 11 and 16 years of age, by which time maximum lung volumes have been attained. In boys, the growth spurt occurs between 13 and 18 years and lung growth and lung volume measurements peak between 20 and 25 years. Lung architecture (including air sacs, alveoli, bronchioles through to trachea) are all larger in men compared to women. Men have increased muscle strength and vital capacity and therefore have larger ventilatory capacity compared to women.

1.17 Lung function and sarcopenia

Air flow during forced expiration is a consequence of respiratory muscle strength and airways resistance. The lungs' elasticity constantly exerts an

inward force against the stiffer chest wall and respiratory muscles. The intrathoracic airways are compressed when exposed to raised intrathoracic pressure generated by forced expiration. Therefore during forced expiration, airway resistance is dynamic and changes with lung volume, effort and air flow. At a particular point, the intraluminal pressure equates to the pressure surrounding the airway. Beyond this point, the pressure falls below the surrounding pressure, and the affected airway segment is compressed, limiting the flow. Hence increased effort raises both the driving pressure and the airway resistance, flow then becomes subject only to pulmonary recoil pressure which is itself dependent on lung volume (87). With ageing, expiratory flow rates decrease. This is associated with reduced respiratory muscle function and increased airways resistance (secondary to reduced chest wall and lung parenchyma compliance). As a result, there is increased air trapping, increased functional residual capacity (FRC) and increased work of breathing (88). Figure 6 illustrates the changes that occur with lung volume with increasing age.

Figure 6: Changes in lung volumes with ageing (88)



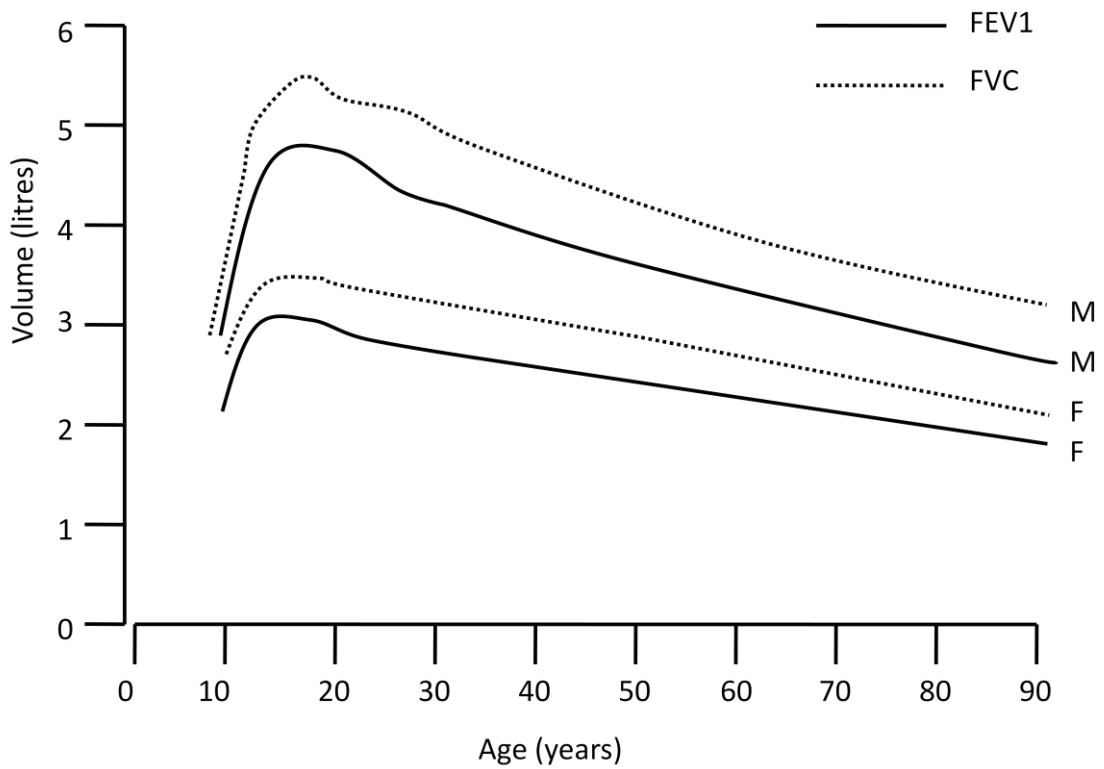
TLC: total lung capacity; VC vital capacity; IRV: inspiratory reserve volume; ERV: expiratory reserve volume; FRC: functional residual capacity; RV: residual volume.

Age-related airway compliance changes contribute to the declining ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) with ageing. See Figure 7. This leads to increased airflow obstruction during forced

expiration. Consequently, many older people may meet the spirometric criteria for obstructive airways disease despite no other clinical evidence of lung pathology.

Figure 7: FEV1 and FVC changes with ageing (based upon data from 746 subjects with no cardio-respiratory symptoms who had never smoked)

(88)



M: males; F: females

An additional explanation is that older people may be unable to generate and sustain sufficient expiratory pressure to reach and hold maximum flow as lung volume falls from total lung capacity (TLC) to residual volume (RV)

particularly in the initial phase of expiration when flow is more effort dependent secondary to reduced expiratory muscle strength (EMS). Older people particularly those with indicators of frailty may be unable to generate and sustain sufficient expiratory pressure to reach and hold maximum flow as lung volume falls. This may be secondary to expiratory muscle weakness. Therefore, expiratory muscle weakness may be an expression of the more generalised sarcopenia often found in frail older people. It has been previously recognised that skeletal muscle strength and EMS decrease at a similar rate with ageing. This study used grip strength, a measure of skeletal muscle strength, to reflect EMS in investigating the relationship between EMS and lung function.

1.18 **Research looking at muscle strength and lung function**

There is an increasing interest in not only looking at sarcopenia in terms of limb function and strength but also with regard to lung function (89). Previous studies have looked at lung function in older patients and postulated that changes occurring with increasing ages are related to increased lung compliance (or decreased elastic recoil) and reduced chest wall compliance (or increased chest wall stiffness) (89). The decreased expiratory phase of lung function produced by the decreased elastic recoil of the lungs in passive expiration is also contributed to by a reduced action of the expiratory muscles (lateral internal intercostals and abdominal muscles) in active expiration. Expiratory muscles also play an important part in non-ventilatory functions including coughing,

talking and swallowing. Alternative measures of respiratory muscle strength used in previous studies include measuring maximum inspiratory and expiratory pressures (89). Expiratory type II muscle fibres appear to atrophy with age according to one post mortem study (90).

In addition to the overall decline in muscle mass and strength previously noted, it has also been demonstrated that there is a decline in respiratory muscle mass and strength. Several studies have shown that with increasing age there is a decrease in respiratory muscle strength (91).

Peak expiratory flow has been used as a research tool in assessing respiratory muscle strength. It has been used in studies looking at malnutrition, chronic medical diseases in particular COPD, smokers and ex-smokers and surgical patients. However few studies have looked at spirometry in healthy individuals without known lung disease. A positive correlation between skeletal muscle strength and spirometry has been found in healthy men and women (92).

FEV1 has been considered to be a strong predictive factor in determining physical performance in older patients with COPD (93;94). COPD has been shown to be associated with reduced muscle mass, performance and respiratory function including FEV1 (93-95). A study of 71 subjects with COPD aged over 65 years underwent a timed six minute walking test, and

appendicular lean mass and FEV1 were measured. The study showed that respiratory function was strongly associated with physical performance in older people with COPD (93).

Decreased muscle mass has been inversely associated with the Medical Research Council dyspnoea score and the Activity component of the Saint George Respiratory Questionnaire (95-97).

A study involving 289 Indian female subjects, 30 females 20-25 years of age and 259 females aged 55-80 years of age. It measured amongst other anthropological measures FVC, PEFr and hand grip strength. It showed a significant correlation of lung function with age ($p < 0.01$) and hand grip strength with age ($p < 0.01$). Additionally a significant positive correlation of FVC and PEFr with hand grip strength. However this study did not exclude co-morbidities or smoking history in the subject group (98).

Studies have commonly used measurements of maximal static inspiratory pressure (PI_{max}) and maximal static expiratory pressure (PE_{max}) to measure respiratory muscle strength. However participants need to be able to learn the manoeuvres. A moderate positive correlation between maximal inspiratory pressure, a measure of respiratory muscle strength, body weight and fat-free mass was shown in 54 patients with COPD whilst having in-patient pulmonary

rehabilitation (94). An alternative measurement which does not require so much cooperation from participants is the diaphragm thickness (tdi) in the area of apposition of the diaphragm to the rib cage using two dimensional (2D) ultrasound (99).

1.19 Lung function with ageing

In older age, the rate of decline in lung function is similar between men and women. It is due to decreased muscle strength, reduced compliance of the rib cage, deterioration in lung parenchyma, reduced elastic recoil and increased chest wall rigidity thought to be secondary to endogenous and external factors. See Figure 8. Total lung capacity is unchanged with older age. However Functional Residual Capacity (FRC) and Residual Volume (RV) increase, and Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1) and Peak Expiratory Flow (PEF) decreases (100). Increased airway size and reduced alveolar surface limits efficient gas exchange and premature closure of smaller airways may cause a ventilation perfusion mismatch.

The international Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommends that spirometry is an essential diagnostic tool in Chronic Obstructive Lung Disease (COPD). More patients are being investigated and diagnosed with COPD than in the past (101). COPD is a leading cause of morbidity and mortality worldwide responsible for an increasing

social and economic burden. Estimates of prevalence, morbidity and mortality vary across countries and this variation may be due to differences in diagnostic criteria, surveying and analysis of results. COPD is more prevalent in smokers and ex-smokers than in non-smokers and higher in those over 40 years of age than those younger than 40 years of age (101). Spirometry is used to monitor the response to treatment, assess disability and used in respiratory rehabilitation (102-103). It measures the volume or flow of air a subject can inhale or exhale over a period of time.

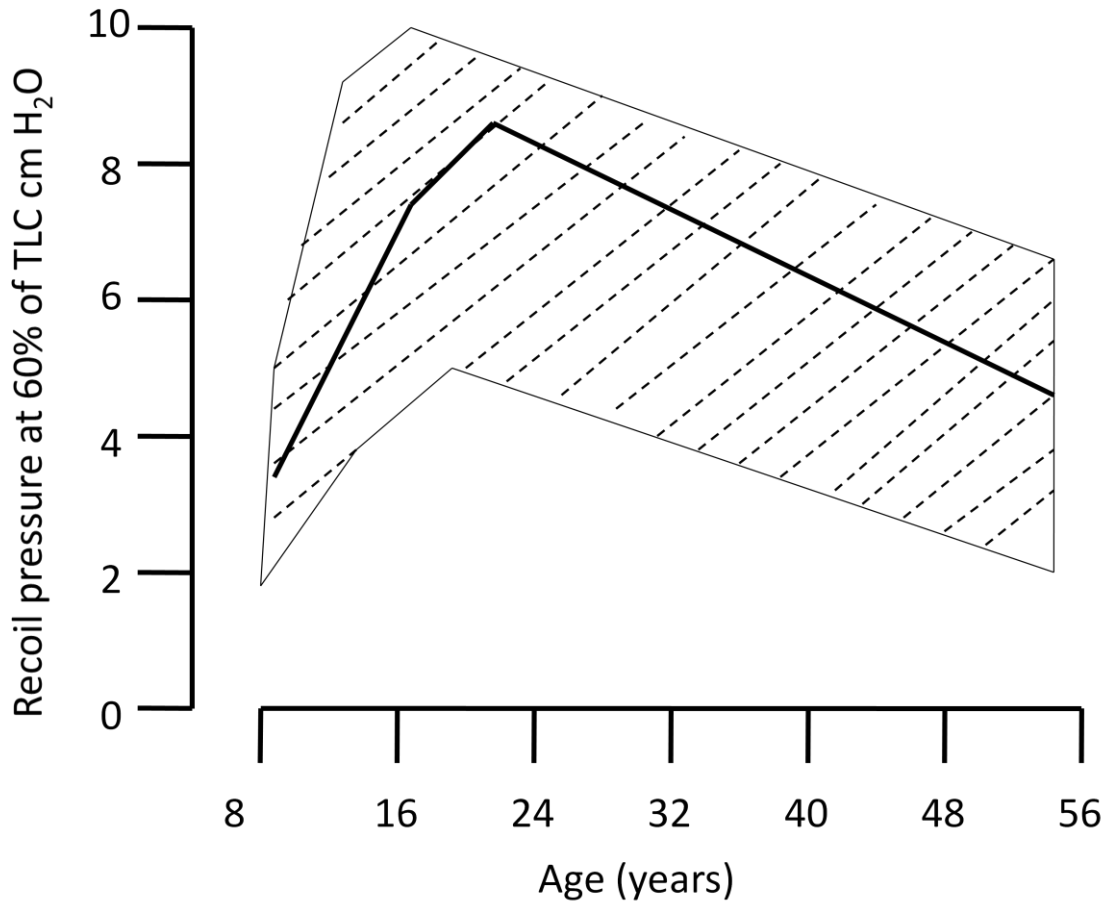
It is being increasingly recognised that obstructive airways disease is being over-diagnosed because of the current predictive spirometry criteria being used in older people. The Global Initiative for Chronic Obstructive Lung Disease definition for stage 1 COPD is FEV1/FVC of $<70\%$ and FEV1 predicted $>80\%$ and stage 2 COPD as FEV1/FVC $<70\%$ and FEV1 predicted of $<80\%$. These definitions are set regardless of age in order to simplify the diagnosis. However given that FEV1/FVC falls with age, the fixed criteria for defining COPD becomes less accurate with increasing age (104). Normal ageing may mimic COPD partly because of loss of elastic tissue in the lung parenchyma, increasing the airways dynamic collapse in expiration that may simulate true obstruction when examining FEV1 as well as a rise in residual volume (104).

In a study of 71 healthy elderly recruited participants who had never smoked and were able to perform spirometry, about 35% had an FEV1/FVC $<70\%$ and

would have been classified as having stage 1 COPD. Of those over 80 years old about 50% would have been classified as having COPD and about one third had an FEV1<80% predicted (104).

In older people it is recognised that the normal predicted values are likely to be different to that of younger people, for example FEV1/FVC ratio being 0.65-0.7 compared to 0.7-0.8 in younger people. Older people in spirometry guidelines are defined as patients over 70 years old.

Figure 8: The decline in static elastic recoil with normal ageing. The shaded area showing $\pm 1SD$ of plotted means (88).



1.20 Spirometry in older people

Spirometry has generally been used in research in older people with known lung disease (such as asthma or COPD) alongside walking speed and activity of daily living to assess physical functioning. Very little research has been done looking at lung function with increasing age without lung disease (105).

A study recruited 715 elderly participants with respiratory symptoms. 81.8% of participants were able to perform spirometry according to the ATS criteria of spirometry whereas 18.2% were unable to do so. Age alone was not found to be a significant marker for being unable to perform spirometry, however reduced cognition and immobility made it less likely that these patients could perform spirometry well (106).

1.21 **Determinants of spirometry**

Predicted values tend to be based on local values, although sometimes these are based on those calculated by the European Respiratory Society or the European Community Health and Respiratory Survey (ECHRS) or on International values. These are all calculated based on values using healthy people varying in gender, height, age and ethnicity using spirometric data in which patients were able to complete 3 blows within 5% or 150ml of each other (107-109). Another study used data from the 1995/1996 Health Survey for England to derive new spirometric reference equations for the English population. Of note, a large number of patients over 75 years old were excluded as they were unable to reproduce acceptable spirometric standards set by the study (107-109).

Lung size varies between ethnic groups. This is partly due to differences in trunk length compared to standing height. However it thought that there is no

significant difference in alveolar size or airways dimensions (108). The Global Lung Function Initiative (GLI) has devised equations for multi-ethnicities across different ages based on 74,187 healthy non-smokers, 57.1% were female and the participants were aged between 3 and 95 years old (109).

Other factors that can contribute to lung size include nutrition, physical activity during childhood, high altitude and exercises that develop shoulder girdle muscles (108). Cognitive impairment, as evidenced by a MMSE <24/30 and inability to copy intersected pentagons has been shown to predict inability to perform spirometry. Alternative measures such as CLOX has not been shown to perform better than these (110).

Patients' height is characteristically measured without shoes, with feet together, standing as tall as possible with eyes looking directly ahead using a stadiometer. Performing standing height is the basis for many reference equations used in spirometry. However, in patients unable to do this because of kyphoscoliosis, chest wall deformity, degenerative conditions of the spine or neurological or muscular disease, arm span or ulna length may be used instead (100). The premise for these alternative measures are that arm span or ulna length do not decrease with age and may be more representative of height at maturity (111). Arm span is measured from finger tip to finger tip. Ulna length is measured from between the point of the elbow (olecranon process) and the midpoint of the styloid process of the wrist. An alternative method has been to

use knee height to estimate height in patients where arm span was difficult to measure (112).

A small study looked at whether slow vital capacity (SVC) was better than forced vital capacity (FVC) measurements in older people. SVC was not found to be superior to FVC in patients with reduced cognition (MMSE<24) but was useful in patients who tended to cough when performing spirometry (113).

1.22 Spirograms

Interpretation of lung values requires comparing actual values to predicted values and looking at the shape of the spirogram. Expectations in the repeatability of spirometry include patients being able to complete 3 blows within 5% or 150ml of each other. Spirometry allows the measurement of expiratory flow rate versus volume. In a normal healthy subject, the spirogram produced would show a rapid rise in expiratory flow rate to maximal expiratory flow followed by a uniform decline until all air is expelled. In a subject with airflow obstruction, there would be a less rapid rise to maximal expiratory flow followed by a more concave dip in the second part. In patients with more severe airflow obstruction, there would be a rapid decline in flow after maximal expiratory flow had been reached. A restrictive picture would be more apparent if there was a global decrease in lung volume but with a normal shape flow rate versus volume curve (101).

1.23 **Pitfalls in spirometry**

Older individuals and some young people find spirometry a difficult technique to master. The predominant problems hindering performance include fatigue, dyspraxia and cognitive impairment (103). A common reason for repeatability not being achieved is patient technique. This can only be corrected by observing what the patient does and looking at the spirogram. Not all patients can repeat spirometry to improve technique because of increased fatigability with repetition. For others it may be too physically demanding such as post myocardial infarction, hence these patients are excluded for the first month (114). Additionally, spirometry is inappropriate in those with significant cognitive impairment (MMSE<24) and requires reasonable executive functioning. Several cognitive tests have been carried out including CLOX, MMSE and Intersecting pentagons in relation to spirometry. CLOX has not been shown to perform any better than MMSE or intersected pentagons (IP) therefore MMSE is the standard normally used (110).

Other problems with patients' technique include inadequate inspiration, reduced blast effort in expiration, delayed onset of maximal expiratory effort, incomplete emptying of the lungs, additional breath during expiration, poor lip seal allowing for leaks, slow start to blow, expiration through the nose rather than through the mouth, glottic closure, obstruction of the mouthpiece by teeth or tongue and poor posture. Operator problems include lack of knowledge and training in the instrument used and poorly maintained and calibrated spirometer (101).

Acceptability of expiratory blow criteria includes a satisfactory start and end of test. This requires observation that the subject understands the instructions and performs the manoeuvre with maximum inspiration, good start, smooth exhalation and maximal effort. The subject may cough during expiration, but so long as this doesn't interfere with the measurement of an accurate result, the spirogram can be accepted (102).

1.24 **Predicted values in spirometry**

Several prediction equations have been used locally, regionally, nationally and internationally (European Respiratory Society or the European Community Health and Respiratory Survey (ECHRS)) to estimate predicted spirometric values according to age, gender, ethnicity and body size based on the appropriate population. Several of these equations are based on populations up to 75 years of age and have not been done in older age groups. Therefore it is likely that these equations are not representative if looking at recruited subjects in their 80s and 90s (107).

This is evidenced by one UK prediction tool that used sample numbers across age groups as follows: 931 (in 16-24 age group), 1422 (in the 25-34 age group), 1333 (in the 35-44 age group), 969 (in the 45-54 age group), 676 (in the 55-64 age group), 486 (in the 65-74 age group), 185 (in the 74-84 age group) and 33 (in the over 85 age group) (107).

1.25 Summary of key points

- Sarcopenia is defined by the loss of muscle mass, strength and physical performance.
- There are several mechanisms leading to sarcopenia across the life course including endogenous and exogenous factors.
- The consequences of sarcopenia have socio-economic impact on society and have several consequences for the individual.
- COPD may be over diagnosed in older people.
- Few studies have incorporated numbers representative of the increasingly healthy older population in predicted values for spirometry.
- Very little research has been done in older individuals using spirometry and grip strength measurements except in smokers, those with COPD or cardio-respiratory disease.
- Spirometry has previously not been used to measure respiratory muscle strength.
- This study looked at spirometry as a surrogate marker for respiratory muscle strength.

The primary aim of this study was to evaluate the association between grip strength and lung function in older hospitalised patients.

2. Method

2.1 Study design

This was a prospective study on hospital in-patients over 70 years of age measuring lung function and grip strength.

2.2 Study setting

The study was carried out on four acute older people's wards at Southampton General Hospital over a six month period from April 2012 to September 2012.

2.3 Participants

2.3.1 Inclusion and exclusion criteria

The inclusion criteria for recruitment were: age over 70 years; a history of never smoking or trivial smoking less than 1 year; no history, symptoms or signs of respiratory disease; negative for bronchial obstruction on the European Community and American Thoracic Society (ECAT) questionnaire.

Exclusion criteria were met: if any participant was unable to meet the inclusion criteria, MMSE \leq 24 or had any contraindication to performing spirometry according to the Association for Respiratory Technology and Physiology

(ARTP) guidelines. Contraindications to performing spirometry from the ARTP guidelines included: haemoptysis; pneumothorax; unstable angina; recent myocardial infarction in the last 1 month; pulmonary embolism; thoracic, abdominal or cerebral aneurysms; recent eye surgery; nausea or vomiting; recent thoracic or abdominal surgery. Additionally if participants appeared non-specifically unwell or nursing staff had concerns about participation that day then they were not approached.

2.3.2 Sample size

The sample size for this exploratory study was 50 participants. This number was appropriate for assessing the feasibility of recruiting participants and conducting the measurements, and was achievable within the researcher's time frame.

2.3.3 Recruitment

All eligible patients approached for recruitment, were given a patient information sheet to keep and given at least 2 hours to read and ask further questions (Appendix 6.1). This provided information on the purpose of the study, readings that would be taken including body measurements, spirometry and grip strength, as well as risks and benefits involved in participation. Patients with sensory impairment were given additional opportunity to go through the sheets either with sections of the document being read to them or the opportunity of

going through this with next-of-kin. Each participant was taken through a brief questionnaire to ensure that they had no symptoms that day that would affect either carrying out the spirometry or exclude them from the study (Appendix 6.2). Any positive response to the ECAT questionnaire excluded recruitment to the study. Participants were also asked about any contraindication to performing spirometry according to ARTP guidelines: haemoptysis, pneumothorax, unstable angina, recent myocardial infarction, pulmonary embolism, thoracic, abdominal or cerebral aneurysms, recent eye surgery, nausea or vomiting, recent thoracic or abdominal surgery (114). This was confirmed on review of notes prior to performing spirometry with the participants' permission.

2.3.4 Consent

Each participant was given the opportunity to read the consent form. Consent of those with visual impairment was taken by reading through each point in turn. Some participants found it difficult to write their initials by each point but were encouraged to do this and sign at the bottom of the form if in agreement with the study terms. See example of consent form in Appendix 6.3.

2.4 Development of data collection proforma

2.4.1 Case record review

Patients reviewed, approached for participation, consented and agreed to participate were recorded on a log book. See Appendix 6.4.

2.4.2 Clinical assessment

2.4.2.1 Body height

The majority of older participants were unable to stand tall to take true height readings. The reasons for this included loss of balance (previous strokes), immobility (chair bound), osteoporosis, arthritis, pain (cellulitis or peripheral vascular disease) and spinal curvature. In order to measure standing height participants would need to stand against a stadiometer without footwear, upright with heels together and heels, calf, buttocks and back against the stadiometer with eyes facing directly ahead. Sitting height was considered but again may be affected by osteoporosis or kyphoscoliosis of the spine. Lastly arm span was also considered, requiring the participant to hold arms equidistant to the shoulders but limited by old shoulder injuries (tendonitis, dislocation, arthritis). In the final analysis height was derived from ulna length using a nomogram (115). All participants had ulna length measured (see Figure 9).

Figure 9: Ulna length measurement (116)



2.4.2.2 Body weight

Body weight was measured using sitting scales on the ward at the patient's bedside. This was done with the patient wearing light nightwear and without footwear. The scales were locally calibrated on a regular basis.

2.4.2.3 Body mass index

Body mass index (BMI) was calculated using weight/height^2 (kg/m^2).

2.4.2.4 Malnutrition Universal Screening Tool

Malnutrition Universal Screening Tool was calculated on the basis of the information recorded in the clinical records at the time regarding weight loss and

the weight and height and dietary intake. See Appendix 6.5 for how this was calculated.

2.4.2.5 Barthel Index Score

The Barthel score is based upon 10 items that measure a person’s activities of daily living. This tool was used as a measure of the participant’s current functioning at the time of recruitment. The higher the score is the more independent the individual is. The scoring system that was used gives a potential maximum of 100. See Figure 10 below.

Figure 10: Barthel Index Score of Activities of Daily Living (117)

<p>Feeding 0 = unable 5 = needs assistance 10 = independent</p> <p>Bathing 0 = dependent 5 = independent</p> <p>Grooming 0 = needs help with personal care 5 = independent</p> <p>Dressing 0 = dependent 5 = needs help can do about half unaided 10 = independent</p> <p>Bowels 0 = incontinent 5 = occasional incontinence 10 = continent</p> <p>Bladder 0 = incontinent or catheterised and dependent 5 = occasional incontinence 10 = continent</p>	<p>Toilet use 0 = dependent 5 = needs some assistance 10 = independent</p> <p>Transfers 0 = unable 5 = major help (one or two people) 10 = minor help (verbal or physical) 15 = independent</p> <p>Mobility 0 = immobile 5 = >50 yards 10 = walks with one 15 = independent</p> <p>Stairs 0 = unable 5 = needs help 10 = independent</p> <p>Total score (0-100)</p>
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2.4.2.6 MMSE

MMSE was used as a screening tool to exclude patients with a significant degree of cognitive impairment that would be unlikely to be able to perform spirometry correctly. It has been used as an established cognitive screening tool in previous spirometry studies in older people (111;118). See Appendix 6.6. Drawing the Intersecting pentagons was evaluated separately as a marker of executive function.

2.4.2.7 Demographic data

Data were abstracted from the medical notes of participants regarding age, date of birth, gender, co-morbidities, number of medications, living arrangements pre-admission and post-admission (home, residential care and nursing care) and length of hospital stay. The hospital patient administration system was interrogated to determine the number of deaths during the 1 year post-discharge.

2.4.2.8 Grip strength

A Jamar dynamometer was used to measure grip strength. See Figure 11. The researcher washed her hands and explained the procedure to the patient. The patient was asked to remove any watches or bracelets that may be uncomfortable prior to the procedure. The dynamometer was cleaned before use with an alcohol wipe. The participant's hand dominance and serial number of the dynamometer were recorded. The patient was asked to sit comfortably in

his bedside chair with a back support and fixed arm rests and asked to sit with feet flat on the floor. The same chair type was used for each participant as this was standard on each of the wards. The patient was asked to rest his arms comfortably on the chair arm with the wrist over the end of the chair's arm, thumb facing upwards. The dynamometer was placed so that the thumb went round one side and fingers around the other side. Comfort was checked prior to any measurements being taken. Any known pain or arthritis was asked about prior to readings and documented. The red needle was moved to "0" on turning the dial. Measurements were started in the right hand and then repeated alternating between each hand. The researcher supported the weight of the dynamometer by resting it on her palm without restricting the patient from squeezing it. The patient was encouraged to squeeze as long and tightly as possible until the needle stopped rising. This was done using verbal encouragement "Now squeeze... harder, harder...and stop squeezing". Measurements from the dial were recorded to the nearest 1kg. Three measurements were recorded for each hand.

Figure 11: Jamar dynamometer being used



2.4.2.9 Spirometry

The researcher washed her hands and introduced herself to the patient. The patient was encouraged to be comfortable prior to performing spirometry. This included the ERS guidelines that clothes were non-restrictive particularly for full chest and abdominal expansion and patients had not eaten a large meal within 2 hours of testing. The patient was also encouraged to use the toilet if he or she wished prior to spirometry, as the procedure could cause urinary incontinence. The researcher ensured that spirometry was conducted when the patient had been rested and without unnecessary distraction. For example, prior to family visiting and informing nursing staff to avoid interruption with observations.

Equipment was cleaned using an alcohol wipe. Disposable mouth pieces were used for each patient. The patient was asked to put his feet firmly on the floor and ensure sitting in an upright supported position. The patient was shown how to hold the mouth piece. Optimal spirometry technique was demonstrated by the researcher and repeated if necessary. Any questions the patient had were answered and patients were reminded that results were for research purposes and not for diagnostic purposes. The patient was then asked to perform the technique. This was done with both verbal encouragements “Blow as hard and fast as you can. Blow...blow....keep going, keep blowing...almost there... and stop”, and also with visual demonstration at the same time for those less able to follow instructions.

FEV1/FVC and PEF were recorded. The best of five readings was taken. The researcher observed for any fatigability or problematic technique and recorded this. SVC was then demonstrated to the patient visually and verbally. “Breathe in.... slow normal breath out...keep going... and stop.” The patient was then asked to do the best of three SVC. See Figure 12.

Figure 12: The Microlab Portable Spirometer



Repeatability was considered to be adequate when there was a difference of ≤ 0.15 L between the maximum and the next largest FVC and between the maximum and next largest FEV₁. In patients with FVC ≤ 1 L a difference of ≤ 0.10 L was used (119-120). SVC attempts were considered to be acceptable if the individual breathed in to TLC then breathed out until flow had ended for at least 1 second. SVC measurements were considered to be repeatable if the two highest attempts varied by ≤ 0.2 L (114).

At the outset of the study, the intention was to measure PEF, FEV1, FVC and FEV1/FVC. After measuring spirometry on the first 10 patients I decided to introduce SVC as an outcome measure, therefore 40 patients had this measured of the 50 recruited. SVC was included as I felt this may be an easier technique for patients' to achieve and therefore in some instances may be more representative of the patients' actual lung functioning rather than their technique.

2.5 Data analysis

2.5.1 Statistical tests

Data was entered onto the IBM SPSS Statistics software (Southampton) and double checked by a statistician. This software was used to analyse the data obtained from recruited patients. Data were separated according to gender prior to analysis.

2.5.2 Feasibility of recruitment

One of the outcomes of this study was to assess the feasibility of recruiting hospitalised older patients to the study. Reasons for declining participation in the study were documented.

2.5.3 Feasibility of performing grip strength and spirometry

Grip strength was considered acceptable if participants were able to complete 3 measurements in each hand. Spirometry was considered acceptable if there was acceptable technique, met acceptable measurements as above and the spirograms were of reasonable shape within 5 attempts.

2.5.4 Participants characteristics

Mean and standard deviation, median and inter-quartile ranges and number and percentages were used to describe the participants' demographic and clinical characteristics. Demographic characteristics were adjusted for linear regression analysis using weight and height separately rather than BMI to give a clear breakdown of whether weight or height had any significance against grip strength or lung function.

2.5.5 Grip strength and Lung function

Mean and standard deviation was calculated for grip strength and lung function in women and men separately as normally distributed data.

2.5.6 The association of grip strength and lung function

This study looked at the impact of whether there was an association between grip strength and FEV1, FVC, FEV1/FVC, PEF and SVC using linear

regression and then adjusting these results for age, height and weight. 50 measurements were recorded for grip strength and FEV1, FVC, FEV1/FVC and PEF. 40 measurements were recorded for SVC as this was a measurement introduced after starting the study introduced as this may be more feasible for participants to undertake.

Normality of variables was assessed using visual inspection of histograms and skewness. Variables have been summarised using means and standard deviations (SD), medians and inter-quartile ranges (IQR) and frequency and percentage distributions for categorical variables. Comparing means between men and women groups, independent sample t test was used. Non-parametric testing using the Mann Whitney test was used to compare gender groups.

2.6 Ethics approval

Southampton and South West Hampshire Research Ethics Committee gave approval for this study having submitted a written amendment to a larger on-going study. See Appendix 6.7.

2.7 Quality assurance of data collected

2.7.1 Training in use of tools

Training in the use of the Jamar hand dynamometer was obtained from an experienced researcher. The method of grip strength assessment using the

dynamometer was based on a literature review of grip strength assessment and followed a standard protocol (49). The researcher had practice sessions and discussions with an experienced researcher to standardise her technique for grip strength assessment. Initial assessments were observed for technique. Then the researcher checked inter-observer variability (IOV) of grip strength assessment with this experienced researcher, and also her own intra-observer variability (IOV) in a group of 7 volunteer participants.

Training in the calibration and use of the portable spirometer was given by an experienced researcher. The researcher had practise sessions and discussions with the experienced researcher on the use of the spirometer prior to assessment. An assessment of competence in obtaining informed consent, calibration and measuring lung function was carried out using the portable spirometer on a volunteer. The experienced researcher confirmed that the researcher had gained competence in the procedure for research.

The researcher was familiar with the Barthel Score (Figure 10), the MUST nutritional assessment tool (Appendix 6.5) and the MMSE.

2.7.2 Inter- and Intra-observer variability

The purpose of this study was to ensure that grip strength measurements were done accurately and reproducible if carried out by another researcher in the

future. 7 healthy volunteers from the researcher's host institution agreed to participate and gave verbal consent. Grip strength was assessed sitting in the same chair according to the protocol used in this study and was measured to the nearest 1 kg. Measurements were taken, three times in each hand, alternating between hands. The researcher and the experienced researcher assessed the volunteers' grip separately in all 7 participants during the morning of the test day. The researcher and experienced researcher alternated the order in which they approached participants. This was to minimise the impact of the participant learning and/or tiring effects on the assessment of observer differences. A single dynamometer was used and had been previously calibrated against known weights prior to use.

Maximum grip strength was used for all analyses. A two sample t test was used to determine if there was any difference between the mean grip strength values obtained from the participants by the researcher and experienced researcher (inter-observer variability). A one sample t test was used to determine any difference between the values obtained by the researcher (intra-observer variability). An alpha value of 0.05 with a 95% confidence interval was used to reject the null hypothesis of no difference in the mean between and within the researchers' when a hypothesised mean difference of zero was used. No significant statistical differences in measurements between investigators were found (see Figure 13).

2.7.3 Calibration of instruments

The Jamar hand dynamometer was checked against known weights every 3 months and calibrated annually. The Micro-lab 3300 portable spirometer was calibrated on a daily basis using a 3 litre syringe using the in-built calibration program.

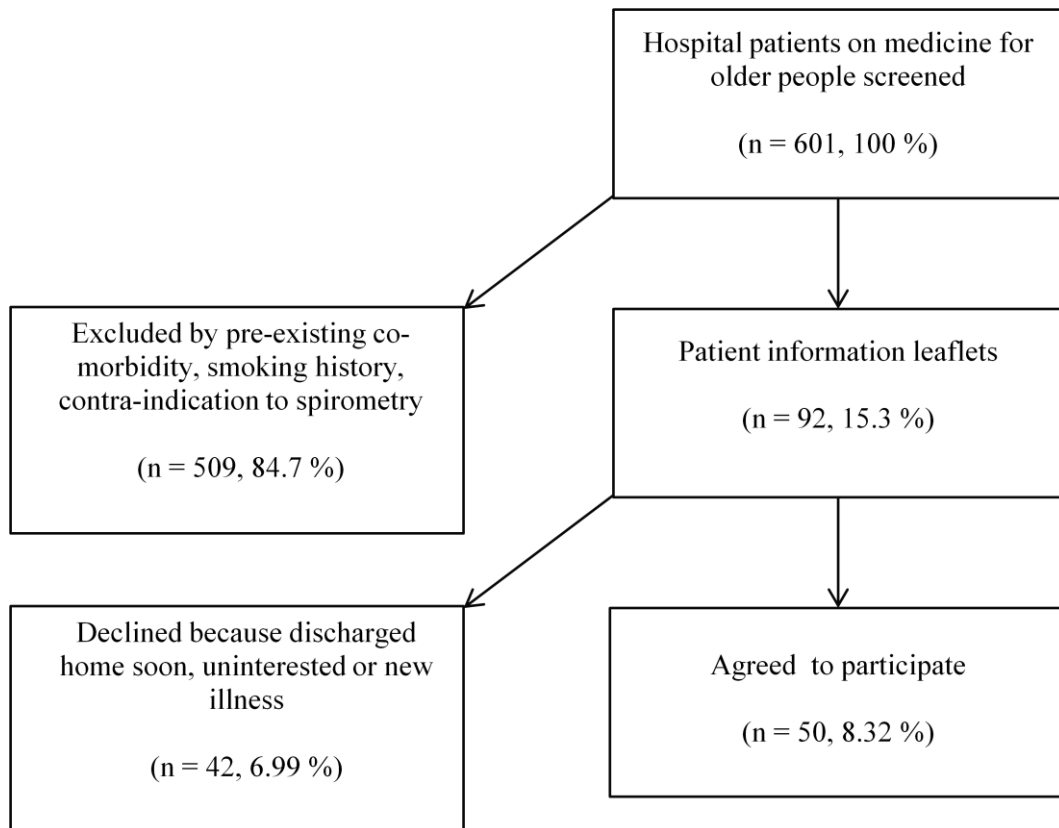
3. Results

3.1 Recruitment

Over a six month period, between April and September 2012, 601 patients were screened. Based upon the exclusion criteria, patients with acute respiratory illnesses such as COPD exacerbation, pneumonia or bronchiectasis exacerbation (n=58), any prior respiratory disease (n=48), smoking or previous significant smoking history (greater than 1 year) (n=109), acute illness or concerns from nurses of acute illness (n=13) and significant cognitive impairment (known moderate or severe dementia) (n=281) were excluded (total n=509). Some patients had one or more exclusion criteria.

Patients that did not meet the exclusion criteria were approached with information leaflets (n=92) and given time to consider participating in the study. Of these, patients declined participating on the grounds of discharge home soon (n=17), lack of interest or anticipation that it would be too much for them (n=19), or new illness since being given the information leaflet (n=6): this included the specific spirometry exclusion criteria of possible pulmonary embolism (n=2), myocardial infarction (n=3) and sepsis (n=1). Fifty subjects consented to take part in the study (men n=20, women n= 30) (Figure 14).

Figure 14: Flow chart for the recruitment into the study



3.2 Clinical Assessment

Men and women were of similar ages in this study ($p=0.438$) (Table 3). Men were taller than women participants although there was no significant difference ($p=0.806$). Men were heavier than women participants but with no significant difference ($p=0.643$). BMI was similar between men and women participants ($p=0.364$). MUST score was slightly higher in women inferring increased risk of malnutrition but there was no significant difference between men and women ($p=0.133$). Barthel index score was significantly higher in men inferring greater independence in this group compared to women ($p=0.001$). MMSE was

marginally higher in women compared to men ($p=0.036$) inferring higher cognitive function although all participants had MMSE ≥ 24 . There was no significant difference between men and women in their ability to complete intersected pentagons, used as a marker of executive function to perform spirometry. See Table 3.

Table 3: Participant Characteristics

Characteristics	Men(n=20)	Women(n=30)	p value
Age, y ^a	86.3(4.92)	87.5(4.76)	<i>0.438</i>
Height, m ^a	1.71(0.68)	1.60(0.65)	<i>0.806</i>
Weight, kg ^a	74.9(15.1)	66.0(16.4)	<i>0.643</i>
BMI, kg/m² ^a	25.6(5.25)	26.0(6.36)	<i>0.364</i>
MUST (%) ^c			<i>0.133</i>
0	18(90)	23(77)	
1	0(0)	3(10)	
2	2(10)	4(13)	
Barthel score ^b	87.5(62.5,100)	65(47,79)	<i>0.001</i>
MMSE ^b	25.5(24,27.8)	26.5(25,29)	<i>0.036</i>
IP (%) ^c	14(70)	19(63.3)	<i>0.203</i>

Footnote

^a Mean (SD) using T test; ^b Median (IQR) using Mann Whitney test; ^c Number (%) using Chi-squared test. y: year; m: metres; kg: kilograms; BMI: body mass index; kg/m² (kilogram/metre²); MUST: malnutrition universal screening tool; MMSE: mini mental state examination; IP: intersected pentagons.

3.3 Demographic data

Both men and women had similar numbers of co-morbidities ($p=0.959$). The women had a larger numbers of falls in the last year and a greater number had a history of osteoporosis and arthritis. The men had a higher proportion of malignancy, hypertension and depression. Men and women were on a similar number of medications ($p=0.062$). See Table 4.

Women were in hospital for longer than men (mean 29.5 (SD 18) days compared to mean 20.5 (SD 19.5) days, $p=0.541$). 15 men were admitted from home with no care needs, 5 had carers, 11 were discharged back home independently, 8 required a care package, 1 was discharged to a residential care home. 16 women were admitted from home with no care needs, 13 required a care package, 1 was admitted from a nursing home, 5 were discharged independently back home, 19 were discharged home with a care package, 3 were discharged to a residential home, 3 were discharged to a nursing home. 1 year after the study, the majority of patients were still alive, 3 men (15%) and 5 women (20%) had died. See Table 5.

Table 5: Pre-admission and Post-admission destination of participants

Pre-/post-admission status	Men(n=20)	Women(n=30)
Duration of stay, days ^a	20.5(19.5)	29.5(18)
From own home ^b	15(75)	16(53.3)
From own home with carers ^b	5(5)	13(43.3)
From residential home ^b	0(0)	0(0)
From Nursing home ^b	0(0)	1(3.3)
Discharge to own home ^b	11(55)	5(16.7)
Discharge to own home with carers ^b	8(40)	19(63.3)
Discharge to residential home ^b	1(5)	3(10)
Discharge to nursing home ^b	0(0)	3(10)

Footnote

^a Mean (SD); ^b Number (%).

3.4 Grip strength

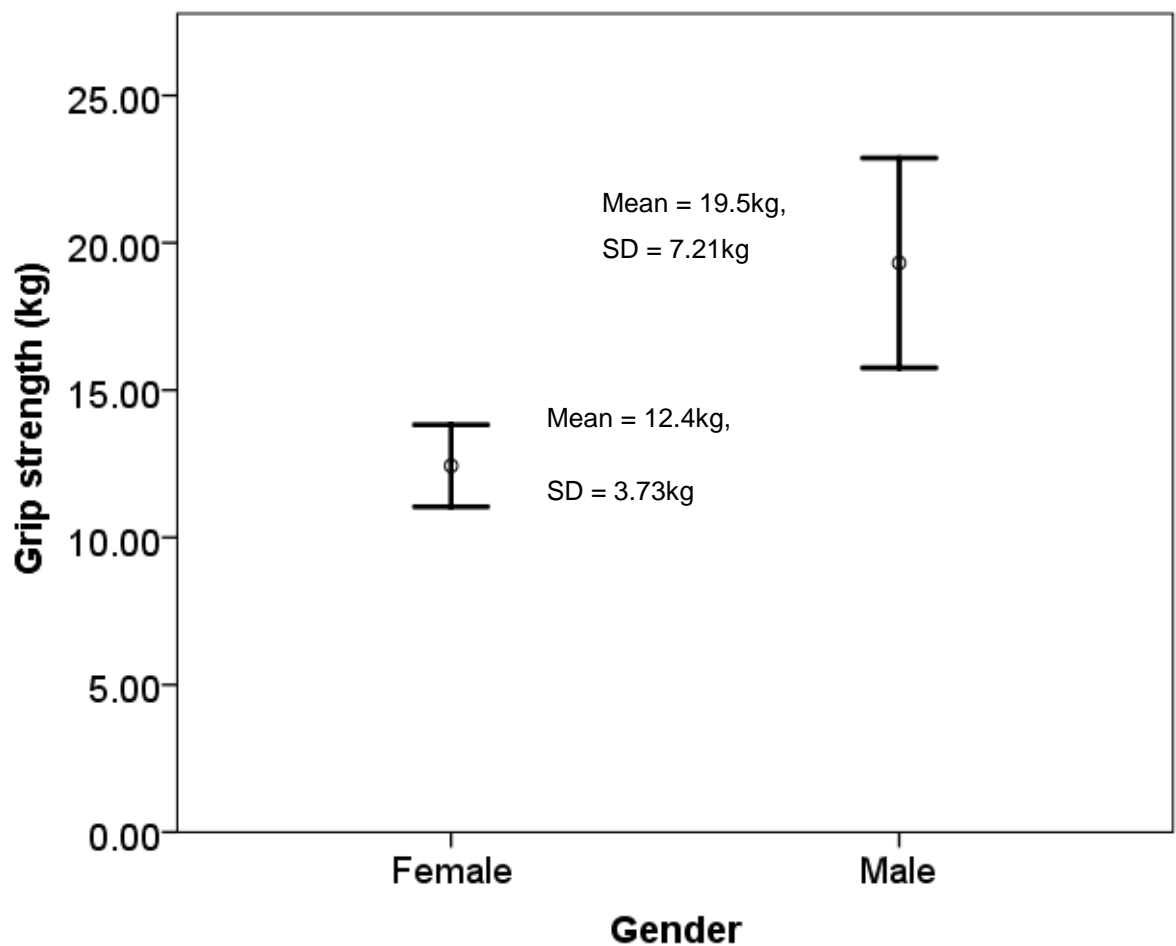
3.4.1 Feasibility of grip strength

Grip strength was easy to measure in all patients including in those who may have mild cognitive impairment or those with arthritis. Results were reproducible and the best grip measurements were taken, therefore this was a feasible assessment.

3.4.2 Grip strength

Grip strength was measured on all participants and was normally distributed. Maximum grip was significantly stronger in the men compared to the women ($p=0.026$). See Figure 15. The range of grip strength in men was 29 kg (10kg to 39kg) whereas in the women this was 18kg (4kg to 22kg).

Figure 15: Grip strength in men and women



3.5 Spirometry

3.5.1 Feasibility of spirometry

Spirometry itself was easy to demonstrate to patients at the bedside. However the difficulty was in reproducibility of the results and the need for patients to rehearse technique without becoming fatigued. Hence after review of 10 patients I introduced SVC which was more easy for patients to demonstrate and more reproducible. For each spirometric value only the best results were taken.

3.5.2 FEV1

All spirometry values were normally distributed. FEV1 was significantly larger in men compared to women ($p=0.018$). The range of FEV1 in men was 2.07l (0.65l to 2.72l) and in women was 1.24l (0.51l to 1.75l). See Table 6.

3.5.3 FVC

FVC was also significantly larger in men than women ($p=0.010$). The range of FVC in men was larger (2.57l (0.72l to 3.29l)) compared to the women (1.62l (0.65l to 2.27l)).

3.5.4 FEV1/FVC

FEV1/FVC were not significantly different between men and women ($p=0.881$). The range of FEV1/FVC in men was 54% (44% to 98%). The range of FEV1/FVC in women was 46% (53% to 99%).

3.5.5 PEF

PEF was significantly larger in men compared to women ($p=0.004$). The range of PEF in men was 349l/m (97l/m to 446l/m) compared to the range of PEF in women 195l/m (72l/m to 267l/m).

3.5.6 SVC

SVC was significantly larger in men compared to women ($p=0.003$). The range of SVC in men was 2.86l (0.72l to 3.58l) compared to 1.14l in women (0.46l to 1.60l).

3.6 Grip Strength and spirometry

A significant association was found in men between grip strength and FEV1 although this attenuated after adjustment for age, height and weight. In women a significant association was found between grip strength and PEF and between grip strength and SVC which was robust to adjustment. No other

significant relationships were found. FEV1, FVC and SVC were significantly larger in men compared to women (Table 7).

4. Discussion

4.1 Summary of findings

Hand grip strength was significantly stronger in men than women in this study. Similarly FEV1, FVC, PEF and SVC were larger in men compared to women probably due to larger body sizes as expected. These findings are in keeping with other studies comparing gender differences.

Higher values for FEV1 were significantly associated with stronger grip strength in men but the significance was attenuated after adjustment for age, height and weight. No significant association between FEV1 and grip strength was found in women. A recent study inferred a relationship between grip strength and FEV1 in patients who were healthy subjects and patients with COPD. This study demonstrated that a decrease in grip strength was associated with a decrease in FEV1 however it did not adjust for age or body size (119).

FVC in men and women were not found to be significantly associated with grip strength in this study. However there was a trend for men with higher FVC to have stronger grip strength. Similar in a study with COPD participants higher FVC was associated with stronger grip strength (119).

The ratio of FEV1/FVC did not have a significant association with grip strength. This was an unexpected result. As it was presumed that patients that were weaker would have reduced FEV1 and FVC therefore would have an obstructive picture similar to patients with COPD. Current studies that use FEV1/FVC do so only in the context of patients with lung pathology such as COPD or smokers or a mixed group and do not compare this to grip strength or adjust for body size.

Greater PEFr and SVC were found to be significantly associated with stronger grip strength in women but not men. PEFr and SVC may be more significant in women in this study reflecting stronger patients generating higher intra-thoracic pressure at the start of spirometry and pushing harder against thoracic cage recoil at end-expiration. Greater PEFr has been found to be non-significantly associated with stronger grip strength in patients with COPD (105).

4.2 Participant characteristics

Men were taller and heavier than women but not significantly different. BMI were similar in men and women. MUST scores were slightly higher in women than men. Barthel was significantly higher in men compared to women participating, suggesting an increased level of independence which may also be reflected in their greater grip strength and greater body size. Cognition as measured by the MMSE was significantly better in women compared to men although all participants met the baseline criteria of ≥ 24 points to be eligible for

the study. Men and women were similarly able to draw intersecting pentagons as part of the MMSE. This may infer a similar executive function or praxis between men and women. The number of co-morbidities, medications and recruited participants living one year after the study was similar between men and women.

Women were admitted on average for longer than men. Women required a higher level of care pre-admission and post-discharge than men. This may have been because these participants were widowed or living alone. Marital status wasn't recorded in the demographic data and would have been an interesting parameter to have collected to see if this contributed to the length of hospital stay. Delays in discharge planning may have contributed to length of hospital stay. Increased length of stay may also reflect increased frailty in the recruited participants.

4.3 **Recruitment**

A large number of potential participants were excluded to minimise confounders and these included active or ex-smokers, patients with acute or chronic lung pathology, acute illnesses with chronic co-morbidities and cardiac disease. There were a number of patients with dementia who had to be excluded because of the need for written informed consent and active participation in grip strength and lung function measurements. Patients that met exclusion criteria

from the questionnaire with potential acute cardiac or respiratory illnesses were automatically excluded. Therefore this study may not be representative of the older population as a whole.

Some patients that declined participation had already had a long hospital stay and were concerned that recruitment would delay their discharge despite reassurance. Some individuals declined participation because of the consent process. Perhaps in increasing access for older people to participate we may need to re-evaluate making the consent forms and information more succinct for those with sensory impairment or available in alternative formats. We tried to overcome this problem by giving increased time for patients to read through the forms, be assisted by families and reading through the forms for the patients but this was time consuming for participants. This study relied more on their willingness to participate therefore which is always a limitation in studies in hospitalised patients.

4.4 **Grip strength**

The measurement of grip strength was feasible in all participants. Lower grip strength was associated with female gender, older patients, those with higher MUST scores, smaller body size and lower Barthel scores. These results are similar to those previously reported in a study comparing grip strength to physical functioning and SF-36 scores (60).

4.5 Lung function

Spirometry was easy to demonstrate and perform at the bed side. However it presented more issues in conforming to the ATS guidelines and patients being able to reproduce results 5 times without fatigability. I accepted the best value of 3 attempts and to quality assure this data two observers reviewed the spirograms of each patient separately and together to see if the spirograms reflected adequate performance.

FEV1, FVC, SVC and PEF were significantly higher in men rather than women. This is mainly due to the higher lung volumes in men but also may reflect the increased muscle strength in men which enables them to generate increased intra-thoracic pressure and to push harder against thoracic cage recoil at end-expiration. Additionally greater height and weight may also have been contributing factors to their ability to generate higher intra-thoracic pressures. However, the ratio of FEV1/FVC was not found to be significantly different between men and women. There was considerable variability in the ratio among both men and women. This may reflect several factors including patients' ability to perform the test.

SVC appeared to be a more practical and applicable lung function measure in this older patient group. All patients asked to perform this were able to do it meet the criteria set out in the methods. Ten measurements were not completed as these patients had gone home by the time this measure had been

established as a useful test to perform. Therefore, if carried out in a larger population, a more significant relationship between SVC and strength may have been found.

4.6 **Strengths and weaknesses of the study**

This study had several strengths. Data were collected by a single researcher, with trained competency confirmed with IOVs, and using standardised protocols and calibrated instruments.

At the outset of this study I planned on recruiting 50 patients and achieved this number. Part of the reason for recruiting a relatively small number of patients was to ensure that this study was feasible both in time taken to carry out by one researcher and also to ensure that data collection could be completed. I tried to minimise other co-morbidities which may have influenced results through using a strict exclusion criteria. To further evaluate the relationships found between lung measurements and grip strength further studies of a larger number would be required.

Spirometry assessment can be improved through rehearsal. However, many patients were unable to repeat lung function tests up to five times. Therefore rehearsal could not be obtained consistently and all attempts between a minimum of three and up to five were recorded. A younger participant group

may have been able to rehearse the technique and then perform spirometry but this wasn't possible in this relatively frail subject group. Further research in a larger group could set limits to exclude lung function tests with FEV1/FVC over 90% or under 60% and abnormal spirogram patterns.

All participants agreed that grip strength and spirometry were easier to perform than anticipated. A greater difficulty in recruitment to the study was that many found the consent process more of a concern than the actual testing. It was not possible to collect data at a set period in the day which would have limited participation much further, this study may not have accounted for any diurnal variation in grip strength or lung function. There is limited data available from studies looking at grip strength and diurnal variation to suggest when it should be measured and if there is any significant difference in measurements taken at different times of the day. Lung function is likely to be worse in the early morning however this has mainly been considered in patients with COPD, asthma or smokers. All the data was collected from late morning into the afternoon and it was felt that the risk of diurnal variation affecting the results would be very limited. This may a consideration for future study.

It was determined that to exclude participants with inadequate spiograms would limit the sample size further. Also that excluding these results did not have a significant difference on the overall results.

However, we tried to avoid reduced performance in subjects by consideration of visiting at a time that was convenient to the patient and allowing some flexibility to a time that was convenient to them when they would be at their best.

4.7 **Future research**

A further consideration was whether this population recruited was representative of the older population. Firstly, those recruited represented only 8% of those patients considered for the study. Secondly the population of community dwelling older people may be different to those admitted to hospital. In order to research this further, older people in the community who are well and without lung disease or symptoms would need to be recruited to a separate study to explore the relationship of grip strength and lung function. A larger sample size may have aided any association between grip strength and lung function reach a level of statistical significance.

Community dwelling older people may be more likely to wish to participate if seen to be helping prevent ill health in the future in themselves by promoting research in ageing, and may be physically more able and have increased endurance therefore being able to rehearse the spirometry technique prior to yielding any results.

Considerations for future research may need to consider further mechanisms affecting the ageing lung. This may include further work looking at the biochemical markers associated with ageing, imaging of the lungs, expiratory muscle pressures and additional spirometry measures including additional measures of FEV at the earlier part of forced expiration to increase accuracy of results before fatigability sets in.

5. Conclusion

Men had significantly stronger grip strength and larger FEV1, FVC, PEFr and SVC compared to women probably because of larger body size. There was a significant association between grip strength and PEFr and grip strength and SVC after adjustment for age, height and weight in women which may reflect stronger patients generating higher intra-thoracic pressure at the start of spirometry and pushing harder against thoracic cage recoil at end-expiration. In men a significant relationship was found between grip strength and FEV1 which was attenuated after adjustment for age, height and weight this requires further evaluation.

Appendices

Appendix 6.1 Patient Information Sheet

PATIENT INFORMATION SHEET

A research study to evaluate the use of mealtime assistance on an acute medical ward for older people

We would like to invite you to take part in a research study. Before you decide we would like you to read the following information in order for you to understand why the research is being done and what it will involve.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Take time to decide whether or not you wish to take part.

PART ONE

What is the purpose of the study?

The aim of this study is to see if the use of volunteers helping as mealtime assistants can increase the amount and quality of food patients eat. We want to know if this approach is practical and if patients and staff find it helpful.

Why have I been chosen?

We are asking all patients admitted to two acute medical wards for older people, over a two-year period, to be part of this study.

Do I have to take part?

No, it is up to you to decide whether or not to take part and you will have at least 2 hours to make that decision. If you do, you will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

For some patients the nursing staff will help with meals, whilst for others it will be trained volunteers who provide the meal-time assistance. This may include making sure you can reach your food or helping to feed you. They will only assist if you are happy and it is safe to do so. The nursing staff will have overall responsibility for mealtime assistance.

Using different ways of assisting with meal times on the two wards will allow the research team to compare the two ways of working to see which offers the most benefit to patients and their health. To measure this we would like to collect a variety of data from you both during your hospital stay and at six months after your discharge from hospital.

1. Use of your routinely collected hospital information

We would like to collect existing data from your medical records (both paper and computer records), which would have been obtained during your time in hospital. This would include blood results, weight, nutrition score, medication being taken, information about how you manage at home, any previous and current illness and discharge details. In addition to this we will talk to your nurse and obtain information about your level of activity at the moment.

2. Body measurements

If you agree we would also like to conduct some simple tests for which you can remain clothed and be in bed, and which take about 10-15 minutes to measure. These include measuring

- a) the circumference and length of your arm, and the thickness of your skin on your arm.
- b) your strength by getting you to grip a measuring handle with your hands.
- c) the composition of muscle and water in your body, using a quick and simple test called bio-impedance, which involves placing a sticker on

your hand and foot, to pick up small electrical messages from your body (rather like an ECG heart tracing).

If you agree we would like to do all of these tests in the next few days, when you are ready for discharge and when you actually leave hospital, so we can compare the results.

3. Blood tests

We would like to check the levels of three vitamins in your blood, by taking a small amount of extra blood when you are having a routine blood test. After analysis no blood samples will be retained.

A few participants will have additional blood taken on two occasions whilst in hospital for measurement of immune functioning and repeat vitamin levels. Again, these would only require a small amount of extra blood taken when you are having routine blood tests and after analysis no blood samples will be retained.

4. Questionnaires

We would like to ask you some more questions about your memory, mood, appetite, concentration and sleep at the moment. We will also be recording food and drink intake on a few days for everyone in the ward, and may monitor staff activity. When you are ready to leave the hospital, we would like to ask you and/or your next of kin to complete a short questionnaire telling us about your experience of the food, your satisfaction with mealtimes and your well-being.

Additionally we hope to interview a few patients or relatives from each ward for around 20 minutes (either on the ward or in a private room, according to their choice) about their views on mealtimes and nutrition in hospital in more depth.

Finally we would also like to visit you at home about six months after your hospital discharge to ask you how your health has been. We would contact your GP prior to this to check your current location, and the appropriateness of

contacting you or your next of kin. A trained researcher will visit you at a convenient time for no more than one hour. During this time some of the questionnaires and physical tests will be repeated.

5. Breathing tests

We would like to check how well your lungs are working. You will be asked to breathe out as hard and as much as you can into a machine that will measure your lung function. This test will be repeated up to 5 times on one occasion. The strength of your hands will be tested at the same time by asking you to squeeze a measuring handle.

6. Additional optional tests

a) A few participants in each ward will have their mobility over an 8 hour period assessed using a small activity monitor attached to their leg, on three days whilst they are in hospital. Specific consent will be asked for this, part of which is a medical student project supervised by the research team.

b) A few participants will have a more detailed assessment of physical performance, taking no more than 30 minutes. The strength of your leg will be measured by sitting on a chair and straightening it at the knee against resistance. You will also be asked to walk 3 metres, stand up from a chair and stand one leg whilst being timed. If you are unwilling or unable to perform any of these tasks, they will not be attempted.

Expenses and Payment

There is no payment for participants in this study.

Are there any risks or disadvantages associated with taking part?

There are no risks for those patients (or relatives) agreeing to just the use of routine data, bioimpedance or assessment of well-being and grip strength. Bio-impedance cannot be done on individuals who have a pacemaker or similar electronic device. Some individuals may find the body measurements slightly uncomfortable but this is a quick measurement to take and the researcher would stop at your request. The vitamin and immune status will be assessed as part of a routine blood test although will require approx a small additional blood sample.

Specific consent would be obtained for the activity monitor, which is very small and light, so little burden and no associated risks. Lung function tests cannot be performed on patients who have had a recent pneumothorax, heart attack or stroke, or recent abdominal or eye surgery, or who have unstable angina.

The individual interviews will be anonymised but we recognise that this will be an additional task lasting around 20 minutes, and patients and carers will be selected from those that are willing to consent to this specifically.

What are the possible benefits of taking part?

There are benefits from participating in a research study e.g. you and your clinical team will have information about your health and body composition that would not be part of your usual care. The information that is obtained during this study will allow us to determine if there is any benefit to specific meal time assistance and then make recommendations to improve future patient care.

What happens when the research study stops?

Usual mealtime assistance on both wards will resume.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered will be addressed. More detailed information on this is given in part two of the sheet.

Will my taking part in the study be kept confidential?

Yes, we will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART TWO

What if new information becomes available?

A member of the research team will tell you and discuss whether you would like to continue in the study. If you decide not to continue in the study your care will continue as usual on the ward. If you decide to continue in the study we may ask you to sign an updated consent form. If at any time the research team consider it to be in your best interest to withdraw from the study, this would be discussed with you and your care would continue as usual on the ward. If for any reason the research study stopped we would inform you.

What will happen if I don't want to carry on with the study?

You can let us know at any time if you do not wish to participate in the study. No further assessments would be made but we would like to retain the use of anonymised routine data and any data already collected. Similarly it would be important for this study to be able to record patient outcomes such as discharge details.

What if there is a problem?

If you have any cause for concern regarding your participation in the trial, please contact one of the researchers in the first instance (see contact details at the end of this sheet). If this is unsatisfactory, they will be able to direct you to an alternative person who will be able to help.

If you have a complaint, which cannot be resolved by these measures, you may wish to complain formally. You can do this through the NHS Complaints Procedure. Details can be obtained from Southampton University Hospital Trust. Southampton University Hospital Trust sponsors this study and provides indemnity against clinical negligence during the study.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. We will inform your GP and Hospital Consultant that you are participating in the study. Additionally we will contact your GP prior to the six month follow-up phone-call.

We will keep a record of your contact details so that we can contact you for follow-up but these will be stored securely and only accessed by direct members of the research team. Any other information about you will have your name and address removed so that you cannot be recognised from it. In the analysis of results, your data will be used anonymously. Our procedures for handling, processing, storing and destroying data relating to your participation in the study are compliant with the Data Protection Act 1998. In accordance with

this Hospital's regulations we are required to keep your data secure for 15 years. For the purposes of monitoring research there is a possibility that the hospital's Research and Development department will audit the data that we have collected.

What will happen to the results of the research study?

The results of the research will be published in medical scientific journals. Research staff may also present the results at conferences and local meetings. You will not be identified in any report produced.

Who is organising and funding the research?

This research is being funded by the National Institute of Health Research, part of the Department of Health.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the local research ethics committee and has been reviewed by the research and development team at Southampton University Hospitals NHS Trust.

This information sheet is for you to keep. If you are interested in participating in this study, please speak to your nurse who will contact the research team. Thank you very much for reading this information and considering taking part in the study.

Appendix 6.2 Patient Questionnaire

Mealtime assistance in Older People (MOP)

Grip Strength & Spirometry Sub-study

COLLECTION SHEET

RESPIRATORY SYMPTOMS

(Any answer of 'Yes' gives a Positive result = 1, 'No' gives a Negative result = 2)

Current health (during the last four weeks):

1. Climbing stairs or on walking do you ever
 - a. wheeze?
 - b. get chest tightness?
 - c. get breathless?
2. Do you wake from sleep
 - a. breathless?
3. In the morning are you
 - a. wheezy?
 - b. breathless?
4. Have you been breathless, had chest tightness, a cough or wheeze at any time?
5. Have you ever been told you had asthma, emphysema or bronchitis, fibrosis or asbestos lung disease?

Result (Positive = 1, Negative = 2)

CONTRAINDICATIONS TO SPIROMETRY

(Any answer of 'Yes' means excluded from Spirometry)

Circle any answers of 'Yes'.

Have you had any of the following?

1. Haemoptysis
2. Pneumonia
3. Pneumothorax
4. Recent myocardial infarction
5. Recent pulmonary embolism
6. Thoracic, abdominal or cerebral aneurysms
7. Recent eye surgery
8. Recent thoracic or abdominal procedures

Result (Excluded = 1, Included = 2)

SPIROMETRY

Minimum of 2 attempts, maximum of 5. Results must be within 5 % of each other.

	1	2	3	4	5
FEV ₁					
FVC					
FEV1/FVC (%)					

Maximum FEV1

Maximum FVC

Maximum FEV1/FVC

(%)

Calibration check (DD/MM/YY)

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GRIP STRENGTH

Arthritis of hands (Yes = 0, No = 1)

Jamar Number

Hand dominance (*L = 1, R = 2,*

both = 3)

Grip strength (0.0 kg)

3 X both sides alternately

RIGHT

		•	
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		•	
--	--	---	--

		•	
--	--	---	--

LEFT

		•	
--	--	---	--

		•	
--	--	---	--

		•	
--	--	---	--

Maximum grip

		•	
--	--	---	--

Calibration check (DD/MM/YY)

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Appendix 6.3 Consent form

PATIENTS INFORMED CONSENT FORM

A research study to evaluate the use of mealtime assistance on an acute medical ward for older people

LREC number:

Participant ID:

Name of Principal Investigator: Dr Helen Roberts

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1.	I have read the information sheet version 5 dated 18 th May 2011 for the above study and have been given a copy to keep. I have been able to ask questions about the study and I understand why the research is being done. I have been informed about any risks or inconveniences involved and the conditions under which the study is to be conducted.	<input type="checkbox"/>
2.	I understand that I can withdraw from the study at any time without my medical treatment or legal rights being affected.	<input type="checkbox"/>
3.	I agree to my Physician being informed of my participation in this study and my GP being contacted to check the appropriateness of a follow-up contact and any changes in my contact details.	<input type="checkbox"/>
4.	I understand that relevant sections of my medical notes and data collected during the study, maybe looked at by responsible individuals from the research team, from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	<input type="checkbox"/>
5.	I agree for someone from the research team to look at my records to obtain the information as described in the use of routinely collected hospital data part of the information sheet.	<input type="checkbox"/>
6.	I agree that if I withdraw from this study, all data that has been collected up to this point can still be used, in an anonymised form in the final analysis.	<input type="checkbox"/>
7.	I agree to participate in the body measurements assessment, as outlined in the information sheet.	<input type="checkbox"/>

8.	I agree to participate in the questionnaires assessment as outlined in the information sheet.	<input type="checkbox"/>
9.	I agree that additional blood can be taken during up to 2 routine blood tests. I understand what this blood will be used for and that all samples will be disposed of after analysis.	<input type="checkbox"/>
10.	I agree to follow up data being collected after discharge from hospital and understand that this may include home visits for further assessments and blood tests as detailed in the information sheet.	<input type="checkbox"/>
11.	I agree to participate in further assessment of my physical performance via the leg strength and mobility tests outlined in the information sheet.	<input type="checkbox"/>
12.	I agree to my interview being audio taped and I understand that transcripts of my interview will be anonymised.	<input type="checkbox"/>
13.	I agree to have lung function tests and the results being used by the research team.	<input type="checkbox"/>
14.	I agree to have my mobility monitored by an Activpal (an activity monitor, attached to my leg for an eight hour period, three times during my hospital admission) and the results being used by the research team.	<input type="checkbox"/>

.....

Name of patient Date Signature

.....

Person taking consent Date Signature
(If not researcher)

.....

Researcher Date Signature

Original for investigator site file/researcher
1 copy for participant
1 copy for medical record/hospital notes

Appendix 6.4 Log book of case records

(Available in Electronic Supplementary Document)

Appendix 6.5 Malnutrition Universal Screening Tool

(Available in Electronic Supplementary Document)

Appendix 6.6 Mini Mental State Examination

(Available in soft bound copy)

Appendix 6.7 Ethics Amendment

(Available in soft bound copy)

Appendix 6.8 UHS Translational Research Conference Abstract

Is there a relationship between grip strength and lung function with ageing?

S Holmes¹, S Allen² and H Roberts¹

Academic Geriatric Medicine¹, University of Southampton; Medicine for the Elderly²,
The Royal Bournemouth Hospital and Bournemouth University.

Aims

To determine the association between grip strength and lung function in older in-patients.

Background:

With increasing age the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) declines. This change is attributed to the age-related compliance changes that occur in the airways, leading to an increase in obstruction to airflow during forced expiration. Consequently, many older people meet the prevailing spirometric definitions for obstructive airways disease despite having no other evidence of airways disease. However, older people particularly those with indicators of frailty may be unable to generate and sustain sufficient expiratory pressure to reach and hold maximum flow as lung volume falls from total lung capacity (TLC) to residual volume (RV) particularly in the initial phase of expiration when flow is more effort dependent. Thus expiratory muscle weakness might be an expression of the more generalized sarcopenia often found in frail older people. We hypothesise that older people with low grip-strength might have lower FEV1/FVC ratios than age-sex-height matched controlled subjects with well preserved grip strength.

Methods:

This pilot study has started to recruit 50 in-patients from Medicine for Older People at Southampton General Hospital that meet the following inclusion criteria: age above 75 years, never smoked or trivial experimentation with smoking (<1 year), no history symptoms or signs of respiratory disease and negative for bronchial obstruction on the ECAT questionnaire, MMSE \geq 24, willing and able to consent to participate, able to perform hand grip and forced spirometry. Recruitment is on-going and data collection is feasible among these frail patients.

Appendix 6.9 UHS Translational Research Conference Poster

(Available in Electronic Supplementary Document)

Appendix 6.10 BGS Autumn Meeting Abstract

Abstract for the British Geriatric Society (BGS) Autumn Meeting

Introduction

Age-related airway compliance changes contribute to the declining ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) with ageing. This leads to increased airflow obstruction during forced expiration. Consequently, many older people meet the spirometric criteria for obstructive airways disease despite no other evidence. Older people may be unable to generate and sustain sufficient expiratory pressure to reach and hold maximum flow as lung volume falls. This study used grip strength (GS) to reflect expiratory muscle strength (EMS) in investigating the relationship between EMS and lung function (LF).

Methods

Patients on acute Medicine for Older People wards were recruited who met the inclusion criteria: age above 70 years; never smoked; no history, symptoms or signs of respiratory disease; Mini Mental State Examination (MMSE) ≥ 24 ; willing and able to consent to participate; able to perform hand grip and forced spirometry. Outcome measure was LF (FEV1, FVC, FEV1/FVC, peak expiratory flow rate (PEFR) and slow vital capacity (SVC)), covariates were GS, age, weight, height. Unadjusted and adjusted (for age, height, weight) linear regressions were used for analysis.

Results

50 patients (men=20, women=30) were recruited. Significant relationships were found in men between GS and FEV1 (unadjusted $\beta=0.032$, 95%CI=(0.001,0.063), $p=0.047$) although attenuated after adjustment; in women between GS and PEFr (unadjusted $\beta=6.881$, 95%CI=(1.537,12.226), $p=0.013$); (adjusted $\beta=6.938$, 95%CI=(1.268,12.607), $p=0.018$), and in women between GS and SVC (unadjusted $\beta=0.052$, 95%CI=(0.006,0.099), $p=0.028$); (adjusted $\beta=0.050$, 95%CI=(0.0005,0.100), $p=0.048$). No other significant relationship was found.

Conclusions

The relationship of GS with PEFr and SVC in women might reflect stronger patients generating higher intra-thoracic pressure at the start of spirometry and pushing harder against thoracic cage recoil at end-expiration. No significant relationship was found with FEV1/FVC and GS in this small study. Further research is needed to evaluate the relationship between LF and GS.

Appendix 6.11 BGS Autumn Meeting Poster

(Available in Electronic Supplementary Document)

Appendix 6.12 Good Clinical Practice

(Available in soft bound copy)

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