Correlates of Frailty in Old Age:
Falls, Underweight and Sarcopenia

LEE Shun Wah Jenny

A Thesis Submitted in Fulfilment
of the Requirements for the Degree of

Doctor of Medicine

The Chinese University of Hong Kong

February 2015

Dedications

To my geriatrics patients, their families, and their caregivers.

And to all the future geriatricians-to-be.

Also to my father who lived to the ripe old age of 85.

Acknowledgement

First and foremost, I would like to acknowledge Professor Jean Woo, my teacher in medical school, my supervisor in clinical service, and my mentor in research, who has given me the many opportunities in my career I needed, and framed my concepts in so many areas in geriatrics. Without her introducing me to research these studies would never have existed.

I have to acknowledge Professor Timothy Kwok and his research team in the Department of Medicine & Therapeutics and the Jockey Club Centre of Osteoporosis Care and Control, in particular Mr Jason Leung, who have provided support to many of the analyses and advised me on numerous occasions on statistical matters, and Ms Hazel Mok, who has constantly been a source of friendship and support.

I would like to thank Dr Patsy Chau for her many inputs and advice in the nursing home cohort papers. Her careful scrutiny of data has saved me many mistakes in analyses and results compilation.

My sincere gratitude goes to my colleagues and friends in the Department of Medicine & Geriatrics in Shatin Hospital, during my stay in which all these studies were completed. I thank Dr Elsie Hui for allowing me the freedom to continue with research activities, Dr Christopher Lum for his encouragement, and Dr Maria Tang for her warmth and support over the years. I am grateful to the entire Division of Geriatrics in the Department of Medicine & Therapeutics of The Chinese University of Hong Kong, not forgetting the support provided by Ms Lai Fong Chiu and Joyce Ho, for refreshing my tired brain with many happy tea time chats. I thank Dr Kar Ming Au of the Community Outreach Service Team in the Prince of Wales Hospital, and Dr May Tang, for their passion towards better care for end of life elderly patients which has deeply inspired me.

My heartfelt thanks go to my many junior colleagues and young friends, in particular Dr Mark Tam, Dr Angeline Lo and Dr Ernie Tse, for they have taken such good care of my patients to allow the peace of mind I required to finish this thesis. They and many others have also been my constant source of inspiration, for they have shared with me, through their vibrant youthful minds and over many delightful lunch gatherings, the energy and stamina I needed to compose this work. I wish them all the best with their careers, in whichever paths they should choose.

Last, but definitely not the least, I would like to thank Dr Tung Wai Auyeung, my closest friend and associate, in all the aspects in life that one can imagine.

Abstract

This thesis is focused on frailty in old age. The frailty syndrome is the newest geriatric syndrome and can be aptly called the ultimate geriatric syndrome due to the complexity of its causes and the wide range of adverse outcomes it may lead to in older persons. Several of the important correlates of frailty, namely falls, underweight and sarcopenia, are discussed in the context of their relationship with frailty. These entities are geriatric syndromes in their own rights, sharing many common risk factors and arriving at adverse health outcomes either directly or via the pathway of frailty. In the publications that arose from this work, the risk factors of falls, in particular the relationship between medications and chronic diseases in causing falls; risk factors and outcomes of sarcopenia, in particular its relation to diabetes mellitus and other chronic diseases; and how underweight poses survival risks in both community-living and institutionalized older people, are discussed. The final publication of this series of studies demonstrated the reversibility of the frailty syndrome, showing that not all who were in the pre-frailty stage will decline. Risk factors associated with improvement or decline in the pre-frail stage were identified in the local population, and a period of relative stability opened for possible interventions was observed. This thesis thus examines the complex interplay of these syndromes in old age. It is hoped that these publications will enable further research into the underlying mechanisms of frailty and to elucidate modifiable risk factors, hence enabling older people, in particular those in the pre-frail stage, to live healthier and longer lives.

List of abbreviations

ABI	Ankle-brachial index
ACEI	Angiotensin converting enzyme inhibitors,
ADL	Activities of daily living
ANCOVA	Analysis of covariance
ALM	Appendicular lean mass
ASM	Appendicular skeletal muscle mass
ASM/Ht^2	Height-adjusted appendicular skeletal muscle mass (ASM/Ht^2)
AWGS	Asia Working Group for Sarcopenia
BIA	Bioelectrical Impedance Analysis
BMI	Body mass index
CCB	Calcium channel blocker
CES–D scale	Center for Epidemiologic Studies Depression scale
CFS	Clinical Frailty Scale
CHS	Cardiovascular Health Study
CI	Confidence interval
COPD	Chronic obstructive pulmonary diseases
CSHA	Canadian Study of Health and Aging
CSI-D	Community Screening Instrument of Dementia
CT	Computerized Axial Tomography
DM	Diabetes mellitus
DXA	Dual X-Ray Absorptiometry

EWGSOP	European Working Group on Sarcopenia in Older People
GDS	Geriatric Depression Scale
GS	Gait speed
HOMA-IR	Homeostatis Model Assessment of Insulin Resistance
HR	Hazard ratios
HS	Handgrip strength
ICD	International Classification of Disease
IL-6	Interleukin-6
IWGS	International Working Group on Sarcopenia
LBP	Low back pain
MDS	Minimum Data Set
MDS/RAI	Minimum Data Set/Resident Assessment Instrument
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
NS	Not significant
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PASE	Physical Activity Scale of the Elderly
RAF	Relative abdominal fat
SAS	Statistical Analysis System
SD	Standard deviation
SES	Socio-economic status

SF-12	Short form 12 Quality of Life Score
SMI	Skeletal muscle index
SOF	Study of Osteoporotic Fracture
SPPB	Short Physical Performance Battery
SPSS	Statistical package for the social sciences
TNFα	Tumour necrosis factor α
UK	United Kingdom
US	United States
WHO	World Health Organization
WHR	Waist-hip ratio

Table of Content

List of Tables

List of Figures

Chapter 1

Introduction

1.1 What are Geriatric Syndromes?

Geriatric syndromes are clinical presentations commonly seen in older people that are associated with adverse health outcomes or poor quality of living in late life. They are often not explicitly linked to any single disease but are the results of reduced reserve in multiple systems. (Tinetti et al., 1995) As a result, they may appear ill-defined, yet pose diagnostic challenges to clinicians because the presenting problem (e.g. delirium or a fall) may be related to a distant infection (e.g. urinary tract infection), rather than a primary problem in the brain. This is the basis of the so-called "atypical presentation" of illnesses in older patients. In addition, these syndromes often share similar sets of causes, which make their relationships to each other complicated.

1.2 Outcomes of Geriatric Syndromes

There are ample evidence that geriatric syndromes can predict mortality (Afilalo et al., 2009), institutionalization, prolonged hospitalization (Anpalahan & Gibson, 2008; Alarcón et al.,1999), and poor hospitalization, surgical or cancer treatment outcomes (Alarcón et al., 1999; Liu & Leung, 2000; Makary et al., 2010; Lee et al., 2010;

Extermann et al., 2005; Koroukian et al., 2010) in older people. (Kane et al., 2011; Inouye et al., 2007) The outcome of several geriatric syndromes will be specifically discussed in the following chapters.

1.3 Geriatric Syndromes as a Disease Model

If we try to classify geriatric syndromes according to models of diseases as described by Inouye et al. (Inouye et al., 2007), it would be obvious that they constitute the most complex model in which multiple intrinsic and extrinsic risk factors interact with each other, causing the older individual to present with one particular clinical phenotype, or presentation. It is therefore obvious that interventions at multiple levels have to be employed in order to prevent further decline, or revert the defect. One of the difficulties in geriatric medicine is that many of the risk factors are not reversible, such as old age and pre-existing organ degenerations, and that makes the study and management of geriatric syndromes much more complex than general adult medicine.

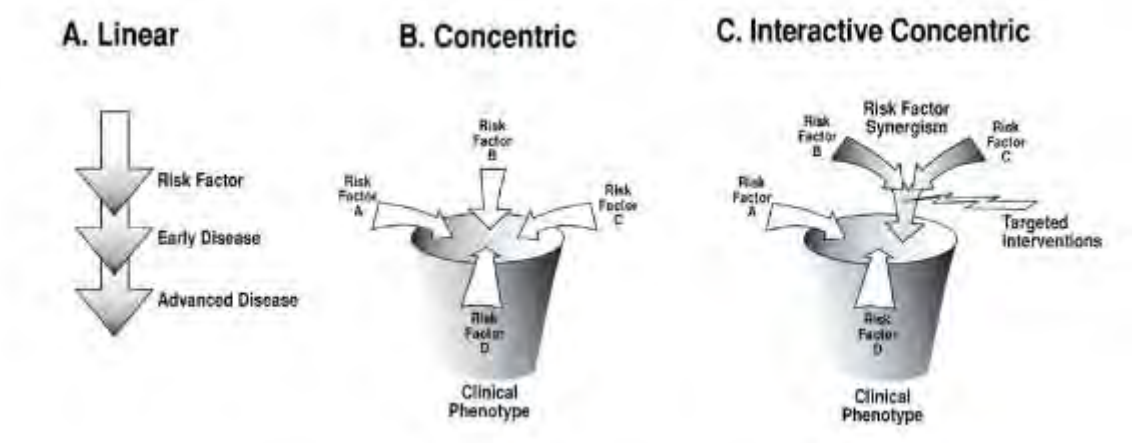


Figure 1.1 Different conceptual models of diseases or syndromes: adopted from: Inouye et al., 2007

1.4 Traditional and new geriatric syndromes

Geriatrics syndromes are not new concepts. Sir Bernard Isaac (1924-1995), a forerunner in British geriatric medicine, has coined the term “geriatric giants” or the Geriatric “I”s: immobility, instability (falls), incontinence and impaired intellect/memory. These, together with “iatrogenicity”, are the traditional geriatric syndromes.

However, in the recent one or two decades, new “giants” have emerged. Multiple morbidities, under-nutrition, sarcopenia, frailty, impaired homeostasis, chronic inflammation, pressure ulcer and functional decline are some of the more recently proposed geriatric giants. (Kane et al., 2011; Inouye et al., 2007) They too shared common risk factors which will be discussed below.

1.5 Underlying risk factors

Intrinsic factors

Ageing

Ageing as a natural process causes degeneration in biological systems, resulting in decline in vision, cognition, changes in body composition thus loss of body mass, decline in physical performance, and increase pain in degenerative joints. These degenerative processes will take place even in someone who suffers from no disease, and therefore is

free from any pathological processes. One example is the occurrence of cataracts, which, without intervention, will lead to diminished visual acuity, and put an older person at risk of falls. By the same token, degeneration of knee joints and age-related loss of muscle (sarcopenia) will predispose the person to limitations of mobility, loss of independent functioning in instrumental or basic daily care, falls, fractures, and even hospitalization secondary to injuries thus sustained.

Medical Illnesses

Pathological processes that a person has acquired as a result of genetic predisposition, unhealthy lifestyle, or injuries during the life course will aggravate the damages done to the individual during the natural ageing processes. An example is diabetes mellitus developed due to genetic tendency, unhealthy eating and the lack of exercise in the decades preceding old age. This will aggravate or accelerate cataract develop and lead to earlier risk of falls due to decline in vision. Its associated obesity will also accelerate the toll of knee osteoarthritis, leading to earlier physical limitations.

Extrinsic factors

Environment and drugs

Younger adults are able to compensate for environmental perturbations or risks by

adaptation. Older adults were less able to compensate due to marginal reserves in multiple systems, thus are more prone to adverse effects of extrinsic risk factors such as extremes of temperatures, insufficient lighting or obstacles during locomotion. They are also more prone to the adverse effects of medications due to reduced body water, thus reduced volume of distribution for water-soluble drugs; increased in body fat proportion, thus delayed clearance of drugs; and reduced liver and renal metabolism due to ageing or other diseases.

Social changes

Older adults are also more subjected to adverse social conditions such as social isolation, depression, poverty and limitation in food choices. Unhealthy lifestyle such as smoking would have been present for decades and damages to organs well-established. Regular physical exercise is often not possible due to musculoskeletal degeneration or cardio-pulmonary function decline. Maintaining exercise is difficult especially for older women who frequently did not acquire the habit in younger days.

In the following chapters, four geriatric syndromes and their complex inter-play in old age will be discussed.

Chapter 2

Falls

2.1 Introduction

Millions of people fall each day all over the world, and most of them would be toddlers. A fall can be part of the learning process for these very young children, or it can be a result of trying out new techniques, such as falls sustained while learning to ride the bicycle or skating. However, falls are very serious events in old age. Falls are one of the traditional geriatric syndromes, frequently also termed “instability”. Instability can result in falls, injuries, fractures, hospitalization, and occasionally death due to injuries or their complications. Instability can also be attributed to dizziness or syncope, which is another geriatric giant on its own.

2.2 Definition

A fall is defined as any unexpected loss of balance resulting in coming to rest on the ground or floor. Recurrent fallers were defined as those subjects with 2 or more falls in the past year.

2.3 Falls as a geriatric syndrome

Falls or instability is one of the traditional geriatric syndromes. It satisfies all the criteria of being one with a high prevalence rate in the older population, has multiple interacting risk factors, and results in many adverse outcomes in old age.

Prevalence

Approximately 18 to 60% of older community dwellers all over the world fall each year. (Ho et al., 1996; Hanlon et al., 2002; Cesari et al., 2002; Rubernstein & Josephson, 2002; Chu et al., 2005). Institutionalized elderly had an even higher prevalence of falls up to 45 – 70% per year. (Gryfe et al., 1977; Tinetti et al., 1987) Among the latter, fall rate differs between those with different mobility levels, with the bedridden having the lowest fall rate (4.1 per 100 person-years), increasing to 17.0 per 100 person-years in those who could ambulate by themselves. More mobile residents tended to have more serious fall-related injuries. (Thapa et al., 1996)

Outcomes

Not all falls in old age will result in serious injuries, but approximately 20% leads to soft tissue injury, 5% results in fractures, and 1% will sustain a hip fracture. (Tinetti et al., 1988; Chu et al., 2007; Kannus et al., 2005) Apart from the pain, subsequent surgical risk,

and a period of immobilization, a hip fracture will have other long-lasting consequences: the risk of admission to institutionalized care was increased up to 10.2 times compared with someone without a fall (Tinetti et al, 1997; Donald & Bulpitt, 1999), 8-33% would have died within the end of the first year (Donald & Bulpitt, 1999; Roche et al., 2005) , and the higher mortality risk persisted up to 10% after the fracture (Bliuc et al., 2009). Even non-injurious falls can leave a psychological impact: older people with a history of fall will have fear of further falls, which limits their mobility and functional independence, leading to loss of health-related quality of life, anxiety and depression. (Chu et al., 2007; Costa et al., 2012; van Haastregt et al.,2008; Scheffer et al.,2008)

2.4 Risk factors

Risk factors of falls have been studied in different older populations. Physical disabilities, poor vision, cognitive impairment, and presence of certain conditions such as depression, stroke and cardiovascular diseases were commonly identified risk factors. (Ho et al.,1996; Prudham & Evans, 1981; Campbell et al.,1981; O'Loughin et al.,1993; Lord et al., 1994; Lawlor et al.,2003; Tinetti et al.,1988) Frailty was found to be an independent risk factor of both falls and fractures. (Ensrud et al., 2007; Ensrud et al., 2009)

Risk Factors in older adults in different settings

Risk factor profiles for falls appeared to be different in different older populations: community-living vs. nursing home residents, and fall risk factors have not been reported among the Hong Kong nursing home population. In view that the local population is getting older and in view that Hong Kong has a high rate of institutionalization, amounting to 7% of the population over the age of 65 (Thematic Household Survey Report No. 40. Hong Kong [Census and Statistics Department, the Government of the Hong Kong Special Administrative Region], 2009), fall prevention by identifying risk factors in this population is in need.

Are Medications risk factors?

Medications, in particular anti-hypertensives and sedatives, have often been cited as one of the major extrinsic associated factors for falls in older adults, (Tinetti et al., 1988; Cumming et al., 1991; Ho et al., 1996; Koski et al., 1996; Lawlor et al.,2003; Woolcott et al., 2009; Ensrud et al., 2002; Leipzig et al., 1999) but opinion has not been consistent. Some have found medications to be unrelated to falls (Graafmans et al., 1996) while others concluded such findings were inconsistent across studies, including meta-analyses. (Ganz et al., 2007) Few studies, however, have attempted to compare the relative importance of medications and their indications in the association with falls. One earlier study which attempted to do this had concluded that drugs were more related to falls than

diagnoses. (Granek et al., 1987) However, that was conducted in a nursing home population which was likely to be of older age and physically more ill than community living older people. Findings therefore could not be generalized to the latter group. In addition, the use of psychogenic medications differ between age groups and prescription pattern differ between countries, (Ohayon, 2002) it is therefore important to examine the local older population and in both the community and the institutionalized settings for this question.

Table 2.4.1 Classes of medications reported to have association with falls in older adults

Medication class	**Reference**
Sedatives or hypnotics	Tinetti et al., 1988; Ensrud et al., 2002; Woolcott et al., 2009; Cumming et al., 1991; Koshi et al., 1996
Anti-depressants	Ensrud et al., 2002; Woolcott et al., 2009
Anticonvulsants	Ensrud et al., 2002; Deandrea et al., 2010
Anti-hypertensives (diltiazem, calcium channel blockers)	Cumming et al., 1991; Koski et al., 1996
Diuretics	Cumming et al., 1991
Laxatives	Cumming et al., 1991
Digitalis	Koski et al., 1996
Peripheral vasodilators	Koski et al., 1996
Anti-inflammatory drugs	Koski et al., 1996

Chapter 3

Underweight

3.1 Introduction

While there is a growing global epidemic of obesity among younger and middle aged adults, and even among children, the main concern in older adults in this regard is the loss of weight as the individual ages. Progressive weight loss in old age is a strong predictor of mortality, as well as a marker of frailty (Fried et al., 2001).

3.2 Definition

World Health Organization (WHO) definition

The desirable weight for any adult has been defined by the World Health Organization (WHO) according to the following classification in the body mass index (BMI).

Table 3.2.1 BMI classifications defined by the WHO

Category	BMI (kg/M^2)	BMI (Asia Pacific definition) (kg/M^2) (WHO, Australia 2000)
Underweight	<18.5	<18.5
Normal	18.5 - 25	18.5 – 22.9
Overweight	25.1 - 30	23 – 24.9
Obese	>30	≥ 25

Special consideration has been given to Asia-Pacific populations, in which the relationship between BMI and cardio-metabolic risks were different as compared to the white and black populations, mainly due to a difference in body built and body fat proportion. As a result, a modified classification of the BMI was provided for Asians (Table 3.2.1). However, it must be noted that the BMI is a tool for cardio-metabolic risk assessment, and therefore it was validated against the occurrence of these diseases. One has to bear in mind that the BMI is more a screening tool for over-nutrition, rather than one for under-nutrition. In both the general WHO definition and the WHO Asia-Pacific definition, a BMI <18.5 kg/m^2 is classified as "underweight".

Other definitions

In geriatrics literature, underweight has often been classified differently from the WHO classification. The range of BMI defined as "underweight" or "low" in old age literature ranges from <18.5 kg/m^2 the lowest, to 22 kg/m^2 the highest. (Sergi et al., 2005; Kimyagarow et al., 2010)

3.3 The problem of age-disparity in the BMI

Although BMI is widely used in public health promotion and education, in general we make no distinction between the BMI of a middle age adult and an older adult. In the

non-elderly adult population, underweight is often not a risk factor whereas overweight or obesity is a major health concern, giving rise to higher mortality risk or cardiovascular events risk. (Wändell et al., 2009; Kramer et al., 2013) In recent meta-analysis, there is a tendency for overweight (BMI 25 to <30 kg/m2) to be protective towards all-cause mortality, with the protective effect being more prominent among those age ≥ 65 years, and the ill-effect of obesity (BMI up to ≥ 35 kg/m2) towards the same outcome not significant statistically when compared with the normal weight, among those over 65 years old. (Flegal et al., 2013) A higher than normal BMI will call for weight reduction, to prevent the cardio-metabolic complications of obesity such as diabetes mellitus, ischaemic heart disease, hypertension and stroke. However, when these conditions are already present, and that the individual has already survived with these conditions into the seventh, eighth or even the ninth decade, weight reduction may cause more harm than good. (Bales & Buhr, 2008) One controversial point regarding the underweight category in the WHO BMI classification is its relationship with all-cause mortality. While a few large middle-age cohorts did report a higher mortality risk in the underweight (Gu et al., 2006; Adams et al., 2006), only rarely has specific causes of death been linked to underweight. (Jee et al., 2006)

3.4 Weight loss or underweight as a geriatric syndrome

Weight loss or underweight is a geriatric syndrome. Apart from the almost universal fact that people lose weight as they grow into their seventies or eighties, there is the fact that this weight loss is associated with adverse outcomes.

Mortality

There has been increasing evidence to suggest that any kind of intentional or unintentional weight loss may be related to higher mortality risk in old age, even among the obese. (Bales & Buhr, 2008; Wang et al., 1997; Ryan et al., 1995; Kiely et al., 2000; Sullivan et al., 2001; Flacker & Kiely, 2003; Ho et al., 1994) While recently there have been controversies regarding the benefit of weight reduction among obese or overweight young or middle age adults, (Klenk et al., 2014; Poobalan et al., 2007; Harrington et al., 2009) epidemiology studies in older populations have consistently demonstrated that who are overweight and no weight loss had the highest survival rate (Janssen et al., 2005; Takata et al., 2007). This phenomenon of "survival of the fattest" is further exaggerated among the frailer nursing home population, in which the obese survived even longer than the overweight. (Grabowski et al., 2005) One explanation for this "geriatric paradox" seen between obesity and mortality may be that the BMI reflects more the lean mass, whereas abdominal fatness may be more reflected by waist circumference, (Seidell & Visscher,

2000) though other studies on this matter has also adjusted for the waist circumference or the waist-hip-ratio, and found it to be unrelated to mortality in older people. (Woo et al., 2001)

Functionality

Apart from the higher mortality, underweight is also associated with low muscle mass and age-related muscle loss or sarcopenia. However, the relationship between BMI and functionality may vary between populations, depending on the range of BMI. Very high BMI (e.g. >30 or 35 kg/m^2) may cause physical limitations due to difficult to move about and the gravity effect on degenerative weight-bearing joints in Western populations with more obesity. (Davison et al., 2002; Bannerman et al., 2002) Yet in populations with a smaller body build and which tend to be leaner, a low, instead of high, BMI was more predictive of mobility decline. (Ho et al., 1997; Woo et al., 2001) It is worth noting that despite baseline body weight, weight loss in old age is predictive of mobility and functional decline. (Bannerman et al., 2002)

Falls and Fractures

Underweight is associated with low bone mineral density in both men and women. (Coin et al., 2000) In addition, low BMI is also a risk factor for hip fracture in older women, the

risk being doubled in those with BMI of 20kg/m^2, when compared with those with BMI of 25kg/m^2. (De Laet et al., 2005) Weight loss, in particular involuntary weight loss in older women, was also associated with increased fractures including hip fractures. (Ensrud et al., 1997; Ensrud et al., 2003) One of the mechanisms for this was likely the bone mineral density loss associated with weight loss in hormone-deficient, post-menopausal women. This bone mineral loss could not be regained during subsequent weight gain and hence accounted for the increased fracture rate. (Villalon et al., 2011) Thus both underweight and weight loss is directly related to higher fracture risk in the older adult. In fact, BMI has been included as one of the important clinical factors that contribute to better hip fracture prediction in addition to bone mineral density. (Kanis et al., 2007)

Frailty and Sarcopenia

Weight loss was an integral part of the frailty phenotype as defined by Fried et al. (Fried et al., 2001) Weight loss was also strongly related to age-related muscle loss or sarcopenia, and those with low BMI were almost always found to have low muscle strength and muscle mass. (Lau et al., 2005; Iannuzzi-Sucich et al., 2002) It is difficult for an underweight elderly to regain muscle mass simply by increasing energy intake, as most of the regained weight would be fat rather than muscle. (Newman et al., 2005) In fact, apart

from underweight, any weight loss might be considered a warning sign in an older person, as anorexia can be an early signal of many occult infections (e.g. tuberculosis) and malignancies.

Chapter 4

Sarcopenia

4.1 Introduction

Sarcopenia is a relatively new geriatric syndrome. Its name was derived from the Greek word “sarx”, meaning “flesh”, and “penia”, meaning “loss”. The first publication with the term “sarcopenia” in its title has only appeared in 1993. (Evans & Campbell, 1993) Sarcopenia describes age-related muscle loss or lean mass loss, and contributes to the decline in physical function in old age. This loss of muscle mass and strength is at least as common in old age as its counterpart, osteoporosis, including a high prevalence in the older populations and an increasing prevalence with advancing age: the loss in muscle mass amounts to 1-2% per year after the age of 50. (Hughes et al., 2002) However, only recently, sarcopenia has become a key component of another yet newer geriatric syndrome, frailty, which will be discussed in the next chapter.

4.2 Definition

Cut-off value

The definition of sarcopenia has been problematic. In the earlier studies, researchers have defined sarcopenia as muscle mass below 2 standard deviations (SD) of the mean value of

the healthy young population, after the fashion of osteoporosis. (Lau et al., 2005; Baumgartner et al.,1998) However, some argued that being a "proto-illness", cut-points should be defined by the value below which risks of undesirable outcomes began to increase. (Woo et al., 2009; Lauretani et al., 2003) When the muscle mass of the normal young population was not available, or as some have suggested, that there may be a secular drop in the muscle mass in the younger generation because of urbanization and changes in lifestyle, the lowest 20% or 25% of muscle strength in the study population has often been adopted arbitrarily as the cut-off value (Szulc et al., 2004; Visser et al., 2000), or lower two quintiles in muscle mass. (Davison et al., 2002)

Methods of measurement

Mass

To complicate this further, the method of measurement has also been under debate: the most common method of measurement is the Dual X-Ray Absorptiometry (DXA) in the literature, but increasingly Bioelectrical Impedance Analysis (BIA) has been used, in particular in large population studies and in community settings, where the BIA machine can be brought to the subject on the site. However, accuracy of the BIA measurements depends highly on the environment and skin condition of the subject, and the validation equation also varied between different machines, making comparisons between studies

problematic. (Roberts et al., 2011; Mijnarends et al., 2013) Occasionally the Computerized Axial Tomography (CT) was used to demonstrate cross-sectionally the distribution of fat and muscle, especially in the calf or thigh areas. The CT has the ability to distinguish between muscle and fat infiltrating muscles, thus avoiding the over-estimation of muscle mass in obese subjects as measured by the DXA. (Pahor et al., 2009) In short, all three methods have their advantages and deficits. At present, most of the older cohorts reported used DXA measurements, but there is an increasing use of BIA in literature.

Strength

The most common measurement of muscle strength used in literature and in clinical practice is grip strength. Grip strength has excellent correlation with lean body mass. (Roberts et al., 2011) However, it has been noted that the decline in strength with ageing is faster than the decline in muscle mass, (Ferrucci et al., 1997; Lauretani et al., 1985; Delmonico et al., 2009) and that the decline in strength correlated better with physical performance than the decline in mass. (Visser et al., 2000) It is due to this reason that some researchers proposed the term “dynapenia” (Clark & Manini, (2008) to supplement the notion of loss in strength in addition to mass in changes in the quality on top of the quantity of muscle in old age. To this effect, recent definitions of sarcopenia include not

only measurement of muscle mass, but often, muscle strength in the form of grip strength. (Cruz-Jentoft et al., 2010a; Fielding et al., 2011; Chen et al., 2014)

Performance

Physical performance can be regarded as a function of muscles. In this regard, the lower limbs have some of the largest muscles in the body and are responsible for mobilization of the body in many daily functions, including walking and stairs climbing. In geriatrics, strength and balance in the lower limbs are particularly important because apart from allowing for activities of daily living (ADL) independence, they are also involved in the righting reflex and thus falls prevention. To reflect the function of the lower limbs muscles, a measure of physical performance is often added in definitions or studies of sarcopenia. (Cruz-Jentoft et al., 2010a; Fielding et al., 2011; Chen et al., 2014)

A battery of tests called the Short Physical Performance Battery (SPPB) serves to evaluate the strength, endurance, balance and gait by testing the ability to stand with the feet in the side-by-side, semi-tandem, and tandem position, each for 10 seconds, time to walk 8 feet, and time to perform the chair-rise without help of armrests for 5 times. (Guralnik et al., 1994) It does not require any special equipment apart from a stop watch and a chair, and is considered a standard measure of physical performance in both clinical setting and

research. (Cruz-Jentoft et al., 2010a; Working Group on Functional Outcome Measures for Clinical Trials, 2008)

Gait speed, one of the tests in the SPPB, has now become one of the most common used physical performance measures in both literature and clinical settings. It has good predictive power towards adverse outcomes such as new disabilities, (Guralnik et al., 2000) mobility limitations and mortality. (Cesari et al., 2009) Gait speed measurements are done at usual pace, over a distance of either 8 feet or 6 meters. Some researchers include the accelerating phase and therefore the speed may be lower. Others asked the subject to walk through an 8-metre strip but only take the time after the subject crossed a line marking the first metre, thus excluding the accelerating phase.

Area of measurement and adjustments

Early studies in sarcopenia has adopted the appendicular skeletal muscle mass (ASM) and used the height-adjusted ASM (ASM/m^2) as a standard for measurement muscle mass. (Baumgartner et al., 1998) The ASM is derived from the summation of the lean mass of the four limbs as seen on a DXA scan, with the limbs being “cut” from the trunk at defined landmarks. Sarcopenia defined by this method correlated significantly with physical disability, independent of age, comorbidities and fat mass. (Baumgartner et al.,

1998) However, others have suggested that since the DXA cannot distinguish muscle mass and the fat infiltrated into muscles, it may over-estimate the muscle mass in obese subjects. These researchers suggested to use weight-adjusted muscle mass (skeletal muscle mass/total body mass x 100) (Janssen et al., 2002), or the residuals method which takes into account the fat mass in addition to the height, which is more accurate than the height-adjusted method in women (who tend to have more body fat) and in obese or overweight individuals. (Newman et al., 2003)

Operational definition

The need of an operational definition used by all has been long recognized. However, owing to the variations in measurement methods and differences in concept about the cut-off values across different research centres, coming to a consensus is difficult. Since 2010 researchers have devoted concerted efforts in establishing some commonly accepted operational definitions for sarcopenia. At present there are 3 published consensus definitions from 3 groups: the European Working Group on Sarcopenia in Older People (EWGSOP) in Europe, the International Working Group on Sarcopenia (IWGS) including researchers from both Europe and America, and the Asia Working Group for Sarcopenia (AWGS) in Asia. They are listed below:

Table 4.2.1 Consensus definitions from 3 groups: the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS) and the Asia Working Group for Sarcopenia (AWGS)

	A. Muscle mass	B. Muscle strength	C. Physical performance
EWGSOP (Cruz-Jentoft et al., 2010a) Diagnosis: A + (B or C)	ASM/height2 (by 2SD below mean of young population) Men: 7.26kg/m2 Women: 5.5 kg/m2 ASM/height 2 (lowest 20% of study population) Men: 7.25kg/m2 Women: 5.67kg/m2	Men: <30 kg Women: <20 kg Men: BMI ≤ 24 : ≤29 kg BMI 24.1 – 26: ≤30 kg BMI 26.1 – 28: ≤30 kg BMI >28: ≤32 kg Women: BMI ≤ 23 : ≤17 kg BMI 23.1 – 26: ≤17.3 kg BMI 26.1 – 29: ≤18 kg BMI >29: ≤21 kg	Gait speed ≤0.8m/s
IWGS (Fielding et al., 2011) Diagnosis: A + C	ALM/Height2 Men: ≤7.23 kg/m2 Women: ≤5.67 g/m2	Not mentioned	Gait speed <1.0m/s
AWGS (Chen et al., 2014) Diagnosis: A + (B or C)	ASM/height2 DXA: Men: <7.0 kg/m2 Women: < 5.4 kg/m2 BIA: Men: <7.0 kg/m2 Women: < 5.7 kg/m2	Men: <26 kg Women: <18kg	Gait speed ≤0.8m/s

ALM = appendicular lean mass

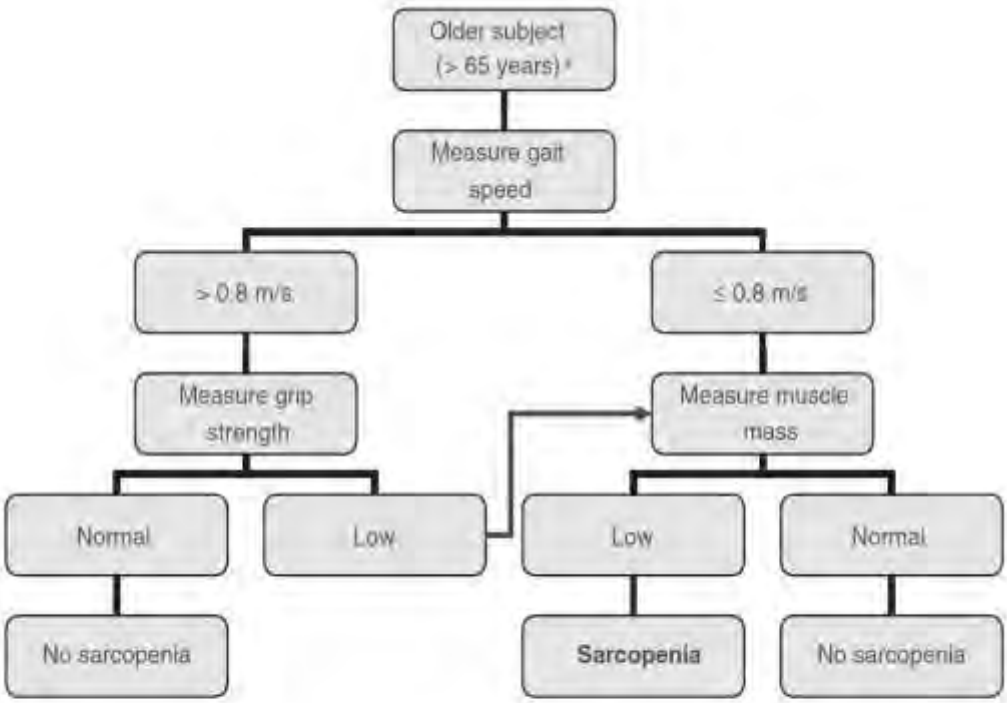


Figure 4.2.1 EWGSOP-suggested algorithm for sarcopenia case finding in older individuals. (Cruz-Jentoft et al., 2010a)

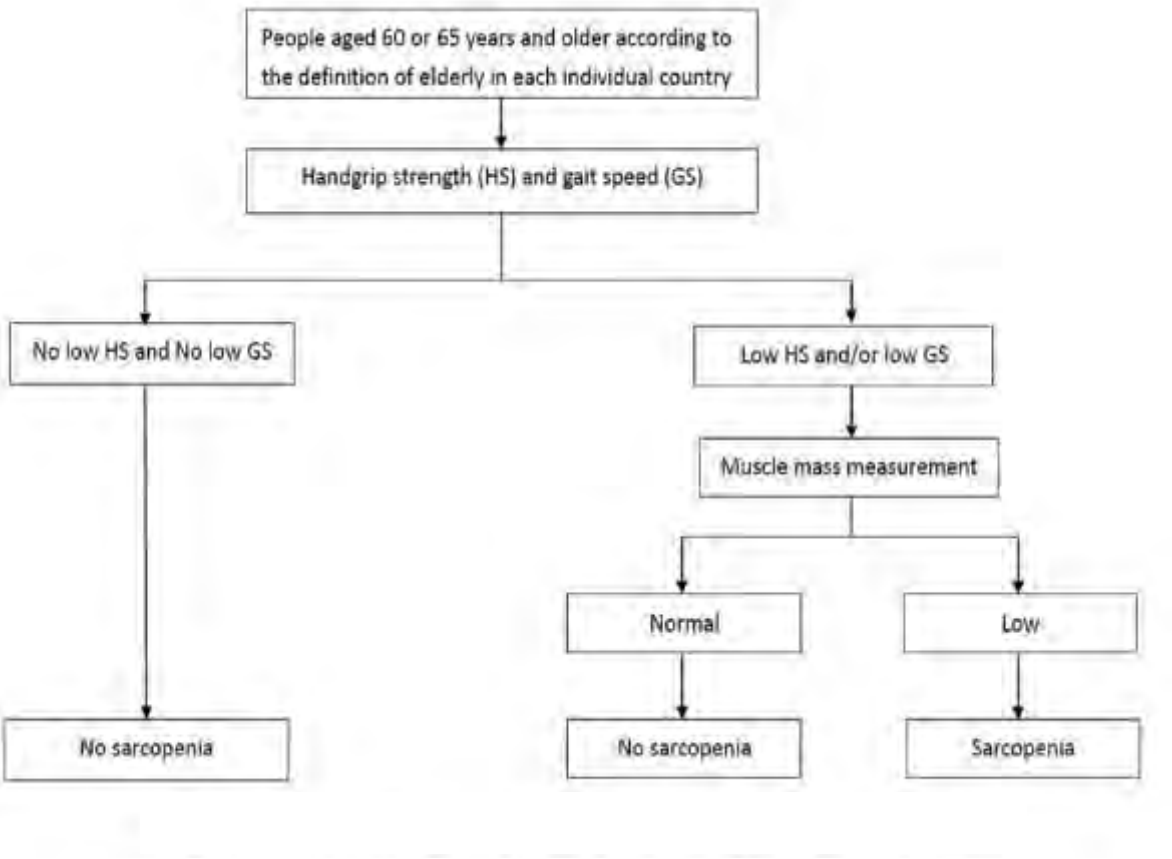


Figure 4.2.2 Recommended diagnostic algorithm of Asian Working Group for Sarcopenia (Chen et al., 2014)

Screening

The IWGS suggested screening for sarcopenia in older people who have impaired physical functioning, such as inability to rise from a chair without assistance, who cannot walk without assistance, and in those who has gait speed below 1m/s, DXA for muscle mass assessment are recommended. (Fielding et al., 2011) The AWGS suggested screening in older people aged 60 – 65 years and above, with the following presentations: recent functional decline or functional impairment, unintentional weight loss for over 5% in a month, depressive mood or cognitive impairment, repeated falls, under-nutrition, or

are suffering from chronic conditions such as chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions. (Chen et al., 2014) The EWGSOP did not have any target screening groups at present, apart from those over 65 years of age and with a slow walking speed.

4.3 Sarcopenia as a geriatric syndrome

Sarcopenia is appropriately called a geriatric syndrome: it is common in the aged population, has multiple contributing factors involving multiple systems, and is well-documented to be associated with many adverse outcomes in old age. The prevalence of sarcopenia ranges from 8.8 (women) to 13.5 (men) % in those between 60-70 years old, up to 50% in those over 80 years of age. (Rolland et al., 2008; Fielding et al., 2011) Adverse outcomes that have been associated with sarcopenia in the literature included disability (Evans & Campbell, 1993; Visser et al., 1998; Janssen et al., 2004; von Haehling et al.,2010), falls (von Haehling et al.,2010; Landi et al.,2012b), hospitalization (Cawthon et al., 2009), ADL limitations (Cruz-Jentoft et al., 2010b), poor quality of life (Cruz-Jentoft et al., 2010b), and mortality (Landi et al., 2012a; Landi et al., 2013).

4.4 Risk factors

Intrinsic

Age, gender, and ethnicity

Every year of advancing age is associated with 1-2% of muscle mass loss. (von Haehling et al., 2010) Muscle power and strength, which are sensitive to the physical performance, decline at an even faster rate. Men lose muscle at a faster rate than women, though they have a larger peak muscle mass. (Gallagher et al., 1997) Owing to this gender difference, sarcopenia research should be, and is often done, separately for the genders. Ethnicity or genetics also play an important role in sarcopenia. Black individuals have more muscle than white people, and their rates of muscle and strength loss with age are different. (Goodpaster et al., 2006) Little is known about Asians because the earlier sarcopenia studies were nearly all conducted in black and white people. There is an urgent need to have data on how Asians are affected by this new geriatric syndrome.

Nutrition

Underweight and low caloric intake have long been recognized as risk factors for sarcopenia. A low BMI has been a consistent significant risk factor in sarcopenia studies in different cohorts. (Iannuzzi-Sucich et al., 2002; Szulc et al., 2004)

As nutrition can be altered by interventions, it is possible that sarcopenia can be prevented

or “treated” partially at least by nutritional interventions.

Cytokines and hormones

Inflammatory cytokines such as Interleukin-6 (IL-6) and tumour necrosis factor α (TNFα) have been found to be associated with both natural ageing and sarcopenia. (Di Iorio et al., 2006; Morley & Baumgartner, 2004; Visser et al., 2002) The decline in sex hormones, in particular testosterone, has been found to be associated with age-related muscle loss and strength loss. (Iannuzzi-Sucich et al., 2002; Szulc et al., 2004; Baumgartner et al., 1999; Auyeung et al., 2011a) However, testosterone decline seemed to be more related to sarcopenia in men than in women. (Baumgartner et al., 1999)

Chronic diseases

Chronic diseases play an important role in the development of disability and geriatric syndromes. Diseases such as chronic heart failure and chronic obstructive lung diseases increase inflammatory cytokine levels (von Haehling et al., 2009; Broekhuizen et al., 2005; Luo et al., 2005) and theoretically should also contribute to sarcopenia. However, the only chronic disease that has been specifically studied with respect to sarcopenia is diabetes. (Park et al., 2009; Park et al., 2007) Both of these papers were conducted in a US cohort which consisted of only black and white older people. In view of the paucity of

studies in this area at that time, there is a need to study how chronic diseases affect sarcopenia and muscle loss in Asian populations.

Extrinsic

Smoking and exercise

A sedentary lifestyle is associated with a higher rate of muscle loss in old age and lower muscle mass in both older men and women. (Szulc et al., 2004; Baumgartner et al., 1999) Smoking, on the other hand, was associated with lower muscle mass. (Szulc et al., 2004) As exercise can be promoted and programmes can be prescribed, current research is focusing on studying the type of exercise that can benefit muscle and sarcopenia most in the elderly.

Chapter 5

Frailty

5.1 Introduction

Frailty is a very recently developed concept in geriatrics, having only appeared on the scene since twenty or so years ago. (Fried et al.,2001) It is not to be confused with the general English word “frail”, which though describes an individual with weak health, is not clearly defined in any way. Frailty syndrome in geriatrics describes a state of the lack of reserve in multiple systems that lead to vulnerability to adverse outcomes. These systems encompass physical, cognitive, psychological, social and nutritional aspects. Frailty thus can be considered as the ultimate geriatric syndrome because it can be both the presentation and underlying cause of other geriatric syndromes, e.g. falls, underweight and sarcopenia.

5.2 Definition

Frailty is a pre-disability state, which means that the presence of disability should not be considered as a diagnostic criterion for frailty. (Morley et al., 2013) Frailty is a dynamic state. Thus it is possible for an individual to “transit” from one category of frailty to another. (Morley et al., 2013) Frailty is also a reversible state, which implies that with

improvement either with or without interventions, it is also possible for someone to recover from a more frail state to a less frail state. (Morley et al., 2013) Frailty is to be distinguished between a broader definition of the term, which describes the state of an individual, and a specific medical / geriatric syndrome. (Morley et al., 2013) Frailty differs from multi-morbidity: "physical frailty focuses on specific areas for which a general treatment approach can be developed, whereas multi-morbidity moves the focus to the management of each condition separately." (Morley et al., 2013)

The current definition recommended by a consensus group comprised of delegates from 6 major international, European, and US societies is: "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death." (Morley et al., 2013)

There are at least 8 major validated models of frailty. (Morley et al., 2013) Some focused more on the physical aspects (Fried et al., 2001), and the others put emphasis on multiple system deficits. (Rockwood et al., 1994) Three of the most commonly used models in frailty research are described below.

The Cardiovascular Health Study (CHS) frailty phenotype

Table 5.2.1 Fried's phenotype for frailty

Characteristic	Definition
Shrinkage (unintentional weight loss)	10 lbs lost unintentionally in prior year; or ≥5% of body weight in prior year (by direct measurement of weight)
Weakness	Grip strength in the lowest 20% at baseline, adjusted for gender and body mass index.
Self-reported exhaustion	Self-reported exhaustion, identified by two questions from the CES–D scale, (Orme et al., 1986) is associated with stage of exercise reached in graded exercise testing, as an indicator of O^2 max, and is predictive of cardiovascular disease.
Slowness	The slowest 20% of the population was defined at baseline, based on time to walk 15 feet, adjusting for gender and standing height.
Low physical activity level	A weighted score of kilocalories expended per week was calculated at baseline based on each participant's report. The lowest quintile of physical activity was identified for each gender.

An individual is classified as Robust, Pre-frail, or Frail according to the number of phenotypes present: none of the phenotypes = Robust; one or two phenotypes = Pre-frail; and three or more phenotypes = Frail. The model was validated in 5317 US older adults ≥65 years old (the Cardiovascular Healthy Study cohort), the ethnicity of which was 86% white, 15% black. Frailty thus classified was marginally predictive of falls at 3 and 7

years, but highly predictive of mobility decline, disabilities in activities of daily living, first hospitalization and death at 3 and 7 years. (Fried et al., 2001)

One problematic issue with the Fried's criteria for frailty phenotype is that the normative data of the parent population has to be obtained, and that value may differ somewhat, depending on the recruitment strategy of the cohort.

The Deficits Model

Rockwood et al. defined frailty using a multiple accumulative deficits approach. In this dynamic model, frailty is a balance between the assets and accumulated deficits an older individual possesses, and there is a constant change in this balance. (Rockwood et al., 1994)

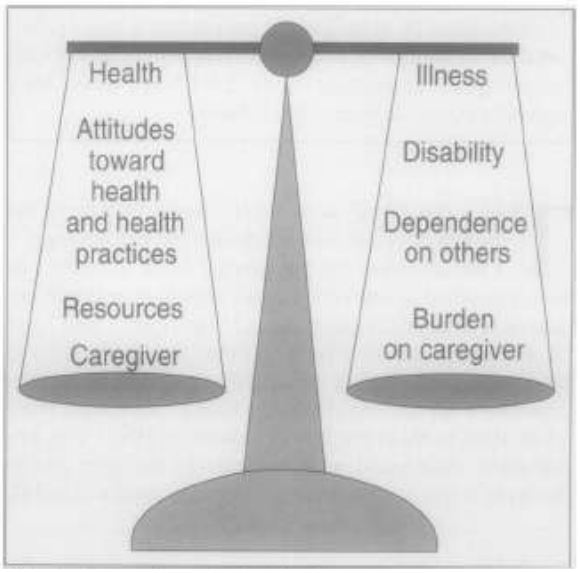


Figure 5.2.1 Dynamic model of frailty in elderly people, in which the balance between assets (left) and deficits (right) determines whether a person can maintain independence in the community.

Items considered in this model not only include physical performance or measurements, but also include the availability of social resources and caregiver, or in short, both medical and social aspects.

Based on this concept, Rockwood et al. developed three approaches in the calculation of deficits in defining the degree of frailty for any individual elderly person. The first approach was a criteria-specific scale (the Frailty Scale), which took into consideration 4 aspects: mobility, ADL independence, continence and cognition. (Rockwood et al., 1999) The score ranged from 0 to 3, with the higher number denoting higher frailty. The second approach was to define frailty as a fraction which describes the number of deficits present in the person out of 70 possible deficits (the Frailty Index). This approach, although correlated well with adverse outcomes, was too mathematical and highly time-consuming, thus unsuitable for clinical use. (Rockwood et al., 2002) Rockwood's group later summarized their model using the Clinical Frailty Scale (CFS), which was derived from the Canadian Study of Health and Aging (CSHA) cohort and was validated in 2305 people over the age of 6. Outcomes defined for this scale were death or institutionalization in 5 years. (Rockwood et al., 2005)

Figure 5.2.2 The CSHA Clinical Frailty Scale

1. Very fit	robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2. Well	without active disease, but less fit than people in category 1
3. Well, with treated comorbid disease	disease symptoms are well controlled compared with those in category 4
4. Apparently vulnerable	although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms
5. Mildly frail	with limited dependence on others for instrumental activities of daily living
6. Moderately frail	help is needed with both instrumental and non-instrumental activities of daily living
7. Severely frail	completely dependent on others for the activities of daily living, or terminally ill

The Clinical Frailty Scale does not involve any physical performance measurements and are based instead on information about the presence or absence of disease, disease or symptoms control, and dependency on others for activities of daily living.

The FRAIL scale

In 2008, the Geriatric Advisory Panel of the International Academy of Nutrition and

Aging (IANA), consisting of European, Canadian and American researchers came to a consensus regarding a suitable screening instrument for frailty in older adults. (von Kan et al., 2008a) This was the FRAIL scale:

Table 5.2.3 The Frail scale (von Kan et al., 2008a)

Fatigue
Resistance (ability to climb 1 flight of stairs)
Ambulation (ability to walk 1 block)
Illnesses (greater than 5)
Loss of Weight (5%)
0 = robust; 1 or 2 = pre-frail; 3 or more = frail

This instrument, as well as some of the others, is recommended to be used by geriatricians to identify persons at risk of the physical frailty syndrome, as these persons may be in need of more assessment and focused management. It is suggested that all persons aged ≥70 years, or with significant unintentional weight loss (≥5% in past one year) should be screened for frailty. (Morley et al., 2013)

5.3 Frailty as a geriatric syndrome

The association between frailty and adverse health outcomes in older individuals has been well-studied. Physical frailty as defined by the Fried's criteria was predictive of falls, hip fractures, non-spine fractures and death within one year. (Ensrud et al., 2007) The same frailty phenotype, as well as a more simple frailty measure, the Study of Osteoporotic

Fracture (SOF) Index (3 components: weight loss, inability to rise from a chair, and poor energy), also predicted falls, disability, non-spine fracture, and death in 1-3 years. (Ensrud et al., 2009) Hospitalizations, institutionalizations and disability were other outcomes used to validate frailty measurement instruments. (Fried et al., 2001; Rockwood et al., 1999; Rockwood et al., 2002; Rockwood et al., 2005; Kielyet al., 2009; Lopez et al., 2012; Gobbens et al., 2012)

5.4 Risk factors

Frailty is the latest identified geriatric syndrome. I consider it the ultimate geriatric syndrome because it was associated with most of the other earlier geriatric syndromes and can be viewed as the final pathway by which an older person reaches the end of life. If we consider frailty in a global manner the list of its risk factors will include all the items listed in the other geriatric syndromes discussed earlier, and its outcome would have included all the adverse outcomes mentioned for the other geriatric syndromes as well.

Intrinsic

Older age is an obvious risk factor for frailty. However, age per se is not a major component and in fact if we studied the various definitions proposed for frailty at present, age was not included in any of them. Old age, but with adequate reserve in the functional,

mental and social systems, would not place a person in a frailty state. Gender, however, is a different matter. Numerous studies have reported that at the same age, women were more likely to be frail than men. It is not clear at present why this is so, but it has also been noted that despite being more frail, women tolerate frailty better, with a longer life expectancy. It is therefore of interest to researchers in geriatrics to look for the mechanism of this phenomenon. We shall see later in one of the studies arising from this work that it was the reversibility of frailty that may account for this phenomenon.

Sarcopenia and underweight

One of the most common frailty definitions used is the frailty phenotype, which is essentially the description of physical frailty. (Fried et al., 2001) Weakness as indicated by low grip strength was one of the basic criteria in this definition, and slowness in walking speed being the other. As we have seen in the consensus definitions of sarcopenia, both of these measurements are also measurements of sarcopenia. Therefore one can view frailty as the clinical representation of sarcopenia, but in combination with other elements. Again, another criterion in this frailty phenotype, and also in the FRAIL scale is weight loss or low body weight. Underweight is itself a geriatric syndrome but is also a risk factor or component of frailty.

Chronic diseases

Illnesses that develop during the course of ageing are important contributors to the emergence of frailty. Apart from having the total number of illnesses counted in one of the frailty criteria (the FRAIL scale), medical illnesses have not been featured in any of the other current frailty definitions. The presence of chronic diseases may not be modifiable but their control may be. It is therefore important to study which of the common chronic diseases in old age may be associated with frailty, and then to examine whether their control may modify the progression of frailty. It is with this in mind that studies on the relationship between several medical conditions and frailty have been conducted. These shall be discussed in the latter part of this thesis.

Extrinsic

Low physical activity is considered as a criterion for physical frailty in the Fried's definition. (Fried et al., 2001) This is a modifiable risk factor and has great potential of becoming an intervention for the prevention or recovery of frailty. Apart from being an intervention in research, more importantly physical exercise or activities can be promoted as a public health measure among the older population. Another possibly modifiable factor would be nutrition. It has been observed that muscle strengthening or hypertrophy in old age in response to nutrition input or exercise training are less effective when

compared with that in younger age. However, for nutrition interventions to be successful it has to reduce frailty via the pathway of increasing muscle strength and bulk, thereby improving physical performance and ADL independence.

At the moment researchers are still in the early stage of frailty intervention trials. As of to date, only a handful of studies have embarked on this endeavor, with the publications mostly protocols, and the small number of studies with results, inconclusive. (Fairhall et al., 2008; Li et al., 2010; Cameron et al., 2013; Mazya et al., 2013)

Chapter 6

Hypothesis, Subjects and Methods

6.1 Overview

Frailty, being the ultimate geriatric syndrome, encompasses most of the deficits that lead to adverse outcomes commonly seen in old age. Frailty shares an intricate relationship with its three correlates, i.e. falls, under-nutrition and sarcopenia. All four shared common intrinsic and extrinsic risk factors, and they are often both the cause and result of each other. A schematic diagram showing their inter-dependent relationship is as follows:

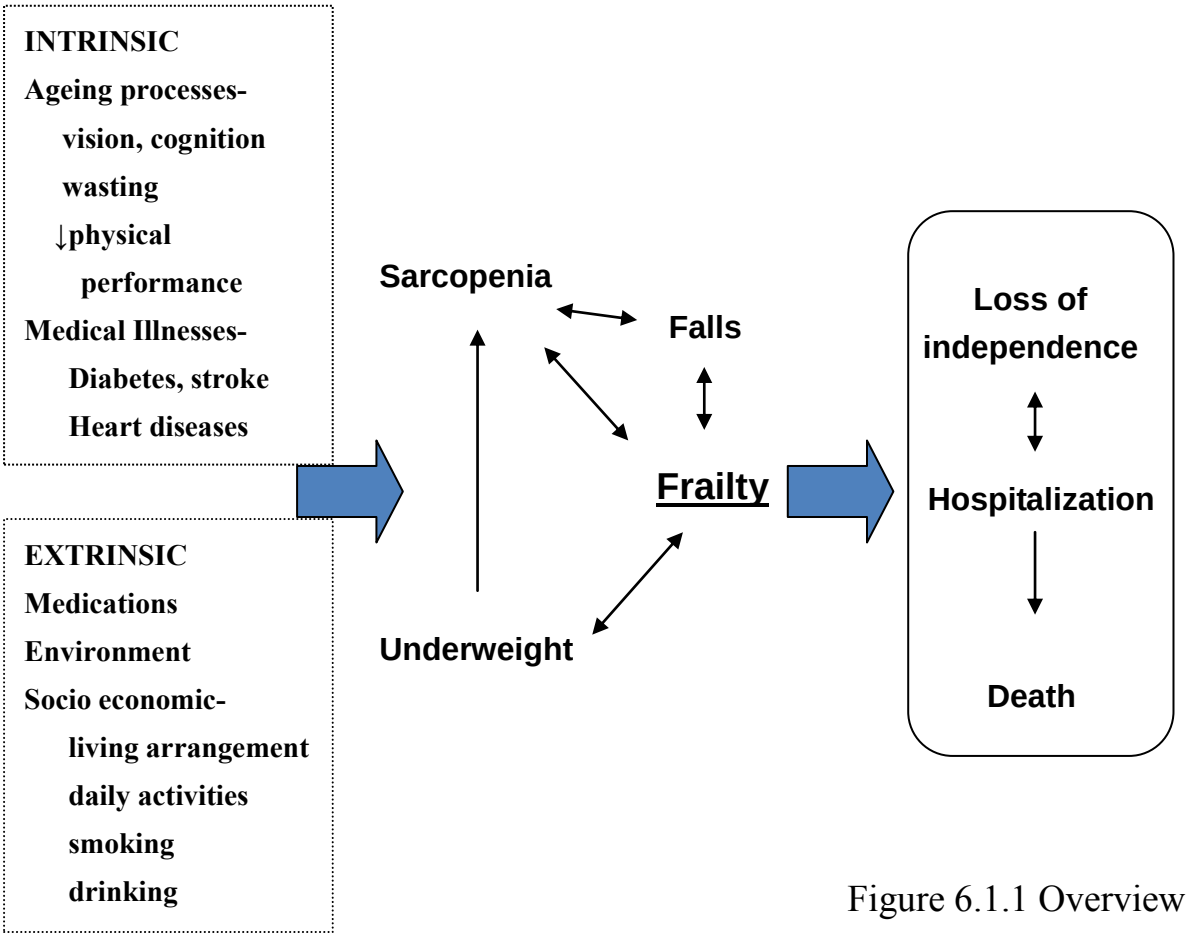


Figure 6.1.1 Overview

In the process of studying the cause and consequence of frailty, I have attempted to answer questions concerning both the frailty syndrome and its three correlates. I shall present the hypotheses I had concerning each, in relationship to either their risk factors, outcomes that they share with frailty, or both.

6.2 Hypotheses

Falls

In the study of falls, it was customary for researchers to segregate their study population into two groups: the more independent community-living older adult population, and the more dependent nursing home population. As the two populations differ considerably in their physical and cognitive impairment, it would be of interest to examine whether they share common risk factors despite these differences. Medications, in particular psychogenic medications, have been identified as culprits for falls. Yet they are prescribed for a reason, and the underlying condition for which they are prescribed may in fact be the true risk factor for the falls instead. Intrinsic ageing processes such as impairment in balance and vision are other risk factors for falls, but these are usually implicated only among community living older people.

Hypothesis

- Falls in older people in different care settings are more related to intrinsic medical

problems and physiological decline, rather than extrinsic factors such as medications

Underweight

While being overweight is a health concern in younger adults and the middle-aged, recent findings in cohorts of older people overseas have showed that the BMI with the best survival rates may in fact be in the overweight range. Since Asians have more body fat then Caucasians at the same BMI, this observation may or may not be true among Asians. Underweight and under-nutrition is an important risk factor for both sarcopenia and the frailty syndrome, both of which contribute to falls. We therefore embarked to examine whether the validity of this finding among local older people, in both the community and nursing home settings. This finding will affect the recommendations and interventions we make in the future regarding the prevention of frailty, sarcopenia and falls.

Hypothesis

- Being underweight, rather than overweight, is more detrimental to survival among older people in both community and nursing home settings

Sarcopenia

Sarcopenia is a new research area in which only very little data in Asians is available. Little is known about how chronic diseases affect the prevalence and progression of

sarcopenia.

Hypothesis

- Age-related muscle loss (sarcopenia) is related to chronic medical conditions and unfavourable lifestyle in old age
- Sarcopenia is associated with unfavourable health outcomes in older people

Frailty

Frailty is the ultimate geriatric syndrome. Apart from being the consequence of falls and injuries, loss of weight, and loss of muscle mass and strength, frailty can also lead to falls, its weakness and fatigue lead to decrease in physical activities which in turn results in loss of weight and muscle performance.

Hypothesis

- Frailty and transitions between different frailty states are influenced by both chronic diseases and cognition

6.3 Subjects

In the course of confirming these hypotheses, data collected by our team from two cohorts were examined:

1. Community cohort

A community-living cohort consisted of 2000 men and 2000 women living in Hong Kong were recruited. To ensure an even distribution of subjects across different age range, their age was stratified into 3 groups with approximately 33% in each of the following: 65-69, 70-74, >=75 years. The cohort was not randomised but was recruited by advertisements and recruitment talks in elderly activity centres. Participants were invited to attend a health check carried out in the School of Public Health of the Chinese University of Hong Kong between August 2001 and December 2003 by placing recruitment notices in community centers for the elderly and in housing estates. Talks were also given at these centers explaining the purpose, procedures and investigations to be carried out. Only ethnic Chinese subjects were recruited. We excluded those who (1) were unable to walk without assistance of another person; (2) had had a bilateral hip replacement; (3) were not competent to give informed consent. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants gave written consent.

2. Nursing home cohort

Ten private and four subsidized homes with at least 100 residents were randomly

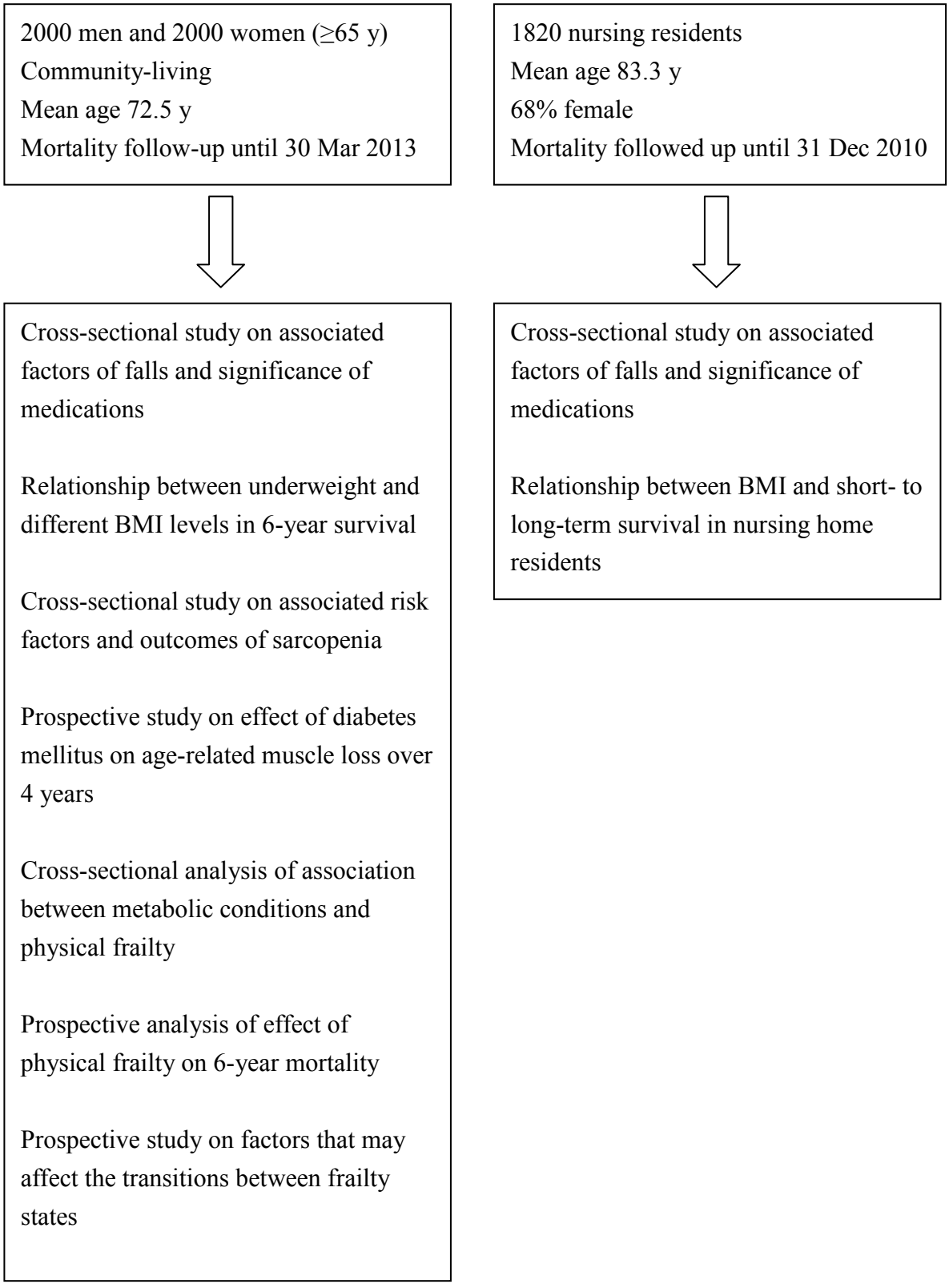
selected from among the 533 private nursing homes and 130 subsidized nursing homes in Hong Kong in 2001. The ratio of private and subsidized homes was chosen to reflect the excess of private homes. Of the 1914 residents in these residential care facilities, 1820 of them were successfully assessed between December 2001 and August 2002, using the Chinese version of the Minimum Dataset—Residential Assessment Instrument version 2.0 (MDS-RAI 2.0) (Morris et al., 1990; Morris et al., 1997; Chou et al., 2001), with a response rate of 95%. Reasons for unsuccessful assessments of the remaining 94 residents included hospitalization, moved to other facilities, and home leave during the period of study. The mean age of these residents were 83.3 years, 68% were female. The study was approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong.

In the falls study, participants who were bedridden were excluded, since the fall rate and risk factors would be very different for these residents when compared with those who were mobile. Bedridden was defined as being obliged to remain in bed all or most of the time, as defined in one item of the MDS-RAI (2.0). After exclusion, 1710 participants remained in the analysis.

In the study on how BMI affected survival in nursing home residents, only data of

1614 residents were included in this analysis: four were excluded due to invalid Hong Kong identity numbers and therefore untraceable mortality status; 202 were excluded due to missing or erroneous data on their body weight or height. Among those included in this analysis, 546 (33.8%) resided in subsidized homes while 1068 (66.2%) were from private homes.

Figure 6.3.1 Flow chart of the two cohorts and the related studies discussed in this thesis:



6.4 Methods

6.4.1 Community cohort analyses

The baseline assessment was conducted from 2001-2003. A second interview and assessment was conducted between 2003 and 2005, during which 3427 participations returned. A third interview and assessment was conducted between 2005 and 2007, during which 3153 participants returned. Mortality status was followed up until 30 Mar 2013. Questionnaires and physical measurements were conducted by a team of research assistants located in the Jockey Club Centre of Osteoporosis Care and Control of The Chinese University of Hong Kong. All research assistants underwent training regarding the use of the various questionnaires and scales involved in these studies. Physical measurements were conducted using standardized procedures. Body composition measurements were performed using a DXA machine located in the same centre, and has been operated by the same technician throughout the study.

The Questionnaire

Demographic and social data

At baseline, a questionnaire containing information regarding demographics, smoking habit (never, ex- and current smoker), alcohol intake, exercise habit (takes walks for exercise daily or almost daily) and history of falls (any falls and recurrent falls in the past 12 months). Self-rated health was graded by each subject on a scale of 1 to 5, with 1 =

excellent and 5 = poor. (Goldstein et al., 1984) Physical activity levels were scored using the Physical Activity Scale of the Elderly (PASE). (Washburn et al., 1993) This is a 12-item scale measuring the average number of hours per day spent in leisure, household and occupational physical activities over the previous 7-day period. Activity weights for each item were determined based on the amount of energy spent, and each item score was calculated by multiplying the activity weight with daily activity frequency. A summary score of all the items reflects the daily physical activity level. It has been validated and proven to be a reliable tool in measuring the physical activity of older people. Mood symptoms were assessed by the Geriatric Depression Scale, with a score of ≥ 8 out of 15 indicative of depressed mood. (Yesavage et al., 1983) Quality of life was assessed by the Short Form 12 mental and Short Form 12 physical subscores. (Ware et al., 1994)

Cognitive function was assessed by the Mini-Mental State Examination (MMSE). (Folstein et al., 1975) Cognitive impairment was defined by having a Community Screening Instrument of Dementia (CSI-D) cognitive score. 28.40. (Chan et al., 2003; Prince et al., 2003) Socio-economic status was assessed by asking the participants to mark their self-perceived position on a ladder with ten rungs, with the lowest and highest rungs representing the lowest and highest socio-economic status in society.

Medical conditions and Medications

The presence or absence of disease was based on the subjects' report of their physician's diagnoses, supplemented by the identification of drugs brought to the interviewers. Heart disease includes coronary heart disease, heart failure and myocardial infarction. I have conducted a random check on the accuracy of the self-reported medical diagnoses by cross checking them with the diagnoses in the electronic medical records of the Hong Kong Hospital Authority for 200 participants, and have found them to have at least 95% correspondence. Participants were instructed to bring to the centre at each assessment their current medications, including any over-the-counter supplements. The names of the medications were recorded and classified.

Physical measurements

Body weight was measured, with subjects wearing a light dressing gown, by the Physician Balance Beam Scale (Health-o- Meter, Arlington Heights, Ill., USA). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Blood pressure was measured on both arms and ankles, and the lower ankle-brachial index (the ratio of the systolic blood pressure of the posterior tibial artery to that of the brachial artery, the ABI) of the two sides was used for analysis. An ABI of < 0.9 was defined as low and reflects a state of generalized atherosclerosis. (Newman et al., 1991) The

waist-hip ratio (WHR) was defined as the ratio between the waist (the narrowest circumference around the trunk midway between the lower rib cage and the pelvis) and the hip (the largest circumference around the buttocks posteriorly and the symphysis pubis anteriorly). WHR was taken to be high if > 0.9 in men and >0.85 in women. (Alberti et al., 1998) Body Mass index (BMI) was calculated by the formula BMI = weight (kg)/ height $(m)^2$, and categorized into underweight (<18.5), normal (18.5 – 23), overweight (23-25) and obese (≥25) according to the World Health Organization Asia Pacific criteria. (WHO, Australia, 2000)

Physical performance

A battery of 5 physical performance tests was conducted for each participant: 5 chair-stands (time taken for the subject to stand up with folded arms from a chair 5 times), grip strength (average of both hands, using Jamar Hand dynamometer 5030 J1, Sammons Preston, Inc., Bolingbrook, Ill., USA), time taken for "normal and narrow (within 20 cm width)" a 6-metre walk, and the stride length (6 metres divided by the number of steps taken during the walk). The performance was summarized into a composite physical frailty score (0-20), according to quartiles of performance, with 0 being the most frail and 20 the most robust. Weakness or low grip strength, and slowness or slow walking speed had been included as two of the five frailty characteristics defined by Fried at al. (Fried et

al., 2001)

Measurement of Muscle Mass and Fat Mass

We measured muscle mass using DXA, using a Hologic Delphi W4500 (Hologic Inc, Bedford, Massachusetts, USA) at the baseline, then again at the 2-year and 4-year follow-up visits. In previous studies, the DXA-estimated appendicular skeletal mass (ASM) had been found to be a reasonably good predictor of total body skeletal mass quantified by multi-slice magnetic resonance imaging in healthy adults ($R^2 = 0.96$). (Kim et al., 2002) In our cohort, ASM was calculated by the summation of muscle mass measured in the four limbs, with the operator adjusting the cut lines of the four limbs according to specific anatomical landmarks as described by Heymsfield et al.. (Heymsfield et al., 1990) In delineating the trunk for measurement of the trunk fat, a line was drawn just below the chin to separate the head from the trunk. Another line was drawn between the head of the humerus and the scapula through the glenoid fossa to separate the arm from the trunk, and another passed through the femoral necks and just below the ischium to separate the pelvis from the leg.

In the measurement of the abdominal fat, the upper border of the abdominal region was defined by a horizontal line drawn through the lower one third of the vertical height

between the left midpoint acromion and the external end of left iliac crest. The lower border of the abdominal region was defined by a horizontal line through the external ends of the iliac crests. The method was adopted from that of Bertin et al.. (Bertin et al., 2000) The abdominal height was reduced to the lower one third instead of the lower half as in the report by Bertin et al. because the latter method would have included the lungs and heart due to the smaller body size in the Chinese population. We were not able to use the method of measuring abdominal fat as defined by the region between the L1 and L4 vertebrae because many subjects had scoliosis and low bone mass, making the delineation of the upper or lower borders of these vertebrae difficult from a whole-body DXA scan. The relative abdominal fat (RAF) was calculated as the proportion of abdominal fat within whole body fat (RAF= abdominal fat/whole body fat×100%). The maximum coefficient of variation for fat is 1.47%.

All data used in the analysis were on participants who clearly fitted within the DXA field-of-view. During the course of the study, the Hologic Body composition step phantom was scanned daily to ensure proper calibration for fat and non-fat compartments. The maximum coefficient of variation for lean mass is 0.84%. To adjust for body size, ASM was adjusted to height using the formula: height-adjusted ASM (kg/m^2) = ASM (kg)/height $(m)^2$, as proposed by Baumgartner et al.. (Baumgartner et al., 1998)

Frailty status

Frailty status at both baseline and follow-up visits was categorized into three groups: robust, pre-frail and frail, based on the Fried's frailty criteria. (Fried et al., 2001) The five components of the Fried's criteria were: 1) low physical activity (defined as the lowest quintile of the Physical Activity Scale for the Elderly score), 2) fatigue (defined as answering 'No' to the question: " Do you feel full of energy?" in the Geriatric Depression Scale), 3) shrinkage (significant weight loss of ≥ 5% between the first visit and the year 2 visit, two years apart), 4) weakness (defined as the lowest quintile in gender-specific grip strength), and 5) slowness (defined as the lowest quintile of gender-specific walking speed). Robust was defined as having none of these features, pre-frailty as having 1 to 2 features, and frailty as having three or more of these features. The lowest quintile cut-off values for grip strength, walking speed and physical activity in the baseline assessment was also used as the cut-off values in the follow-up assessment.

Follow-up procedures

Follow-up was done every 4-monthly by phone then every 2-yearly by a mailed reminder for a follow-up body check appointment until the end of 4 years (a total of three follow-up visits) or death, whichever occurred earlier. Phone reminders were given again close to

the appointment dates, and defaulters were given a second appointment to enhance attendance rates.

Mortality Status and hospitalizations

Mortality status was ascertained by annual death registry search in the Death Registry of the Hong Kong Government. Mortality status was checked by the participants' Hong Kong Identity Card number, which is unique to each Hong Kong resident. Cardiovascular causes of death were identified by the cause of death reported on the death certificate, and classified according to the International Classification of Disease (ICD) version 10 codes as those ranging from 100 to 199. The number of all-cause hospitalizations between the visits was obtained from the Hong Kong Hospital Authority records, which covered >93% of the hospitalizations in the Hong Kong population. (Yip & Law, 2002)

Statistical Analysis

In the study of the correlates of falls in community living older adults, and the effect of medication versus medical conditions on falls, statistical analysis was performed using SPSS version 11.5. Multiple logistic regression analysis was used to calculate age and sex adjusted odds ratios for all variables. Variables with $p<0.05$ were chosen to be entered into the final model for each of the significant medications. Fallers (fell at least once) were

compared with non-fallers, and recurrent fallers (fell at least twice) were compared with those with one or no falls. A p value of < 0.05 was taken as statistical significant. Significance was stratified into 3 levels in the final models.

In the study of BMI and weight in survival of the community cohort, data analysis was performed by using SPSS version 17.0 (IBM Corp, Somers, NY, USA). As body composition differs with gender, all statistical tests were done separately for men and women. Characteristics of decedents and survivors were compared. Unpaired t tests were used for continuous variables and chi-square tests for categorical variables. Crude mortality was plotted against quintiles of different adiposity measurements. All-cause and cardiovascular mortality as on February 28, 2009 were analyzed using Cox regression, adjusted for covariates that were relevant to mortality in older individuals (age, physical activity, smoker status, history of cancer, diabetes, heart disease, measures of socio-economic status and medications. To adjust for the effect of lifelong obesity, recalled weight change since early adulthood at 25 years of age was further adjusted for. The lowest quintile of all adiposity measures was used as the comparison group. Early deaths within 12 months of the baseline assessment were excluded to avoid bias due to reverse causality.

In analyzing the associated factors of sarcopenia, the absolute difference in height-adjusted ASM between those with and without each condition was compared by unpaired t test. Psychosocial well-being scores and physical activity scores were examined in tertiles of height-adjusted ASM and compared by analysis of variance, using the highest tertile as the reference group. Physical performance measures were examined against tertiles of height-adjusted ASM and adjusted to age, using analysis of covariance. All tests were two-sided and a p value of < 0.05 was taken as statistically significant.

In the prospective study of the effect of diabetes mellitus on sarcopenia and age-related muscle loss, data analysis was performed using statistical package SAS, version 9.1 (SAS Institute, Inc., Cary, NC, USA). As body composition differs with gender, all statistical tests were carried out separately for men and women. Characteristics of subjects with diabetes and those without were compared. Two-samples independent t-tests were used for continuous variables and v2-tests for categorical variables. Body composition changes at 4 years were compared by using analysis of covariance (ANCOVA), adjusting for age. Multivariate linear regressions were used to examine the relationship between appendicular lean mass loss and diabetes, adjusting for age, physical activity, smoker status, BMI and diabetes-related conditions (low ankle–brachial index, hypertension, heart disease and stroke) and total body mass loss, indifferent models. All tests were

two-sided and a P-value of < 0.05 was taken as statistically significant.

In the study on association between physical frailty and metabolic risk factors, and the relationship between physical frailty and 6-year mortality, data analysis was performed using SPSS version 16.0, done separately for men and women. Cox regression analysis was used to examine the relationship between 6-year mortality and the composite physical performance score. Age, physical activity, smoker status, the presence of cognitive impairment and metabolic conditions were subjected to multiple linear regression analysis to study their effect on the composite physical performance score. All tests were 2-sided and a p value of <0.05 was taken as statistically significant.

In the study on factors affecting the transition of frailty states, the change in frailty status between the baseline and follow-up visits was used as the outcome. The number and proportions of participants in the robust, pre-frail and frail categories at both visits were reported according to gender. The numbers of those in each frailty category who had remained stable, improved or declined after two years with respect to their frailty status were also listed. Comparison of the gender, age, and baseline frailty status of those who did or did not return for the follow-up visit was made. Continuous variables were compared using Students' t-test and categorical variables, by the Chi-square test.

Age-adjusted logistic regression for each possibly related covariate, and multiple step-wise logistic regressions were used to identify significant factors associated with changes in frailty status. As others have reported that baseline frailty status significantly influenced the probability of transitions and the directions of transitions between frailty statuses, 12 regressions were done separately for frailty groups as categorized at baseline (robust, pre-frail, and frail). Directions of change examined included 1) pre-frail to frail, 2) pre-frail to robust, 3) robust to pre-frail or frail, and 4) frail to pre-frail or robust. Because women and men had different prevalence of frailty and might have different rates and associated factors for these transitions, separate models were performed for the genders. Covariates included age, smoking, BMI, MMSE, social economic status, and medical conditions (diabetes, heart disease, COPD, osteoarthritis, history of hip fracture, stroke and cancer), and number of hospitalization in the intervening years between the two visits. The latter was categorized into none, one to two, three to four, and five or more episodes. Analysis was performed using the Analysis was performed with the statistical package SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). All tests were 2-sided and significance level was set at $p<0.05$. Participants with missing data that renders it impossible to classify their frailty state and baseline and at the follow-up visits were excluded from analysis.

6.4.2 Nursing home cohort analyses

The MDS-RAI questionnaire

Participants in the nursing home cohort were assessed the Chinese version of the Minimum Dataset—Residential Assessment Instrument version 2.0 (MDS-RAI 2.0). (Morris et al., 1990; Morris et al., 1997; Chou et al., 2001) The MDS-RAI captures detailed information on each resident including demographic information, medical diagnoses and medications, physical and cognitive functional status, and their dietary, nutrition and behavioral patterns. Data were collected by two trained research assistants. Medical and social information was collected from the residents or from a proxy if the former were too frail to be interviewed. Proxies included personal care workers, other front-line nursing staff, family members or close friends. The participant's file at the facilities was also consulted for background social and medical history. Participants' daily routines were confirmed with care home staff to ensure reliability and validity of the information gathered.

Definitions

Falls

A fall was defined as any unexpected loss of balance resulting in coming to rest on the ground or floor within the previous 180 days.

Walking aids

Walking with aids was defined as able to ambulate with cane, walker or crutch. Dementia was defined as having a diagnosis of Alzheimer's disease or any dementia other than Alzheimer's disease.

Restraint

A physical restraint was defined as a mechanical appliance inhibiting a resident's freedom of movement. (Stillwell et al., 1991; Karlsson et al., 1997) Restraints noted in the dataset included bed rails on either or both sides, trunk restraint by means of using safety vest or belt, limb restraint, and chairs with a detachable table top that prevented the resident from getting up. Any restraint use in the past seven days was recorded.

Activities of daily living and cognitive impairment

The MDS ADL Self-Performance Hierarchy scale was used to describe the actual performance level of each resident across a spectrum of ADLs (activities of daily living). (Morris et al., 1999) Multiple MDS items concerning ADLs and dependency levels in performing these activities were used to formulate a score that ranged from 0 (=independent) to 6 (=totally dependent), according to methods proposed by Morris et al.

The MDS Cognitive Performance Scale was used as a measure of the participant's cognitive function. Multiple cognitive items in the MDS were extracted to generate a score that ranged from 0 (=intact cognition) to 6 (=very severe impairment), according to the methods of Morris et al. (Morris et al., 1994)

Mortality status

Mortality status was ascertained by death registry search in the Death Registry of the Hong Kong Government. The data used in the BMI in survival of nursing home residents study was obtained last on 31 Dec 2010.

Statistical analysis

In the falls study, analysis was carried out with the SPSS (version 12.0) in two steps. In the first step, univariate analysis was performed with potential associated factors. In the second stage, age, sex use of physical restraints and all other factors with a p-value of <0.1 in the univariate analysis were examined by logistic regression in a multivariate model. P-values were calculated by Student's t-test for continuous variables, chi-square test for categorical variables, and Somers' D test for ordinal variables. A p-value of <0.5 was taken as statistically significant.

Relationship between mortality (6 month, 1 year, 2 year, 4 year and 9 year) and significant weight loss (≥5% over 30 days or ≥10% over 180 days), and BMI, was studied by Cox regression with both variables in the same model, adjusted for age, gender, medical conditions (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus), tube-feeding, 25% food left uneaten, swallowing problem, and the level of functional impairment as represented by the category on the ADL hierarchy scale. In model 1, BMI was used as a continuous variable, while in model 2, BMI was used as an ordinal variable according to the Asia Pacific cut-off values described above, (World Health Organization (2000)), with the underweight group as reference. To study whether the association between BMI and weight loss would vary according to the duration of survival, in each model, separate Cox regressions were performed with the dependent variable being the survival time censored at different time points: 182 days (6 months), 1, 2, 4 and 9 years after the date of the MDS assessment. Statistical Analysis was conducted using the SPSS software version 16.0 (SPSS Inc., Chicago, IL). A p value of <0.05 was taken as statistically significant.

Chapter 7

Results

7.1 Intrinsic and extrinsic factors associated with falls in older people in nursing homes

In the study of risk factors associated with falls in older people in nursing homes in Hong Kong, 1820 residents were recruited. The mean age was 83.5 ± 8.4, 68% were women, and 12.7 % had a history of one or more falls in the past 180 days. Regarding the intrinsic risk factors related to falls, 81% had visual problems, 75% had some balance problems, 45% had to use an aid for walking, and 53% had at least mild degree of cognitive impairment according to the MDS-Cognitive Performance Scale. Regarding the extrinsic problems, in particular the use of sedative medications which had been found to be an important risk factor for falls, 53% were on between one to four medications, and 37% were on 5 or more medications. The baseline characteristics of the entire sample are shown in Table 7.1.1.

Table 7.1.1. Demographics, outcomes and potential confounders for falls in past 180 days among all 1820 participants

Variable	Definition	N = 1820
Age, mean (SD)		83.5 (8.4)
Women, n (%)		1232 (67.7)
Falls in past 180 days, n (%)	One or more falls	232 (12.7)
Hip fracture in past 180 days, n (%)		5 (0.3)
Visual problems, n (%)	Impaired vision or side vision, experience vision problems	1470 (80.8)
Balance problems, n (%)	No	452 (24.8)
	Unsteady, able to rebalance	536 (29.5)
	Requires physical support	259 (14.2)
	Unable to stand	573 (31.5)
Bedfast all the time, n (%)		110 (6)
Using walking aids, n (%)		821 (45.1)
Number of medications, n (%)	0	176 (9.7)
	1-4	962 (52.9)
	5 or above	682 (37.4)
mean (SD)		3.96 (2.68)
Number of emergency room attendances in past 90 days, n (%)	0	1643 (90.3)
	1 or above	177 (9.7)
MDS-ADL hierarchy scale, n (%)	0 (independent)	732 (40.2)
	1-4 (Supervision, limited, extensive impairment 1 & 2)	415 (22.8)
	5,6 (Dependent, total dependent)	673 (36.9)
MDS-Cognitive Performance Scale, n (%)	0 (intact)	368 (20.2)
	1 (Borderline intact)	485 (26.6)
	2 (Mild impairment)	423 (23.2)
	3-6 (Moderate to severe impairment)	544 (30.0)
MDS-mortality prediction score, n (%)	0 (low predicted mortality)	771 (42.2)
	1-6 (some predicted mortality)	1049 (57.6)
Hypnotic use in past 7 days, n (%)		95 (5.2)
Walks to toilet most nights, n (%)		931 (51.2)

Among these 1820 residents, 110 were bedridden most of the time. As their risks of falls would be very different from those who were mobile, only the 1710 non-bedridden residents were included in the further analyses. Among these, 29.6% had a diagnosis of dementia, 10.6% had heart diseases (ischaemic heart disease, congestive heart failure), 37.6 % had eye diseases (cataract, glaucoma, diabetic retinopathy, and macular degeneration), 32.6% had previous stroke, 8.2% had Parkinson's disease, and 10.7% had leg or back pain. Their mean number of medications was four. Nearly 21% of participants had received psychotropic medications in the previous week. Restraint use, a practice that was commonly employed for falls prevention in Hong Kong nursing homes, but had been reported to be associated with more serious falls-related injury elsewhere, was present in 68% of the participants in the previous week.

Among 1710 residents, 216 had a history of at least 1 fall in the past 180 days. The characteristics of fallers and non-fallers were compared in Table 7.1.2. Fallers were more likely to be older, had dementia and eye diseases, and were on psychotropic medications. They also had more medications, and were more likely to have suffered a hip fracture in the past 180 days, and were in physiotherapy in their nursing homes.

Table 7.1.2. Characteristics of fallers vs. non-fallers.

Characteristic	Fallers (n = 216)	Non-fallers (n = 1494)	p value
Demographics			
Female sex	137 (63.4)	1017 (68.1)	0.187
Education (n = 1706)			
No schooling	132 (61.4)	891 (59.8)	
Some primary school	69 (32.1)	472 (31.6)	
Above primary	14 (6.5)	128 (8.6)	
Age, yr (mean, sd)	84.7 (7.5)	83.1 (8.6)	0.012*
Mobility			
Walks with cane/ walker	114 (52.8)	695 (46.5)	0.085
Wheelchair as primary mode of locomotion	66 (30.6)	443 (29.7)	0.786
Functional scales			
MDS Cognitive Performance Scale			0.199
Mildly impaired (0,1)	115 (53.2)	714 (47.8)	
Moderately impaired (2,3,4)	78 (36.1)	622 (41.6)	
Severely impaired (5)	9 (4.2)	51 (3.4)	
Very severely impaired (6)	14 (6.5)	107 (7.2)	
MDS Self-performance Hierarchy Scale			0.514
Mildly impaired (0,1,2)	111 (51.4)	767 (51.3)	
Moderately impaired (3.4)	41 (19.0)	211 (14.1)	
Severely impaired (5,6)	64 (29.6)	516 (34.5)	
Rehabilitation programs			
Dementia care unit	1 (0.5)	0 (0)	-
Occupational therapy	14 (6.5)	107 (7.2)	0.715
Physiotherapy	88 (40.7)	501 (33.5)	0.037*
Medical history			
Diabetes	45 (20.8)	344 (23.0)	0.473
Heart disease (IHD, CHF)	16 (7.4)	165 (11.0)	0.104

Dementia	79 (36.6)	427 (28.6)	0.016*
Eye disease (cataract, diabetic retinopathy, glaucoma, macular degeneration)	108 (50.0)	535 (35.8)	0.000*
Depression	12 (5.6)	76 (5.1)	0.771
Stroke/ hemiparesis	66 (30.6)	491 (32.9)	0.498
Parkinson's disease	15 (6.9)	126 (8.4)	0.457
Foot problems	20 (9.3)	206 (13.8)	0.066
Back / lower limb pain	23 (10.6)	160 (10.7)	0.978
Hip fracture in past 180 days	2 (0.9)	2 (0.1)	0.024*
Medications			
Number of medications, mean (SD)	4.4 (2.7)	4.0 (2.7)	0.023*
Psychotropic drugs	62 (28.7)	294 (19.7)	0.002*

IHD= ischaemic heart disease, CHF = congestive heart failure

Univariate analysis of possible risk factors of falls and other relevant factors were presented in Table 7.1.3. Among intrinsic risk factors, older age, having dementia and eye diseases and the need to use a walking aid were associated with increased risk of falls. Among extrinsic risk factors, higher number of medications and the use of any psychotropic medications were associated with falls. The use of restraints was not associated with less falls.

Table 7.1.3. Univariate analysis of possible risk factors of falls in the past 180 days

Variable	Mean (SD)/ N (%)	OR	95% CI	p value
Age (per yr increase)	83.3 (8.5)	1.023	1.005, 1.042	0.012*
Female sex	1154 (67.5)	0.813	0.604, 1.095	0.174
Walks with aids	809 (47.3)	1.285	0.965, 1.710	0.086*
Wheelchair mostly for locomotion	509 (29.8)	1.044	0.766, 1.423	0.786
Conditions				
Dementia	506 (29.6)	1.441	1.069, 1.943	0.017*
Poor short term memory	958 (56.0)	1.216	0.909, 1.626	0.188
Diabetes mellitus	389 (22.7)	0.880	0.620, 1.248	0.473
Heart disease (IHD, CHF)	181 (10.6)	0.644	0.378, 1.099	0.107
Eye disease (cataract, glaucoma, diabetic retinopathy, macular degeneration)	643 (37.6)	1.793	1.345, 2.388	0.000*
Visual impairment	1333 (78.0)	1.158	0.812, 1.653	0.417
History of hip fracture	133 (7.8)	0.942	0.547, 1.621	0.828
Leg or back pain	183 (10.7)	0.994	0.626, 1.578	0.978
History of stroke / hemiparesis	557 (32.6)	0.899	0.660, 1.224	0.499
Parkinson's disease	141 (8.2)	0.810	0.465, 1.412	0.458
Medications				
Number of medications (per 1 item increase)	4 (2.7)	1.061	1.008, 1.117	0.024*
Any psychotropics	356 (20.8)	1.643	1.192, 2.266	0.002*
Restraint use	1163 (68.0)	0.829	0.614, 1.117	0.218

* $p < 0.05$

SD = standard deviation, OR = odds ratio, CI = confidence interval, IHD = ischemic heart disease, CHF = congestive heart failure

In the multivariate model of risk factors for falls in this nursing home cohort, intrinsic factors including older age, female gender, and having dementia and eye diseases persisted to be significant risk factors, whereas extrinsic factors such as the number of medications lost its significance. Among extrinsic factors, only the

use of psychotropic medications remained significant. Restraints were not associated with less falls. Factors intrinsic to the older persons seemed more important as risk factors for falls than extrinsic factors such as psychotropic medications.

Table 7.1.4 Multivariate model of risk factors for falls among non-bedridden nursing home residents

Factors	Number included in analysis (% of total)	Adjusted OR for falls in last 180 days	95% CI	p-value
Age (per yr increment)	1710 (100)	1.026	1.005-1.046	0.012*
Female Sex	1154 (67.5)	0.654	0.477-0.898	0.009*
Walk with aids	809 (47.3)	1.253	0.927-1.692	0.142
Dementia	506 (29.6)	1.464	1.048-2.044	0.025*
Eye diseases	643 (37.6)	1.746	1.293-2.359	<0.001*
Psychotropic medications (hypnotics, antidepressants, anxiolytics)	356 (20.8)	1.516	1.059-2.170	0.023*
Restraints	1163 (68)	0.731	0.534-1.000	0.050
Number of medications (per 1 item increment)	1710 (100)	1.048	0.992-1.108	0.094

*p<0.005; OR=odds ratio; CI=confidence interval

7.2 Associated factors of falls and significance of medications in a community cohort of older persons

In this cross-sectional study, baseline characteristics of 4000 community living older men and women were examined as possible risk factors for falls in the

previous 12 months. Their mean age was 72.5 years, and 50% were women. Among participants, 789 (19.7%) reported having at least 1 fall in the previous 12 months, and among those, 235 (5.9% of 4000) had more than 1 fall. Other characteristics were shown in Table 7.2.1. Falls in this study include any falls reported by the participants (i.e. including both cold and hot falls). The survey did not collect information regarding whether the falls were associated with acute infections such as urinary tract infections.

Table 7.2.1. Baseline characteristics of 4000 community-dwelling men and women

Characteristic	n	mean ± SD or percentage
Age, years	4000	72.49 ± 5.18
Female Sex, %	2000	50 %
Education level		
no education	856	21.4%
primary education	2007	50.2%
secondary education or above	1137	28.4%
Living with someone	3454	86.4%
Walks unaided	3994	99.9%
Takes daily walks	2458	61.5%
Current smoker	275	6.9%
Self-rated health		
excellent or good	1889	47.2%
fair	1815	45.4%
poor or very poor	296	7.4%
MMSE score		
<18	131	3.3%
18-24	1197	29.9%
>24	2672	66.8%
PASE score (0-400)	4000	91.39 ± 42.93
BMI	4000	23.69 ± 3.30

Number of medications		
0	1803	45.1%
1 - 4	2106	52.7%
5 - 7	91	2.3%

SD = standard deviation, MMSE = Mini-Mental State Examination, PASE = Physical Activity Scale of the Elderly, BMI = body mass index

Association between falls and medications

Table 7.2.2 shows the age- and sex-adjusted odds ratios of various medications in relation to falls and recurrent falls. Use of aspirin, calcium channel blockers, anti-diabetics (including sulphonylureas, biguanide and insulin), nitrates, non-steroidal anti-inflammatory drugs (NSAIDs) and statins was associated with an increased risk of recurrent falls. Aspirin, anti-diabetics, nitrates, NSAIDs and paracetamol use was associated with increased risk of any number of falls. Psychotropic drugs including benzodiazepines, antidepressants and antipsychotics were not significantly associated with either any or recurrent falls.

Table 7.2.2. Age-sex adjusted associations between medications and falls in previous 12 months among 4000 community dwelling older persons age 65 or over

Medications	N (%)	Any falls (n=789)			Recurrent falls (n=235) †		
		OR	95% CI	p value	OR	95% CI	p value
ACEI	453 (11.3)	0.984	0.764, 1.268	0.903	1.183	0.784, 1.786	0.423
Aspirin	448 (11.2)	1.386	1.096, 1,752	0.006*	1.636	1.135, 2.360	0.008*
Beta-blocker	645 (16.1)	1.135	0.922, 1.397	0.232	1.313	0.941, 1.833	0.109
CCB	719 (18.0)	0.998	0.815, 1.224	0.988	1.477	1.083, 2.016	0.014*
Anti-diabetics	430 (10.8)	1.292	1.017, 1.641	0.036*	1.852	1.301, 2.636	0.001*
Nitrate	255 (6.4)	1.849	1.393, 2.456	0.000*	2.040	1.330, 3.131	0.001*
NSAID	173 (4.3)	1.461	1.030, 2.072	0.034*	1.955	1.185, 3.227	0.009*
Paracetamol	83 (2.1)	1.628	1.002, 2.645	0.049*	1.173	0.503, 2.738	0.711
Statin	236 (5.9)	1.194	0.870, 1.638	0.272	1.673	1.052, 2.661	0.030*
Psychotropics	49 (1.2)	1.382	0.726, 2.630	0.324	0.955	0.293, 3.108	0.938
Diuretics	381 (9.5)	1.047	0.808, 1.358	0.728	0.794	0.499, 1.264	0.331

†comparisons are between subjects with no or 1 fall and those with ≥2 falls

*$p < 0.05$

OR = odds ratio, CI = confidence interval, ACEI = angiotensin converting enzyme inhibitors, CCB = Calcium channel blocker, NSAID = non-steroidal anti-inflammatory agent, psychotropics = benzodiazepines, antidepressants, antipsychotics, diuretics = thiazide, loop and potassium sparing diuretics

Table 7.2.3 shows the age- and sex-adjusted odds ratios of other factors that may contribute to falls and recurrent falls, including medical diagnoses, cognitive function, social factors, physical activity score, self-rated health, and physical measurements. Factors significantly associated with recurrent falls include: diabetes, eye diseases (cataract and/or glaucoma), heart diseases (history of myocardial infarction, angina and congestive heart failure), lower body musculoskeletal pain (low back pain, hip and knee pain), self-rated health, and average stride length. The same variables, apart from the addition of a history of stroke, were associated with any falls in the previous year.

Table 7.2.3. Age-sex adjusted associations between medical diagnoses, cognitive function, social factors, physical activity, neuromuscular functions and falls in previous 12 months among 4000 community dwelling older persons age 65 or over

Risk factors	N (%)	Any falls (n=789)			Recurrent falls (n=235) †		
		OR	95% CI	p value	OR	95% CI	p value
Medical diagnoses							
Stroke	175 (4.4)	1.641	1.159, 2.324	0.005*	1.178	0.627, 2,213	0.611
Parkinson's disease	16 (0.4)	1.623	0.518, 5.086	0.406	3.022	0.669, 13.643	0.151
COPD	333 (8.3)	0.927	0.686, 1.251	0.619	1.290	0.806, 2.065	0.289
Diabetes	579 (14.5)	1.274	1.030, 1.575	0.026*	1.424	1.013, 2.001	0.042*
Any eye disease (glaucoma, cataract)	1646 (41.2)	1.293	1.098, 1.524	0.002*	1.536	1.165, 2.026	0.002*
Any heart disease (MI, angina, CHF)	696 (17.4)	1.636	1.350, 1.982	0.000*	1.896	1.401, 2.565	0.000*
Any lower musculoskeletal pain (LBP, hip, knee pain)	2317 (57.9)	1.349	1.141, 1.594	0.000*	1.661	1.230, 2.242	0.001*
Cognitive function							
MMSE score (0-30)	4000 (100)	1.022	0.998, 1.046	0.068	0.989	0.953, 1.026	0.549
Sociodemographic factors							
Living with someone	4000 (100)	0.840	0.673, 1.047	0.121	0.760	0.539, 1.070	0.115

Average drinks / wk in past year among drinkers	522 (13.1)	1.015	0.990, 1.042	0.239	0.862	0.706, 1.054	0.148
Smoke years in ever smokers	1466 (36.7)	0.997	0.992, 1.002	0.221	1.000	0.992, 1.009	0.930
Current smoker	275 (6.9)	0.744	0.515, 1.073	0.114	1.109	0.591, 2.081	0.747
Physical activities, self-rated health and number of medications							
PASE score (0-400)	4000 (100)	1.000	0.998, 1.002	0.801	0.999	0.995, 1.003	0.572
Self-rated health (1-5, 1=best, 5=worst)	4000 (100)	1.196	1.078, 1.326	0.001*	1.266	1.063, 1.509	0.008*
Number of medications (per each additional drug)	4000 (100)	1.085	1.025, 1.149	0.005*	1.197	1.095, 1.309	0.000*
Physical Measurements							
BMI	4000 (100)	1.010	0.987, 1.035	0.389	1.023	0.984, 1.065	0.251
Average stride length (per 0.1 m increment)	4000 (100)	0.795	0.715, 0.883	0.000*	0.707	0.595, 0.830	0.000*

†comparisons are between subjects with no or 1 fall and those with ≥2 falls

*$p < 0.05$

OR = odds ratio, CI = confidence interval, COPD = chronic obstructive pulmonary diseases, MI = myocardial infarction, CHF = congestive heart failure, LBP = low back pain, MMSE = Mini-Mental State Examination, PASE = Physical Activity Scale for the Elderly, BMI = body mass index

Tables 7.2.4 showed the multivariate models demonstrating the association between each medication and falls with adjustment to significant non-drug factors. Female sex, heart diseases and shorter stride length were highly associated with falls history ($p<0.005$). Eye disease was moderately associated with falls in the nitrates model ($p=0.009$), while lower body musculoskeletal pain, previous stroke and eye disease were slightly associated with falls in all medication models. The only medication with any significant association with any falls was nitrate, showing borderline significance (OR 1.489, $p=0.027$).

Table 7.2.4. Final model: Association between medications, significant age-sex adjusted risk factors and history of any falls in the previous 12 months

Risk factors	Aspirin	Anti-diabetics	Nitrates	NSAIDs	Paracetamol
	OR (95% CI) p value				
Medication	1.022 (0.753, 1.387) p=0.890	1.169 (0.755, 1.809) p=0.484	1.489 (1.046, 2.120) p=0.027‡	1.417 (0.980, 2.048) p=0.064	1.392 (0.844, 2.297) p=0.196
Age (per yr increase)	0.997 (0.981, 1.014) p=0.741	0.997 (0.981, 1.014) p=0.747	0.996 (0.980, 1.013) p=0.677	0.997 (0.981, 1.014) p=0.754	0.997 (0.981, 1.014) p=0.743
Female sex	1.413 (1.176, 1.697) p=0.000*	1.411 (1.175, 1.696) p=0.000*	1.413 (1.176, 1.698) p=0.000*	1.419 (1.181, 1.706) p=0.000*	1.418 (1.180, 1.704) P=0.000*
Any eye disease	1.207 (1.044, 1.396) p=0.011‡	1.206 (1.043, 1.395) p=0.012‡	1.215 (1.051, 1.405) p=0.009 †	1.207 (1.043, 1.395) p=0.011‡	1.205 (1.042, 1.393) p=0.012‡
Any heart disease	1.558 (1.246, 1.948) p=0.000*	1.579 (1.270, 1.961) p=0.000*	1.440 (1.143, 1.814) p=0.002*	1.604 (1.291, 1.993) p=0.000*	1.569 (1.264, 1.946) p=0.000*

Lower musculoskeletal pain	1.230 (1.036, 1.461) p=0.018‡	1.233 (1.039, 1.465) p=0.017‡	1.228 (1.034, 1.458) p=0.019‡	1.217 (1.025, 1.446) p=0.025‡	1.221 (1.028, 1.450) p=0.023‡
Diabetes	1.208 (0.954, 1.528) p=0.116	1.086 (0.744, 1.585) p=0.668	1.235 (0.975, 1.563) p=0.080	1.241 (0.980, 1.573) p=0.073	1.220 (0.964, 1.544) p=0.097
History of stroke	1.493 (1.030, 2.163) p=0.034‡	1.517 (1.059, 2.172) p=0.023‡	1.509 (1.054, 2.161) p=0.025‡	1.523 (1.064, 2.180) p=0.021‡	1.518 (1.061, 2.173) p=0.023‡
Self-rated health (per score increase)	1.094 (0.982, 1.219) p=0.104	1.094 (0.982, 1.219) p=0.105	1.093 (0.981, 1.218) p=0.107	1.092 (0.980, 1.217) p=0.110	1.092 (0.980, 1.217) p=0.110
Stride length (per 0.1 m increase)	0.842 (0.755, 0.938) 0.002*	0.842 (0.756, 0.938) p=0.002*	0.839 (0.753, 0.935) p=0.001*	0.847 (0.760, 0.944) p=0.003*	0.844 (0.758, 0.941) p=0.002*
Number of medications (per each additional drug)	0.967 (0.894, 1.045) p=0.397	0.963 (0.895, 1.036) p=0.309	0.940 (0.871, 1.014) p=0.112	0.953 (0.886, 1.025) p=0.199	0.962 (0.896, 1.034) p=0.292

* $p<0.005$, † $p<0.01$, ‡$p<0.05$

OR = odds ratio, CI = confidence interval, NSAID = non-steroidal anti-inflammatory agent

Table 7.2.5 showed multivariate models on recurrent falls. Female sex and shorter stride length were again strongly associated with recurrent falls. Eye disease was moderately associated with falls, while heart diseases and lower musculoskeletal pain showed a slight association. Among medications, only anti-diabetics showed a moderate association (OR 2.9, p=0.01).

In this study, intrinsic factors such as gender, decline in physical performance (reduced stride length), eye diseases, heart diseases and degenerative processes and the resultant pain were more associated with falls. Medications, or the total number of medications, when entered into the same model with the diseases for which they were prescribed, were mostly unrelated to falls, with the exception of anti-diabetic medications.

Table 7.2.5. Final model: Association between medications, significant age-sex adjusted risk factors and history of recurrent falls in the previous 12 months

Risk factors	Aspirin	Ca channel blockers	Anti-diabetics	Nitrates	NSAIDs	Statin
	OR (95% CI) p value					
Medication	1.013 (0.635, 1.617) p=0.957	1.218 (0.847, 1.750) p=0.288	2.909 (1.287, 6.575) p=0.010†	1.214 (0.711, 2.073) p=0.477	1.595 (0.938, 2.713) p=0.085	1.173 (0.689, 1.995) p=0.557
Age (per yr increase)	1.008 (0.981, 1.036) p=0.553	1.008 (0.981, 1.036) p=0.573	1.008 (0.981, 1.036) p=0.559	1.008 (0.981, 1.036) p=0.581	1.009 (0.981, 1.036) p=0.540	1.009 (0.982, 1.037) p=0.532
Female sex	1.660 (1.207, 2.285) p=0.002*	1.648 (1.197, 2.268) p=0.002*	1.638 (1.190, 2.253) p=0.002*	1.661 (1.207, 2.286) p=0.002*	1.673 (1.216, 2.303) p=0.002*	1.649 (1.197, 2.271) p=0.002*
Any eye disease	1.398 (1.102, 1.774) p=0.006†	1.396 (1.100, 1.772) p=0.006†	1.393 (1.097, 1.769) p=0.007†	1.402 (1.105, 1.780) p=0.005†	1.395 (1.099, 1.771) p=0.006†	1.398 (1.101, 1.774) p=0.006†
Any heart disease	1.514 (1.063, 2.156) p=0.022‡	1.553 (1.100, 2.192) p=0.012‡	1.600 (1.133, 2.259) p=0.008†	1.453 (1.007, 2.096) p=0.046‡	1.577 (1.117, 2.227) p=0.010‡	1.508 (1.068, 2.127) p=0.019‡

Lower musculoskeletal pain	1.466 (1.078, 1.993) p=0.015‡	1.469 (1.080, 1.997) p=0.014‡	1.491 (1.096, 2.027) p=0.011‡	1.462 (1.075, 1.988) p=0.015‡	1.440 (1.058, 1.960) p=0.020‡	1.469 (1.080, 1.997) p=0.014‡
Diabetes	1.141 (0.782, 1.665) p=0.493	1.151 (0.790, 1.677) p=0.464	0.508 (0.235, 1.097) p=0.085	1.153 (0.791, 1.680) p=0.460	1.193 (0.816, 1.744) p=0.362	1.153 (0.791, 1.682) p=0.459
Self-rated health (per score increase)	1.085 (0.904, 1.303) p=0.380	1.082 (0.901, 1.299) p=0.399	1.086 (0.904, 1.304) p=0.377	1.085 (0.904, 1.303) p=0.383	1.083 (0.902, 1.300) p=0.392	1.087 (0.905, 1.305) p=0.372
Stride length (per 0.1 m increase)	0.771 (0.646, 0.920) p=0.004*	0.768 (0.643, 0.917) p=0.004*	0.770 (0.646, 0.919) p=0.004*	0.770 (0.645, 0.919) p=0.004*	0.781 (0.654, 0.932) p=0.006	0.769 (0.645, 0.919) p=0.004*
Number of medications (per each additional drug)	1.076 (0.950, 1.218) p=0.252	1.044 (0.922, 1.183) p=0.495	1.038 (0.925, 1.165) p=0.528	1.061 (0.943, 1.194) p=0.326	1.053 (0.940, 1.180) p=0.373	1.062 (0.942, 1.198) p=0.325

* $p<0.005$, † $p<0.01$, ‡$p<0.05$

OR = odds ratio, CI = confidence interval, Ca Channel Blocker = calcium channel blocker, NSAID = non-steroidal anti-inflammatory agent

7.3 Relationship between underweight and different BMI levels in 6-year survival among community-living older adults

After a mean follow-up of 72.3 ± 11.7 months, 286 (14.3%) men and 97 (4.9%) women had died. Those who died within the first year after the baseline visit were excluded from the analysis (15 men and 7 women) to eliminate bias in body fat changes close to the time of death (reverse causality). Decedents in both men (n = 271) and women (n = 90) were older, had lower MMSE (Mini-Mental State Examination) scores and were more likely to have a past history of cancer at baseline. In men, those who died also had lower physical activity scores and were more likely to have diabetes (Table 7.3.1).

Men who died within the follow-up period had significantly lower BMI, lower whole body fat %, and lower relative abdominal fat. There was no difference in the waist circumference and waist hip ratio between the survivors and the decedents (Table 7.3.1). In women, no difference in any of the adiposity measurements was observed between survivors and decedents.

Table 7.3.1. Characteristics of decedents and survivors

	Men		Women	
	Decedents (n = 271)	Survivors (n = 1714)	Decedents (n = 90)	Survivors (n = 1903)
Age	75. (5.4)	71.9 (4.8) *	74.9 (6.2)	72.5 (5.3) *
Physical activity score	84.0 (45.2)	99.5 (50.8) *	85.2 (33.2)	85.4 (33.2)
Smoker status (%)†				
Never	24.7	37.9	77.8	91.1
Ex smoker	60.9	50.5	16.7	7.2
Current smoker	14.4	11.6	5.6	1.7
MMSE	26.2 (3.7)	27.1 (2.6) *	23.3 (4.1)	24.3 (3.9) *
Diabetes (%)	21.8	13.4 *	15.6	14.2
Heart disease (%)	20.7	17.8	15.6	16.6
History of cancer (%)	6.6	3.9 *	8.9	4.3 *
Adiposity Measurements				
BMI	22.8 (3.5)	23.6 (3.0) *	24.0 (4.1)	23.9 (3.4)
Whole body fat %	23.6 (5.3)	24.5 (4.9) *	33.8 (7.0)	34.6 (5.2)
Waist (cm)	87.1 (13.0)	87.4 (8.9)	87.1 (10.2)	85.6 (9.4)
Waist Hip ratio	0.93 (0.07)	0.92 (0.07)	0.93 (0.09)	0.92 (0.08)
Relative Abdominal Fat (%)	14.7 (2.7)	15.2 (2.4)*	14.0 (2.1)	14.0 (2.0)

Numbers expressed as mean (sd)

* $p < 0.05$, † p for trend < 0.05

MMSE = Mini-Mental State Examination score, BMI = body mass index

Figure 7.3.1 showed the crude mortality rates of both men and women across the quintiles of four obesity measures (whole body fat % for general adiposity, waist circumference, WHR and relative abdominal fat for abdominal adiposity). The lowest quintile in whole body fat % and relative abdominal fat had the highest crude mortality in men, while higher quintiles of both whole body fat % and relative

abdominal fat (RAF) were associated with lower mortality, (whole body fat%, p for trend < 0.05; relative abdominal fat, p for trend < 0.01). Waist circumference and WHR had a U shape relationship with mortality with the lowest rate at the third quintile and second quintile respectively. None of the obesity measures bore any significant relationship with mortality in women.

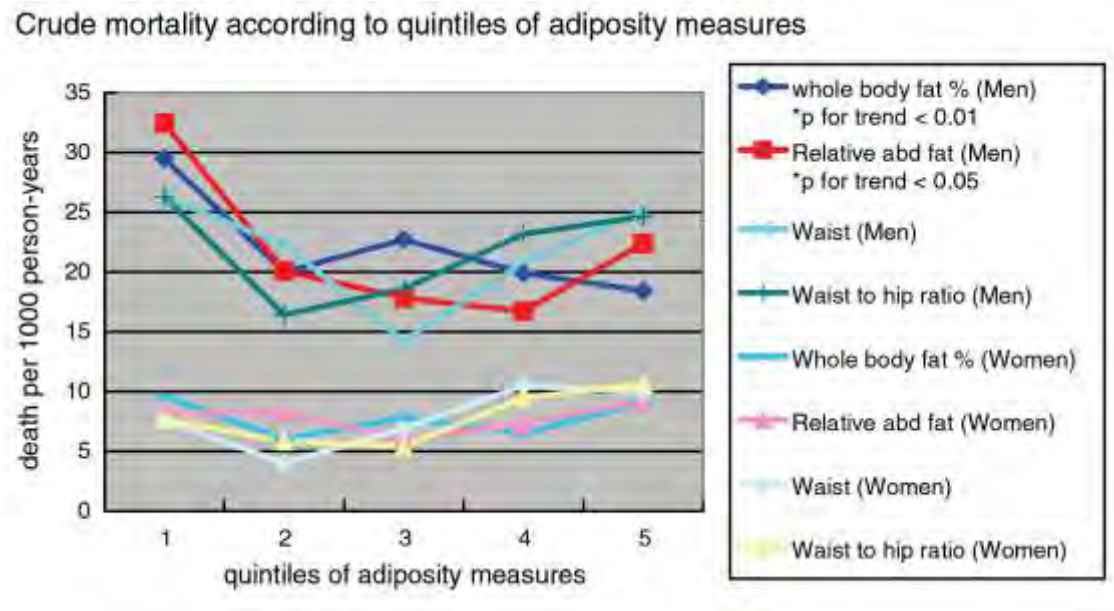


Fig. 7.3.1. Relationship between crude mortality rate and quintiles of adiposity measurements

Table 7.3.2 showed the hazard ratios (HR) of all-cause and cardiovascular mortality according to quintiles of whole body fat %, relative abdominal fat, waist circumference and WHR. In men, each of the 4 upper quintiles of RAF was associated with a significantly lower HR for all-cause mortality after adjustment

for age, physical activity, history of cancer, diabetes and smoker status. Only the highest 2 quintiles of whole body fat % showed similar protective effect. Waist circumference and WHR quintiles however were not related to all-cause mortality. No relationship between these measures of obesity and all-cause of mortality was found in women, nor was there any relationship found between any of the three abdominal adiposity measurements and cardiovascular mortality in both genders. Further adjustment for weight change since the age of twenty five slightly attenuated the protective effect of the highest two quintiles of whole body fat % and the 2nd to 4th quintiles of relative abdominal fat %, but the relationship remained significant. The highest quintile in relative abdominal fat % ceased to be protective after this adjustment (Table 7.3.3).

Table 7.3.2. Hazard ratios of all-cause mortality according to adiposity measurement quintiles

Quintile	Whole body fat %		Relative abdominal fat		Waist circumference		Waist Hip ratio	
	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality
Men								
1st	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2nd	0.72 (0.50, 1.04)	1.33 (0.57, 3.09)	0.62 (0.43, 0.89) †	0.82 (0.37, 1.80)	0.85 (0.59, 1.21)	0.97 (0.38, 2.44)	0.68 (0.46, 1.00)	1.25 (0.54, 2.91)
3rd	0.81 (0.56, 1.18)	1.48 (0.61, 3.45)	0.58 (0.40, 0.85) †	0.72 (0.32, 1.66)	0.58 (0.38, 0.88) *	1.82 (0.80, 4.16)	0.78 (0.53, 1.14)	1.02 (0.42, 2.48)
4th	0.63 (0.43, 0.92) *	0.91 (0.37, 2.26)	0.52 (0.36, 0.77) †	0.58 (0.25, 1.38)	0.83 (0.57, 1.19)	1.40 (0.59, 3.30)	0.92 (0.64, 1.33)	1.27 (0.55, 2.93)
5th	0.54 (0.38, 0.78) †	1.09 (0.49, 2.43)	0.67 (0.47, 0.96) *	1.31 (0.64, 2.68)	0.87 (0.60, 1.25)	1.54 (0.67, 3.53)	0.86 (0.60, 1.23)	1.56 (0.71, 3.42)
Women								
1st	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2nd	0.72 (0.37, 1.42)	0.48 (0.09, 2.50)	1.10 (0.58, 2.09)	0.45 (0.09, 2.33)	0.55 (0.24, 1.23)	0.79 (0.13, 4.77)	0.76 (0.37, 1.55)	0.77 (0.17, 3.46)
3rd	1.05 (0.56, 1.98)	0.57 (0.11, 3.05)	0.75 (0.38, 1.50)	0.22 (0.03, 1.92)	1.00 (0.51, 1.97)	1.52 (0.33, 6.93)	0.74 (0.36, 1.52)	0.83 (0.19, 3.73)
4th	0.83 (0.43, 1.62)	1.04 (0.27, 3.98)	0.94 (0.49, 1.82)	0.66 (0.16, 2.78)	1.44 (0.76, 2.71)	2.06 (0.49, 8.70)	1.12 (0.60, 2.10)	0.67 (0.15, 3.03)
5th	1.22 (0.66, 2.25)	0.55 (0.10, 2.91)	1.20 (0.65, 2.24)	0.93 (0.25, 3.50)	1.31 (0.70, 2.44)	0.33 (0.03, 3.14)	1.18 (0.63, 2.21)	0.42 (0.07, 2.32)

By Cox Regression, adjusted for age, physical activity, smoker status, history of cancer, diabetes and heart disease.

*p <0.05, †p < 0.01

Table 7.3.3. Hazard ratios of all-cause mortality according to adiposity measurement quintiles in men, further adjusted for weight changes since age 25, in addition to age, physical activity, smoker status, history of cancer, diabetes and heart disease

Quintile	Whole Body Fat %	Relative Abdominal Fat	Waist Circumference	Waist Hip ratio
1st	1.00	1.00	1.00	1.00
2nd	0.73 (0.50, 1.08)	0.65 (0.44, 0.95) *	0.94 (0.65, 1.38)	0.74 (0.49, 1.11)
3rd	0.86 (0.57, 1.29)	0.62 (0.41, 0.92) *	0.69 (0.44, 1.07)	0.87 (0.58, 1.31)
4th	0.65 (0.42, 1.00) *	0.59 (0.39, 0.89) *	1.11 (0.73, 1.68)	1.13 (0.77, 1.67)
5th	0.58 (0.38, 0.90) *	0.74 (0.49, 1.11)	1.16 (0.73, 1.85)	1.01 (0.68, 1.51)

*p <0.05

The relative abdominal fat quintile with the highest adjusted HR for all-cause mortality was the first or lowest quintile, and that with the lowest adjusted HR, the fourth quintile. Common obesity measurements of the 5 quintiles in relative abdominal fat (men) were shown for clinical reference (Table 7.3.4). The corresponding waist circumference in the lowest quintile of relative abdominal fat was 77.2 cm, the BMI 20.2, and a whole body fat % of 18.9%. The same parameters in the quintile with best survival rates (the fourth quintile) was 90.53 cm, the BMI 24.6, the waist-hip ratio 0.94 and whole body fat % 26.4 %.

Table 7.3.4. Clinical arthropometric measurements of men according to quintiles of relative abdominal fat

Quintiles of relative abdominal fat	Waist (cm)	Body mass index	Waist Hip Ratio	Whole body fat %
1st *	**77.2 (7.5)**	**20.2 (2.6)**	**0.9 (0.1)**	**18.9 (4.9)**
2nd	86.3 (6.5)	22.9 (2.3)	0.9 (0.1)	22.9 (2.3)
3rd	88.8 (9.1)	23.9 (2.4)	0.9 (0.1)	25.4 (3.6)
4th*	**90.5 (6.8)**	**24.6 (2.6)**	**0.9 (0.1)**	**26.4 (3.6)**
5th	94.6 (7.3)	25.7 (2.8)	1.0 (0.1)	27.3 (3.7)

Numbers expressed as mean (sd).
***** The lowest quintile of relative abdominal fat has the highest mortality.
The 4th quintile of relative abdominal fat had the lowest all-cause mortality.

7.4 Relationship between BMI and short- to long-term survival in nursing home residents

Of the 1614 nursing home residents included in this analysis, 69.5% were female. The mean age was 83.7±8.4 years. Approximately half (49.4%) of the residents were mildly impaired in ADLs as defined by the MDS-ADL scale while 36.1% were severely impaired. The mean BMI was 21.7±4.8; a quarter of the residents were underweight (BMI<18.5 kg/m2) and another quarter approximately were obese (BMI > 25 kg/m2). Overall, 36.7% of the participants were either overweight or obese. Half of them had left 25% of their food uneaten at meals, and 1.5% were recorded to have significant weight loss (≥5% over previous 30 days or ≥10% over previous 180 days). In terms of medical diagnoses, 30% suffered from dementia, 22% suffered from diabetes mellitus, 11% had heart diseases, 7.6% had hip fracture and 4% had a

diagnosis of cancer. Polypharmacy (>4 drugs) was found in 53%. (Table 7.4.1)

Compared with residents who were alive by the end of 9-year, residents deceased by then were older, more impaired in ADLs, more likely to be underweight, on tube-feeding and had swallowing problems. They also had more of the studied medical conditions and were more likely to be suffering from dementia and heart disease at baseline. (Table 7.4.1)

Table 7.4.1. Baseline characteristics of nursing home residents (n = 1614)

Characteristic	**Total, N (%)**	**Dead at 9 yr, N(%)**	**Alive at 9 yr, N(%)**	**p-value[#]**
Age, yr (mean, sd)	83.7 (8.4)	84.8 (7.9)	79.8 (8.9)	<0.001***
Female	1122 (69.5)	865 (68.6)	257 (72.8)	0.129
Activities of Daily Living Hierachy scale				
Mildly impaired (0,1,2)	797 (49.4)	556 (44.1)	241 (68.3)	<0.001***
Moderately impaired (3,4)	234 (14.5)	196 (15.5)	38 (10.8)	
Severely impaired (5,6)	583 (36.1)	509 (40.4)	74 (21.0)	
Nutrition and Feeding				
BMI (kg/m^2) <18.5	421 (26.1)	381 (30.2)	40 (11.3)	<0.001***
18.5 – 22.9	601 (37.2)	471 (37.4)	130 (36.8)	
23.0 – 25.0	211 (13.1)	165 (13.1)	46 (13.0)	
>25	381 (23.6)	244 (19.3)	137 (38.8)	
Tube feeding	90 (5.6)	83 (6.6)	7 (2.0)	0.001***
Swallowing problems	65 (4.0)	59 (4.7)	6 (1.7)	0.012*
25% food left uneaten after each meal	826 (51.2)	643 (51.0)	183 (51.8)	0.778
Weight loss of ≥5% over 30 days or ≥10% over 180 days	24 (1.5)	21 (1.7)	3 (0.8)	0.263
Medical conditions				
Number of medical conditions present				<0.001***

0	651 (40.3)	474 (37.4)	179 (50.7)	
1	700 (43.4)	570 (45.2)	130 (36.8)	
2	231 (14.3)	191 (15.1)	40 (11.3)	
3	30 (1.9)	26 (2.1)	4 (1.1)	
4	2 (0.1)	2 (0.2)	0 (0.0)	
Dementia	491 (30.4)	426 (33.8)	65 (18.4)	<0.001***
Cancer	70 (4.3)	58 (4.6)	12 (3.4)	0.328
Renal failure	44 (2.7)	38 (3.0)	6 (1.7)	0.180
Heart disease	171 (10.6)	150 (11.9)	21 (5.9)	0.001***
Diabetes	362 (22.4)	271 (21.5)	91 (25.8)	0.088
Hip fracture	122 (7.6)	95 (7.5)	27 (7.6)	0.942
Polypharmacy (≥ 4 drugs)	857 (53.1)	664 (52.7)	193 (54.7)	0.502

p-value for the difference between those who were dead and alive at 9-year
* p-value<0.05, ***p-value<0.001

The number (%) of residents with significant weight loss among the different BMI categories were: 9 (2.1%) out of 421 underweight residents, 11 (1.8%) out of 601 normal weight residents, 1 (0.5%) out of 211 overweight residents, and 3 (0.8%) out of 381 obese residents. The proportions of those with weight loss among the different BMI categories were not statistically significant (Chi square test p>0.05).

Mortality rates at different time points from the baseline assessment were: 6.3% at 6 months, 14.3% at 1 year, 27.1% at 2 years, 47.3% at 4 years and 78.1% at 9 years. At 9-year, the mortality rates among those who were underweight, normal weight, overweight and obese were 90.5%, 78.4%, 78.2% and 64.0% respectively. Figure 7.4.1 shows the survival curves of residents in the four BMI categories over 9 years, using univariate analysis. Those in the obese category had the highest survival rate while

those in the underweight category, the lowest survival rate.

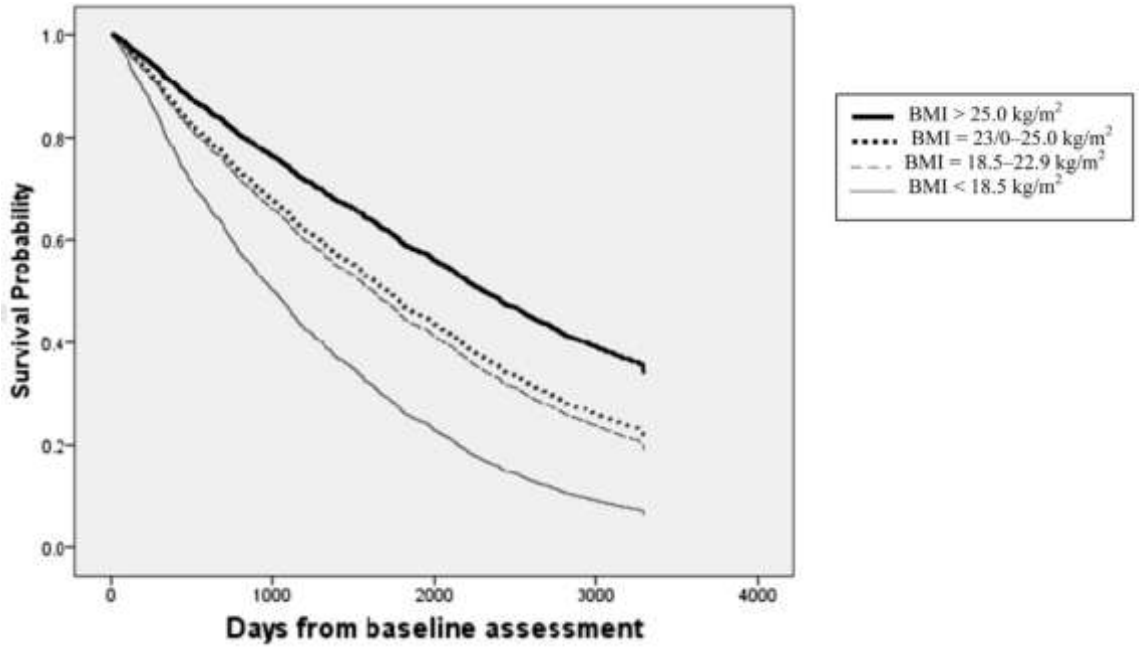


Figure 7.4.1 Survival curves according to baseline BMI categories

Table 7.4.2 describes the two Cox regression models used to examine the relationship between both significant weight loss and BMI, and mortality, with different periods of observation. Both significant weight loss and BMI were entered at the same time into the models, with adjustment for other factors which might be related to mortality. The survival benefit of the higher BMI tended to be more prominent with longer duration of observation.

In model 1, BMI was used as a continuous variable. Significant weight loss was not associated with higher mortality at all time points, whereas each unit of increase in BMI significantly reduced the risk of mortality between 5 to 10% at various time

points. (Table 7.4.2, model 1)

In model 2, BMI was entered as a categorized variable, and mortality risk was presented for each BMI category, as compared to the underweight (BMI<18.5kg/m2) group. Significant weight loss was again not associated with higher mortality risk. Higher BMI were associated with lower risk as compared to the underweight group: at 6 months those had normal weight, were overweight and obese had 50 to 64% lower mortality risk; at 1 year, 37 to 66% lower risk, at 2 years, 37 to 63 % lower risk, at 4 years, 36 to 58% lower risk, and at 9 years, 35 to 53% lower risk. (Table 7.4.2, model 2)

Table 7.4.2 Likelihood of death at different time points by Cox regression, in relation to different BMI and significant weight loss

	6 months		1 year		2 years		4 years		9 years	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Model 1										
Significant weight loss	0.00 (0.00, 0.00)	0.958	1.12 (0.49, 2.57)	0.788	1.00 (0.53, 1.91)	0.991	1.16 (0.69, 1.94)	0.586	1.16 (0.75, 1.79)	0.507
BMI (per kg/m^2 increment)	**0.91 (0.86, 0.95)**	**<0.001**	**0.90 (0.87, 0.93)**	**<0.001**	**0.91 (0.89, 0.93)**	**<0.001**	**0.93 (0.91, 0.95)**	**<0.001**	**0.95 (0.93, 0.96)**	**<0.001**
Model 2										
Significant weight loss	0.00 (0.00, 0.00)	0.956	1.19 (0.52, 2.72)	0.680	1.08 (0.57, 2.04)	0.818	1.20 (0.71, 2.00)	0.51	1.17 (0.76, 1.81)	0.482
BMI (kg/m^2)										
<18.5	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
18.5 – 22.9	**0.50 (0.31, 0.80)**	**0.004**	**0.63 (0.47, 0.85)**	**0.002**	**0.63 (0.51, 0.78)**	**<0.001**	**0.64 (0.54, 0.76)**	**<0.001**	**0.65 (0.57, 0.75)**	**<0.001**
23 - 25	**0.36 (0.17, 0.78)**	**0.009**	**0.39 (0.24, 0.64)**	**<0.001**	**0.44 (0.31, 0.62)**	**<0.001**	**0.51 (0.40, 0.66)**	**<0.001**	**0.62 (0.52, 0.75)**	**<0.001**
>25	**0.43 (0.23, 0.79)**	**0.006**	**0.34 (0.22, 0.53)**	**<0.001**	**0.37 (0.27, 0.50)**	**<0.001**	**0.42 (0.34, 0.52)**	**<0.001**	**0.47 (0.39, 0.55)**	**<0.001**

Significant weight loss = loss ≥5% over 30 days or ≥10% over 180 days

Adjusted for age, gender, medical conditions (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus), tube-feeding, left 25% food uneaten, swallowing problem, and the activities of daily living hierarchy scale.

7.5 Cross-sectional study on associated risk factors and outcomes of sarcopenia

In this study we analysed data from the community cohort consisted of 2,000 men and 2,000 women. Their education levels varied between no education (21.4%), primary education (50.2%) to secondary education or above (28.4%). Most of them were independent in ambulation and all of them were community dwelling, with 86.4% living with either a family member or friend. Only 6 subjects walked with assisted devices. The mean height-adjusted ASM was 7.19 and 6.05 kg/m 2 in men and women respectively. Table 7.5.1 shows the height-adjusted ASM across age groups. Height-adjusted ASM was associated with older age, with the trend being more apparent in men (Table 7.5.1).

Table 7.5.1. Height-adjusted appendicular skeletal muscle mass (kg/m 2) stratified by age and gender

	Men				Women			
	n	ASM/Ht^2	difference from youngest age group (mean, 95% CI)	p value	n	ASM/Ht^2	difference from youngest age group (mean, 95% CI)	p value
Age, years								
65–69	664	7.36 (0.82)	–		669	6.11 (0.03)	–	
70–74	707	7.23 (0.78)	−0.13 (−0.21, −0.04)	0.004*	665	6.13 (0.03)	0.02 (−0.05, 0.10)	0.537
>74	629	6.99 (0.84)	−0.037 (−0.46, −0.28)	0.000*	666	5.93 (0.03)	−0.18 (−0.26, −0.10)	0.000*

* $p < 0.05$ when compared with youngest age group mean of same gender values are mean (standard error).

Lifestyle Factors and Chronic Medical Conditions

Table 7.5.2 shows the relationship between different lifestyle factors, chronic illnesses and height-adjusted ASM. Among lifestyle factors, current smoking was highly associated with lower height-adjusted ASM while ex-smoking, drinking and daily walks for exercise did not show any significant relationship to muscle mass. Physical activity as stratified by quartiles

of the PASE score was positively associated with muscle mass in both men and women, with those having least activities having significantly lower muscle mass. Underweight (defined as BMI <18.5), chronic obstructive pulmonary disease (COPD) and atherosclerosis (defined as ankle-brachial blood pressure ratio <0.9) were associated with lower height-adjusted ASM. On the other hand, diabetes, hypertension and heart diseases were associated with higher height-adjusted ASM. The associations between muscle mass and chronic diseases were consistent between men and women.

Table 7.5.2. Comparison of height-adjusted appendicular skeletal muscle mass (ASM/Ht^2) with respect to lifestyle factors and medical conditions

	Men				Women			
	n	ASM/Ht^2 kg/m^2	mean difference (95% CI)	p value[a]	n	ASM/Ht^2 kg/m^2	mean difference (95% CI)	p value[a]
Drinker								
Yes	159	7.23	0.04 (−0.09, 0.17)	n.s.	1	6.76	0.68 (−0.75, 2.09)	n.s.
No	1,838	7.19			1,999	6.05		
Ever smoker[b]								
Current	238	7.03	−0.19 (−0.31, −0.07)	0.002*	37	5.76	−0.3 (−0.54, −0.07)	0.012*
Ex smoker	1,038	7.12	0.05 (−0.02, 0.13)	n.s.	153	5.94	−0.173 (−0.21, 0.03)	n.s.
Never	724	7.22			1,810	6.07		
Daily walks for exercise								
Yes	1,337	7.19	0.00 (−0.08, 0.08)	n.s.	1,121	6.03	0.04 (−0.10, 0.02)	n.s.
No	663	7.19			879	6.08		
PASE scores[b]								
Lowest quartile	487	7.07	−0.27 (−0.37, −0.17)	0.000*	504	5.94	−0.22 (−0.31, −0.13)	0.000*
Second quartile	516	7.16	−0.18 (−0.28, −0.08)	0.011*	446	5.99	−0.18 (−0.27, −0.08)	0.001*
Third quartile	500	7.22	−0.13 (−0.23, −0.02)	0.032*	557	6.12	−0.04 (−0.13, 0.05)	n.s.
Highest quartile	497	7.34			493	6.16		
COPD								
Yes	232	6.90	−0.32 (−0.49, −0.20)	0.000*	101	5.89	−0.16 (−0.31, −0.02)	0.025*
No	1,768	7.23			1,899	6.06		
ABI								
< or = 0.9	95	6.89	−0.31 (−0.48, −0.14)	0.022*	180	5.94	−0.12 (−0.23, −0.01)	n.s.
> 0.9	1,904	7.21			1,819	6.06		
BMI								
≤18.5	115	5.89	−1.28 (−1.47, −1.29)	0.000*	100	5.04	−1.06 (−1.15, −0.97)	0.000*
≥18.5	1,885	7.27			1,900	6.11		
Diabetes								
Yes	293	7.41	0.25 (0.15, 0.35)	0.000*	286	6.16	0.12 (0.04, 0.21)	0.003*
No	1,707	7.16			1,714	6.03		
Hypertension								
Yes	836	7.34	0.25 (0.18, 0.32)	0.000*	871	6.13	0.13 (0.07, 0.19)	0.000*
No	1,164	7.09			1,129	6.00		
Heart disease								
Yes	366	7.30	0.12 (0.03, 0.22)	0.003*	330	6.17	0.14 (0.05, 0.22)	0.001*
No	1,634	7.18			1,670	6.04		

PASE = Physical activity scale of the elderly; ASM = appendicular skeletal muscle mass; CI = confidence interval, COPD = chronic obstructive airway diseases; ABI = ankle-brachial index; BMI = body mass index; n.s. = not significant.

[a] Comparisons were done by analysis of covariance, adjusted to age.

[b] p values are comparisons to never smokers and highest quartile in PASE scores respectively.

* $p < 0.05$.

Physical Performance Measures

Table 7.5.3 shows the results of physical performance measures across tertiles of height-adjusted ASM and their associations after adjustment to age. Among men, only weaker grip strength was associated with lower muscle mass. Speed of walking and chair-stands did not demonstrate any association with muscle mass. On the other hand,

women in the lowest tertile of muscle mass performed significantly better in all three lower limb performance tests though poorer in grip strength, when compared with those in the highest tertile. Grip strength among all tests showed the strongest association with muscle mass in both men and women.

Table 7.5.3. Comparison of physical performance measures across tertiles of height-adjusted appendicular skeletal muscle mass

	Men, kg/m^2			Women, kg/m^2		
	high >7.52	intermediate 6.83–7.52	low <6.83	high >6.33	intermediate 5.69–6.33	low <5.69
Grip strength, kg	33.52 (0.25)	31.43 (0.23)	28.66 (0.24)	21.39 (0.17)	20.40 (0.16)	18.98 (0.14)
p	–	0.000*	0.000*	–	0.000*	0.000*
Five chair-stands test, s	12.33 (0.14)	12.75 (0.16)	12.87 (0.16)	13.57 (0.22)	13.50 (0.21)	13.18 (0.16)
p	–	0.197	0.409	–	0.580	0.023*
Six-meter walk speed, m/s	1.05 (0.01)	1.02 (0.01)	0.99 (0.01)	0.90 (0.01)	0.93 (0.01)	0.92 (0.01)
p	–	0.355	0.141	–	0.003*	0.002*
Step length, m	0.58 (0.00)	0.58 (0.00)	0.57 (0.00)	0.49 (0.00)	0.49 (0.00)	0.50 (0.00)
p	–	0.918	0.616	–	0.040*	0.000*

Comparisons used the highest tertile height-adjusted ASM group as reference group by analysis of covariance, adjusted to age. Figures expressed are mean (standard error). CI = Confidence interval; ASM = appendicular skeletal muscle mass.
* $p < 0.05$.

Psychosocial and Physical Activities

Comparing to those in the highest tertile of height-adjusted ASM, men in the lowest tertile of muscle mass had poorer physical well-being but the association was not significant in women. Neither the Geriatric Depression Score nor the mental well-being score was related with muscle mass (Table 7.5.4).

Table 7.5.4. Comparison of psychosocial well-being scores across tertiles of height-adjusted appendicular skeletal muscle mass

	Men, kg/m^2			Women, kg/m^2		
	high >7.52	intermediate 6.83–7.52	low <6.83	high >6.33	intermediate 5.69–6.33	low <5.69
SF-12 physical subscore	51.45 (0.26)	50.56 (0.29)	49.57 (0.32)	46.60 (0.34)	46.51 (0.33)	46.67 (0.35)
p	–	0.033*	0.000*	–	0.844	0.879
SF-12 mental subscore	56.00 (0.25)	55.73 (0.27)	55.75 (0.26)	55.09 (0.31)	55.30 (0.29)	54.75 (0.31)
p	–	0.473	0.500	–	0.608	0.424
GDS score	2.85 (0.10)	2.92 (0.11)	3.14 (0.11)	2.96 (0.12)	2.99 (0.11)	3.11 (0.11)
p	–	0.601	0.054	–	0.832	0.318

Comparisons used the highest tertile height-adjusted ASM group as reference group by analysis of variance. Figures expressed as mean (standard error). CI = Confidence interval; ASM = appendicular skeletal muscle mass; SF-12 = Short Form 12 quality of life score; GDS = Geriatric Depression Scale.
* $p < 0.05$.

7.6 Prospective study on effect of diabetes mellitus on age-related muscle loss over 4 years

Among the 4000 participants of the community cohort, all had a baseline DXA measurement and 3153 (74.95%) returned for the 4th year DXA measurements. Among those who did not return, 248 (6.2%) was due to death and 599 (15.0%) defaulted. Those who did not return were older, had lower physical activity, lower total body mass, lower appendicular lean mass (ALM) and were more likely to have ankle: brachial index (ABI) <0.9 at baseline. Women who did not return were more likely to have high waist-hip ratio, and men who did not return were more likely to be current smokers and have a history of stroke. A similar proportion of participants with diabetes did and did not return for the 4th year measurement.

At baseline, diabetic adults were more likely to have hypertension, heart disease, low ABI and high waist-hip ratio (Table 7.6.1). There was no difference in physical activity scores

among those with or without diabetes, in both men and women. Among the 3153 subjects with baseline and 4th year DXA measurements, 442 (14.0%) were diabetic. Both diabetic men and women had higher total body lean mass and total lean mass % (total lean mass / total body mass) than those without diabetes but diabetic participants had lower appendicular lean to total body lean mass ratios.

Table 7.6.1. Comparison of baseline characteristics between DM and non-DM subjects

	Men			**Women**		
	No DM (N=1344)	**DM (N=222)**	**p-value**	**No DM (N=1367)**	**DM (N=220)**	**p-value**
	Mean (SD)/ Freq (%)	**Mean (SD)/ Freq (%)**	**p-value of t-test/ chi square**	**Mean (SD)/ Freq (%)**	**Mean (SD)/ Freq (%)**	**p-value of t-test/ chi square**
Age	71.7 (4.7)	72.0 (4.6)	0.439	72.0 (5.1)	72.4 (4.9)	0.235
PASE score	100.7 (50.1)	100.1 (54.5)	0.864	86.8 (33.6)	88.1 (32.1)	0.601
Body Mass Index	23.3 (3.1)	24.7 (2.8)	<.001	23.9 (3.4)	24.3 (3.3)	0.104
Total body mass (kg)	61.4 (9.1)	64.9 (8.2)	<.001	54.4 (8.4)	55.6 (8.5)	0.052
Total body fat mass (kg)	15.1 (4.6)	16.6 (4.3)	<.001	19.2 (5.1)	19.0 (5.1)	0.629
Total body lean mass (kg)	44.2 (5.3)	46.1 (4.8)	<.001	33.8 (4.0)	35.1 (4.3)	<.001
Trunk fat mass (kg)	8.5 (3.0)	9.9 (2.8)	<.001	9.9 (2.9)	10.2 (2.7)	0.141
Trunk lean mass (kg)	21.6 (2.7)	22.7 (2.5)	<.001	17.0 (2.1)	17.9 (2.3)	<.001
Appendicular fat mass (kg)	5.7 (1.8)	5.9 (1.8)	0.171	8.5 (2.5)	8.0 (2.7)	0.007
Appendicular lean mass (kg)	19.3 (2.6)	19.9 (2.3)	<.001	13.8 (1.9)	14.3 (2.0)	0.002
Total Lean Mass / total body mass %	71.3 (4.1)	72.5 (4.7)	0.001	62.6 (5.0)	63.6 (5.0)	0.005
Appendicular lean mass / total body lean mass %	43.5 (1.5)	43.2 (1.5)	0.003	40.9 (1.6)	40.5 (1.7)	0.004
Smoker status			0.364			0.434
Never smokers	506 (37.7%)	86 (38.7%)		1249 (91.4%)	199 (90.5%)	
Ex- smokers	686 (51.0%)	118 (53.2%)		94 (6.9%)	19 (8.6%)	
Current smokers	152 (11.3%)	18 (8.1%)		24 (1.8%)	2 (0.9%)	
Hypertension	499 (37.1%)	148 (66.7%)	<.001	540 (39.5%)	154 (70.0%)	<.001
Stroke	50 (3.7%)	21 (9.5%)	<.001	46 (3.4%)	8 (3.6%)	0.837
Heart disease	222 (16.5%)	53 (23.9%)	0.008	209 (15.3%)	48 (21.8%)	0.015
ABI < 0.9	40 (3.0%)	7 (3.2%)	0.888	101 (7.4%)	24 (10.9%)	0.073
High gender-specific waist-hip ratio	839 (62.4%)	174 (78.4%)	<.001	1086 (79.5%)	195 (88.6%)	0.001

DM = diabetes mellitus; PASE = Physical Activity Scale for the elderly; ABI = ankle-brachial index

Changes in body composition over time were presented in Table 7.6.2. Both diabetic and non-diabetic participants had significant loss of total body mass and ALM after 4 years, irrespective of gender ($p<0.001$). Those with diabetes had higher total body mass loss than those without diabetes (-2.3 vs. -0.9% in men, $p<0.001$; -2.4 vs. -1.2% in women, $p=0.005$). Both diabetic and non-diabetic participants lost total body lean mass, trunk lean mass and appendicular lean mass over time, but those with diabetes had higher loss than those without the disease. Non-diabetic men lost ALM at a rate of 1.5% over 4 years, while non-diabetic women lost ALM at a rate of 1.9% over the same period. The difference in lean mass loss was more marked in the limbs (-3.0 vs. -1.5% in men, $p<0.001$; -3.4 vs. -1.9% in women, $p<0.001$) than in the trunk (-2.7 vs. 1.9% in men, p 0.003; -2.5 vs. -1.9% in women, p 0.034).

Table 7.6.2. Comparison of body composition changes over 4 year between DM and non-DM subjects

	Men							Women						
	No DM (N=1344)		DM (N=222)		Difference			No DM (N=1367)		DM (N=220)		Difference		
Body composition changes at 4 yr	**Mean (SD)**	**%**	**Mean (SD)**	**%**	**Mean (SE)**	**%**	**p-value[a]**	**Mean (SD)**	**%**	**Mean (SD)**	**%**	**Mean (SE)**	**%**	**p-value[a]**
Total body mass (g)	-576 (2,977) ‡	-0.9	-1,482 (3,147) ‡	-2.3	-887 (216)	-1.3	<.001	-670 (2,923) ‡	-1.2	-1,297 (2,882) ‡	-2.4	-597 (211)	-1.1	0.005
Total body fat mass (g)	107 (2,130)	0.7	-269 (1,997)	-1.6	-370 (153)	-2.3	0.016	-70 (2,155)	-0.4	-332 (2,109) *	-1.8	-241 (155)	-1.4	0.120
Total body lean mass (g)	-709 (1,540) ‡	-1.6	-1,251 (1,912) ‡	-2.7	-530 (115)	-1.1	<.001	-606 (1,311) ‡	-1.8	-957 (1,313) ‡	-2.8	-343 (95)	-1.0	<0.001
Trunk fat mass (g)	-22 (1,381)	-0.3	-291 (1,318) †	-3.0	-264 (99)	-2.7	0.008	-107 (1,304) †	-1.1	-262 (1,286) †	-2.6	-143 (94)	-1.5	0.128
Trunk lean mass (g)	-398 (913) ‡	-1.9	-604 (1,083) ‡	-2.7	-200 (68)	-0.8	0.003	-324 (757) ‡	-1.9	-443 (743) ‡	-2.5	-116 (55)	-0.6	0.034
Appendicular fat mass (g)	137 (830) ‡	2.4	35 (771)	0.6	-101 (60)	-1.8	0.089	43 (926)	0.5	-58 (952)	-0.7	-93 (67)	-1.2	0.168
Appendicular lean Mass (g)	-278 (836) ‡	-1.5	-601 (1,030) ‡	-3.0	-315 (62)	-1.6	<.001	-258 (683) ‡	-1.9	-475 (694) ‡	-3.4	-212 (50)	-1.5	<.001

% = % change from baseline, *p<0.05; †p<0.01; ‡p<0.001, age adjusted p-value comparing with baseline

[a] p-value of ANCOVA, age adjusted for DM vs. no DM within gender

Multivariate Analyses

Table 7.6.3 shows the relationship of ALM loss over time in relation to diabetes, adjusted for age, physical activity, smoking status, BMI, total body mass change and diabetes-related conditions. The ALM loss in men and women with diabetes was higher than those without diabetes by 1.380% and 1.387% respectively. The difference was attenuated after additional adjustment for total body mass loss over the same period in model 2, but association between diabetes and ALM loss remained significant. Having diabetes was associated with an additional 0.85% of ALM loss in men and 0.96% loss in women. Total body mass loss over time was strongly associated with ALM loss in men and women irrespective of diabetes status (2.664 (0.086) % per additional 5 kg total body mass loss in men, $p<0.001$; 2.635 (0.089) % in women, $p<0.001$). There was no significant interaction effect between age and diabetes ($p>0.30$) on ALM change, in both men and women. Further adjustment for changes in physical activity score (PASE) over four years (Model 3) showed that the effect of diabetes was only slightly attenuated. The change in PASE score was significant in the multivariate model only in men but not in women.

Table 7.6.3. Multivariate linear regression models showing relationship between ALM % change over time and diabetes, adjusted for age, physical activity, smoking status, BMI, total body mass change and diabetes-related conditions

	ALM % change over 4 years (SE)	
	Men (N=1566)	**Women (N=1587)**
Diabetes (vs. no diabetes)		
Model 1	-1.380 (0.326) ‡	-1.387 (0.360) ‡
Model 2	-0.846 (0.256) †	-0.962 (0.289) ‡
Model 3	-0.783 (0.256) †	-0.951 (0.289) †

*p<0.05; †p<0.01; ‡p<0.001

Model 1: adjusted for age, PASE score, smoker status (never, ex- and current), low ankle-brachial index, stroke, hypertension, heart disease, BMI; model 2: additionally adjusted for total body mass % change over 4 years; model 3: additionally adjusted for PASE score change over 4 years.

7.7 Cross-sectional analysis of association between metabolic conditions and physical frailty, and the latter's relationship to mortality

Among the 2000 men and 2000 women assessed, the prevalence of diabetes, hypertension and heart disease were similar among men and women. Compared with women, men had significantly more strokes (5.5% vs. 3.3%, p = 0.001) but lower prevalence of low ankle-brachial index (4.8% vs. 9.0%, p<0.001) and high waist-hip ratio (64.9% vs. 81.5%, p<0.001). Men were more likely to be smokers, had higher education level and higher physical activity scores. (Table7.7.1)

Table 7.7.1. Comparison of baseline characteristics between men and women

	Men (n = 2000)	**Women** (n = 2000)	**p-value**
Age (year)	72.3 ± 5.0	72.5 ± 5.3	NS
Body Weight (kg)	62.4 ± 9.3	54.5 ± 8.4	< 0.001
Body Mass Index	23.4 ± 3.1	23.9 ± 3.4	< 0.001
<18.5	5.8	5.0	
18.5 – 23.0	38.0	35.6	
23.0 – 24.9	26.2	23.8	
25 – 29.9	28.1	31.4	
30 or above	2.0	4.3	
Current Smokers	11.9%	1.9%	< 0.001
Years of Education			< 0.001
0 years	5.2%	37.7%	
1-6 years	55.2%	45.2%	
7-12 years	26.1%	11.3%	
> 12 years	13.6%	6.0%	
PASE Score	97.2 ± 50.2	85.3 ± 33.1	< 0.001
CSI-D cognitive score ≦ 28.40	4.9%	25.3%	< 0.001
MMSE score	26.9 ± 2.7	24.2 ± 3.9	< 0.001
Appendicular Skeletal Mass (kg)	19.1 ± 2.6	13.8 ± 1.9	< 0.001
Diabetes Mellitus	14.7%	14.3%	NS
Hypertension	41.8%	43.6%	NS
Stroke	5.5%	3.3%	0.001
Heart disease	18.3%	16.5%	NS
ABI < 0.9	4.8%	9.0%	< 0.001
High gender-specific waist-hip ratio	64.9%	81.5%	< 0.001
Composite physical performance score	12.2 ± 4.1	12.2 ± 4.3	NS

Values are expressed as mean ± standard deviation or percentage; CSI-D= Community Screening Instrument of Dementia; MMSE = Mini-mental Status Examination; PASE = Physical Activity Scale for the elderly; ABI = ankle-brachial index; NS = not significant Statistical comparison by unpaired student-t test for continuous variables and Chi-square test for categorical variables

In both men and women, all metabolic conditions examined (diabetes, hypertension, heart

disease, stroke, low ABI and high WHR) were significantly associated with the composite physical frailty score, both before and after adjustment for appendicular skeletal mass. (Table 7.7.2)

Table 7.7.2. Univariate analysis of composite physical performance score, unadjusted and after adjustment for appendicular skeletal muscle mass

Covariates	**Mean ± SD/ %**	**Unit**	**Mean difference per unit change of covariates (95% CI)**			
			unadjusted	**p value**	**adjusted for ASM**	**p value**
Men						
Cognitive impairment	4.9%	Yes/ no	-0.16 (-3.74, -2.12)	<0.001	-0.14 (-3.33, -1.75)	< 0.001
Age (year)	72.3 ± 5.0	5	-2.15 (-1.90, -1.55)	< 0.001	-1.95 (-1.75, -1.35)	< 0.001
PASE score	97.2 ± 50.2	50.2	10.49 (0.50, 1.00)	< 0.001	9.54 (0.50, 1.00)	< 0.001
Diabetes	14.7%	Yes/ no	-3.08 (-1.29, -0.29)	0.002	-0.09 (-1.54, -0.56)	< 0.001
Hypertension	41.8%	Yes/ no	-0.12 (-1.31, -0.60)	< 0.001	-0.14 (-1.53, -0.83)	< 0.001
Heart Disease	18.3%	Yes/ no	-0.08 (-1.42, -0.40)	< 0.001	-0.09 (-1.57, -0.57)	< 0.001
Stroke	5.5%	Yes/ no	-0.11 (-2.81, -1.25)	< 0.001	_0.12 (-2.82, -1.30)	<0.001
ABI < 0.9	4.8%	Yes/ no	-0.11 (-3.00, -1.33)	< 0.001	-0.93 (-2.59, -0.966)	< 0.001
High Waist – Hip Ratio	64.8%	Yes/ no	-0.06 (-0.84, -0.10)	0.013	-0.12 (-1.37, -0.63)	< 0.001
Current smoker	11.9%	Yes/ no	0.01 (-0.41, 0.69)	NS	0.03 (-0.18, 0.89)	NS
Women						
Cognitive impairment	25.3%	Yes/ no	-0.21 (-2.50, -1.66)	< 0.001	-0.21 (-2.46, -1.62)	<0.001
Age (year)	72.5 ± 5.3	5.3	-2.12 (-1.86, -1.48)	< 0.001	-2.01 (-1.80, -1.43)	< 0.001
PASE score	85.3 ± 33.1	33.1	8.28 (0.99, 1.32)	< 0.001	7.61 (0.66, 1.32)	< 0.001
Diabetes	14.3%	Yes/ no	-0.08 (-1.55, -0.48)	< 0.001	-0.09 (-1.65, -0.60)	< 0.001
Hypertension	43.6%	Yes/ no	-0.03 (-0.66, 0.09)	NS	-0.05 (-0.77, -0.02)	0.038
Heart Disease	16.5%	Yes/ no	-0.08 (-1.55, -0.42)	0.001	-0.08 (-1.63, -0.51)	< 0.001
Stroke	3.3%	Yes/ no	-0.06 (-2.53, -0.44)	0.005	-0.06 (-2.41, -0.34)	0.009
ABI < 0.9	9.0%	Yes/ no	-0.11 (-2.22, -0.92)	< 0.001	-0.09 (-2.05, -0.76)	< 0.001
High Waist – Hip Ratio	81.5%	Yes/ no	-0.08 (-2.12, -1.17)	< 0.001	-0.18 (-2.44, -1.49)	< 0.001
Current smoker	1.9%	Yes/ no	0.01 (-1.23, 1.55)	NS	0.02 (-0.90, 1.85)	NS

PASE = Physical Activity Scale for the elderly; ABI = ankle-branchial index; BMI = body mass index; ASM = Appendicular skeletal mass; CI = Confidence interval; NS = not significant

In multivariate linear regression analysis, the relationship between various metabolic conditions and the composite physical performance score was studied with adjustment for age, cognitive impairment, appendicular skeletal mass and physical activities. Diabetes, hypertension, heart disease stroke and high WHR were all associated with lower composite physical frailty scores in men, independent of the effect of cognitive impairment and muscle mass, while low ABI was not related. In women, diabetes, heart disease, stroke and high WHR was associated with lower physical performance, while both hypertension and low ABI were not related. (Table 7.7.3)

Table 7.7.3. Multivariate analysis of composite physical performance score with adjustment for metabolic factors, cognitive impairment, and appendicular skeletal muscle mass

Covariates	**Mean ± SD/ %**	**Unit**	**Mean difference per unit change (95% CI)**	**p value**
Male				
ASM (kg)	19.1 ± 2.6	2.6	0.43 (0.49, 0.83)	< 0.001
Cognitive impairment	4.9%	Yes/ no	-0.07 (-2.05, -0.60)	< 0.001
Age (year)	72.3 ± 5.0	5.0	-1.7 2 (-1.55, -1.23)	< 0.001
PASE score	97.2 ± 50.2	50.2	5.82 (0.30, 0.60)	< 0.001
Metabolic/ atherosclerotic conditions				
Diabetes	14.7%	Yes/ no	-0.04 (-0.90, -0.00)	0.049
Hypertension	41.8%	Yes/ no	-0.05 (-0.78, -0.12)	0.008
Heart Disease	18.3%	Yes/ no	-0.05 (-1.05, -0.14)	0.010
Stroke	5.5%	Yes/ no	-0.08 (-2.20, -0.81)	< 0.001
ABI < 0.9	4.8%	Yes/ no	-0.03 (-1.31, 0.17)	NS
High Waist – Hip Ratio	64.8%	Yes/no	-0.09 (-1.08, -0.40)	< 0.001
Female				
ASM (kg)	13.8 ± 1.9	1.9	0.17 (0.20, 0.55)	< 0.001
Cognitive impairment	25.3%	Yes/ no	-0.12 (-1.54, -0.75)	< 0.001
Age (year)	72.5 ± 5.3	5.3	-1.57 (-1.44, -1.07)	< 0.001
PASE score	85.3 ± 33.1	33.1	4.30 (0.36, 0.73)	< 0.001
Metabolic/ atherosclerotic conditions				
Diabetes	14.3%	Yes/ no	-0.05 (-1.15, -0.17)	0.009
Hypertension	43.6%	Yes/ no	0.02 (-0.20, 0.51)	NS
Heart Disease	16.5%	Yes/ no	-0.05 (-1.20, -0.17)	0.009
Stroke	3.3%	Yes/ no	-0.05 (-2.07, -0.20)	0.018
ABI < 0.9	9.0%	Yes/ no	-0.01 (-0.70, 0.49)	NS
High Waist – Hip Ratio	81.5%	Yes/no	-0.11 (-1.64, -0.76)	< 0.001

PASE = Physical Activity Scale for the elderly; ABI = ankle-branchial index; BMI = body mass index; ASM = Appendicular skeletal mass; CI = Confidence interval
NS = not significant

After a mean follow-up period of 72.0 ± 12.7 months, 271(13.5%) men and 90(4.5%) women had died. Lower physical performance score was associated with higher mortality after 6 years of follow-up, in both men and women, with exclusion of early deaths that occurred within the first twelve months after the physical assessment. Adjustment for age and cognitive function attenuated the relationship but it remained significant, particularly in men. Further adjustment for metabolic and atherosclerotic risk factors resulted in a small reduction in the detrimental effect of physical frailty in men (HR reduced from 1.103 to 1.098), but not in women (HR increased from 1.058 to 1.061). (Table 7.7.4)

Table 7.7.4. Change of impact of composite physical performance score on 6-year mortality by Cox regression analysis per 1 point decrease in physical performance score

	Change of unadjusted HR (95% CI)	p value	age-adjusted HR (95% CI)	p value	additional adjustment for cognitive status HR (95% CI)	p value	additional adjustment for metabolic & atherosclerotic risk factors	p value
Men								
Excluded early deaths up to 12 months from baseline	1.160 (1.124,1.196)	<0.001	1.108 (1.070, 1.146)	<0.001	1.103 (1.067, 1.142)	<0.001	1.098 (1.060, 1.137)	<0.001
Women								
Excluded early deaths up to 12 months from baseline	1.097 (1.043, 1.154)	<0.001	1.063 (1.008, 1.123)	0.025	1.058 (1.002, 1.117)	0.042	1.061 (1.005, 1.122)	0.032

Metabolic and atherosclerotic risk factors included diabetes, hypertension, stroke, heart disease, ABI < 0.9 and high gender-specific waist hip ratio.

7.8 Prospective study on factors that may affect the transitions between frailty states

In this study, in order to obtain the weight change in the previous two years as one of the components of the frailty syndrome, the second year visit of the community cohort was considered the “baseline” visit in the analysis, and the fourth year visit, the “follow-up” visit.

A total of 1519 men (87.0% of 1745 at baseline) and 1499 women (89.1% of 1682 at baseline) attended both visits with complete frailty data. Table 7.8.1 compared the characteristics of participants who did or did not return (either deceased or defaulted) for the

follow-up visit. Those who did not return for the follow-up were older, had lower MMSE scores, have more hospitalizations after the baseline visit, and were more likely to be frail at baseline. Men who did not return for the follow-up visit were also more likely to be past or current smokers and to have a history of COPD, hip fracture or cancer.

Table 7.8.1. Characteristics of subjects who did and did not return for follow-up visit (deceased or defaulted)

	Men		**Women**	
	Did not return (n=226)	**Returned (n=1519)**	**Did not return (n=183)**	**Returned (n=1499)**
Age	76.6 (5.4)	73.5 (4.7)*	76.4 (5.8)	73.8 (5.0)*
MMSE	26.3 (3.3)	27.3 (2.5)*	23.3 (4.2)	24.6 (3.8)*
SES ladder HK	4.3 (2.0)	4.5 (1.8)	4.6 (2.2)	4.6 (1.9)
Smoking		*		
Never	56 (24.8%)	574 (37.8%)	161 (88.0%)	1371 (91.5%)
Past	141 (62.4%)	802 (52.8%)	20 (10.9%)	107 (7.1%)
Current	29 (12.8%)	143 (9.4%)	2 (1.1%)	21 (1.4%)
BMI				
underweight (<18.5)	18 (8.0%)	81 (5.3%)	9 (4.9%)	73 (4.9%)
normal (18.5 - <23)	91 (40.3%)	576 (37.9%)	73 (39.9%)	548 (36.6%)
overweight (23-24.9)	64 (28.3%)	419 (27.6%)	45 (24.6%)	354 (23.7%)
Obese (25 or above)	53 (23.5%)	442 (29.1%)	56 (30.6%)	522 (34.9%)
Diabetes	39 (17.3%)	215 (14.2%)	24 (13.1%)	211 (14.1%)
Heart disease	49 (21.7%)	289 (19.0%)	37 (20.2%)	251 (16.7%)
COPD	41 (18.1%)	157 (10.3%)*	13 (7.1%)	79 (5.3%)
Osteoarthritis	16 (7.1%)	99 (6.5%)	26 (14.2%)	162 (10.8%)
Hip fracture	3 (1.3%)	4 (0.3%)*	3 (1.6%)	18 (1.2%)
Stroke	15 (6.6%)	79 (5.2%)	4 (2.2%)	52 (3.5%)
Cancer	24 (10.6%)	89 (5.9%)*	12 (6.6%)	75 (5.0%)
Hospital admission since baseline till death or follow-up visit		*		*
0	69 (30.5%)	978 (64.4%)	90 (49.2%)	1033 (69.0%)
1-2	77 (34.1%)	390 (25.7%)	51 (27.9%)	377 (25.2%)
3-4	37 (16.4%)	99 (6.5%)	24 (13.1%)	66 (4.4%)
5 or above	43 (19.0%)	52 (3.4%)	18 (9.8%)	22 (1.5%)
Frailty – baseline		*		*
Robust	53 (23.5%)	736 (48.5%)	47 (25.7%)	586 (39.1%)
Pre-frail	131 (58.0%)	719 (47.3%)	95 (51.9%)	789 (52.6%)
Frail	42 (18.6%)	64 (4.2%)	41 (22.4%)	124 (8.3%)

*p<0.05 of t-test for continuous variables and chi-square for categorical variables.
MMSE = Mini-mental state examination score, SES = socio-economic status, BMI = body mass index, COPD = chronic obstructive pulmonary disease

Table 7.8.2 showed the change in status between baseline and follow-up. At baseline, 48.7% of men and 52.5% of women were in the pre-frail group, and 6.0% men and 9.8% women were frail. By the end of two years, 66 (3.7%) men and 20 (1.1%) women had died. Mortality increased significantly with increasing frailty at baseline for both men and women (both p<0.001). Default rate also increased with baseline frailty (both p<0.001). There was no difference between the percentage of defaulters and the deceased across the different frailty states (p>0.05). At the follow-up visit, slightly more than half of those in the pre-frail state at baseline had remained in the same state, while 11.1% of men and 6.6% of women worsened into frailty, and a quarter of both genders recovered into the robust state. Only 4.5% of pre-frail men and 1.2% of pre-frail women had died. Among the frail at baseline, one-third had remained frail, about half had recovered into the pre-frail state, but 15.1% of men and 4.2% of women had died. Among the robust, two-thirds had remained robust, while one-third had worsened into the pre-frail state, and very few had declined into frailty or died. Men tended to worsen into frailty more than women.

Table 7.8.2. Status at follow-up including deaths and no follow-up

Frailty Status–baseline	**Status – follow-up at 2 Y, n (%)**					
	Robust	**Pre-frail**	**Frail**	**Deceased**	**Defaulted**	**Total**
Male	657	727	135	66	160	1745
Robust	456 (57.8%)	266 (33.7%)	14 (1.8%)	12 (1.5%)	41 (5.2%)	789
Pre-frail	199 (23.4%)	426 (50.1%)	94 (11.1%)	38 (4.5%)	93 (10.9%)	850
Frail	2 (1.9%)	35 (33.0%)	27 (25.5%)	16 (15.1%)	26 (24.5%)	106
Female	622	773	104	20	163	1682
Robust	381 (60.2%)	199 (31.4%)	6 (1.0%)	2 (0.3%)	45 (7.1%)	633
Pre-frail	235 (26.6%)	496 (56.1%)	58 (6.6%)	11 (1.2%)	84 (9.5%)	884
Frail	6 (3.6%)	78 (47.3%)	40 (24.2%)	7 (4.2%)	34 (20.6%)	165

p-value: male:<0.0001, female:<0.0001

Age-adjusted models

Table 7.8.3 showed the age-adjusted odds ratios (ORs) of factors possibly associated with directions of change in frailty status after two years. Different factors were associated with the transitions in frailty states among men and women. Among pre-frail men, having normal and overweight BMI was protective against worsening, while hospitalizations and having previous stroke was associated with worsening or less improvement. Among pre-frail women, having osteoarthritis and a history of stroke was associated with higher chance of worsening, while having diabetes and heart disease was associated with less improvement.

Table 7.8.3. Age-adjusted odds ratio of possible associated factors for transitions in frailty status after two years

	Male				**female**			
	Pre-frail worsening	**Pre-frail improvement**	**Robust worsening**	**Frail improvement**	**Pre-frail worsening**	**Pre-frail improvement**	**Robust worsening**	**Frail improvement**
MMSE	0.98(0.90,1.06)	**1.10(1.02,1.18)***	0.99(0.92,1.06)	0.90(0.74,1.09)	0.96(0.90,1.03)	1.02(0.98,1.07)	0.98(0.94,1.04)	0.96(0.88,1.05)
SES ladder HK	0.96(0.85,1.08)	1.02(0.92,1.12)	0.97(0.89,1.05)	1.05(0.78,1.40)	0.94(0.81,1.09)	1.03(0.94,1.13)	**0.89(0.81,0.98)***	0.84(0.67,1.04)
Smoking								
Non	1	1	1	1	1	1	1	1
Past	0.75(0.46,1.24)	1.01(0.70,1.46)	0.95(0.69,1.32)	0.57(0.18,1.82)	1.75(0.79,3.89)	0.99(0.52,1.88)	1.36(0.66,2.80)	0.58(0.18,1.89)
Current	1.53(0.73,3.23)	0.63(0.33,1.21)	1.29(0.75,2.23)	0.21(0.02,1.80)	3.07(0.63,14.80)	2.44(0.76,7.83)	0.26(0.03,2.15)	-
BMI								
underweight (<18.5)	1	1	1	1	1	1	1	1
normal (18.5 - <23)	**0.47(0.23,0.99)***	1.24(0.59,2.61)	1.25(0.42,3.76)	0.27(0.04,1.60)	0.86(0.32,2.31)	0.84(0.42,1.65)	0.93(0.32,2.75)	1.25(0.22,7.09)
overweight (23-24.9)	**0.36(0.16,0.81)***	1.45(0.68,3.08)	1.18(0.39,3.59)	0.78(0.09,6.45)	0.72(0.26,2.00)	0.92(0.46,1.86)	0.57(0.19,1.75)	1.01(0.17,6.05)
Obese (25 or above)	0.65(0.31,1.38)	1.26(0.59,2.70)	1.77(0.59,5.35)	0.26(0.04,1.75)	0.57(0.20,1.62)	0.73(0.37,1.45)	0.93(0.32,2.75)	0.65(0.11,3.77)
Diabetes	0.86(0.45,1.62)	0.84(0.52,1.35)	1.54(0.97,2.42)	0.43(0.12,1.62)	1.35(0.67,2.71)	**0.50(0.31,0.82)†**	0.99(0.58,1.69)	0.63(0.23,1.77)
Heart disease	1.13(0.66,1.93)	1.08(0.71,1.65)	1.14(0.76,1.71)	1.12(0.35,3.60)	1.10(0.55,2.20)	**0.64(0.42,0.99)***	1.61(1.00,2.57)	0.84(0.31,2.22)
COPD	1.69(0.92,3.09)	0.70(0.39,1.28)	0.61(0.34,1.11)	1.15(0.33,4.06)	1.11(0.37,3.29)	0.84(0.44,1.63)	**2.66(1.10,6.44)***	2.05(0.35,12.05)
Osteoarthritis	1.03(0.42,2.55)	1.08(0.55,2.11)	1.29(0.70,2.37)	0.35(0.05,2.46)	**2.11(1.01,4.44)***	1.11(0.67,1.84)	0.99(0.58,1.69)	0.76(0.22,2.56)
Hip fracture	-	-	-	-	0.95(0.12,7.83)	0.62(0.13,3.00)	-	0.70(0.11,4.61)
Stroke	1.79(0.84,3.82)	**0.40(0.17,0.92)***	1.53(0.74,3.15)	**0.18(0.04,0.84)***	**2.81(1.01,7.77)***	0.49(0.20,1.23)	**3.86(1.42,10.50)†**	0.35(0.10,1.27)
Cancer	0.75(0.30,1.88)	1.07(0.48,2.37)	**2.03(1.03,4.00)***	2.20(0.44,11.02)	0.98(0.29,3.33)	1.39(0.71,2.70)	0.79(0.32,1.95)	2.25(0.42,12.12)
Hospital admission								
0	1	1	1	1	1	1	1	1
1-2	**1.71(1.02,2.88)***	0.66(0.43,1.02)	1.24(0.87,1.76)	1.17(0.37,3.72)	**2.62(1.46,4.73)†**	0.71(0.49,1.02)	1.36(0.89,2.05)	0.41(0.16,1.03)
3-4	**2.50(1.23,5.10)***	1.06(0.57,1.96)	0.88(0.40,1.92)	0.65(0.12,3.66)	**4.07(1.59,10.42)†**	**0.24(0.08,0.68)†**	**6.32(1.99,20.09)†**	0.31(0.07,1.27)
5 or above	**5.33(2.16,13.15)‡**	0.50(0.16,1.51)	**3.04(1.24,7.44)***	1.30(0.11,15.24)	2.73(0.32,23.37)	0.18(0.02,1.48)	3.09(0.51,18.85)	**0.03(0.004,0.33)†**

‡ $p < 0.001$, † $p<0.01$ * $p<0.05$

MMSE = Mini-mental state examination score, SES = socio-economic status, BMI = body mass index, COPD = chronic obstructive pulmonary disease

Among robust men, a history of cancer and five or more hospitalizations during the two years between visits were associated with worsening. In robust women, having COPD and a history of stroke was associated with worsening, while higher socio-economic status was protective.

Among frail men, a history of stroke lowered the chance of any improvement by 82%. In frail women, having 5 or more hospitalizations in the intervening years reduced the chance of any improvement by 97%.

Multivariate models

Table 7.8.4 showed the step-wise multiple logistic regression models of the four different directions of change in frailty status. Older age was consistently associated with either higher risk of decline or lower chance of improvement, except in the improvement of frail men. Among the pre-frail, higher MMSE score was protective while a history of stroke reduced the chance of improvement by 60% in men and increased the likelihood of decline by three fold in women. In addition, having diabetes reduced the chance of improvement by 50% in pre-frail women. Having three or four hospitalizations within the intervening two years also significantly reduced the chance of improvement. Any hospitalization increased the risk of worsening up to five times in both pre-frail men and women. Additional factors associated with decline in pre-frail women included a history of osteoarthritis.

In robust men, having a history of cancer increased the risk of worsening by two times. In robust women, hospitalizations, COPD or stroke were risk factors for decline. In frail men, a history of stroke reduced the chance of improvement by 82%. We were not able to find any significant factors associated with improvement in frail women in our model, apart from younger age.

Table 7.8.4. Multiple step-wise logistic regressions: factors significantly associated with transitions in frailty status over 2 years

	Male				**female**			
	Pre-frail worsening	**Pre-frail improvement**	**Robust worsening**	**Frail improvement**	**Pre-frail worsening**	**Pre-frail improvement**	**Robust worsening**	**Frail improvement**
Age (per 1 year increase)	1.13 (1.08, 1.18)	0.86 (0.82, 0.90)	1.12 (1.07, 1.16)		1.14 (1.08, 1.21)	0.91 (0.88, 0.94)	1.08 (1.03, 1.12)	0.90 (0.83, 0.97)
Hospital admission								
0	1.0				1.0	1.0	1.0	
1-2	1.70 (1.01, 2.85)				2.51 (1.35, 4.68)	0.78 (0.53, 1.15)	1.48 (0.95, 2.30)	
3-4	2.28 (1.10, 4.74)				5.12 (1.90, 13.76)	0.20 (0.06, 0.67)	6.36 (1.95, 20.74)	
5 or above	5.08 (1.98, 13.08)				-	0.28 (0.03, 2.26)	3.87 (0.62, 24.14)	
Stroke		0.40 (0.17, 0.92)		0.22 (0.05, 0.93)	3.11 (1.05, 9.18)		3.53 (1.24, 10.09)	
MMSE (per 1 unit increase)		1.09 (1.01, 1.18)			0.91 (0.84, 0.99)			
Cancer			2.02 (1.03, 4.00)					
Osteoarthritis					2.28 (1.04, 5.02)			
Diabetes						0.48 (0.29, 0.80)		
SES ladder (per 1 unit increase)							0.89 (0.81, 0.99)	
COPD							3.49 (1.38, 8.78)	

MMSE = Mini-mental state examination score, SES = socio-economic status, COPD = chronic obstructive airway disease

Chapter 8

Discussion

8.1 Intrinsic factors are more important than extrinsic ones in falls among older people in nursing homes

When compared with those in three other countries (Finland, Sweden and Israel), Hong Kong nursing home residents were found to be the least disabled in terms of activities of daily living and had the lowest fall rate. (Chi, 2004) This could be either due to a difference in case-mix and / or prevalence in restraint use. As the characteristics are different and the nursing practice is different, it is possible that potential risk factors for falls might too be somewhat different from those in other countries. To my knowledge, this is the first paper to describe the characteristics of fallers and restraints among nursing home residents in Hong Kong.

In this study, I have excluded from the analysis residents who were completely bedridden as very severe physical limitations and little mobility would have lower fall rates, and it was those who were still able to ambulate despite some physical impairment that were most likely to fall. In fact, Kallin et al reported that the ability to get up from a chair was associated with being a faller in Sweden geriatric care settings. (Kallin et al., 2004) I did not find a difference between the fallers and non-fallers in terms of the MDS ADL self-performance scale. In addition, I found that physical impairment such as the need to

have a walking aid for ambulation was not necessarily related to falls, provided that the resident was cognitively intact and was free from eye diseases.

The most important factor in our analysis was having eye diseases, followed by being on psychotropic drugs which included anti-depressants, hypnotics and anxiolytics, and having dementia. Having eye conditions such as cataracts, glaucoma, or diabetic retinopathy, in particular cataracts, could be considered as part of normal ageing. The other eye conditions, together with dementia, are diseases that are fairly common in old age. It could be concluded from this study that in falls among frail older nursing residents, most of the factors associated with falls were intrinsic factors included age-related degenerative changes and acquired diseases.

Although it was not the focus of the study, it must be mentioned that restraint use in our cohort was unrelated to falls. Even if restraints do reduce falls, they nevertheless impinge on the autonomy and quality of life of the individual and enhance immobility. Previous reports had demonstrated that restraint removal in the nursing home did not necessarily lead to increased falls and could actually reduce injurious falls. (Capezuti et al., 1998; Cali et al., 1995; Ejaz et al., 1994) Another prospective cohort had also shown that physical restraint use was actually associated with more serious injuries. (Tinetti et al., 1992) In one survey, Hong Kong had one of the highest restraint rates among eight other countries

(Denmark, France, Iceland, Italy, Japan, Spain, Sweden and USA); (Tinetti et al., 2004; Woo et al., 1992) the marginal protection offered by restraints in our results and the very high restraint rate calls for sensible reduction of restraints in the local nursing home population.

8.2 Associated factors of falls and significance of medications in community-living older adults

Previous studies have demonstrated the relationship between falls and various types of medications. Few had addressed the possible confounding effect of the underlying medical illnesses. Medications being implicated as the culprit of falls in older adults included sedatives or hypnotics (Tinetti et al., 1988; Ensrud et al., 2002; Woolcott et al., 2009; Cumming et al., 1991; Koshi et al., 1996), anti-depressants (Ensrud et al., 2002; Woolcott et al., 2009); anticonvulsants (Ensrud et al., 2002; Deandrea et al., 2010), anti-hypertensives including diltiazem, calcium channel blockers (Cumming et al., 1991; Koski et al., 1996) and diuretics (Cumming et al., 1991), laxatives (Cumming et al., 1991), digitalis (Koski et al., 1996), peripheral vasodilators (Koski et al., 1996), and anti-inflammatory drugs. (Koski et al., 1996) Some have concluded that risks of falling in older people were in general more related to drugs than to diagnoses. (Granek et al., 1987) Others have reported that having more than three or four drugs of any type would increase the risk of falls. (Leipzig et al., 1999)

However, in a prospective study, the findings suggested that intrinsic factors of the older person such as mobility impairment were more likely to predict falls, rather than high-risk medications. (Graafmans et al., 1996) This importance of intrinsic degenerative problems in causing falls was echoed in two local Hong Kong studies. (Chu et al., 2005; Ho et al., 1996) This debate on which was more important in falls: intrinsic problems vs. medications, has continued over the past two to three decades. A more recent meta-analysis has refuted the long-standing belief among geriatricians regarding the harmfulness of "high-risk" medications, in particular sedatives and those that can cause orthostatic hypotension. In this meta-analysis of studies published from 1966 to 2004, medications, visual impairment and cognitive impairment, were not found to be consistently related to falls in older people. Even orthostatic hypotension had failed to predict falls. (Ganz et al., 2007)

Alternatively, risk factors associated with falls in older adults could be grouped under "pre-disposing factors" and "precipitating factors". In this context, underlying conditions such as cognitive and visual impairment, and even long term medications, could be considered as pre-disposing factors, while acute illnesses such as an urinary tract infection or chest infection, or a stroke, will be the precipitating factors of a fall. This classification of risk factors distinguishes falls as a geriatric syndrome, for among younger adults, these precipitating factors would not commonly be sufficient to cause a fall.

In the current study, when I studied medications together with their indications and other significant non-drug risk factors, I found that most of the medications had failed to demonstrate association with falls. This suggested that underlying medical illnesses and non-drug factors, rather than medications, were responsible for falls in functionally independent community-dwelling older persons.

Our study had shown that heart diseases were associated with falls, while medications used in these diseases were not. Subjects with cardiovascular diseases are more prone to cerebral white matter disease, which has been found to be related to gait and balance impairments and falls in high-functioning older persons. (Starr et al., 2003; Whitman et al., 2001)

An exception in the results was anti-diabetic medications. Anti-diabetic medications were found to be related to recurrent falls, but having diabetes mellitus was not. Diabetes on treatment had been found to be an independent risk factor of falls, (Maurer et al., 2005; Hanlon et al., 2002) though the association was less robust among those on oral agents when compared with insulin-treated diabetics. (Schwartz et al., 2002) Our cohort contained a significant proportion of subjects with diabetes who were not on drug treatment (25.7%), allowing direct comparison between those with and without anti-diabetic drugs. Our findings suggested that being on anti-diabetic drugs or having diabetes requiring drug

control could be a risk factor for falls. More advanced diabetes or hypoglycaemic side-effects of drugs could be the cause of falls among older diabetic patients. Arguably, the risk of falls could be associated with the severity of the disease, rather than the drugs.

When I considered the relationship between falls and psychotropic medications in these two cohorts from different settings, I found that falls in the nursing home were more related to psychotropic medications and patients who had falls in the nursing home also had more medications. In contrast to the nursing home population, the community cohort of older adults did not appear to have this association between falls and medications. This might have been explained by the different in certain important characteristics of the participants: the nursing home residents were approximately ten years older, with more females (67% vs. 50% in the community cohort), were much less mobile (45% using walking aids vs. only 0.1% in the community cohort), and most importantly, were much more cognitively impaired (53% vs. 3.3% in the community cohort). The proportion of participants having polypharmacy as defined by taking 5 or more medications were also much high in the nursing home study (37% vs. 2% in the community participants). As age, female gender, poorer mobility and cognition were all known risk factors for falls, these differences between the cohorts might account for the difference observed in the relationship between psychotropic medications and falls in these two studies. Polypharmacy could lead to iatrogenesis or drug-drug interactions, which might be another

reason that the relationship between psychotropic medications and falls was less significant among those on fewer drugs, such as those in our community cohort.

The dosage of psychotropic medications or whether multiple psychotropic medications were prescribed in the same individual might also account for the differential relationship observed between these medications and falls in the cohorts. As more nursing home residents were cognitively impaired, it was possible that more of them suffered from the psychological and behavior symptoms of dementia, and might therefore be on higher dosages of these medications, or on multiple medications. Unfortunately, we did not collect the data regarding dosages or the number of psychotropic medications, which precluded any exploration on this issue.

Although the results in our two studies differ, there was evidence that the cessation or at least a reduction of psychotropic medications might be able to reduce falls in older persons. In a recent review, four randomized controlled trials using psychotropic medications withdrawal or review as interventions demonstrated various degrees of falls reduction. (Nill and Wee, 2012) Results ranged from a 66% falls reduction ((Campbell et al., 1999) to a non-significant reduction. Among these, however, only the Campbell study had the number of falls over a 44 weeks period as the primary outcome. This study did suggest if medications were removed, there might be benefit, although whether these medications

could be avoided in the long term might be doubtful, given the participants underlying medical or psychiatric conditions.

Among the intrinsic factors identified as significant contributors to falls in our cohort, shorter stride length was a good indicator of falls risk. Stride length is a measurement of balance, gait and muscular power. Changes in stride length had been associated with reductions in falls after fall intervention. (Tinetti et al., 1996) It is easy to measure, requires no special equipment and can be done in virtually any setting. Its value as a falls risk assessment tool is worthy of further examination.

Female sex has often been associated with increased falls. (Prudham & Evans, 1981; O'Loughlin et al., 1993; Koski et al., 1996; Tinetti & Speechley, 1989) This association had persisted after adjustment for all the other significant factors for falls in our study including stride length, a surrogate for neuromuscular function and stature, and had remained to be the strongest. Whether it was due to recall bias difference between the two genders as suggested previously, (Cumming & Klineberg, 1994) or there are other gender specific risk factors yet unknown will need to be answered in a prospective study. However, in the nursing home cohort study described in 7.1, female gender was associated with a statistically significant 35% lower likelihood of falls.

Interestingly, increase in age was not associated with increased falls amongst our subjects after adjustment of underlying medical illnesses, medications, visual impairment and stride length. The relative high physical independence and good health of our cohort may contribute to this finding. In a frailer population such as the nursing home population in study 7.1, the effect of age on falls was more prominent and each additional year in age was associated with 3% increase in falls risk in the multivariate model.

In summary, in this study of falls among older community-dwellers, intrinsic factors including diseases again seemed to contribute more to falls than extrinsic factors such as medications. This study lends support to the literature that falls in old age were more likely to be due to intrinsic falls risk than extrinsic ones.

8.3 More fat benefits survival among community-living older adults

In this study utilizing data from the community cohort, I found that underweight or low BMI was associated with higher all-cause mortality in older men. In particular, when I examined the amount of abdominal fat and its relationship with mortality, higher abdominal fat proportion was associated with a lower mortality. This is in contrast with the observation in the young and middle-age adults, where over-nutrition or a high BMI was detrimental to cardiovascular health and hence mortality.

Our results showed that mortality did not increase with increase in abdominal obesity in

older men. This finding is in line with that of previous authors (Reis et al., 2009) which showed higher waist circumference or waist-hip ratio conferred survival benefits, but in contrary with those of others. (Lindqvist et al., 2006; Price et al., 2006; Pischon et al., 2008; Jacobs et al., 2010) Waist circumference does not take into consideration the distribution of fat, as it only measures the waist; a large waist circumference could imply central fat accumulation, overall fatness or a large body size. The waist-hip ratio does not take into account the loss of gluteal muscles with aging, to the effect that a stable waist circumference with a decreasing hip circumference due to gluteal muscle loss would result in an increasing waist-hip ratio. On the other hand, DXA-measured abdominal fat describes more accurately fat distribution and hence may be more suitable to address the question on the effect of central fat versus peripheral fat. We and others have shown that adiposity (Adams et al., 2006; Flicker et al., 2010) and truncal adiposity (Auyeung et al., 2010) may be beneficial for survival in old age, even for those with history of cardiovascular disease (Lea et al., 2009). Our present results showed that in contrary to findings in middle aged adults, higher proportion of abdominal fat may also be beneficial for survival in men older than 65 years of age.

The proportion of abdominal fat (relative abdominal fat) has a more linear relationship with mortality than waist circumference, waist hip ratio, or whole body fat % (p for trend <0.01, >0.05, >0.05 and <0.05 respectively). This highlights the need to review current

nutrition guidelines for older adults that advocate weight control or reduction. In fact, the negative impact of obesity should be reviewed when the individual reaches the age of 65. The waist circumference cut-offs for metabolic risks in midlife may not be applicable to old age, when overall mortality within a shorter life expectancy is considered.

As quintiles of relative abdominal fat showed a reverse relationship (p trend <0.01) with all-cause mortality in older men, we further described the phenotype of the men having the amount of relative abdominal fat associated with lowest mortality. According to the WHO classification of BMI (Ko et al., 2005; WHO, Australia, 2000), and criteria for metabolic syndrome in Asian populations, these men were in a group at risk of metabolic diseases: mean waist 90.53 cm (> 90cm cut-off for obesity), mean BMI 24.6 (> 23.5, in overweight range), mean waist-hip ratio 0.94 (> 0.9 for obesity), and mean whole body fat 26.38 % (≥ 25%, in high body fat range). According to the BMI and the waist circumference, these men should belong in a group with moderate metabolic risk, yet our results showed that instead of having adverse effects, older men having these markers of obesity actually survived longer. Obesity criteria have been mostly developed using younger adult data. Heim et al have shown that waist-circumference cut-off for disability outcomes could be higher in older adults (Heim et al., 2010).

The relationship between obesity and mortality may be altered by age or by frailty (Kopple,

2005) In older, healthy individuals without chronic diseases, the risk of obesity may remain similar to that in middle aged adults (Adams et al., 2006; Schooling et al., 2006). However, our results showed that beyond the age of 65, even in a cohort of high functioning older adults, obesity operated in a different direction regarding longevity than in midlife. Possible explanations are that in older or frail individuals, infections and acute illnesses become significant causes of death, and those with greater fat or energy reserve tend to survive acute illnesses better. Indeed, weight loss in old age might be a marker of risk of mortality (Newman et al., 2001). In contrary, those with end stage chronic diseases tend to be more cachexic, therefore those with more adiposity should be the ones with less severe chronic diseases. However, this still does not explain why central fat is more protective than fat elsewhere.

The obesity paradox had remained robust in our model: higher overall fatness (whole body fat %) and abdominal adiposity (relative abdominal fat) remained protective against mortality. More importantly, all adiposity measurements, both general and abdominal, did not affect cardiovascular mortality, even with adjustment for recalled weight change in adulthood.

Findings in women might be limited to inadequate numbers of deaths during follow-up, or that mortality in older women might genuinely be independent of fat or thinness. A

previous report from our group using trunk fat did not observe any relationship between that and mortality in women, which could have been due to the inclusion of breast fat (Auyeung et al., 2010). Using a more defined abdominal region in the present study, we confirmed the absence of relationship even with the exclusion of breast fat.

8.4 Higher BMI benefits short- to long-term survival in nursing home residents

Consistent with the other study in 7.3, I found that survival was lowest among nursing home residents with BMI in the underweight range. In fact, short-, intermediate- and long-term mortality up to 9 years was all lower among nursing home residents with BMI >18.5 kg/m^2, when compared with those with BMI < 18.5 kg/m^2 . More remarkably, the mortality risks were lowest in those within the obesity range BMI (by Asia Pacific cut-off). In addition, the survival benefit of the obese group became more significant over the other BMI groups with longer periods of observation. At 9 years, when compared with those with normal weight (BMI 18.5 – 22.9 kg/m^2 using Asia Pacific cut-off), those who were obese (BMI > 25 kg/m^2) had significantly lower mortality (HR =0.71, 95% CI=0.61-0.84), whereas those who were underweight (BMI < 18.5 kg/m^2) had significantly higher mortality (HR =1.53, 95% CI=1.33-1.76). This survival benefit of the obese had been reported in certain Western nursing home populations (Veronese et al., 2013; Grabowski et al., 2005) as well as in a Chinese long term care facility population (Lin et al., 2010). However, studies varied in their definition of the obese, with BMI values ranging from > 25 kg/m^2 in the Chinese study to >28 or 30 kg/m^2 in Western populations. Studies among

Asian nursing home populations were scarce, and only one studied mortality according to the Asia Pacific BMI cut-offs (Lin et al., 2010). Our results supported the idea that among Asian nursing home residents, being overweight or obese were beneficial to survival, and that having a BMI in the underweight range was detrimental to survival, whether short or long term.

The survival benefits of the overweight and obese older adults in this study also echoed similar findings reported among community-living older persons reported in the recent decade or so, among Western as well as Asian populations including earlier studies from our group (Lee et al., 2012; Auyeung et al., 2010; Janssen et al., 2007; Tamakoshi et al., 2010; Jee et al., 2006; Takata et al., 2007). Though it was not always consistently protective, BMI within the overweight range (23 – 24.9 kg/m^2) and obesity range (> 25 kg/m^2) among Asians often had the lowest mortality rate in community-living cohorts. (Nagai et al., 2010; Auyeung et al., 2010; Jee et al., 2006; Takata et al., 2007) (Table 8.4.1) Among studies not demonstrating this effect, being overweight or obese was at least not harmful towards all-cause mortality (Auyeung et al., 2010; Flegal et al., 2005; Wang et al., 2013; Nagai et al., 2010), unless perhaps only among the very obese according to the Asian cut-offs (BMI ≥ 30 or 32 kg/m^2) (Tamakoshi et al., 2010; Jee et al., 2006) Comparing with that of community-living older people, the survival benefit of adiposity in nursing home residents seemed even more pronounced, showing that the lowest mortality was found in

the obese group instead of in the overweight group as in community cohorts. Since similar findings had been reported in white nursing home cohorts with higher mean BMI (mean BMI 23.1 to 25.4 kg/m^2 vs. 21.7 kg/m^2 in our cohort) and with a lower percentage of underweight individuals (8.5 to 11% in other cohort vs. 26% in our cohort), (Cereda et al., 2011; Kaiser et al., 2010; Veronese et al., 2013) it appears that the survival benefit of adiposity remains valid across different ethnic groups and different BMI ranges.

Table 8.4.1. Studies showing association between BMI and mortality in nursing home residents and community-living older adults in Asia and elsewhere

	N	Follow-up duration	Mortality	BMI cut-offs used (kg/m^2)	Findings (Hazard Ratios for mortality)
Nursing home cohorts					
Italian nursing home residents (Volpato et al., 2004)	344	3.5 years	All-cause	BMI tertiles (mean±sd) 19.3 ± 1.8 23.6 ± 1.0 29.3 ± 3.0	 1.00 (reference) 0.72 (0.49–1.06) 0.94 (0.61–1.43)
Existing US nursing home residents, >88% white (Grabowski et al., 2005)	5899	1 year	All-cause	<19 (thin) 19-28 (normal) >28 (obese)	**1.40 (1.11 – 1.77)** 1.00 (reference) **0.75 (0.57, 0.98)**
White nursing home residents in Germany (Kaiser et al., 2010)	200	1 year	All-cause	<20 (low) 20-30 (normal) >30 (high)	**3.4 (1.6 – 7.0)** 1.0 (reference) 0.5 (0.2 – 1.3)
Israel nursing home residents (Kimyagarow et al., 2010)	82	1 year	All-cause	<22 (low) 22-27 (normal) >27 (high)	1.45 (0.61–4.94) 0.97 (0.36–2.47) (Reference) 0.89 (0.22–1.85)
Italian nursing home residents (Cereda et	519	5.7 years	All-cause	BMI tertiles ≤21	 **1.53 (1.13–2.06)**

al., 2011)				21 – 25 ≥ 25	1.04 (0.77–1.40) 1.00 (reference)
Italian nursing home residents (Veronese et al., 2012)	181	5 years	All-cause	<20 20 - 24.9 25 - 29.9 ≥30	1.44 (0.95 - 3.60) 1.00 (reference) 0.90 (0.61 - 1.71) **0.43 (0.20 - 0.70)**
Chinese long-term care facility residents (Lin et al., 2010)	354	5 years	All-cause	WHO Asia: <18.5 18.5 – 22.9 22.9 – 25 >25	 1.00 (Reference) 0.75 (0.53–1.07) **0.54 (0.32–0.92)** **0.60 (0.38–0.95)**
Singaporean nursing home residents, 97% Chinese (Chan et al., 2010)	158	2 years	All-cause	<18.5 ≥ 18.5	**2.71 (1.12 – 6.58)** 1.00 (reference)
Community cohorts					
US Combined NHANES I, II and III data, age ≥70 (Flegal et al., 2005)	36859 (all ages)	20 years	All-cause	<18.5 18.5 to <25 25 to <30 30 to <35 ≥35	**1.69 (1.38-2.07)** 1.00 (reference) 0.91 (0.83-1.01) 1.03 (0.91-1.17) 1.17 (0.94-1.47)
Korean men and women (age 30-95) (Jee et al., 2006)	1,213,829	Up to 12 years	All cause	 <18.5 18.5 – 19.9	Men **1.51 (1.45 – 1.57)** **1.28 (1.24 – 1.32)**	Women **1.25 (1.18 – 1.33)** **1.17 (1.11 – 1.23)**

				20.0 – 21.4	**1.21 (1.18 – 1.25)**	1.02 (0.98 – 1.07)
				21.5 – 22.9	**1.12 (1.09 – 1.15)**	1.02 (0.97 – 1.06)
				23.0 – 24.9	1.00 (reference)	1.00 (reference)
				25.0 – 26.4	**0.95 (0.92 – 0.98)**	0.96 (0.92 – 1.01)
				26.5 – 27.9	**0.95 (0.91 – 0.99)**	0.97 (0.92 – 1.03)
				28.0 – 29.9	0.97 (0.92 – 1.03)	1.03 (0.96 – 1.09)
				30.0 – 31.9	1.09 (0.98 – 1.21)	1.07 (0.97 – 1.18)
				≥ 32.0	**1.82 (1.54 – 2.16)**	1.11 (0.99 – 1.26)
Japanese community 80-year-old cohort (Takata et al., 2007)	1282	4 years	All-cause		HR using two different reference groups:	
				<18.5	1.00 (reference)	**1.94 (1.00–3.76)**
				18.5 – 24.9	0.52 (0.27–1.00)	1.00 (reference)
				>25	**0.25 (0.10–0.60)**	**0.48 (0.24–0.96)**
Japanese community older adults (Tamakoshi et al., 2010)	26747	11.2 years	All-cause		Men	Women
				<16.0	**1.78 (1.45–2.20)**	**2.55 (2.13–3.05)**
				16.0 – 16.9	**1.66 (1.41–1.96)**	**1.47 (1.22–1.77)**
				17.0 – 18.4	**1.16 (1.06–1.28)**	**1.42 (1.26–1.59)**
				18.5 – 19.9	**1.12 (1.04–1.22)**	**1.22 (1.11–1.35)**
				20.0 – 22.9	1.00 (reference)	1.00 (reference)
				23.0 – 24.9	0.94 (0.87–1.02)	0.96 (0.88–1.06)
				25.0 – 27.4	0.92 (0.83–1.01)	1.01 (0.92–1.12)
				27.3 – 29.9	0.89 (0.73–1.07)	0.98 (0.84–1.14)
				≥30.0	0.93 (0.67–1.29)	**1.24 (1.01–1.52)**
Japanese community living cohort, age ≥65 (Nagai et al., 2010)	7274 men, 8477 women	12 years	All-cause	BMI	Men	Women
				<18.5	**1.48 (1.23 – 1.78)**	**1.45 (1.15 – 1.83)**
				18.5 – 20.9	1.09 (0.96 – 1.25)	1.17 (0.97 – 1.40)

				21.0 – 22.9	0.98 (0.87 – 1.11)	0.96 (0.81 – 1.15)
				23.0 – 24.9	1.00 (reference)	1.00 (reference)
				25.0 – 27.4	0.88 (0.76 – 1.03)	1.04 (0.86 – 1.25)
				27.5 – 29.9	0.91 (0.71 – 1.17)	1.07 (0.83 – 1.37)
				≥ 30.0	1.22 (0.83 – 1.79)	1.24 (0.92 – 1.68)
Chinese men and women, age ≥65 (Auyeung et al., 2010)	4000	5.3 years	All cause	BMI quintiles	HR (unadjusted)	
				Men Women	Men	Women
				<21.0 <21.1	**1.96 (1.33 – 2.90)**	1.55 (0.72 – 3.30)
				21.0 – 22.7 21.1 – 23.0	1.09 (0.71 – 1.69)	1.00 (reference)
				22.8 – 24.2 23.0 – 24.6	1.21 (0.79 – 1.85)	1.54 (0.72 – 3.29)
				24.2 – 25.9 24.6 – 26.7	1.00 (reference)	1.44 (0.67 – 3.10)
				>25.9 >26.7	1.04 (0.67 – 1.61)	1.54 (0.72 – 3.29)
Chinese hypertensive patients, age ≥60 (Wang et al., 2013)	9186	3.7 years	All-cause		(reference = overall study population)	
				<18.0	**1.87 (1.39, 2.51)**	
				18-19.9	1.02 (0.80, 1.30)	
				20-21.9	1.07 (0.88, 1.29)	
				22-23.9	0.96 (0.80, 1.15)	
				24-25.9	0.82 (0.67, 1.01)	
				26-27.9	0.81 (0.63, 1.04)	
				28-29.9	0.92 (0.66, 1.28)	
				≥ 30	0.83 (0.51, 1.35)	

Bold numbers denoted statistical significant of $p<0.05$

We found that mortality risk was reduced by 5 to 10% over various periods per each BMI unit increment (Table 7.4.2). In older people, though fat proportion increases with age, higher BMI might also be the result of higher muscle mass, (Iannuzzi-Sucich et al., 2002; Lee et al., 2007) which may contribute to functional benefits and better survival. Fat, being an energy reserve during periods of poor intake in stress or illness, is often given as a possible explanation for the obesity paradox observed in community-living older people. This function of fat may become even more important in long term care settings where poor intake due to physiological changes in aging such as earlier satiety, slower gastric emptying, and lower levels of orexigenic hormones (e.g. ghrelin) are common. (Morley, 2012)

Although both weight loss and a low BMI reflect under-nutrition, I found that BMI was more useful as a survival predictor than weight loss in our study. While the latter had been found to be a good short-term mortality predictor in many nursing home settings, it may have lost its sensitivity as a mortality predictor in populations where a significant proportion was already underweight at baseline, such as in our cohort. It has been suggested that the relationship of low BMI and higher mortality would be lost if body cell mass as measured by bio impedance was adjusted for. (Volpato et al., 2004) This earlier study was, however, conducted in a nursing home cohort with a higher mean BMI than our current cohort. It is possible that in those with a very low BMI, the percentage of weight

loss as a trigger for higher mortality could be lower than 5% in a month or 10% over 6 months.

Prediction of mortality among long term care residents is important for individual prognosis as well as for planning of long term care services. Recently, physical performance measures such as gait speed and handgrip strength (Toots et al., 2013; Ling et al., 2010;) have been found to be useful in mortality prediction in both community and long term care settings among very old adults. These functional tests, together with BMI measurements, may be able to provide quick and simple prognostication of survival in the nursing home population. For community living older adults, a specific physical performance battery, or physical frailty as in the study to be discussed in 8.7, were also able to predict mortality.

This paper confirms that low BMI or underweight is a significant geriatric syndrome that is linked to higher mortality in old age, independent of many of the chronic diseases (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus) and unfavourable physical conditions (being on tube-feeding, poor appetite, swallowing problem, and high dependency in activities of daily living), that are relevant to mortality in this age group.

8.5 Associated risk factors and outcomes of sarcopenia

The mean height-adjusted ASM was 7.19 kg/m^2 in older Chinese men. This was much

lower than that found in White and Black populations (Davison et al., 2002; Newman et al., 2003). The mean height-adjusted ASM in older Chinese women was 6.05 kg/m^2, slightly lower than that in White women but much lower than that in Black women (Newman et al., 2003). This is perhaps not surprising as Asian have a smaller body built and a higher tendency towards accommodation of adiposity even in middle age. It was for this reason that the WHO had a different BMI cut-off for Asian countries with regard to metabolic risks.

The consequence of sarcopenia could be traced back to again the same intrinsic and extrinsic factors as the other geriatric syndromes studied in this thesis. Among the intrinsic factors, underweight, discussed in the previous section (8.3 and 8.4) appears to be a consistent and significant risk factor. Other risk factors pertaining to old age were chronic systemic diseases, such as COPD, and degeneration or metabolic damage to the arterial system, as represented by the degree of atherosclerosis.

Underweight was strongly associated with sarcopenia, which reaffirmed the findings of Lau et al. (Lau et al., 2005). In addition, we found that COPD and atherosclerosis were also associated with lower muscle mass. The chronic activation of inflammatory cytokines in COPD (Di Francia et al., 1994; De Godoy et al., 1996) might have contributed to muscle wastage, as inflammatory cytokines such as tumor necrosis factor, interleukin-1 and 6 and

oxidative stress have been shown to be important catabolic factors (Dinarello, 1996; Boots et al., 2003; Morley et al., 2001). Disuse muscle atrophy due to restricted exercise tolerance in COPD could be another mechanism. Atherosclerosis was associated with low muscle mass in our study and the effect was likely to be mediated through cytokines such as low insulin-like growth factor I (Ceda et al., 2005), an important modulator of muscle mass and function.

Extrinsic factors, in particular life style factors, such as smoking and physical exercise, also appeared to be important in the development of sarcopenia. We found that current but not past history of cigarette smoking might be a risk factor of sarcopenia among older Asians. The relationship was particularly strong in men. Lau et al. (Lau et al., 2005) had reported a suggestive effect of smoking on sarcopenia in Chinese women but that did not reach statistical significance. Using a much larger cohort, we were able to establish that association. Whether smoking is indeed a risk factor needs to be determined by a prospective study.

Regular load-bearing exercise and daily walks were not associated with higher muscle mass both in Lau et al.'s (Lau et al., 2005) and our study respectively. However, the PASE score, a more detailed record on time and physical exertion involved in recreational, household and social/voluntary work in a week did review a highly significant relationship

between physical inactivity and low appendicular muscle mass. Past studies have shown that progressive resistive exercise could increase muscle size and strength (Charette et al., 1991; Frontera et al., 1990) while endurance training alone might not. (Klittgaard et al., 1990) On the other hand, findings of a longitudinal study suggested that leisure time physical activities were not likely to be able to prevent sarcopenia. (Raguso et al., 2006) Being cross-sectional, our results could not establish a causal relationship between these activities and sarcopenia. Prospective interventional studies will be required to determine the intensity and type of exercise or activities most useful to counteract age-related muscle loss.

The most direct consequence of sarcopenia is a decline in physical performance. We found that among Chinese, sarcopenia in older women was less associated with poor physical performance than in older men. In contrast to women, men performed similarly in most physical function tests across all tertiles of muscle mass. Previous groups (Davison et al., 2002; Zoico et al., 2004; Lebrun et al., 2006) had reported that in non-Asian older women, high body fat rather than low muscle mass might be more important in predicting functional limitations, while Janssen et al. (Janssen et al., 2002) were able to find association between sarcopenia and poor function in both men and women. On the other hand, this sex difference in the effect of sarcopenia on physical performance could also be related to the method of adjustment for body size. As reported by Newman et al. (Newman

et al., 2003), among his female subjects, the association of sarcopenia and lower physical functions was apparent only in the residuals method but not in the height-adjustment method. The inverse relationship between lower limb muscle performance and appendicular muscle mass among women suggested that factors other than age and muscle mass were in place. The search for these factors in women could be important as weight-bearing activities contribute heavily to ambulation and independence in activities of daily living.

In clinical or population screening settings it is impossible to have the DXA readily available for muscle mass assessment. There is therefore a need to look for a simple clinical method to substitute for a DXA measurement. At the time of the writing and publication of this paper (August 2007), the definition of sarcopenia was still under debate and no consensus had been reached until several years later. It was still uncertain then which would be the best surrogate muscle measurement in place of the DXA scan. In this paper, I found that grip strength alone among all physical performance tests was strongly associated with appendicular muscle mass in both genders, suggesting that this simple test could serve as a convenient surrogate marker of muscle mass in future epidemiology studies among community-dwelling older Asians.

To the best of our knowledge, this was the largest body composition study in older Asians

using DXA measurements at the time of publication. Following the study of Lau et al. (Lau et al., 2005), this study provided further information regarding sarcopenia among Asians utilizing a much larger cohort and included more variables such as a detailed physical activity record, several physical performance measures that reflected upper and lower limb strength, and quality of life measurements.

8.6 The effect of diabetes mellitus on age-related muscle loss over 4 years

In this paper, one chronic disease common among older adults, diabetes mellitus, was examined for its effect on the progression of sarcopenia. Our results suggested that diabetes was associated with increased lean mass loss and in particular, appendicular lean mass loss in older adults over a period of 4 years. This concurred with the findings of Park et al. (Park et al., 2007) in which a similar association was found in white and black older adults. Diabetes was associated with a higher prevalence of disability and more rapid decline in functions (Maggi et al., 2004; McGuire et al., 2006; Gregg et al., 2002). As appendicular lean mass was associated with poorer physical function in old age (Fantin et al., 2007; Janssen et al., 2002), it is possible that higher appendicular lean mass loss in diabetes contributes partly to this phenomenon. This is the first study on the effect of diabetes mellitus on sarcopenia in Asians and the second cohort to report this finding internationally.

Despite the overall good physical state of this community-living cohort at baseline, there

was a loss of total body mass in both diabetic and non-diabetic participants over time. This is in keeping with the notion the weight loss is an inherent phenomenon in ageing, which often results in the geriatric syndrome of underweight. However, I noted that the magnitude of body mass loss was higher among our participants with diabetes. Diabetes associated weight loss had been previously reported (Wedick et al., 2002), and was found to be associated with adverse health outcomes. Low body mass and weight loss, as geriatric syndrome, has also been reported as risk factors for mortality, disability and institutionalization in old age. (Wedick et al., 2002; Alibhai et al., 2005; Auyeung et al., 2010) Our results suggested that diabetes was associated with excessive loss of weight through excessive loss of both body fat and lean mass, especially in men, and therefore accelerates the progression of both the syndromes of underweight and sarcopenia. As both of these were highly correlated with the frailty syndrome, it is therefore logically to conclude that diabetes mellitus contributed to all three syndromes, including frailty as a common end.

In our cohort, diabetes was consistently associated with higher appendicular lean mass (ALM) loss in both men and women, independent of the diabetes-related conditions studied (low ABI, high BMI, heart disease, stroke and hypertension). The average difference in ALM loss between diabetic and non-diabetic participants was 1.6% per 4 years (0.40% per year) in men, and 1.5% per 4 years (0.38% per year) in women. This

difference was comparable to or slightly greater than that reported in white and black populations, (Park et al., 2007) which averaged about 1% per 3 years (0.33% per year), with men and women considered together. As lean mass, especially ALM, is associated with activities of daily living, (Janssen et al., 2002) and Asians have a greater increase in diabetes prevalence in comparison with other populations, (McBean et al., 2004) the impact of diabetes on ALM loss may lead to higher diabetes-related healthcare burden in Asian populations, and would have a greater contribution to the frailty syndrome among older people in these populations.

In our cohort, the absolute amount of total lean mass, ALM and total lean mass % were higher in diabetic participants but the relative proportion of lean mass in the limbs (ALM/total lean mass) was lower in diabetic participants. Higher lean mass in diabetes was also found in white and black populations. (Park et al., 2007) Increased fat infiltration of muscles in diabetes (Morley, 2008) might account for the higher total lean mass when measured by DXA, which could not distinguish between muscle and muscle infiltrated by fat. Whether diabetes causes higher fat infiltration in trunk lean mass (e.g. internal organs) when compared with appendicular lean mass could not be answered using DXA measurements. More appropriate methods would be cross-sectional CT scans or MRI scans of the relevant limb muscle groups.

There were multiple possible mechanisms of more rapid loss of ALM observed in older adults with diabetes, most of which involved alterations in protein synthesis and protein breakdown sin muscles. The relationship between diabetes, insulin resistance and sarcopenia is a complex one. Increase in mitochondrial efficiency was noted in muscles of aged rats, (Iossa et al., 2004) and the associated reduced utilization of energy substrates, in particular fatty acids, could lead to deposition of intracellular adiposity and lipotoxicity, which might be the cause of insulin resistance in old age in humans, which may in turn precipitate diabetes mellitus in older people. A large cross-sectional study involving adults over the age of 20 have demonstrated that each 10% increase in skeletal muscle index (SMI) was associated with 11% relative reduction in insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR). (Srikanthan & Karlamangla, 2011) This result gave rise to the notion that lower muscle mass was associated with higher insulin resistance and might in fact contribute to the occurrence of diabetes mellitus. This was confirmed in a more recent prospective study which found that higher skeletal muscle index (SMI) was associated with lower incidence of the metabolic syndrome over a period of 24 months. (Park and Yoon, 2013)

On the other hand, insulin is an anabolic stimulus for protein synthesis in muscles, provided that blood supply and amino acids are available. (Fujita et al., 2006) However, aged muscles are less sensitive to the anabolic effects of amino acids (namely leucine) and

insulin, which may be one of the causes of muscle loss in old age. (Guillet and Boirie, 2005) Lower bioavailable testosterone and Insulin-like Growth Factor – 1 in older diabetic men might also contribute to lower protein synthesis, while higher pro-inflammatory cytokines, higher angiotensin II levels might contribute to increased muscle breakdown, resulting in loss of muscle mass. (Rolland et al., 2008; Morley, 2008)

While physical activities had been associated with muscle mass in older populations (Baumgartner et al., 1999) in cross-sectional studies, such as in the earlier study discussed in 8.6, physical activities as reflected by the PASE score used in this study only mildly attenuated the association between ALM loss and diabetes, and only in men. The PASE score captures all activities including activities of daily living such as shopping, walking and doing home chores and was not used exclusively for resistive or aerobic exercise. This might have limited its association with the decline in muscle mass.

8.7 Association between metabolic conditions and physical frailty, and the latter's relationship to mortality

Frailty is the ultimate geriatric syndrome that was tightly related to all three syndromes discussed earlier. Being complex, frailty is described by a variety of measures; being new, frailty as a syndrome has not yet been clearly defined. Some researchers included mainly physical performances, (Rolland et al., 2006) others included limitations in activities of daily living (Rockwood et al., 1999), or a combination of impairment in fitness and

function. (Hubbard et al., 2010) Our results suggested that poorer physical performance in the four tests used (grip strength, gait speed, chair-stairs, and stride length) was related to higher risk of death after 6 years, confirming the findings of others that physical frailty was associated with higher mortality, (Rolland et al., 2006) and not only in women, but also in men.

However, not all frailty criteria included individual medical conditions, and even those that did, include only the total number of medical conditions plus the above. (van Kan et al., 2008a; van Kan et al., 2008b) Apart from being the components of a measure of biological age (Goggins et al., 2005) and putting older individuals at risk of cognitive dysfunction, (Sinclair & Viljoen, 2010) our results suggested that metabolic conditions themselves are associated with physical frailty, independent of sarcopenia and cognitive impairment in old age, and that they might contribute to frailty on their own accord.

Our results suggested that among all the metabolic conditions, high waist-hip ratio had the highest impact on physical frailty, independent of the other commonly co-existing disorders. This is accordance with the results of others and earlier studies from our group that adiposity, though associated with longer survival, (Auyeung et al., 2010; Flicker et al., 2010) might give rise to increased physical frailty or disability. (Blaum et al., 2005; Woo et al., 2007; Houston et al., 2005) It is therefore important to identify the intersecting point at

which adiposity is best for both survival and function.

Low ABI ceased to be significant in the multivariate model, after adjustment for diabetes, cardiovascular diseases and general factors such as age, physical activities, cognitive impairment and smoking. Although peripheral artery disease has been found to be associated with disability, its effect was largely explained by the presence of diabetes, diabetic neuropathy, and diabetes-related cardiovascular diseases. (Dolan et al., 2002) On the other hand, low ABI at our cut-off may not reflect atherosclerosis severe enough to affect our physical frailty measurements.

The exact mechanisms for how each metabolic condition was linked to physical frailty were not known. Most proposed underlying mechanisms for explaining physical frailty due to individual conditions also involved other commonly co-existing metabolic conditions: for example, stroke and heart disease partially explained the relationship between diabetes and disability, (Gregg et al., 2002) and diabetes, heart disease and peripheral artery disease partially explained the relationship between obesity and frailty. (Blaum et al., 2005) Increased rate of sarcopenia might be a cause for diabetes-related physical frailty as reported in our other report, (Lee et al., 2010) while increased inflammation (Barzilay et al., 2007) and cytokines (Ferrucci et al., 1999) might also be underlying mechanisms shared by diabetes, obesity and atherosclerosis. Oxidative stress might be yet another possible

underlying mechanism linking metabolic conditions to physical frailty. (Semba et al., 2007) Higher oxidative stress associated with metabolic and atherosclerotic conditions (Kedziora-Kornatowska et al., 2004; Helmersson et al., 2004) had been implicated in the decline of muscle mass (sarcopenia) and muscle strength via oxidative protein damage, thus compromising physical performance. The tests used in this physical performance score were not strenuous thus should not be particularly affected by cardiopulmonary function. The slowness or weakness detected could be signs of reduced physical reserve that is reflected even in mild everyday activities such as getting up from a chair, walking, and gripping.

It is worth noting that physical activity as reflected by the PASE score was associated with better physical performance in both men and women, even after adjustment for all the metabolic conditions and relevant covariates. Physical activities in the PASE included basic and instrumental activities of daily living, hobbies or leisure activities, in addition to exercise. The message is thus clear that any physical activity, not just formal exercise, might be able to retard physical frailty in old age. This is contrast to the effect of the PASE score in sarcopenia: in the sarcopenia studies discussed in 8.5 and 8.6, PASE was only associated with baseline muscle mass but not the degree of muscle loss in longitudinal follow-up.

In survival analysis, metabolic and atherosclerotic risk factors slightly attenuated the impact of physical frailty on mortality in men, but not in women. This could be due to the higher prevalence of smoking among men, which caused a higher background load of vascular dysfunction, thus making the presence of metabolic and atherosclerotic risk factors more hazardous. The lack of effect of these risk factors in women might be attributed to the lower background vascular dysfunction due to fewer smokers, or that death in older women were not as strongly associated with vascular risks as in men. In frailty criterion, genders are usually not considered. However, in view of this difference in vascular risks or impact on mortality, perhaps some consideration should be given to gender, when mortality prediction is concerned.

In this study in frailty, again we see the importance of the intrinsic effects of ageing (gender and diseases), and the extrinsic effects of lifestyle (smoking, physical activities). Further prospective studies are warranted to examine the effect of metabolic conditions on frailty, or indeed, whether any of these conditions have strong enough impact on frailty that it may worth a place in the frailty criterion. The addition of some metabolic conditions to the current frailty criteria may help to identify those who are at risk of frailty and thus allow early interventions. As it is unlikely that physical frailty can result in metabolic conditions, it would be prudent to conclude that the latter contribute significantly to the former. However, when mortality prediction was considered as an outcome of physical

frailty, these conditions exerted only very modest additional impact. We conclude therefore that metabolic conditions contributed significantly to physical frailty, but not to the impact of physical frailty on mortality.

8.8 Prospective study on factors that may affect the transitions between frailty states

This is the first study to report frailty transitions among Asians, and the third cohort in the published literature to study this entity. We found that a quarter of pre-frail men and women recovered into the robust state after 2 years, with only 12% men and 7% women progressed into frailty. The large proportion of pre-frail persons remaining stable within a period of two years suggested that there may be a window during which interventions can be applied to reduce the decline rate or to improve the recovery rate.

Men and women in our cohort had different transition rate – pre-frail men tend to progress into frailty more than women (11.1% vs. 6.6%). An earlier study in a Western cohort did not find men to be at higher risk of decline. (Espinoza et al., 2012) This will have to be further confirmed by other studies, but it may imply that the effect of frailty interventions might have different efficacy in men and women and that the same interventions may be less or more helpful in men.

Our results confirmed the findings of Gill et al. that hospitalizations reduce the chance of

recovery from the frailer states. (Gill et al., 2011) In fact hospitalizations also significantly and consistently increased the likelihood of worsening in not only the pre-frail, but also the robust. The detrimental effect of hospitalizations was more consistent in women than in men. It is not clear what may be the underlying mechanism of this gender disparity.

Our study is the first to report the effects of various medical co-morbidities on frailty state changes in men and women separately. Among medical co-morbidities studied, stroke was the most consistent harmful factor in both genders. It reduced the chance of improvement in men and increased worsening in women. Having previous stroke increased the risk of worsening in both the pre-frail and robust states by three times. Cognitive impairment was both detrimental in pre-frail men and women. Cognitive impairment has recently been linked to physical frailty (Houles et al., 2012; Malmstrom et al., 2013; Auyeung et al., 2008; Auyeung et al., 2011b) and interventions that help to maintain or improve cognitive function in the pre-frail might have a role to reduce decline or improve recovery in this group. We also confirmed the findings of Espinoza et al. that diabetes was a harmful condition in the pre-frail. (Espinoza et al., 2012) Diabetes predisposes older individuals to more rapid muscle loss (Park et al., 2009; Lee et al., 2010) and functional decline, (Gregg et al., 2002) and metabolic risk factors are associated with poorer physical performance, (Lee et al., 2011) therefore this finding is not surprising. Unfortunately we had no information on diabetes complications and therefore were not able to analysis

whether uncomplicated diabetes might have the same effect on frailty transitions as complicated diabetes.

Overall, we found more significant factors associated with the change in frailty status in women. Although some were shared by both genders (age, hospitalizations, stroke, and cognitive impairment), some were only apparent among women. The identification of the different risk factors for the two sexes will allow us to select a high risk group for earlier intervention. It is also possible that better management of these risk factors may further increase the recovery rate of the pre-frail, or reduce their decline. Enhancing rehabilitation after hospitalizations may be very important to reduce deterioration in the pre-frail and even the robust.

8.9 Limitations

Nursing homes cohort studies

In the nursing home studies, the results concerning falls were cross-sectional, and hence causal relationships could only be interpreted with caution. This is especially true in the association between falls and restraints. Owing to the different time frames in which the questions were set, the use of restraint in the week surveyed could well be the result of a fall that had occurred prior to that week (though the non-restrained actually fell twice as frequently in the previous month). Only prospective studies in the same population would be able to provide a definite answer to the genuine effect of restraints on falls. Nevertheless,

given the well known harmful effects of restraints, and that not all falls were injurious, as indicated in our sample and also elsewhere, we do not support the use of restraints for falls prevention in nursing homes.

In the prospective study on the effect of BMI on short- to long-term mortality in this cohort, attention must be drawn to the fact that BMI may not reflect the amount of body fat accurately in older people due to sarcopenic obesity. Waist circumference may be a more accurate measure, but is rarely available in the nursing home setting. (Woo et al., 2002; Pischon et al., 2008) The waist circumference with the lowest mortality risk, as validated in a study with body composition data, was in the overweight range among community-living older men, (Lee et al., 2012) but this has never been tested among nursing home residents who are likely to be older and more frail. Studies with body composition data in nursing home setting may be able to delineate whether body fat or muscle contributed more to the survival benefit. Higher BMI would reflect high muscle mass in addition to fat mass, and functionality might be a confounder for lower mortality. (Kaiser et al., 2010) Although our data did not include physical performance measures, the use of the MDS-ADL scale categories might have compensated partially for this deficit. Data of 94 residents not successfully assessed were not captured, thus it was not possible to comment on any patterns distinguishing this group. We did not have major laboratory data or blood pressure measurements which might be important in mortality prediction, nor did we have data at

intermediate evaluations, data on mini-nutritional assessment or global frailty.

Community cohort studies

In the study concerning the relationship between medications and falls, we were unable to find any correlation between the use of psychotropic medications and falls. This could be due to the fact that very few of our subjects (3.5%) were on these agents and the prevalence of these medications was much lower among our subjects than in western studies. (Cumming et al., 1991; Lawlor et al., 2003) Adverse effect of medications could also have been masked by our cohort being relatively healthy and mobile. Being retrospective in nature, our results were subjected to recall bias. (Cumming et al., 1994; Cummings et al., 1988) We also had difficulties in determining whether a specific medication was actually being taken around the time of falls, especially if it was a take-as-required medication or one that had been newly prescribed sometime within the previous 12 months. We had no dosage information on the psychotropic medications, which might have contributed to the difference in relationship we found in the two cohorts (nursing home residents vs. more healthy community dwellers) between these medications and falls. A quantitative study which takes into consideration dosage of medication in each category and their relationship with falls in respective groups of the community and nursing home patients would be very difficult to carry out however.

There are several limitations in the study on BMI, abdominal adiposity and mortality. DXA

could not differentiate between abdominal subcutaneous fat from visceral fat in contrast to CT measurements. Nevertheless, trunk fat as determined by DXA was found to correlate well with insulin resistance and dyslipidemia, and survival. (Auyeung et al., 2010; Hamdy et al., 2006) Our results may reflect the phenomenon of selective survival in which only middle-aged persons more resistive to the hazard of central adiposity survived into old age and were thus included in the present study. Those with serious complications of abdominal obesity or its related metabolic disorders might have premature death prior to age 65 or have become too disabled to be included in our cohort. Our cohort is from a population with relatively little morbid obesity therefore findings should not be generalized into the very obese range.

In the study on the associated factors and outcomes of sarcopenia, I must draw attention to certain limitations of the results. Firstly, being cross-sectional, the results could not be used to establish cause-effect relationship between the associated factors and sarcopenia. Secondly, our subjects were independently living volunteers who were interested in participating in research and therefore were likely to represent only the healthier and more educated amongst the general older population. Finally, our physical performance tests were carried out under test conditions and might not directly translate into functional impairment and disability in daily living, which would be more meaningful outcomes. Nevertheless, our findings suggested possible risk factors of sarcopenia in older Chinese

men and women, and provided physical performance data for which future studies in Asians could be based on.

In the study on the effect of diabetes mellitus and sarcopenia progression, a limitation was that we had no data regarding diabetic control or the duration of diabetes. The diagnoses had relied on self-report, although this had been recognized as a valid method for collecting medical diagnosis in large studies. (Bourdel-Marchasson et al., 1997; McQuire et al., 2006) Weight loss could not be classified as intentional or unintentional. We were unable to demonstrate causality between diabetes and the observed weight and muscle losses. A higher than expected proportion of participants did not return for the 4th year assessment which might have biased our results towards more healthy older adults. Again, since the cohort consisted of community-dwelling and well-functioning older adults, the results should not be generalized to those who are frailer.

In the study on physical frailty and metabolic conditions, it must be noted that the study design was cross-sectional, hence the results can only demonstrate associations between these conditions and physical frailty, but not causal relationships. Although a quarter of the female participants were categorized as possibly cognitively impaired, 37% of them had no formal education, which might have affected the cognitive assessment result.

In the last study on frailty transitions, it must be noted that hospitalizations may be a result of frailty rather than a cause of the decline in frailty state. As we did not study the details of the individual hospitalizations it was also uncertain whether they could be preventable. Our data might have an under-representation of the most frail, since those who defaulted the follow-up visit had significantly more hospitalizations. As in the study on diabetes and sarcopenia progression, we did not have information on diabetic complications, which limited our ability to examine whether better controlled or less complicated diabetes would have less effect on frailty transitions. We defined frailty according to the Fried's criteria, which had been commented to be difficult to adopt by primary care or in clinical practice. However, we hope our study may serve as a starting point for looking at how individual medical conditions may affect the improvement or worsening in frailty in the future.

Chapter 9

Conclusion

From this series of study on the correlates of the frailty syndrome in old age, we conclude that intrinsic factors are often more important than extrinsic factors as reasons for falls in older adults. As reported in the two studies conducted among both nursing home residents and community-living older individuals, factors that are likely not changeable and pertaining to degenerative processes in old age, such as visual impairment, eye diseases and medical diseases were more often and more significantly related to external factors such as medications. It was also prudent to conclude that underweight, as defined by a BMI below 18.5 kg/m^2, were associated with both short- and long-term mortality, in both nursing home residents and community-living older persons, when compared with those with a higher BMI. The survival benefits offered by a higher BMI became more pronounced with increasing age and frailty, as evidenced by the BMI or BMI category of the best survival group in the two discussed studies. Among the older and frailer nursing home cohort, the best survival group had the BMI in the obesity range whereas the range was in the overweight category among community-dwellers. The importance of avoidance of underweight could not be over-emphasized as it was also a risk factor for sarcopenia and frailty. Underweight includes the poverty of both fat and muscle mass. While fat may be protective towards survival, the loss of muscle mass was associated with poorer physical performance, poorer physical well-being, in addition to lower survival over a period of

several years. Sarcopenia, as falls, were associated with common diseases found in old age, such as diabetes mellitus. All of these three geriatric syndromes are important players in the orchestration of frailty, a common pathway that leads to the undesirable results of increasing decompensation, recurrent hospitalizations, followed by death. However, frailty was not an irreversible course, as demonstrated by the last study of the series: the majority of those in the intermediate or pre-frail state do remain stable for a period of time, and some may even improve spontaneously. The factors associated with decline or improvement in this group, thus identified in this study, may prove useful in future frailty intervention trials.

9.1 Future studies

With these conclusions in mind, future studies should be directed toward the prevention or improvement of frailty correlates, or frailty itself. Diabetes mellitus appeared to have a significant role in many of these frailty correlates. It was uncertain however that whether it was the impairment to various organ systems that cause its detrimental effects, or that it was the treatment itself. As in the community cohort study on falls, anti-diabetic medication was in fact more strongly associated with falls than diabetes itself. It raised the question whether tighter control was the key to preventing falls, or the cause of falls. Diabetes was a risk factor for muscle, fat and body weight loss in the prospective sarcopenia study, and was also associated with a lower chance of recovery or higher chance

of decline among the pre-frail. In more recently studies, diabetes or insulin resistance was reported to have certain effects on sarcopenia, the mechanisms of which are still under investigation. Diabetes, being a common disease among the older population with a prevalence of nearly 20%, would warrant further examination as a cause of geriatric syndromes. None of our studies had the data required to delineate diabetic control among the participants. How tight or loss diabetic control should be among older individuals of different physiological status, and how that control would influence the development of frailty would be an important research question for future studies.

At present frailty studies are still at a very early stage, with the concept still nebulous and often unheard of outside of geriatrics research. But I believe frailty is the final pathway via which most older people will pass through, as they move toward their end of life. We know now from the few studies, one being included in this thesis, that at least pre-frailty may be reversible, yet little is known about the mechanism how this may occur. The search for underlying mechanisms of frailty reversal, including examination of the interplay of immune pathways, inflammatory cytokines and hormonal systems, and clinical interventions such as nutrition and physical training, may shed light upon how we may modify frailty.

If funding could be made available, these two would be very worthwhile topics for future studies.

Appendix

Appendix I. Statement of Originality

I, the undersigned (the candidate who submit this thesis), confirm that any reference to or use of previously published materials protected by copyright is explicitly acknowledged in this thesis. Concerning contribution to the studies mentioned in the thesis, a summary is stated as follows:

	Development of Hypothesis	Study design	Data collection	Analysis and data interpretation	Reporting
Lee, J. S., Kwok, T., Leung, P. C., & Woo, J. (2006). Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study. Age and ageing, 35(3), 246-251.	√	√	√	√	√
Lee, J. S., Auyeung, T. W., Kwok, T., Lau, E. M., Leung, P. C., & Woo, J. (2007). Associated factors and health impact of sarcopenia in older Chinese men and women: a cross-sectional study. Gerontology, 53(6), 404-410.	√	√	√	√	√
Lee, J. S., Hui, E., Chan, F., Chi, I., & Woo, J. (2008). Associated factors of falls in nursing home residents in Hong Kong and the role of	√	√		√	√

restraints: a cross-sectional survey using the Resident Assessment Instrument (RAI) 2.0. Aging clinical and experimental research, 20(5), 447-453.					
Lee, J. S. W., Auyeung, T. W., Leung, J., Kwok, T., Leung, P. C., & Woo, J. (2010). The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults. Diabetic Medicine, 27(12), 1366-1371.	√	√	√	√	√
Lee, J. S., Auyeung, T. W., Leung, J., Kwok, T., Leung, P. C., & Woo, J. (2011). Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. The journal of nutrition, health & aging, 15(10), 857-862.	√	√	√	√	√
Lee, J. S., Auyeung, T. W., Leung, J., Kwok, T., & Woo, J. (2014). Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors. Journal of the American Medical Directors Association	√	√	√	√	√

Lee, J. S., Auyeung, T. W., Chau, P. P., Hui, E., Chan, F., Chi, I., & Woo, J. (2014). Obesity Can Benefit Survival—A 9-Year Prospective Study in 1614 Chinese Nursing Home Residents. Journal of the American Medical Directors Association.	√	√	√	√

√ = contribution made by the undersigned

I was involved in the study design, data collection and analysis, manuscripts writing of the studies related to the community cohort recruited in 2001-2003 with follow-up until Mar 2013. For the nursing home cohort recruited in 2001 (supported partially by the SK Yee Memorial Fund, with Professor Jean Woo, supervisor of my MD thesis, as the principal investigator), I was involved in data analysis and manuscripts writing.

_____

LEE, Shun Wah Jenny

Appendix II.

Publications arising from and related to the work of this thesis

---

Lee, J. S., Kwok, T., Leung, P. C., & Woo, J. (2006). Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study. Age and ageing, 35(3), 246-251.

Lee, J. S., Auyeung, T. W., Kwok, T., Lau, E. M., Leung, P. C., & Woo, J. (2007). Associated factors and health impact of sarcopenia in older Chinese men and women: a cross-sectional study. Gerontology, 53(6), 404-410.

Lee, J. S., Hui, E., Chan, F., Chi, I., & Woo, J. (2008). Associated factors of falls in nursing home residents in Hong Kong and the role of restraints: a cross-sectional survey using the Resident Assessment Instrument (RAI) 2.0. Aging clinical and experimental research, 20(5), 447-453.

Lee, J. S. W., Auyeung, T. W., Leung, J., Kwok, T., Leung, P. C., & Woo, J. (2010). The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults. Diabetic Medicine, 27(12), 1366-1371.

Lee, J. S., Auyeung, T. W., Leung, J., Kwok, T., Leung, P. C., & Woo, J. (2011). Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. The journal of nutrition, health & aging, 15(10), 857-862.

Lee, J. S. W., Auyeung, T. W., Kwok, T., Li, M., Leung, J., & Woo, J. (2012). Survival benefit of abdominal adiposity: a 6-year follow-up study with Dual X-ray absorptiometry in 3,978 older adults. Age, 34(3), 597-608.

Lee, J. S., Auyeung, T. W., Leung, J., Kwok, T., & Woo, J. (2014). Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors. Journal of the American Medical Directors Association.

Lee, J. S., Auyeung, T. W., Chau, P. P., Hui, E., Chan, F., Chi, I., & Woo, J. (2014). Obesity Can Benefit Survival—A 9-Year Prospective Study in 1614 Chinese Nursing Home Residents. Journal of the American Medical Directors Association.

Other references

Adams, K. F., Schatzkin, A., Harris, T. B., Kipnis, V., Mouw, T., Ballard-Barbash, R., ... & Leitzmann, M. F. (2006). Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. New England Journal of Medicine, 355(8), 763-778.

Afilalo, J., Karunananthan, S., Eisenberg, M. J., Alexander, K. P., & Bergman, H. (2009). Role of frailty in patients with cardiovascular disease. The American Journal of Cardiology, 103(11), 1616-1621.

Alarcon, T., Barcena, A., Gonzalez-Montalvo, J. I., Penalosa, C., & Salgado, A. (1999). Factors predictive of outcome on admission to an acute geriatric ward. Age and Ageing, 28(5), 429-432.

Alibhai, S. M., Greenwood, C., & Payette, H. (2005). An approach to the management of unintentional weight loss in elderly people. Canadian Medical Association Journal, 172(6), 773-780.

Anpalahan, M., & Gibson, S. J. (2008). Geriatric syndromes as predictors of adverse outcomes of hospitalization. Internal Medicine Journal, 38(1), 16-23.

Auyeung, T. W., Kwok, T., Lee, J., Leung, P. C., Leung, J., & Woo, J. (2008). Functional decline in cognitive impairment–the relationship between physical and cognitive function. Neuroepidemiology, 31(3), 167-173.

Auyeung, T. W., Lee, J. S. W., Kwok, T., Leung, J., Ohlsson, C., Vandenput, L., ... & Woo, J. (2011a). Testosterone but not estradiol level is positively related to muscle strength and physical performance independent of muscle mass: a cross-sectional study in 1489 older men. European Journal of Endocrinology, 164(5), 811-817.

Auyeung, T. W., Lee, J. S. W., Kwok, T., & Woo, J. (2011b). Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. The Journal of Nutrition, Health & Aging, 15(8), 690-694.

Auyeung, T. W., Lee, J. S., Leung, J., Kwok, T., Leung, P. C., & Woo, J. (2010). Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4,000 older adults using DXA. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 65(1), 99-104.

Bales, C. W., & Buhr, G. (2008). Is obesity bad for older persons? A systematic review of

the pros and cons of weight reduction in later life. Journal of the American Medical Directors Association, 9(5), 302-312.

Bannerman, E., Miller, M. D., Daniels, L. A., Cobiac, L., Giles, L. C., Whitehead, C., ... & Crotty, M. (2002). Anthropometric indices predict physical function and mobility in older Australians: the Australian Longitudinal Study of Ageing. Public Health Nutrition, 5(05), 655-662.

Barzilay, J. I., Blaum, C., Moore, T., Xue, Q. L., Hirsch, C. H., Walston, J. D., & Fried, L. P. (2007). Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Archives of Internal Medicine, 167(7), 635-641.

Baumgartner, R. N., Koehler, K. M., Gallagher, D., Romero, L., Heymsfield, S. B., Ross, R. R., ... & Lindeman, R. D. (1998). Epidemiology of sarcopenia among the elderly in New Mexico. American Journal of Epidemiology, 147(8), 755-763.

Baumgartner, R. N., Waters, D. L., Gallagher, D., Morley, J. E., & Garry, P. J. (1999). Predictors of skeletal muscle mass in elderly men and women. Mechanisms of Ageing and Development, 107(2), 123-136.

Bertin, E., Marcus, C., Ruiz, J. C., Eschard, J. P., & Leutenegger, M. (2000). Measurement of visceral adipose tissue by DXA combined with anthropometry in obese humans. International Journal of Obesity & Related Metabolic Disorders, 24(3), 263-270.

Blaum, C. S., Xue, Q. L., Michelon, E., Semba, R. D., & Fried, L. P. (2005). The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. Journal of the American Geriatrics Society, 53(6), 927-934.

Bliuc, D., Nguyen, N. D., Milch, V. E., Nguyen, T. V., Eisman, J. A., & Center, J. R. (2009). Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. Journal of the American Medical Association, 301(5), 513-521.

Boots, A. W., Haenen, G. R., & Bast, A. (2003). Oxidant metabolism in chronic obstructive pulmonary disease. European Respiratory Journal, 22(46 suppl), 14s-27s.

Bourdel-Marchasson, I., Dubroca, B., Manciet, G., Decamps, A., Emeriau, J. P., & Dartigues, J. F. (1997). Prevalence of diabetes and effect on quality of life in older French living in the community: the PAQUID Epidemiological Survey. Journal of the American Geriatrics Society, 45(3), 295-301.

Broekhuizen, R., Grimble, R. F., Howell, W. M., Shale, D. J., Creutzberg, E. C., Wouters, E. F., & Schols, A. M. (2005). Pulmonary cachexia, systemic inflammatory profile, and the interleukin 1beta-511 single nucleotide polymorphism. The American Journal of Clinical Nutrition, 82(5), 1059-1064.

Cameron, I. D., Fairhall, N., Langron, C., Lockwood, K., Monaghan, N., Aggar, C., ... & Kurrle, S. E. (2013). A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. BMC Med, 11, 65.

Campbell, A. J., Reinken, J., Allan, B. C., & Martinez, G. S. (1981). Falls in old age: a study of frequency and related clinical factors. Age and Ageing, 10(4), 264-270.

Campbell, A. J., Robertson, M. C., Gardner, M. M., Norton, R. N., & Buchner, D. M. (1999). Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. Journal of the American Geriatrics Society, 47(7), 850-853.

Capezuti, E., Strumpf, N. E., Evans, L. K., Grisso, J. A., & Maislin, G. (1998). The relationship between physical restraint removal and falls and injuries among nursing home residents. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 53(1), M47-M52.

Cawthon, P. M., Fox, K. M., Gandra, S. R., Delmonico, M. J., Chiou, C. F., Anthony, M. S., ... & Harris, T. B. (2009). Do muscle mass, muscle density, strength and physical function similarly influence risk of hospitalization in older adults?. Journal of the American Geriatrics Society, 57(8), 1411-1419.

Cereda, E., Pedrolli, C., Zagami, A., Vanotti, A., Piffer, S., Opizzi, A., ... & Caccialanza, R. (2011). Body mass index and mortality in institutionalized elderly. Journal of the American Medical Directors Association, 12(3), 174-178.

Cesari, M., Kritchevsky, S. B., Newman, A. B., Simonsick, E. M., Harris, T. B., Penninx, B. W., ... & Pahor, M. (2009). Added Value of Physical Performance Measures in Predicting Adverse Health-Related Events: Results from the Health, Aging and Body Composition Study. Journal of the American Geriatrics Society, 57(2), 251-259.

Cesari, M., Landi, F., Torre, S., Onder, G., Lattanzio, F., & Bernabei, R. (2002). Prevalence and risk factors for falls in an older community-dwelling population. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(11), M722-M726.

Chan, T. S., Lam, L. C., Chiu, H. F., & Prince, M. (2002). Validity and applicability of the Chinese version of community screening instrument for dementia. Dementia and Geriatric Cognitive Disorders, 15(1), 10-18.

Chan, M., Lim, Y. P., Ernest, A., & Tan, T. L. (2010). Nutritional assessment in an Asian nursing home and its association with mortality. The Journal of Nutrition, Health & Aging, 14(1), 23-28.

Charette, S., McEvoy, L., Pyka, G., Snow-Harter, C., Guido, D., Wiswell, R. A., & Marcus, R. (1991). Muscle hypertrophy response to resistance training in older women. Journal of Applied Physiology, 70(5), 1912-1916.

Chen, L. K., Liu, L. K., Woo, J., Assantachai, P., Auyeung, T. W., Bahyah, K. S., ... & Arai, H. (2014). Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. Journal of the American Medical Directors Association, 15(2), 95-101.

Cheng, H., Gary, L. C., Curtis, J. R., Saag, K. G., Kilgore, M. L., Morrisey, M. A., ... & Delzell, E. (2009). Estimated prevalence and patterns of presumed osteoporosis among older Americans based on Medicare data. Osteoporosis International, 20(9), 1507-1515.

Chi, I. (2004). Cross-national comparison of the profiles of nursing home residents. Geriatrics & Gerontology International, 4(s1), S286-S288.

Chou, K. L., Chi, I., Leung, A. C. T., Wu, Y. M., & Liu, C. P. (2001). Validation of Minimum Data set for nursing home in Hong Kong Chinese elders. Clinical Gerontologist, 23(1-2), 43-54.

Chu, L. W., Chi, I., & Chiu, A. Y. Y. (2007). Falls and fall-related injuries in community-dwelling elderly persons in Hong Kong: a study on risk factors, functional decline, and health services utilization after falls. Hong Kong Medical Journal, 13(Suppl 1), 8-12.

Chu, L. W., Chi, I., & Chiu, A. Y. (2005). Incidence and predictors of falls in the Chinese elderly. Ann Acad Med Singapore, 34(1), 60-72.

Clark, B. C., & Manini, T. M. (2008). Sarcopenia≠dynapenia. The journals of gerontology. Series A, Biological sciences and medical sciences, 63(8), 829-834.

Coin, A., Sergi, G., Beninca, P., Lupoli, L., Cinti, G., Ferrara, L., ... & Enzi, G. (2000). Bone mineral density and body composition in underweight and normal elderly subjects.

Osteoporosis International, 11(12), 1043-1050.

Costa, E. M., Pepersack, T., & Levêque, A. (2012). Fear of falling and associated activity restriction in older people. Results of a cross-sectional study conducted in a Belgian town. Arch Public Health, 70(1), 1. doi: 10.1186/0778-7367-70-1

Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., ... & Zamboni, M. (2010a). Sarcopenia: European consensus on definition and diagnosis Report of the European Working Group on Sarcopenia in Older People. Age and Ageing, 39(4), 412-423.

Cruz-Jentoft, A. J., Landi, F., Topinkova, E., & Michel, J. P. (2010b). Understanding sarcopenia as a geriatric syndrome. Current Opinion in Clinical Nutrition & Metabolic Care, 13(1), 1-7.

Cumming, R. G., & Klineberg, R. J. (1994). A study of the reproducibility of long-term recall in the elderly. Epidemiology, 5(1), 116-119.

Cumming, R. G., Miller, J. P., Kelsey, J. L., Davis, P., Arfken, C. L., Birge, S. J., & Peck, W. A. (1991). Medications and multiple falls in elderly people: the St Louis OASIS study. Age and Ageing, 20(6), 455-461.

Cummings, S. R., Nevitt, M. C., & Kidd, S. (1988). Forgetting falls: the limited accuracy of recall of falls in the elderly. Journal of the American Geriatrics Society, 36(7):613-6.

Davison, K. K., Ford, E. S., Cogswell, M. E., & Dietz, W. H. (2002). Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. Journal of the American Geriatrics Society, 50(11), 1802-1809.

De Godoy, I., Donahoe, M., Calhoun, W. J., Mancino, J., & Rogers, R. M. (1996). Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. American Journal of Respiratory and Critical Care Medicine, 153(2), 633-637.

De Laet, C., Kanis, J. A., Odén, A., Johanson, H., Johnell, O., Delmas, P., ... & Tenenhouse, A. (2005). Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis International, 16(11), 1330-1338.

Deandrea, S., Lucenteforte, E., Bravi, F., Foschi, R., La Vecchia, C., & Negri, E. (2010). Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology, 21(5), 658-668.

Delmonico, M. J., Harris, T. B., Visser, M., Park, S. W., Conroy, M. B., Velasquez-Mieyer, P., ... & Goodpaster, B. H. (2009). Longitudinal study of muscle strength, quality, and adipose tissue infiltration. The American Journal of Clinical Nutrition, 90(6), 1579-1585.

Census and Statistics Department, the Government of the Hong Kong Special Administrative Region (2009).Thematic Household Survey Report No. 40. Hong Kong

Di Francia, M., Barbier, D., Mege, J. L., & Orehek, J. (1994). Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine, 150(5), 1453-1455.

Di Iorio, A., Cherubini, A., Volpato, S., Sparvieri, E., Lauretani, F., Franceschi, C., ... & Ferrucci, L. (2006). Markers of inflammation, vitamin E and peripheral nervous system function: the InCHIANTI study. Neurobiology of Aging, 27(9), 1280-1288.

Dinarello, C. A. (1996). Biologic basis for interleukin-1 in disease. Blood, 87(6), 2095-2147.

Dolan, N. C., Liu, K., Criqui, M. H., Greenland, P., Guralnik, J. M., Chan, C., ... & McDermott, M. M. (2002). Peripheral artery disease, diabetes, and reduced lower extremity functioning. Diabetes Care, 25(1), 113-120.

Donald, I. P., & Bulpitt, C. J. (1999). The prognosis of falls in elderly people living at home. Age and Ageing, 28(2), 121-125.

Ejaz, F. K., Jones, J. A., & Rose, M. S. (1994). Falls among nursing home residents: An examination of incident reports before and after restraint reduction programs. Journal of the American Geriatrics Society, 42(9):960-964.

Ensrud, K. E., Blackwell, T. L., Mangione, C. M., Bowman, P. J., Whooley, M. A., Bauer, D. C., ... & Study of Osteoporotic Fractures Research Group. (2002). Central nervous system–active medications and risk for falls in older women. Journal of the American Geriatrics Society, 50(10), 1629-1637.

Ensrud, K. E., Cauley, J., Lipschutz, R., & Cummings, S. R. (1997). Weight change and fractures in older women. Archives of Internal Medicine, 157(8), 857.

Ensrud, K. E., Ewing, S. K., Cawthon, P. M., Fink, H. A., Taylor, B. C., Cauley, J. A., ... & Cummings, S. R. (2009). A comparison of frailty indexes for the prediction of falls,

disability, fractures, and mortality in older men. Journal of the American Geriatrics Society, 57(3), 492-498.

Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., Cauley, J. A., ... & Cawthon, P. M. (2007). Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 62(7), 744-751.

Ensrud, K. E., Ewing, S. K., Stone, K. L., Cauley, J. A., Bowman, P. J., & Cummings, S. R. (2003). Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. Journal of the American Geriatrics Society, 51(12), 1740-1747.

Espinoza, S. E., Jung, I., & Hazuda, H. (2012). Frailty transitions in the San Antonio longitudinal study of aging. Journal of the American Geriatrics Society, 60(4), 652-660.

Evans, W. J., & Campbell, W. W. (1993). Sarcopenia and age-related changes in body composition and functional capacity. The Journal of Nutrition, 123 (2 Suppl), 465-468.

Evans, W. J. (2010). Skeletal muscle loss: cachexia, sarcopenia, and inactivity. The American Journal of Clinical Nutrition, 91(4), 1123S-1127S.

Evans, W. J. (1995). What is sarcopenia?. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 50 (Special Issue), 5-8.

Extermann, M., Aapro, M., Bernabei, R., Cohen, H. J., Droz, J. P., Lichtman, S., ... & Topinkova, E. (2005). Use of comprehensive geriatric assessment in older cancer patients:: Recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Critical Reviews in Oncology & Hematology, 55(3), 241-252.

Fairhall, N., Aggar, C., Kurrle, S. E., Sherrington, C., Lord, S., Lockwood, K., ... & Cameron, I. D. (2008). Frailty Intervention Trial (FIT). BMC Geriatrics, 8, 27.

Fantin, F., Di Francesco, V., Fontana, G., Zivelonghi, A., Bissoli, L., Zoico, E., ... & Zamboni, M. (2007). Longitudinal body composition changes in old men and women: interrelationships with worsening disability. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 62(12), 1375-1381.

Ferrucci, L., Guralnik, J. M., Buchner, D., Kasper, J., Lamb, S. E., Simonsick, E. M., ... & Fried, L. P. (1997). Departures from linearity in the relationship between measures of muscular strength and physical performance of the lower extremities: the Women's Health

and Aging Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 52(5), M275-M285.

Ferrucci, L., Harris, T. B., Guralnik, J. M., Tracy, R. P., Corti, M. C., Cohen, H. J., ... & Havlik, R. J. (1999). Serum IL-6 level and the development of disability in older persons. Journal of the American Geriatrics Society, 47(6), 639-646.

Fielding, R. A., Vellas, B., Evans, W. J., Bhasin, S., Morley, J. E., Newman, A. B., ... & Zamboni, M. (2011). Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. Journal of the American Medical Directors Association, 12(4), 249-256.

Flacker, J. M., & Kiely, D. K. (2003). Mortality-Related Factors and 1-Year Survival in Nursing Home Residents. Journal of the American Geriatrics Society, 51(2), 213-221.

Flegal, K. M., Graubard, B. I., Williamson, D. F., & Gail, M. H. (2005). Excess deaths associated with underweight, overweight, and obesity. Journal of the American Medical Association, 293(15), 1861-1867.

Flegal, K. M., Kit, B. K., Orpana, H., & Graubard, B. I. (2013). Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Journal of the American Medical Association, 309(1), 71-82.

Flicker, L., McCaul, K. A., Hankey, G. J., Jamrozik, K., Brown, W. J., Byles, J. E., & Almeida, O. P. (2010). Body mass index and survival in men and women aged 70 to 75. Journal of the American Geriatrics Society, 58(2), 234-241.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12(3), 189-198.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., ... & McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 56(3), M146-M157.

Frontera, W. R., Meredith, C. N., O'Reilly, K. P., & Evans, W. J. (1990). Strength training and determinants of VO2max in older men. Journal of Applied Physiology, 68(1), 329-333.

Fujita, S., Rasmussen, B. B., Cadenas, J. G., Grady, J. J., & Volpi, E. (2006). Effect of

insulin on human skeletal muscle protein synthesis is modulated by insulin-induced changes in muscle blood flow and amino acid availability. American Journal of Physiology, Endocrinology and Metabolism, 291(4), E745.

Gallagher, D., Visser, M., De Meersman, R. E., Sepúlveda, D., Baumgartner, R. N., Pierson, R. N., ... & Heymsfield, S. B. (1997). Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. Journal of Applied Physiology, 83(1), 229-239.

Ganz, D. A., Bao, Y., Shekelle, P. G., & Rubenstein, L. Z. (2007). Will my patient fall? Journal of the American Medical Association, 297(1), 77-86.

Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2011). The relationship between intervening hospitalizations and transitions between frailty states. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 66(11), 1238-1243.

Gobbens, R. J., van Assen, M. A., Luijkx, K. G., & Schols, J. M. (2012). The predictive validity of the Tilburg Frailty Indicator: Disability, health care utilization, and quality of life in a population at risk. The Gerontologist, 52(5), 619-631.

Goggins, W. B., Woo, J., Sham, A., & Ho, S. C. (2005). Frailty index as a measure of biological age in a Chinese population. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 60(8), 1046-1051.

Goldstein, M. S., Siegel, J. M., & Boyer, R. (1984). Predicting changes in perceived health status. American Journal of Public Health, 74(6), 611-614.

Goodpaster, B. H., Park, S. W., Harris, T. B., Kritchevsky, S. B., Nevitt, M., Schwartz, A. V., ... & Newman, A. B. (2006). The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 61(10), 1059-1064.

Graafmans, W. C., Ooms, M. E., Hofstee, H. M. A., Bezemer, P. D., Bouter, L. M., & Lips, P. T. A. M. (1996). Falls in the elderly: a prospective study of risk factors and risk profiles. American Journal of Epidemiology, 143(11), 1129-1136.

Grabowski, D. C., Campbell, C. M., & Ellis, J. E. (2005). Obesity and mortality in elderly nursing home residents. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 60(9), 1184-1189.

Granek, E., Baker, S. P., Abbey, H., & Robinson, E. (1987). Medications and diagnoses in

relation to falls in a long-term care facility. Journal of the American Geriatrics Society, 35(6):503-11.

Gregg, E. W., Mangione, C. M., Cauley, J. A., Thompson, T. J., Schwartz, A. V., Ensrud, K. E., & Nevitt, M. C. (2002). Diabetes and incidence of functional disability in older women. Diabetes Care, 25(1), 61-67.

Gryfe, C. I., Amies, A., & Ashley, M. J. (1977). A longitudinal study of falls in an elderly population: I. Incidence and morbidity. Age and Ageing, 6(4), 201-210.

Gu, D., He, J., Duan, X., Reynolds, K., Wu, X., Chen, J., ... & Whelton, P. K. (2006). Body weight and mortality among men and women in China. Journal of the American Medical Association, 295(7), 776-783.

Guillet, C., & Boirie, Y. (2005). Insulin resistance: a contributing factor to age-related muscle mass loss?. Diabetes & Metabolism, 31, 5S20-5S26.

Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., ... & Wallace, R. B. (2000). Lower extremity function and subsequent disability consistency across studies, predictive models, and value of gait speed alone compared with the Short Physical Performance Battery. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 55(4), M221-M231.

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., ... & Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. Journals of Gerontology, 49, M85-M85.

Hamdy, O., Porramatikul, S., & Al-Ozairi, E. (2006). Metabolic obesity: the paradox between visceral and subcutaneous fat. Current Diabetes Reviews, 2(4), 367-373.

Hanlon, J. T., Landerman, L. R., Fillenbaum, G. G., & Studenski, S. (2002). Falls in African American and white community-dwelling elderly residents. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(7), M473-M478.

Harrington, M., Gibson, S., & Cottrell, R. C. (2009). A review and meta-analysis of the effect of weight loss on all-cause mortality risk. Nutrition Research Reviews, 22(01), 93-108.

Heim, N., Snijder, M. B., Heymans, M. W., Deeg, D. J., Seidell, J. C., & Visser, M. (2010).

Exploring cut-off values for large waist circumference in older adults: a new methodological approach. The Journal of Nutrition, Health & Aging, 14(4), 272-277.

Helmersson, J., Vessby, B., Larsson, A., & Basu, S. (2004). Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. Circulation, 109(14), 1729-1734.

Heymsfield, S. B., Smith, R., Aulet, M., Bensen, B., Lichtman, S., Wang, J., & Pierson, R. N. (1990). Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. The American Journal of Clinical Nutrition, 52(2), 214-218.

Hill, K. D., & Wee, R. (2012). Psychotropic drug-induced falls in older people. Drugs & Aging, 29(1), 15-30.

Ho, S. C., Woo, J., & Sham, A. (1994). Risk factor change in older persons, a perspective from Hong Kong: weight change and mortality. Journal of Gerontology, 49(6), M269-M272.

Ho, S. C., Woo, J., Yuen, Y. K., Sham, A., & Chan, S. G. (1997). Predictors of mobility decline: the Hong Kong old-old study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 52(6), M356-M362.

Ho, S. C., Woo, J., Chan, S. S., Yuen, Y. K., & Sham, A. (1996). Risk factors for falls in the Chinese elderly population. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 51(5), M195-M198.

Holt, G., Khaw, K. T., Reid, D. M., Compston, J. E., Bhalla, A., Woolf, A. D., ... & Reeve, J. (2002). Prevalence of osteoporotic bone mineral density at the hip in Britain differs substantially from the US over 50 years of age: implications for clinical densitometry. The British Journal of Radiology, 75(897), 736-742.

Houles, M., Canevelli, M., Abellan Van Kan, G., Ousset, P. J., Cesari, M., & Vellas, B. (2012). Frailty and cognition. Journal of Frailty & Aging, 1(2), 56-63.

Houston, D. K., Nicklas, B. J., Ding, J., Harris, T. B., Tylavsky, F. A., Newman, A. B., ... & Kritchevsky, S. B. (2008). Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. The American Journal of Clinical Nutrition, 87(1), 150-155.

Houston, D. K., Stevens, J., & Cai, J. (2005). Abdominal fat distribution and functional

limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. International Journal of Obesity, 29(12), 1457-1463.

Hubbard, R. E., Lang, I. A., Llewellyn, D. J., & Rockwood, K. (2010). Frailty, body mass index, and abdominal obesity in older people. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 65(4), 377-381.

Hughes, V. A., Frontera, W. R., Roubenoff, R., Evans, W. J., & Singh, M. A. F. (2002). Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. The American Journal of Clinical Nutrition, 76(2), 473-481.

Iannuzzi-Sucich, M., Prestwood, K. M., & Kenny, A. M. (2002). Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(12), M772-M777.

Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. Journal of the American Geriatrics Society, 55(5), 780-791.

Iossa, S., Mollica, M. P., Lionetti, L., Crescenzo, R., Tasso, R., & Liverini, G. (2004). A possible link between skeletal muscle mitochondrial efficiency and age-induced insulin resistance. Diabetes, 53(11), 2861-2866.

Jacobs, E. J., Newton, C. C., Wang, Y., Patel, A. V., McCullough, M. L., Campbell, P. T., ... & Gapstur, S. M. (2010). Waist circumference and all-cause mortality in a large US cohort. Archives of Internal Medicine, 170(15), 1293-1301.

Janssen, I., Baumgartner, R. N., Ross, R., Rosenberg, I. H., & Roubenoff, R. (2004). Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. American Journal of Epidemiology, 159(4), 413-421.

Janssen, I., Heymsfield, S. B., & Ross, R. (2002). Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. Journal of the American Geriatrics Society, 50(5), 889-896.

Janssen, I., Katzmarzyk, P. T., & Ross, R. (2005). Body mass index is inversely related to mortality in older people after adjustment for waist circumference. Journal of the American Geriatrics Society, 53(12), 2112-2118.

Janssen, I. (2007). Morbidity and mortality risk associated with an overweight BMI in

older men and women. Obesity, 15(7), 1827-1840.

Jee, S. H., Sull, J. W., Park, J., Lee, S. Y., Ohrr, H., Guallar, E., & Samet, J. M. (2006). Body-mass index and mortality in Korean men and women. New England Journal of Medicine, 355(8), 779-787.

Kaiser, R., Winning, K., Uter, W., Volkert, D., Lesser, S., Stehle, P., ... & Bauer, J. M. (2010). Functionality and mortality in obese nursing home residents: an example of 'Risk Factor Paradox'?. Journal of the American Medical Directors Association, 11(6), 428-435.

Kallin, K., Gustafson, Y., Sandman, P. O., & Karlsson, S. (2004). Drugs and falls in older people in geriatric care settings. Aging Clinical and Experimental Research, 16(4), 270-276.

Kane, R. L., Talley, K. M., Shamliyan, T., & Pacala, J. T. (2011). Common syndromes in older adults related to primary and secondary prevention. Available from: http://www.ncbi.nlm.nih.gov/books/NBK62074/ (Last accessed on 8 Jan 2014)

Kanis, J. A., Johnell, O., Odén, A., Johansson, H., De Laet, C., Eisman, J. A., ... & Tenenhouse, A. (2005). Smoking and fracture risk: a meta-analysis. Osteoporosis International, 16(2), 155-162.

Kanis, J. A., Odén, A., Johnell, O., Johansson, H., De Laet, C., Brown, J., ... & Yoshimura, N. (2007). The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporosis International, 18(8), 1033-1046.

Kannus, P., Sievänen, H., Palvanen, M., Järvinen, T., & Parkkari, J. (2005). Prevention of falls and consequent injuries in elderly people. The Lancet, 366(9500), 1885-1893.

Karlsson, S., Nyberg, L., & Sandman, P. O. (1997). The use of physical restraints in elder care in relation to fall risk. Scandinavian Journal of Caring Sciences, 11(4), 238-242.

Kedziora-Kornatowska, K., Czuczejko, J., Pawluk, H., Kornatowski, T., Motyl, J., Szadujkis-Szadurski, L., ... & Kedziora, J. (2003). The markers of oxidative stress and activity of the antioxidant system in the blood of elderly patients with essential arterial hypertension. Cellular & Molecular Biology Letters, 9(4A), 635-641.

Kiely, D. K., Cupples, L. A., & Lipsitz, L. A. (2009). Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. Journal of the American Geriatrics Society,

57(9), 1532-1539.

Kiely, D. K., & Flacker, J. M. (1999). Resident characteristics associated with mortality in long-term care nursing homes: is there a gender difference?. Journal of the American Medical Directors Association, 1(1), 8-13.

Kim, J., Wang, Z., Heymsfield, S. B., Baumgartner, R. N., & Gallagher, D. (2002). Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. The American Journal of Clinical Nutrition, 76(2), 378-383.

Kimyagarov, S., Klid, R., Levenkrohn, S., Fleissig, Y., Kopel, B., Arad, M., & Adunsky, A. (2010). Body mass index (BMI), body composition and mortality of nursing home elderly residents. Archives of Gerontology and Geriatrics, 51(2), 227-230.

Klenk, J., Rapp, K., Ulmer, H., Concin, H., & Nagel, G. (2014). Changes of Body Mass Index in Relation to Mortality: Results of a Cohort of 42,099 Adults. PloS One, 9(1), e84817.

Klitgaard, H., Mantoni, M., Schiaffino, S., Ausoni, S., Gorza, L., Laurent-Winter, C., ... & Saltin, B. (1990). Function, morphology and protein expression of ageing skeletal muscle: a cross-sectional study of elderly men with different training backgrounds. Acta Physiologica Scandinavica, 140(1), 41-54.

Ko, G. T. C., Cockram, C. S., Chow, C. C., Yeung, V., Chan, W. B., So, W. Y., ... & Chan, J. C. N. (2005). High prevalence of metabolic syndrome in Hong Kong Chinese - comparison of three diagnostic criteria. Diabetes Research and Clinical Practice, 69(2), 160-168.

Kopple, J. D. (2005). The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. The American Journal of Clinical Nutrition, 81(6), 1257-1266.

Koroukian, S. M., Xu, F., Bakaki, P. M., Diaz-Insua, M., Towe, T. P., & Owusu, C. (2010). Comorbidities, functional limitations, and geriatric syndromes in relation to treatment and survival patterns among elders with colorectal cancer. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 65(3), 322-329.

Koski K, Luukinen H, Laippala P, Kivela SL. (1996). Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study. Age and ageing, 25(1), 29-38.

Kramer, C. K., Zinman, B., & Retnakaran, R. (2013). Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Annals of Internal Medicine, 159(11), 758-769.

Landi, F., Cruz-Jentoft, A. J., Liperoti, R., Russo, A., Giovannini, S., Tosato, M., ... & Onder, G. (2013). Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. Age and Ageing, 42(2), 203-209.

Landi, F., Liperoti, R., Fusco, D., Mastropaolo, S., Quattrociocchi, D., Proia, A., ... & Onder, G. (2012a). Sarcopenia and mortality among older nursing home residents. Journal of the American Medical Directors Association, 13(2), 121-126.

Landi, F., Liperoti, R., Russo, A., Giovannini, S., Tosato, M., Capoluongo, E., ... & Onder, G. (2012b). Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. Clinical Nutrition, 31(5), 652-658.

Lau, E. M., Lynn, H. S., Woo, J. W., Kwok, T. C., & Melton, L. J. (2005). Prevalence of and risk factors for sarcopenia in elderly Chinese men and women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 60(2), 213-216.

Lauretani, F., Russo, C. R., Bandinelli, S., Bartali, B., Cavazzini, C., Di Iorio, A., ... & Ferrucci, L. (2003). Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. Journal of Applied Physiology, 95(5), 1851-1860.

Lawlor, D. A., Patel, R., & Ebrahim, S. (2003). Association between falls in elderly women and chronic diseases and drug use: cross sectional study. BMJ: British Medical Journal, 327(7417), 712-717.

Lea, J. P., Crenshaw, D. O., Onufrak, S. J., Newsome, B. B., & McClellan, W. M. (2009). Obesity, End-stage Renal Disease, and Survival in an Elderly Cohort With Cardiovascular Disease. Obesity, 17(12), 2216-2222.

Lebrun, C. E., van der Schouw, Y. T., de Jong, F. H., Grobbee, D. E., & Lamberts, S. W. (2006). Fat mass rather than muscle strength is the major determinant of physical function and disability in postmenopausal women younger than 75 years of age. Menopause, 13(3), 474-481.

Lee, D. H., Buth, K. J., Martin, B. J., Yip, A. M., & Hirsch, G. M. (2010). Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation, 121(8), 973-978.

Leipzig, R. M., Cumming, R. G., & Tinetti, M. E. (1999). Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. Journal of the American Geriatrics Society, 47(1), 30-39.

Li, C. M., Chen, C. Y., Li, C. Y., Wang, W. D., & Wu, S. C. (2010). The effectiveness of a comprehensive geriatric assessment intervention program for frailty in community-dwelling older people: a randomized, controlled trial. Archives of Gerontology and Geriatrics, 50, S39-S42.

Lin W-Y, Albu J, Liu C-S, Huang H-Y, Pi-Sunyer F X, Li C-I, Li T-C, Lin C-C, Huang K-C. (2010). Larger body mass index and waist are associated with lower mortality in the Chinese long-term care facility residents. Journal of the American Geriatrics Society, 58: 2092–2098.

Lindqvist, P., Andersson, K., Sundh, V., Lissner, L., Björkelund, C., & Bengtsson, C. (2006). Concurrent and separate effects of body mass index and waist-to-hip ratio on 24-year mortality in the Population Study of Women in Gothenburg: evidence of age-dependency. European Journal of Epidemiology, 21(11), 789-794.

Ling, C. H., Taekema, D., de Craen, A. J., Gussekloo, J., Westendorp, R. G., & Maier, A. B. (2010). Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. Canadian Medical Association Journal, 182(5), 429-435.

Liu, L. L., & Leung, J. M. (2000). Predicting adverse postoperative outcomes in patients aged 80 years or older. Journal of the American Geriatrics Society, 48(4), 405-412.

Lopez, D., Flicker, L., & Dobson, A. (2012). Validation of the frail scale in a cohort of older Australian women. Journal of the American Geriatrics Society, 60(1), 171-173.

Lord, S. R., Sambrook, P. N., Gilbert, C., Kelly, P. J., Nguyen, T., Webster, I. W., & Eisman, J. A. (1994). Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. The Medical Journal of Australia, 160(11), 684-5.

Luo, F. M., Liu, X. J., Li, S. Q., Wang, Z. L., Liu, C. T., & Yuan, Y. M. (2005). Circulating ghrelin in patients with chronic obstructive pulmonary disease. Nutrition, 21(7), 793-798.

Maggi, S., Noale, M., Gallina, P., Marzari, C., Bianchi, D., Limongi, F., & Crepaldi, G. (2004). Physical disability among older Italians with diabetes. The ILSA study. Diabetologia, 47(11), 1957-1962.

Makary, M. A., Segev, D. L., Pronovost, P. J., Syin, D., Bandeen-Roche, K., Patel, P., ... & Fried, L. P. (2010). Frailty as a predictor of surgical outcomes in older patients. Journal of the American College of Surgeons, 210(6), 901-908.

Malmstrom, T. K., & Morley, J. E. (2013). Frailty and cognition: Linking two common syndromes in older persons. The Journal of Nutrition, Health & Aging, 17(9), 723-725.

Maurer, M. S., Burcham, J., & Cheng, H. (2005). Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 60(9), 1157-1162.

Mazya, A. L., Eckerblad, J., Jaarsma, T., Hellström, I., Krevers, B., Milberg, A., ... & Ekdahl, A. (2013). The Ambulatory Geriatric Assessment–a Frailty Intervention Trial (AGe-FIT)–A randomised controlled trial aimed to prevent hospital readmissions and functional deterioration in high risk older adults: A study protocol. European Geriatric Medicine, 4(4), 242-247.

McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, Hispanics, and Asians. Diabetes Care, 27(10), 2317-2324.

McGuire, L. C., Ford, E. S., & Ajani, U. A. (2006). The impact of cognitive functioning on mortality and the development of functional disability in older adults with diabetes: the second longitudinal study on aging. BMC Geriatrics, 6(1), 8-14.

Mijnarends, D. M., Meijers, J. M., Halfens, R. J., ter Borg, S., Luiking, Y. C., Verlaan, S., ... & Schols, J. M. (2013). Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. Journal of the American Medical Directors Association, 14(3), 170-178.

Morley, J. E., Baumgartner, R. N., Roubenoff, R., Mayer, J., & Nair, K. S. (2001). Sarcopenia. Journal of Laboratory and Clinical Medicine, 137(4), 231-243.

Morley, J. E., Vellas, B., Abellan van Kan, G., Anker, S. D., Bauer, J. M., Bernabei, R., ... & Walston, J. (2013). Frailty consensus: a call to action. Journal of the American Medical Directors Association, 14(6), 392-397.

Morley, J. E. (2012). Anorexia of aging: a true geriatric syndrome. The Journal of Nutrition, Health & Aging, 16(5), 422-425.

Morley, J. E. (2008). Diabetes, sarcopenia, and frailty. Clinics in Geriatric Medicine, 24(3), 455-469.

Morley, J. E., & Baumgartner, R. N. (2004). Cytokine-related aging process. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59(9), M924-M929.

Morris, J. N., Fries, B. E., Mehr, D. R., Hawes, C., Phillips, C., Mor, V., & Lipsitz, L. A. (1994). MDS cognitive performance scale. Journal of Gerontology, 49(4), M174-M182.

Morris, J. N., Fries, B. E., & Morris, S. A. (1999). Scaling ADLs within the MDS. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 54(11), M546-M553.

Morris, J. N., Hawes, C., Fries, B. E., Phillips, C. D., Mor, V., Katz, S., ... & Friedlob, A. S. (1990). Designing the national resident assessment instrument for nursing homes. The Gerontologist, 30(3), 293-307.

Morris, J. N., Nonemaker, S., Murphy, K., Hawes, C., Fries, B. E., Mor, V., & Phillips, C. (1997). A commitment to change: revision of HCFA's RAI. Journal of the American Geriatrics Society, 45(8), 1011-1016.

Nagai, M., Kuriyama, S., Kakizaki, M., Ohmori-Matsuda, K., Sugawara, Y., Sone, T., ... & Tsuji, I. (2010). Effect of age on the association between body mass index and all-cause mortality: the Ohsaki cohort study. Journal of Epidemiology, 20(5), 398.

Newman, A. B., Kupelian, V., Visser, M., Simonsick, E., Goodpaster, B., Nevitt, M., ... & Harris, T. B. (2003). Sarcopenia: alternative definitions and associations with lower extremity function. Journal of the American Geriatrics Society, 51(11), 1602-1609.

Newman, A. B., Lee, J. S., Visser, M., Goodpaster, B. H., Kritchevsky, S. B., Tylavsky, F. A., ... & Harris, T. B. (2005). Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. The American Journal of Clinical Nutrition, 82(4), 872-878.

Newman, A. B., Sutton-Tyrrell, K., Rutan, G. H., Locher, J., & Kuller, L. H. (1991). Lower extremity arterial disease in elderly subjects with systolic hypertension. Journal of Clinical Epidemiology, 44(1), 15-20.

Newman, A. B., Yanez, D., Harris, T., Duxbury, A., Enright, P. L., & Fried, L. P. (2001).

Weight change in old age and its association with mortality. Journal of the American Geriatrics Society, 49(10), 1309-1318.

O'Loughlin, J. L., Robitaille, Y., Boivin, J. F., & Suissa, S. (1993). Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. American Journal of Epidemiology, 137(3), 342-354.

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews, 6(2), 97-111.

Orme, J. G., Reis, J., & Herz, E. J. (1986). Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. Journal of Clinical Psychology, 42(1), 28-33.

Pahor, M., Manini, T., & Cesari, M. (2009) Sarcopenia: clinical evaluation, biological markers and other evaluation tools. Journal of Nutrition Health and Aging, 13(8), 724-728.

Park, B. S., & Yoon, J. S. (2013). Relative Skeletal Muscle Mass Is Associated with Development of Metabolic Syndrome. Diabetes & Metabolism Journal, 37(6), 458-464.

Park, S. W., Goodpaster, B. H., Strotmeyer, E. S., de Rekeneire, N., Harris, T. B., Schwartz, A. V., ... & Newman, A. B. (2006). Decreased muscle strength and quality in older adults with type 2 diabetes The Health, Aging, and Body Composition Study. Diabetes, 55(6), 1813-1818.

Park, S. W., Goodpaster, B. H., Lee, J. S., Kuller, L. H., Boudreau, R., De Rekeneire, N., ... & Newman, A. B. (2009). Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care, 32(11), 1993-1997.

Park, S. W., Goodpaster, B. H., Strotmeyer, E. S., Kuller, L. H., Broudeau, R., Kammerer, C., ... & Newman, A. B. (2007). Accelerated loss of skeletal muscle strength in older adults with Type 2 diabetes: The Health, Aging, and Body Composition Study. Diabetes Care, 30(6), 1507-1512.

Pischon, T., Boeing, H., Hoffmann, K., Bergmann, M., Schulze, M. B., Overvad, K., ... & Riboli, E. (2008). General and abdominal adiposity and risk of death in Europe. New England Journal of Medicine, 359(20), 2105-2120.

Poobalan, A. S., Aucott, L. S., Smith, W. C. S., Avenell, A., Jung, R., & Broom, J. (2007). Long-term weight loss effects on all cause mortality in overweight/obese populations.

Obesity Reviews, 8(6), 503-513.

Price, G. M., Uauy, R., Breeze, E., Bulpitt, C. J., & Fletcher, A. E. (2006). Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. The American Journal of Clinical Nutrition, 84(2), 449-460.

Prince, M., Acosta, D., Chiu, H., Scazufca, M., & Varghese, M. (2003). Dementia diagnosis in developing countries: a cross-cultural validation study. The Lancet, 361(9361), 909-917.

Prudham, D., & Evans, J. G. (1981). Factors associated with falls in the elderly: a community study. Age and Ageing, 10(3), 141-146.

Raguso, C. A., Kyle, U., Kossovsky, M. P., Roynette, C., Paoloni-Giacobino, A., Hans, D., ... & Pichard, C. (2006). A 3-year longitudinal study on body composition changes in the elderly: role of physical exercise. Clinical Nutrition, 25(4), 573-580.

Reis, J. P., Macera, C. A., Araneta, M. R., Lindsay, S. P., Marshall, S. J., & Wingard, D. L. (2009). Comparison of overall obesity and body fat distribution in predicting risk of mortality. Obesity, 17(6), 1232-1239.

Roberts, H. C., Denison, H. J., Martin, H. J., Patel, H. P., Syddall, H., Cooper, C., & Sayer, A. A. (2011). A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age and Ageing, 40(4), 423-9.

Roche, J. J. W., Wenn, R. T., Sahota, O., & Moran, C. G. (2005). Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. British Medical Journal, 331(7529), 1374. doi: 10.1136/bmj.38643.663843.55

Rockwood, K., Mitnitski, A. B., & MacKnight, C. (2002). Some mathematical models of frailty and their clinical implications. Reviews in Clinical Gerontology, 12(2), 109-117.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal, 173(5), 489-495.

Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hébert, R., & Hogan, D. B. (1999). A brief clinical instrument to classify frailty in elderly people. The Lancet,

353(9148), 205-206.

Rolland, Y., Van Kan, G. A., Gillette-Guyonnet, S., & Vellas, B. (2011). Cachexia versus sarcopenia. Current Opinion in Clinical Nutrition & Metabolic Care, 14(1), 15-21.

Rolland, Y., Lauwers-Cances, V., Cournot, M., Nourhashémi, F., Reynish, W., Rivière, D., ... & Grandjean, H. (2003). Sarcopenia, Calf Circumference, and Physical Function of Elderly Women: A Cross-Sectional Study. Journal of the American Geriatrics Society, 51(8), 1120-1124.

Rolland, Y., Lauwers-Cances, V., Cesari, M., Vellas, B., Pahor, M., & Grandjean, H. (2006). Physical performance measures as predictors of mortality in a cohort of community-dwelling older French women. European Journal of Epidemiology, 21(2), 113-122.

Rosenberg, I. H. (1997). Sarcopenia: origins and clinical relevance. The Journal of Nutrition, 127(5), 990S-991S.

Rosendahl, E., Lundin-Olsson, L., Kallin, K., Jensen, J., Gustafson, Y., & Nyberg, L. (2003). Prediction of falls among older people in residential care facilities by the Downton index. Aging Clinical and Experimental Research, 15(2), 142-147.

Rubenstein, L. Z., & Josephson, K. R. (2002). The epidemiology of falls and syncope. Clinics in Geriatric Medicine, 18(2), 141-158.

Ryan, C., Bryant, E., Eleazer, P., Rhodes, A., & Guest, K. (1995). Unintentional weight loss in long-term care: predictor of mortality in the elderly. Southern Medical Journal, 88(7), 721-724.

Scheffer, A. C., Schuurmans, M. J., Van Dijk, N., Van der Hooft, T., & De Rooij, S. E. (2008). Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age and Ageing, 37(1), 19-24.

Schooling, C. M., Lam, T. H., Li, Z. B., Ho, S. Y., Chan, W. M., Ho, K. S., ... & Leung, G. M. (2006). Obesity, physical activity, and mortality in a prospective Chinese elderly cohort. Archives of Internal Medicine, 166(14), 1498-1504.

Schwartz, A. V., Hillier, T. A., Sellmeyer, D. E., Resnick, H. E., Gregg, E., Ensrud, K. E., ... & Cummings, S. R. (2002). Older women with diabetes have a higher risk of falls A prospective study. Diabetes Care, 25(10), 1749-1754.

Seidell, J. C., & Visscher, T. L. (2000). Body weight and weight change and their health implications for the elderly. European Journal of Clinical Nutrition, 54, S33-S39.

Semba, R. D., Ferrucci, L., Sun, K., Walston, J., Varadhan, R., Guralnik, J. M., & Fried, L. P. (2007). Oxidative stress and severe walking disability among older women. The American Journal of Medicine, 120(12), 1084-1089.

Sergi, G., Perissinotto, E., Pisent, C., Buja, A., Maggi, S., Coin, A., ... & Enzi, G. (2005). An adequate threshold for body mass index to detect underweight condition in elderly persons: the Italian Longitudinal Study on Aging (ILSA). The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 60(7), 866-871.

Sinclair, A., & Viljoen, A. (2010). The metabolic syndrome in older persons. Clinics in Geriatric Medicine, 26(2), 261-274.

Srikanthan, P., & Karlamangla, A. S. (2011). Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. The Journal of Clinical Endocrinology & Metabolism, 96(9), 2898-2903.

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., & Whalley, L. J. (2003). Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. Journal of Neurology, Neurosurgery & Psychiatry, 74(1), 94-98.

Sullivan, D. H., Morley, J. E., Johnson, L. E., Barber, A., Olson, J. S., Stevens, M. R., ... & Olave, X. E. (2001). The GAIN (Geriatric Anorexia Nutrition) registry: the impact of appetite and weight on mortality in a long-term care population. The Journal of Nutrition, Health & Aging, 6(4), 275-281.

Szulc, P., Duboeuf, F., Marchand, F., & Delmas, P. D. (2004). Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: the MINOS study. The American Journal of Clinical Nutrition, 80(2), 496-503.

Takata, Y., Ansai, T., Soh, I., Akifusa, S., Sonoki, K., Fujisawa, K., ... & Takehara, T. (2007). Association Between Body Mass Index and Mortality in an 80-Year-Old Population. Journal of the American Geriatrics Society, 55(6), 913-917.

Tamakoshi, A., Yatsuya, H., Lin, Y., Tamakoshi, K., Kondo, T., Suzuki, S., ... & Kikuchi, S.

(2010). BMI and All-cause Mortality Among Japanese Older Adults: Findings From the Japan Collaborative Cohort Study. Obesity, 18(2), 362-369.

Thapa, P. B., Brockman, K. G., Gideon, P., Fought, R. L., & Ray, W. A. (1996). Injurious falls in nonambulatory nursing home residents: a comparative study of circumstances, incidence, and risk factors. Journal of the American Geriatrics Society, 44(3), 273-278.

Tinetti, M. E., Inouye, S. K., Gill, T. M., & Doucette, J. T. (1995). Shared risk factors for falls, incontinence, and functional dependence: unifying the approach to geriatric syndromes. Journal of the American Medical Association, 273(17), 1348-1353.

Tinetti, M. E., McAvay, G., & Claus, E. (1996). Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT trial?. American Journal of Epidemiology, 144(4), 389-399.

Tinetti, M. E., Speechley, M., & Ginter, S. F. (1988). Risk factors for falls among elderly persons living in the community. New England Journal of Medicine, 319(26), 1701-1707.

Tinetti, M. E., & Speechley, M. (1989). Prevention of falls among the elderly. New England Journal of Medicine, 320(16), 1055-1059.

Tinetti, M. E., & Williams, C. S. (1997). Falls, injuries due to falls, and the risk of admission to a nursing home. New England Journal of Medicine, 337(18), 1279-1284.

Tinetti, M. E. (1987). Factors associated with serious injury during falls by ambulatory nursing home residents. Journal of the American Geriatrics Society, 35:644-648.

Tinetti, M. E., Liu, W. L., & Ginter, S. F. (1992). Mechanical restraint use and fall-related injuries among residents of skilled nursing facilities. Annals of Internal Medicine, 116(5), 369-374.

Toots, A., Rosendahl, E., Lundin-Olsson, L., Nordström, P., Gustafson, Y., & Littbrand, H. (2013). Usual Gait Speed Independently Predicts Mortality in Very Old People: A Population-Based Study. Journal of the American Medical Directors Association, 14(7), 529-e1. doi: 10.1016/j.jamda.2013.04.006.

van Geel, T. A., Geusens, P. P., Winkens, B., Sels, J. P. J., & Dinant, G. J. (2009). Measures of bioavailable serum testosterone and estradiol and their relationships with muscle mass, muscle strength and bone mineral density in postmenopausal women: a cross-sectional study. European Journal of Endocrinology, 160(4), 681-687.

van Haastregt, J., Zijlstra, G. A., van Rossum, E., van Eijk, J. T. M., & Kempen, G. I. (2008). Feelings of anxiety and symptoms of depression in community-living older persons who avoid activity for fear of falling. The American Journal of Geriatric Psychiatry, 16(3), 186-193.

Van Kan, G. A., Rolland, Y., Bergman, H., Morley, J. E., Kritchevsky, S. B., & Vellas, B. (2008a). The IANA Task Force on frailty assessment of older people in clinical practice. The Journal of Nutrition Health and Aging, 12(1), 29-37.

van Kan, G. A., Rolland, Y. M., Morley, J. E., & Vellas, B. (2008b). Frailty: toward a clinical definition. Journal of the American Medical Directors Association, 9(2), 71-72.

Verdijk, L. B., Jonkers, R. A., Gleeson, B. G., Beelen, M., Meijer, K., Savelberg, H. H., ... & van Loon, L. J. (2009). Protein supplementation before and after exercise does not further augment skeletal muscle hypertrophy after resistance training in elderly men. The American Journal of Clinical Nutrition, 89(2), 608-616.

Verhoeven, S., Vanschoonbeek, K., Verdijk, L. B., Koopman, R., Wodzig, W. K., Dendale, P., & van Loon, L. J. (2009). Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men. The American Journal of Clinical Nutrition, 89(5), 1468-1475.

Veronese, N., De Rui, M., Toffanello, E. D., De Ronch, I., Perissinotto, E., Bolzetta, F., ... & Sergi, G. (2013). Body mass index as a predictor of all-cause mortality in nursing home residents during a 5-year follow-up. Journal of the American Medical Directors Association, 14(1), 53-57.

Villalon, K. L., Gozansky, W. S., Pelt, R. E., Wolfe, P., Jankowski, C. M., Schwartz, R. S., & Kohrt, W. M. (2011). A Losing Battle: Weight Regain Does Not Restore Weight Loss-Induced Bone Loss in Postmenopausal Women. Obesity, 19(12), 2345-2350.

Visser, M., Harris, T. B., Langlois, J., Hannan, M. T., Roubenoff, R., Felson, D. T., ... & Kiel, D. P. (1998). Body fat and skeletal muscle mass in relation to physical disability in very old men and women of the Framingham Heart Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 53(3), M214-M221.

Visser, M., Kritchevsky, S. B., Goodpaster, B. H., Newman, A. B., Nevitt, M., Stamm, E., & Harris, T. B. (2002). Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition

study. Journal of the American Geriatrics Society, 50(5), 897-904.

Visser, M., Pahor, M., Taaffe, D. R., Goodpaster, B. H., Simonsick, E. M., Newman, A. B., ... & Harris, T. B. (2002). Relationship of Interleukin-6 and Tumor Necrosis Factor-α With Muscle Mass and Muscle Strength in Elderly Men and Women: The Health ABC Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(5), M326-M332.

Visser, M., Newman, A. B., Nevitt, M. C., Kritchevsky, S. B., Stamm, E. B., Goodpaster, B. H., & Harris, T. B. (2000). Reexamining the sarcopenia hypothesis: muscle mass versus muscle strength. Annals of the New York Academy of Sciences, 904(1), 456-461.

Volpato, S., Romagnoni, F., Soattin, L., Blè, A., Leoci, V., Bollini, C., ... & Zuliani, G. (2004). Body Mass Index, Body Cell Mass, and 4-Year All-Cause Mortality Risk in Older Nursing Home Residents. Journal of the American Geriatrics Society, 52(6), 886-891.

von Haehling, S., Morley, J. E., & Anker, S. D. (2010). An overview of sarcopenia: facts and numbers on prevalence and clinical impact. Journal of Cachexia, Sarcopenia & Muscle, 1(2), 129-133.

von Haehling, S., Schefold, J. C., Lainscak, M., Doehner, W., & Anker, S. D. (2009). Inflammatory biomarkers in heart failure revisited: much more than innocent bystanders. Heart Failure Clinics, 5(4), 549-560.

Wändell, P. E., Carlsson, A. C., & Theobald, H. (2009). The association between BMI value and long-term mortality. International Journal of Obesity, 33(5), 577-582.

Wang, S. Y., Fukagawa, N., Hossain, M., & Ooi, W. L. (1997). Longitudinal weight changes, length of survival, and energy requirements of long-term care residents with dementia. Journal of the American Geriatrics Society, 45(10), 1189-1195.

Wang, Y., Wang, Y., Qain, Y., Zhang, J., Tang, X., Sun, J., & Zhu, D. (2013). Association of Body Mass Index with Cause Specific Deaths in Chinese Elderly Hypertensive Patients: Minhang Community Study. PloS One, 8(8), e71223. doi: 10.1371/journal.pone.0071223.

Holt, G., Khaw, K. T., Reid, D. M., Compston, J. E., Bhalla, A., Woolf, A. D., ... & Reeve, J. (2002). Prevalence of osteoporotic bone mineral density at the hip in Britain differs substantially from the US over 50 years of age: implications for clinical densitometry. The British Journal of Radiology, 75(897), 736-742.

Ware J.E., Kosinski M., Keloler S.D. (1994) SF-36 Health Survey: Manual and Interpretational Guide. Boston, MA. The Health Institute, New England Medical Center.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): development and evaluation. Journal of Clinical Epidemiology, 46(2), 153-162.

Wedick, N. M., Barrett-Connor, E., Knoke, J. D., & Wingard, D. L. (2002). The Relationship Between Weight Loss and All-Cause Mortality in Older Men and Women With and Without Diabetes Mellitus: The Rancho Bernardo Study. Journal of the American Geriatrics Society, 50(11), 1810-1815.

Whitman, G. T., Tang, T., Lin, A., & Baloh, R. W. (2001). A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. Neurology, 57(6), 990-994.

Woo, J., Ho, S. C., & Sham, A. (2001). Longitudinal changes in body mass index and body composition over 3 years and relationship to health outcomes in Hong Kong Chinese age 70 and older. Journal of the American Geriatrics Society, 49(6), 737-746.

Woo, J., Ho, S. C., Yu, A. L. M., & Sham, A. (2002). Is waist circumference a useful measure in predicting health outcomes in the elderly? International Journal of Obesity & Related Metabolic Disorders, 26(10), 1349-1355.

Woo, J., Hui, E., Chan, F., Chi, I., & Sham, A. (2004). Use of restraints in long-term residential care facilities in Hong Kong SAR, China: predisposing factors and comparison with other countries. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59(9), M921-M921.

Woo, J., Leung, J., & Kwok, T. (2007). BMI, body composition, and physical functioning in older adults. Obesity, 15(7), 1886-1894.

Woo, J., Leung, J., Sham, A., & Kwok, T. (2009). Defining sarcopenia in terms of risk of physical limitations: a 5-year follow-up study of 3,153 chinese men and women. Journal of the American Geriatrics Society, 57(12), 2224-2231.

Woolcott, J. C., Richardson, K. J., Wiens, M. O., Patel, B., Marin, J., Khan, K. M., & Marra, C. A. (2009). Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Archives of Internal Medicine, 169(21), 1952-1960.

Working Group on Functional Outcome Measures for Clinical Trials. (2008). Functional outcomes for clinical trials in frail older persons: time to be moving. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences, 63(2), 160 – 164.

World Health Organization Western Pacific Region International Association for the Study of Obesity and the International Obesity Task Force. The Asia-Pacific perspective: redefining obesity and its treatment. (2000) Health Communications Australia Pty Limited, Australia.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: a preliminary report. Journal of Psychiatric Research, 17(1), 37-49.

Yip, P. S., & Law, C. K. (2002). Assessment of the future resources and needs for hospitalization in Hong Kong SAR. The International Journal of Health Planning and Management, 17(2), 113-122.

Zamboni, M., Zoico, E., Scartezzini, T., Mazzali, G., Tosoni, P., Zivelonghi, A., ... & Bosello, O. (2003). Body composition changes in stable-weight elderly subjects: the effect of sex. Aging Clinical and Experimental Research, 15(4), 321-327.

Zoico, E., Di Francesco, V., Guralnik, J. M., Mazzali, G., Bortolani, A., Guariento, S., ... & Zamboni, M. (2004). Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. International Journal of Obesity, 28(2), 234-241.

Associated factors of falls in nursing home residents in Hong Kong and the role of restraints: a cross-sectional survey using the Resident Assessment Instrument (RAI) 2.0

Jenny SW Lee[1], Elsie Hui[1], Felix Chan[2], Iris Chi[3] and Jean Woo[1]

[1]Department of Medicine and Therapeutics, Chinese University of Hong Kong, [2]Department of Medicine, Fung Yiu King Hospital, [3]Sau Po Centre of Ageing, University of Hong Kong, Hong Kong SAR

ABSTRACT. ***Background and aims:*** *To identify factors associated with falls in non-bedridden nursing home residents in Hong Kong, and to examine whether restraints are protective against falls.* ***Methods:*** *Cross-sectional survey of 1710 nursing home residents, examining factors associated with falls and use of restraints, as documented in the RAI questionnaire.* ***Results:*** *Vision impairment is highly associated with falls (OR 1.75, 95% CI 1.29-2.34), whereas older age (OR 1.03, 95% CI 1.01-1.05), dementia (OR 1.46, 95% CI 1.05-2.04), and intake of psychotropics (OR 1.52, 95% CI 1.06-2.17) were moderately associated. Women were less likely to fall (OR 0.65, 95% CI 0.48-0.90). Walking with aids and taking more medications were not associated with falls in this population. Restraints were used in 68%. The use of any type of restraint was marginally associated with fewer falls (OR 0.73, 95% CI 0.53-1.00).* ***Conclusions:*** *Men, those with impaired vision, dementia or taking psychotropic drugs were more likely to fall. Restraints are very commonly used in Hong Kong nursing homes. Although their use was associated with fewer falls, their effect on preventing falls could not be established in this cross-sectional study.*

(Aging Clin Exp Res 2008; 20: 447-453)

INTRODUCTION

Falls are common in frail older persons, and result in considerable morbidity and mortality. Approximately 18-60% of older community dwellers all over the world fall each year (1-6). Compared with those living in the community, institutionalized elderly have an even higher prevalence of falls, up to 45-70% per year (7, 8). Among the latter, fall rate differs between those with different mobility levels, with bedridden subjects having the lowest fall rate (4.1 per 100 person-years), increasing to 17.0 per 100 person-years in those who can walk by themselves. More mobile residents tended to have more serious fall-related injuries (9).

A variety of risk factors have been identified for falls among nursing home residents. Intrinsic factors include visual impairment, cognitive impairment, functional impairment, past history of falls, and the use of certain drugs such as neuroleptics, antidepressants and benzodiazepines (10-12). Among those without dementia, orthostatic hypotension and treatment with angiotensin converting enzyme inhibitors have been shown to be risk factors (13).

Physical restraints are often employed to reduce wandering and falls in nursing homes. However, the reduced use of physical restraints does not necessarily result in more falls or fall-related injuries (14), and fall-related fracture rates remain constant, despite a significant reduction in the use of physical restraints in another study (15). In fact, restraint use may even be associated with an increased incidence of serious fall-related injuries (16). Unfortunately, despite these reports, the use of physical restraints in Hong Kong remains one of the highest in comparison with eight other countries, even after adjustment for case-mix, physical and cognitive impairment (17).

Although falls among nursing home residents have been studied in many other countries, risk factors may still differ between places, due to different case-mix and nursing practices. As understanding risk factors is useful in identifying high-risk individuals for targeted interventions, and as we believe fall prevention should not rely solely on the use of restraints, associated factors for falls and the role of physical restraints on falls among nursing home residents in Hong Kong were explored.

Key words: Elderly, falls, nursing home, restraint.

Correspondence: Jenny SW Lee, MRCP, Department of Medicine and Geriatrics, Shatin Hospital, Shatin, Hong Kong SAR. E-mail: jleesw_2000@yahoo.com

Received July 20, 2007; accepted in revised form April 9, 2008.

METHODS

Of the 533 private nursing homes and 130 subsidized nursing homes in Hong Kong in 2001, ten private and four subsidized homes with at least 100 residents were randomly selected, with a sampling ratio of 2.5 private to 1 subsidized homes. This ratio was chosen to reflect the great number of private homes. Of the 1914 residents in these residential facilities, 1820 were successfully assessed with the Minimum Dataset - Residential Assessment Instrument, version 2.0, translated into Chinese (MDS-RAI 2.0) (18-20), with a response rate of 95%.

The MDS-RAI has been translated into Chinese and validated, demonstrating adequate psychometric properties in terms of inter-rater reliability, test-retest reliability, context validity, criterion validity, and clinical validity (20). The 22 sections of the MDS are: 1) Identification Information; 2) Demographic Information; 3) Customary Routine; 4) Face Sheet Signatures; 5) Background Information; 6) Cognitive Patterns; 7) Communication/Hearing Patterns; 8) Vision Patterns; 9) Mood and Behavior Patterns; 10) Psychological Well-Being; 11) Physical Functioning and Structural Problems; 12) Continence in last 14 days; 13) Disease diagnoses; 14) State of health; 15) Oral/Nutritional Status; 16) Oral/Dental Status; 17) Skin Condition; 18) Activity Pursuits; 19) Medications; 20) Special Treatments and Procedures; 21) Discharge Potential and Overall Status; 22) Assessment Information.

Data were collected by two research assistants who were trained in the use of the instrument. Medical and social information was collected from residents or from a proxy if the former were deemed too frail to be interviewed. Proxies included personal care workers, other front-line nursing staff, family members or close friends. Participants' files at the facilities were also consulted for background social and medical history. Participants' daily routines were confirmed with home staff, to ensure the reliability and validity of the information gathered.

Of the 1820 residents interviewed, 583 lived in subsidized homes and 1237 were in private homes. Reasons for unsuccessful assessments included hospitalization, move to other facilities, home leave, and death. Participants who were bedridden were excluded, since the fall rate and risk factors would be very different for this group when compared with those who were mobile. Bedridden was defined as being obliged to remain in bed all or most of the time. After exclusion, 1710 participants remained in the analysis.

Falls

A fall was defined as any unexpected loss of balance resulting in coming to rest on the ground or floor within the previous 180 days. Walking with aids was defined as able to ambulate with cane, walker or crutch. Dementia was defined as a diagnosis of Alzheimer's disease or any dementia other than Alzheimer's disease.

Restraint

A physical restraint was defined as a mechanical appliance inhibiting a resident's freedom of movement (21, 22). Restraints noted in the data included bed rails on either or both sides, trunk restraint by means of using safety vest or belt, limb restraint, and chairs with a detachable table

Table 1 - *Demographics of 1710 non-bedridden nursing home residents and unadjusted odds ratios for falls in past 180 days.*

Variable	Mean (SD)/ n (%)	OR	*p*-value
Age (per yr increase)	83.3 (8.5)	1.023	0.012*
Female sex	1154 (67.5)	0.813	0.174
Walks with aids	809 (47.3)	1.285	0.086*
Wheelchair mostly for locomotion	509 (29.8)	1.044	0.786
Conditions			
Dementia	506 (29.6)	1.441	0.017*
Poor short-term memory	958 (56.0)	1.216	0.188
Diabetes mellitus	389 (22.7)	0.880	0.473
Heart diseases (IHD, CHF)	181 (10.6)	0.644	0.107
Eye diseases (cataract, glaucoma, diabetic retinopathy, macular degeneration)	643 (37.6)	1.793	0.000*
Visual impairment	1333 (78.0)	1.158	0.417
History of hip fracture	133 (7.8)	0.942	0.828
Leg or back pain	183 (10.7)	0.994	0.978
History of stroke/hemiparesis	557 (32.6)	0.899	0.499
Parkinson's disease	141 (8.2)	0.810	0.458
Medications			
Number of medications (per 1 item increase)	4 (2.7)	1.061	0.024*
Any psychotropics	356 (20.8)	1.643	0.002*
Restraint use	1163 (68.0)	0.829	0.218

*$p<0.05$. SD= standard deviation, OR= odds ratio, IHD= ischemic heart disease, CHF= congestive heart failure.

Table 2 - *Characteristics of fallers vs non-fallers.*

Characteristic	Fallers (n=216)	Non-fallers (n=1494)	p-value
Demographics			
Female sex	137 (63.4)	1017 (68.1)	0.187
Education (n=1706)			0.515
No schooling	132 (61.4)	891 (59.8)	
Some primary school	69 (32.1)	472 (31.6)	
Above primary	14 (6.5)	128 (8.6)	
Age, yr (mean, SD)	84.7 (7.5)	83.1 (8.6)	0.012*
Mobility			
Walks with cane/walker	114 (52.8)	695 (46.5)	0.085
Wheelchair as primary mode of locomotion	66 (30.6)	443 (29.7)	0.786
Functional scales			
MDS Cognitive Performance Scale			0.199
Mildly impaired (0,1)	115 (53.2)	714 (47.8)	
Moderately impaired (2,3,4)	78 (36.1)	622 (41.6)	
Severely impaired (5)	9 (4.2)	51 (3.4)	
Very severely impaired (6)	14 (6.5)	107 (7.2)	
MDS ADL Self-performance Hierarchy Scale			0.514
Mildly impaired (0,1,2)	111 (51.4)	767 (51.3)	
Moderately impaired (3,4)	41 (19.0)	211 (14.1)	
Severely impaired (5,6)	64 (29.6)	516 (34.5)	
Rehabilitation programs			
Dementia care unit	1 (0.5)	0 (0)	--
Occupational therapy	14 (6.5)	107 (7.2)	0.715
Physiotherapy	88 (40.7)	501 (33.5)	0.037*
Medical history			
Diabetes	45 (20.8)	344 (23.0)	0.473
Heart diseases (IHD, CHF)	16 (7.4)	165 (11.0)	0.104
Dementia	79 (36.6)	427 (28.6)	0.016*
Eye diseases (cataract, diabetic retinopathy, glaucoma, macular degeneration)	108 (50.0)	535 (35.8)	0.000*
Depression	12 (5.6)	76 (5.1)	0.771
Stroke/hemiparesis	66 (30.6)	491 (32.9)	0.498
Parkinson's disease	15 (6.9)	126 (8.4)	0.457
Foot problems	20 (9.3)	206 (13.8)	0.066
Back/lower limb pain	23 (10.6)	160 (10.7)	0.978
Hip fracture in last 180 days	2 (0.9)	2 (0.1)	0.024*
Medications			
Number of medications, mean (SD)	4.4 (2.7)	4.0 (2.7)	0.023*
Psychotropic drugs	62 (28.7)	294 (19.7)	0.002*

Numbers expressed as n (%) unless otherwise indicated; *$p<0.05$.

top that prevented the resident from getting up. Any restraint use in the past seven days was recorded.

Activities of daily living and cognitive impairment

The MDS ADL Self-Performance Hierarchy scale was used to describe the actual performance level of each resident across a spectrum of ADLs (activities of daily living) (23). Multiple MDS items concerning ADLs and dependency levels in performing those activities were used to formulate a score ranging from 0 (independent) to 6 (total dependence), according to the methods described by Morris et al. (24).

The MDS Cognitive Performance Scale was used to provide a functional view of each participant's cognitive performance. Multiple cognitive items in the MDS were used to generate a score ranging from 0 (intact cognition) to 6 (very severe impairment), according to Morris et al. (24).

Statistical analysis

Analysis was carried out with the SPSS, version 12.0, in two steps. In the first step, univariate analysis was performed with potential associated factors. In the second step, age, sex, use of physical restraints and all factors with a p-value <0.1 in the univariate analysis were analyzed by logistic regression in a multivariate model. P-values were calculated by Student's t-test for continuous variables, the chi-square test for categorical variables, and Somers' D test for ordinal variables. The level of statistical significance was set at $p<0.05$.

Table 3 - *Restraint types and usage (n=1152)**.

Type	n (%)
Partial bedside rails (half rails, or one side only)	785 (68.1)
Full bedrails on both sides	310 (26.9)
Trunk restraints	
< daily	8 (0.7)
daily	210 (18.2)
Limb restraint	
< daily	6 (0.5)
daily	103 (8.9)
Table top restraint	
< daily	2 (0.2)
daily	102 (8.9)

*A resident may have been put on more than 1 type of restraints.

RESULTS

A total of 1710 non-bedridden nursing home residents were included in this analysis. Their mean age was 83.3 years; 67.5% were women, and 47.3% walked with aids. The prevalence of common diseases was as follows: 29.6% with dementia, 10.6% heart disease, 37.6% impaired vision, 32.6% previous stroke, 8.2% Parkinson's disease, and 10.7% leg or back pain. The mean number of medications used was four, 20.8% of subjects having used psychotropic medications in the previous week.

Of these 1710 residents, 216 (12.6%) had had a fall in the last 180 days, four sustaining hip fractures and another four other types of fractures. The fracture rate of all falls was 3.7%. Fallers were significantly older, more likely to be using a cane or walker, were on more medications, had had a hip fracture in the last 180 days, and participated more in physiotherapy. A significantly higher proportion of fallers suffered from dementia and eye problems, which included cataract, diabetic retinopathy, glaucoma, and macular degeneration. ADLs and cognitive functions as measured by the MDS ADL Self-performance Hierarchy scale and the MDS cognitive performance scale were not different between fallers and non-fallers (Table 2).

Restraint had been used in 68% of residents in the previous week. Table 3 lists the number and proportion of the various types of restraints employed. The most common type was bedrails, on either one or both sides. Approximate one-fifth of restrained residents had safety vests or trunk restraints. Those on restraints were older and tended to have less education. They were less likely to be using a walker or a cane, but more likely to be using a wheelchair. They also tended to be on more occupational and physiotherapy. Demented residents were much more likely to be restrained, and those restrained were likewise more commonly put on anti-psychotics and hypnotics. Residents with more ADL and cognitive impairments, as measured by the MDS ADL hierarchy scale and MDS cognitive performance scales, were more often restrained. Restrained residents were much less likely to have fallen in the previous 30 days, although no difference was found for a longer period (Table 4).

Table 5 describes the types and proportions of each type of restraints used by fallers and non-fallers. Only trunk restraints were significantly more common among fallers.

Table 6 shows the multivariate model for associated factors of falls. Impaired vision was highly associated with falls (OR 1.746, $p<0.000$). Older age (OR 1.026, $p=0.012$), dementia (OR 1.464, $p=0.025$), and use of psychotropic drugs (OR 1.516, $p=0.023$) were moderately associated with falls. Women were less likely to have falls than men (OR 0.654, $p=0.009$), but walking with aids and taking more medications were not associated with falls in this population. Restraint use had a marginally protective effect against falls (OR 0.731, $p=0.05$).

DISCUSSION

When compared with nursing home residents in three other countries (Finland, Sweden and Israel), those in Hong Kong were found to be the least disabled in terms of activities of daily living and had the lowest fall rate (25). This may be due either to a difference in case-mix or prevalence of restraint use, or both. As both characteristics and nursing practices in Hong Kong are different, potential risk factors for falls may also be somewhat different from those in other countries. To our knowledge, this is the first paper to describe the characteristics of fallers and restraints among nursing home residents in Hong Kong.

We had excluded from the analysis residents who were completely bedridden, as we believe that very severe physical limitations will actually result in lower fall rates, and those who were still able to ambulate despite some physical impairment were most likely to fall. In fact, Kallin et al. reported that the ability to get up from a chair was associated with being a faller in Sweden geriatric care settings (11). We did not find any difference between fallers and non-fallers in terms of the MDS ADL self-performance scale. In addition, we found that physical impairment, such as requiring walking aids for ambulation, was not necessarily related to falls, provided that the resident was cognitively intact and free of eye diseases.

The most important factor in our analysis was having eye diseases, followed by being on psychotropic drugs including anti-depressants, hypnotics and anxiolytics, and having dementia. Fall prevention in nursing homes should focus on residents with these associated factors. Therapy as prescribed in the nursing home did not seem to make a difference in fall rates. More fallers were in fact on physiotherapy, rather than the reverse. However, as this study is cross-sectional, fallers may also have been interpreted as being started on physiotherapy after they had undergone a fall.

For the sake of simplicity and ease of application in the future, we chose simple, dichotomized variables to identify factors associated with being a faller. Other groups have developed fall prediction models to identify at-risk individuals for early intervention (26). The simple variables we chose may serve as the basis for a simple fall risk identification tool for local nursing home residents.

Restraint use in our cohort was marginally protective for falls, and a history of falls was more significantly associated with trunk restraints. Caution must be taken in this interpretation, however, as fallers were more likely to be put on restraints, and in this cross-sectional study this association between the two was not unexpected. Although restraints do reduce falls, they impinge on the autonomy and quality of life of the individual and increase immobility. Previous reports demonstrate that restraint removal in the nursing home does not necessarily lead to increased falls and may actually reduce injurious falls (14, 15, 27). Another prospective cohort study also showed that physical restraint use was actually associated with

Table 4 - *Characteristics of restrained and non-restrained residents.*

Characteristic	Restrained (n=1152)	Non-restrained (n=558)	*p*-value
Demographics			
Female sex	780 (67.7)	374 (67.0)	0.777
Age, years, (Mean, SD)	83.7 (8.5)	82.6 (8.4)	0.009*
Education (n=1706)			0.021*
No schooling	714 (62.0)	304 (55.7)	
Primary school	347 (29.9)	194 (35.5)	
Above primary	94 (8.1)	48 (8.8)	
Mobility			
Walks with stick/walker	488 (42.4)	321 (57.5)	0.000*
Wheelchair as primary mode of locomotion	421 (36.5)	88 (15.8)	0.000*
Fall history			
Fell in last 30 days	29 (2.5)	32 (5.7)	0.001*
Fell in last 30-180 days	112 (9.7)	47 (8.4)	0.386
Medical history			
Diabetes	268 (23.3)	121 (21.7)	0.465
Heart diseases (IHD, CHF)	126 (10.9)	55 (9.9)	0.496
Dementia	396 (34.4)	110 (19.7)	0.000*
Parkinson's disease	105 (9.1)	36 (6.5)	0.061
Stroke or hemiparesis	388 (33.7)	169 (30.3)	0.160
Eye diseases (cataract, diabetic retinopathy, glaucoma, macular degeneration)	442 (38.4)	201 (36.0)	0.348
Any lower limb or back pain	115 (10.0)	68 (12.2)	0.167
Tube feeding	68 (5.9)	8 (1.4)	0.000*
Medication use			
No. of medications			0.745
0	107 (9.3)	59 (10.6)	
1-4	284 (50.9)	605 (52.5)	
Daily antipsychotic use	164 (14.2)	38 (6.8)	0.000*
Daily hypnotic use	77 (6.7)	16 (2.9)	0.001*
Functional scales			
MDS Cognitive Performance Scale			0.000*
Mildly impaired (0,1)	467 (40.5)	362 (64.9)	
Moderately impaired (2,3,4)	538 (46.7)	162 (29.0)	
Severely impaired (5)	44 (3.8)	16 (2.9)	
Very severely impaired (6)	103 (8.9)	18 (3.2)	
MDS ADL Self-performance Hierarchy Scale			0.000*
Mildly impaired (0,1,2)	519 (45.1)	359 (64.3)	
Moderately impaired (3,4)	172 (14.9)	80 (14.3)	
Severely impaired (5,6)	461 (40.0)	119 (21.3)	
Training programs			
Dementia special care programs	0	1	–
Occupational Therapy	112 (9.7)	9 (1.6)	0.000*
Physiotherapy	463 (40.2)	126 (22.6)	0.000*
Special behavior evaluation program	0	0	–

Numbers expressed as n (%) unless otherwise indicated; *$p<0.05$.

Table 5 - *Restraints use between fallers and non-fallers.*

Restraint type	Fallers (n=216)	Non-fallers (n=1494)	p-value
Full bed rails	31 (14.4)	279 (18.7)	0.123
Other side-rails	91 (42.1)	698 (46.7)	0.206
Trunk restraints	45 (20.8)	179 (12.0)	0.000*
Limb restraints	9 (4.2)	101 (6.8)	0.146
Table top restraints	15 (6.9)	89 (6.0)	0.570
Any type of restraint	139 (64.4)	1024 (68.5)	0.217

Numbers are expressed as n (%). A resident may have been on more than one type of restraint; *$p<0.05$.

more serious injuries (16). Hong Kong has one of the highest restraint rates among eight other countries (Denmark, France, Iceland, Italy, Japan, Spain, Sweden, USA) (17); the marginal protection offered by restraints in our study and the very high restraint rate calls for definite reduction of restraints in local nursing home population.

The MDS ADL and cognitive scales were not related to falls in our cohort, but were highly related to restraints. One would have thought that the factors associated with both (falls and restraints) would be very similar, but in fact they were not. The use of the MDS scales, together with several other simple variables, could perhaps help to identify those who are "at risk" of restraints, so that alternative methods should be sought to prevent the detrimental effects of restraints in these elderly persons.

This study has several limitations. Being cross-sectional, causal relationships could only be interpreted with caution. This is especially true in the association between falls and restraints. Owing to the different timeframes in which the questions were set, the use of restraints in the survey week may well have been the result of a fall that had occurred prior to that week (although the non-restrained actually fell twice as frequently in the previous month). Only prospective studies in the same population would be able to provide a definite answer to the genuine effect of restraints on falls. Nevertheless, in view of the well-known harmful effects of restraints, and the fact that not all falls are injurious, as indicated in our sample and also elsewhere, we do not support the use of restraints for fall prevention in nursing homes.

CONCLUSION

Fall prevention in nursing homes should focus on high-risk groups, i.e. men, those with impaired vision, with dementia, or on psychotropic drugs. In view of the well-known detrimental effects of restraints on the elderly, and only marginal protective effect against falls shown in our study, further prospective trials of restraint reduction are warranted, to enhance restraint reduction programs in nursing homes.

ACKNOWLEDGEMENTS

This study was supported by the SK Yee Memorial Fund.

Author Contributions: JL analyzed the data and wrote the paper. EH and FC arranged and carried out the field study. IC provided the major input in computerizing the RAI, so that data entry could be carried out in the field, and arranged data entry. JW designed the study, organized its execution, and analyzed the data with JL.

Conflict of interest

None declared.

Table 6 - *Multivariate model of risk factors and restraint use in falls among non-bedridden nursing home residents.*

Factors	Number included in analysis (% of total)	Adjusted OR for falls in last 180 days	95% CI	p-value
Age (per yr increment)	1710 (100)	1.026	1.005-1.046	0.012*
Female Sex	1154 (67.5)	0.654	0.477-0.898	0.009*
Walk with aids	809 (47.3)	1.253	0.927-1.692	0.142
Dementia	506 (29.6)	1.464	1.048-2.044	0.025*
Eye diseases (cataract, glaucoma, diabetic eye disease, macular degeneration)	643 (37.6)	1.746	1.293-2.359	0.000*
Psychotropic drugs (hypnotics, antidepressants, anxiolytics)	356 (20.8)	1.516	1.059-2.170	0.023*
Restraints	1163 (68)	0.731	0.534-1.000	0.050
Number of medications (per 1 item increment)	1710 (100)	1.048	0.992-1.108	0.094

*$p<0.05$. OR= odds ratio; CI= confidence interval.

REFERENCES

1. Ho SC, Woo J, Chan SSG, Yuen YK, Sham A. Risk factors for falls in the Chinese elderly population. J Gerontol Med Sci 1996; 51A: M195-8.
2. Hanlon JT, Landerman LR, Fillenbaum GG, Studenski S. Falls in African American and white community-dwelling elderly residents. J Gerontol Med Sci 2002; 57A; M473-8.
3. Cesari M, Landi F, Torre S, Onder G, Lattanzio F, Bernabei R. Prevalence and risk factors for falls in an older community-dwelling population. J Gerontol Med Sci 2002; 57A; M722-6.
4. Rubenstein L, Josephson KR. The epidemiology of falls and syncope. Clin Geriatr Med 2002; 18: 141-58.
5. Chu LW, Chi I, Chiu AYY. Incidence and predictors of falls in the Chinese elderly. Ann Acad Med Singapore 2005; 34: 60-72.
6. Lee JSW, Kwok T, Leung PC, Woo J. Medical illnesses are more important than medications as risk factors of falls in older community dwellers: a cross-sectional study. Age Ageing 2006; 35: 246-51.
7. Gryfe CI, Amies A, Ashley MJ. A longitudinal study of falls in an elderly population:I. Incidence and morbidity. Age Ageing 1977; 6: 201-10.
8. Tinetti ME. Factors associated with serious injury during falls by ambulatory nursing home residents. J Am Geriatr Soc 1987; 35: 644-8.
9. Thapa PB, Brockman KG, Gideon P, Fought RL, Ray WA. Injurious falls in nonambulatory nursing home residents: a comparative study of circumstances, incidence and risk factors. J Am Geriatr Soc 1996; 44: 273-8.
10. Kallin K, Lundin-Olsson L, Jensen J, Nyberg L, Gustafson Y. Predisposing and precipitating factors for falls among older people in residential care. Public Health 2002; 116: 263-71.
11. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Drugs and falls in older people in geriatric care settings. Aging Clin Exp Res 2004; 16: 270-6.
12. Fonad E, Wahlin TB, Winblad B, Emami A, Sandmark H. Falls and fall risk among nursing home residents. J Clin Nurs 2008; 17: 126-34.
13. Eriksson S, Gustafson Y, Lundin-Olsson L. Risk factors for falls in people with and without a diagnosis of dementia living in residential care facilities: a prospective study. Arch Gerontol Geriatr 2008; 46: 293-306.
14. Capezuti E, Strumpf NE, Evans LK, Grisso JA, Maislin G. The relationship between physical restraint removal and falls and injuries among nursing home residents. J Gerontol Med Sci 1998; 53: M47-52.
15. Cali CM, Kiel DP. An epidemiologic study of fall-related fractures among institutionalized older people. J Am Geriatr Soc 1995; 43: 1336-40.
16. Tinetti, ME, Liu WL, Ginter SF. Mechanical restraint use and fall-related injuries among residents of skilled nursing facilities. Ann Intern Med 1992; 116: 369-74.
17. Woo J, Hui E, Chan F, Chi I, Sham A. Use of restraints in long-term residential care facilities in Hong Kong SAR, China: predisposing factors and comparison with other countries. J Gerontol Med Sci 2004; 59: M921.
18. Morris JN, Hawes C, Fries BE, et al. Designing the national resident assessment instrument for nursing facilities. Gerontologist 1990; 30: 293-307.
19. Morris JN, Nonemaker S, Murphy K, et al. A commitment to change: revision of HCFA's RAI. J Am Geriatr Soc 1997; 45: 1011-6.
20. Chou KL, Chi I, Leung ACT, Wu YM, Liu BCP. Validation of minimum dataset for nursing homes for Hong Kong Chinese elders. Clin Gerontol 2001; 23: 43-54.
21. Stillwell E. Nurses' education related to the use of restraints. J Gerontol Nurs 1991; 17: 23-6.
22. Karlsson S, Nyberg L, Sandman PO. The use of physical restraints in elder care in relation to fall risk. Scand J Caring Sci 1997; 11: 238-42.
23. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. J Gerontol Med Sci 1999; 54A: M546-53.
24. Morris JN, Fries BE, Mehr DR, et al. MDS cognitive performance scale. J Gerontol Med Sci 1994; 49: M174-82.
25. Chi I. Cross-national comparison of the profiles of nursing home residents. Geriatr Gerontol Int 2004; 4: S286-8.
26. Rosendahl E, Lundin-Olsson L, Kallin K, Jensen J, Gustafson Y, Nyberg L. Prediction of falls among older people in residential care facilities by the Downton index. Aging Clin Exp Res 2003; 15: 142-7.
27. Ejaz FK, Jones JA, Rose MS. Falls among nursing home residents: an examination of incident reports before and after restraint reduction programs. J Am Geriatr Soc 1994; 42: 960-4.

Clinical Section

Gerontology

Gerontology 2007;53:404–410
DOI: 10.1159/000107355

Received: January 30, 2007
Accepted: June 5, 2007
Published online: August 16, 2007

Associated Factors and Health Impact of Sarcopenia in Older Chinese Men and Women: A Cross-Sectional Study

Jenny S.W. Lee[a] Tung-Wai Auyeung[b] Timothy Kwok[a] Edith M.C. Lau[d]
Ping-Chung Leung[c] Jean Woo[a]

[a]Department of Medicine and Therapeutics, School of Medicine, [b]Department of Community and Family Medicine, School of Public Health, and [c]Jockey Club Center for Osteoporosis Care and Control, The Chinese University of Hong Kong, and [d]Hong Kong Orthopedics and Osteoporosis Center for Treatment and Research, Hong Kong, SAR, China

Key Words
Sarcopenia · Muscle · Chinese · Elderly · Association

Abstract
Background: Sarcopenia is increasingly being recognized as a feature of frailty in old age and is associated with unfavorable health outcomes in Western populations. Little is known about sarcopenia among Asian elderly populations. ***Objectives:*** The study was undertaken to study the association between sarcopenia and common chronic illnesses, lifestyle factors, psychosocial well-being and physical performance. ***Methods:*** 4,000 community-dwelling Chinese elderly ≥65 years were recruited. Medical illnesses, cigarette smoking, alcohol consumption, physical activity level and psychosocial well-being scores were recorded. Physical performance measured included grip strength, timed chair-stands, stride length and a timed 6-meter walk. Muscle mass was measured using dual-energy X-ray absorptiometry. Relationships between appendicular skeletal muscle mass (ASM/ht^2) and multiple variables were analyzed using uni- and multivariate analyses. ***Results:*** Mean ASM/ht^2 was 7.19 and 6.05 kg/m^2 in men and women respectively. Older age, cigarette smoking, chronic lung disease, atherosclerosis, underweight, and physical inactivity were associated with low adjusted ASM, which was in turn associated with poorer physical well-being in men. After adjustment to age, lower appendicular muscle mass was associated with weaker grip strength in both sexes. In men, lower limb tests (chair-stands, walking speed and step length) were not related to ASM, while in women, lower muscle mass was not associated with poorer lower limb muscle performance. ***Conclusions:*** Sarcopenia in community-dwelling older Chinese men and women was associated with cigarette smoking, chronic illnesses, underweight, physical inactivity, poorer well-being and upper limb physical performance.

This study was performed in the Jockey Club Center for Osteoporosis Care and Control, The Chinese University of Hong Kong, Hong Kong.

Introduction

Sarcopenia is increasingly being recognized as a prevalent problem among older persons [1–7] and is one of the major associated factors in frailty [3, 8, 9]. Cigarette smoking [4], poor health [4], low body mass index (BMI)

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0304–324X/07/0536–0404$23.50/0

Accessible online at:
www.karger.com/ger

Jenny S.W. Lee
Department of Medicine and Geriatrics, Shatin Hospital
Ah Kung Kok Street, Shatin, NT, Hong Kong, SAR (China)
Tel. +852 2636 7779, Fax +852 2635 1037
E-Mail jennyleesw@gmail.com

[6] and low testosterone level in men [6] were some of the associated factors identified in Western populations. However, little regarding sarcopenia among Asians has been reported in the literature. Apart from low body weight, associated factors of sarcopenia in the Chinese population have not been established [7].

Though the prevalence of sarcopenia among Chinese as defined by the young normal muscle mass was low according to a previous study [7], a relatively low muscle mass may already adversely affect quality of life and functional abilities. Since body composition varies between ethnic groups and health risks posed by cut-off points could be different across different populations, as in the case of the BMI [10], it would be meaningful to study how older Chinese perform as stratified by their muscle mass.

In conjunction with a cohort study on osteoporosis, we had the opportunity to study muscle mass in a large number of older Chinese men and women using dual-energy X-ray absorptiometry (DXA). Our aim was to establish the relationship between skeletal muscle mass and a large number of potential predictors such as chronic illnesses, lifestyle factors, physical activity level, and to determine how stratifications in muscle mass were related to outcomes such as physical performance measures and psychosocial well-being in a large Asian cohort.

Materials and Methods

4,000 community-dwelling men and women aged 65 years or over were invited to attend a health check carried out in the School of Public Health of the Chinese University of Hong Kong between August 2001 and December 2003 by placing recruitment notices in community centers for the elderly and in housing estates. Talks were also given at these centers explaining the purpose, procedures and investigations to be carried out. Only ethnic Chinese subjects were recruited. We excluded those who (1) were unable to walk without assistance of another person; (2) had had a bilateral hip replacement; (3) were not competent to give informed consent, and (4) had medical conditions (in the judgment of the study physicians) which made it unlikely that they would survive the duration of the study. The sample was stratified so that approximately 33% were in each of the age groups: 65–69, 70–74 and ≥75. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

The Questionnaire

A questionnaire containing information regarding demographics, smoking habit, alcohol intake, exercise habit, self-rated health [11], physical activity level (PASE score) [12], Geriatric Depression Scale [13], quality of life (Short Form 12 mental and Short Form 12 physical subscores) [14], and medical history was administered by trained interviewers. Smokers were classified by having ever smoked more than 5 packs of cigarettes in the past, drinkers by having consumed more than 5 units of alcohol per day ever, and exercise habit was established by asking whether the subject takes walks for exercise daily or almost daily.

The presence or absence of disease was based on the subjects' report of their physician's diagnoses, supplemented by the identification of drugs brought to the interviewers. Heart disease includes coronary heart disease, heart failure and myocardial infarction. Self-rated health was graded by each subject on a scale of 1 to 5, with 1 = excellent and 5 = poor [11]. Physical activity level was assessed using the Physical Activity Scale of the Elderly (PASE) [12]. This is a 12-item scale measuring the average number of hours per day spent in leisure, household and occupational physical activities over the previous 7-day period. Activity weights for each item were determined based on the amount of energy spent, and each item score was calculated by multiplying the activity weight with daily activity frequency. A summary score of all the items reflects the daily physical activity level. It has been validated and proven to be a reliable tool in measuring the physical activity of older people.

Physical Measurements

Body weight was measured, with subjects wearing a light dressing gown, by the Physician Balance Beam Scale (Health-o-Meter, Arlington Heights, Ill., USA). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Blood pressure was measured on both sides and the lower ankle-brachial index (the ratio of the systolic blood pressure of the posterior tibial artery to that of the brachial artery) of the two was used for analysis. The average grip strength was calculated using that of both hands (Jamar Hand dynamometer 5030 J1, Sammons Preston, Inc., Bolingbrook, Ill., USA). Subjects were asked to stand up with folded arms from a chair 5 times and the time required was recorded. The time to walk 6 m at normal pace was measured and the stride length was calculated by dividing the distance with the number of steps taken during the walk.

Measurement of Muscle Mass

We measured muscle mass using DXA, using a Hologic QDR 2000 densitometer (Hologic, Waltham, Wash., USA). In previous studies, the DXA-estimated appendicular skeletal mass (ASM) had been found to be a reasonably good predictor of total body skeletal mass quantified by multi-slice magnetic resonance imaging in healthy adults ($R^2 = 0.96$) [15]. In our cohort, ASM was calculated by the summation of muscle mass measured in the four limbs, with the operator adjusting the cut lines of the limbs according to specific anatomical landmarks as described by Heymsfield et al. [16]. All data used in the analysis were on participants who clearly fitted within the DXA field-of-view. During the course of the study, the DXA systems were regularly matched to quality assurance scans to ensure there was no drift. To adjust for body size, ASM was adjusted to height using the formula: height-adjusted ASM (kg/m^2) = ASM (kg)/height $(m)^2$, as proposed by Baumgartner et al. [1].

Statistical Analysis

In analyzing the relationship between medical conditions and height-adjusted ASM, the absolute difference in height-adjusted ASM between those with and without each condition was compared by unpaired t test. Psychosocial well-being scores and physical activity scores were examined in tertiles of height-adjusted

Table 1. Height-adjusted appendicular skeletal muscle mass (kg/m^2) stratified by age and gender

	Men				Women			
	n	ASM/Ht^2	difference from youngest age group (mean, 95% CI)	p value	n	ASM/Ht^2	difference from youngest age group (mean, 95% CI)	p value
Age, years								
65–69	664	7.36 (0.82)	–		669	6.11 (0.03)	–	
70–74	707	7.23 (0.78)	–0.13 (–0.21, –0.04)	0.004*	665	6.13 (0.03)	0.02 (–0.05, 0.10)	0.537
>74	629	6.99 (0.84)	–0.037 (–0.46, –0.28)	0.000*	666	5.93 (0.03)	–0.18 (–0.26, –0.10)	0.000*

* $p < 0.05$ when compared with youngest age group mean of same gender values are mean (standard error).

ASM and compared by analysis of variance, using the highest tertile as the reference group. Physical performance measures were examined against tertiles of height-adjusted ASM and adjusted to age, using analysis of covariance. All tests were two-sided and a p value of <0.05 was taken as statistically significant.

Results

We studied 2,000 men and 2,000 women aged ≥65, with a mean age of 72.5 ± 5.2 years. Their education levels varied between no education (21.4%), primary education (50.2%) to secondary education or above (28.4%). Most of them were independent in ambulation and all of them were community dwelling, with 86.4% living with either a family member or friend. Only 6 subjects walked with assisted devices. The mean height-adjusted ASM was 7.19 and 6.05 kg/m^2 in men and women respectively. Table 1 shows the height-adjusted ASM across age groups. Height-adjusted ASM was associated with older age, with the trend being more apparent in men (table 1).

Lifestyle Factors and Chronic Medical Conditions

Table 2 shows the relationship between different lifestyle factors, chronic illnesses and height-adjusted ASM. Among lifestyle factors, current smoking was highly associated with lower height-adjusted ASM while ex-smoking, drinking and daily walks for exercise did not show any significant relationship to muscle mass. Physical activity as stratified by quartiles of the PASE score was positively associated with muscle mass in both men and women, with those having least activities having significantly lower muscle mass.

Underweight (defined as BMI <18.5), chronic obstructive pulmonary disease (COPD) and atherosclerosis (defined as ankle:brachial blood pressure ratio <0.9) were associated with lower height-adjusted ASM. On the other hand, diabetes, hypertension and heart diseases were associated with higher height-adjusted ASM. The associations between muscle mass and chronic diseases were consistent between men and women.

Physical Performance Measures

Table 3 shows the results of physical performance measures across tertiles of height-adjusted ASM and their associations after adjustment to age. Among men, only weaker grip strength was associated with lower muscle mass. Speed of walking and chair-stands did not demonstrate any association with muscle mass. On the other hand, women in the lowest tertile of muscle mass performed significantly better in all three lower limb performance tests though poorer in grip strength, when compared with those in the highest tertile. Grip strength among all tests showed the strongest association with muscle mass in both men and women.

Psychosocial and Physical Activities

Comparing to those in the highest tertile of height-adjusted ASM, men in the lowest tertile of muscle mass had poorer physical well-being but the association was not significant in women. Neither the Geriatric Depression Score nor the mental well-being score was related with muscle mass (table 4).

Discussion

The mean height-adjusted ASM was 7.19 kg/m^2 in older Chinese men. This was much lower than that found in White and Black populations [4, 17]. The mean height-adjusted ASM in older Chinese women was 6.05 kg/m^2,

Table 2. Comparison of height-adjusted appendicular skeletal muscle mass (ASM/Ht^2) with respect to lifestyle factors and medical conditions

	Men				Women			
	n	ASM/Ht^2 kg/m^2	mean difference (95% CI)	p value[a]	n	ASM/Ht^2 kg/m^2	mean difference (95% CI)	p value[a]
Drinker								
Yes	159	7.23	0.04 (–0.09, 0.17)	n.s.	1	6.76	0.68 (–0.75, 2.09)	n.s.
No	1,838	7.19			1,999	6.05		
Ever smoker[b]								
Current	238	7.03	–0.19 (–0.31, –0.07)	0.002*	37	5.76	–0.3 (–0.54, –0.07)	0.012*
Ex smoker	1,038	7.12	0.05 (–0.02, 0.13)	n.s.	153	5.94	–0.173 (–0.21, 0.03)	n.s.
Never	724	7.22			1,810	6.07		
Daily walks for exercise								
Yes	1,337	7.19	0.00 (–0.08, 0.08)	n.s.	1,121	6.03	0.04 (–0.10, 0.02)	n.s.
No	663	7.19			879	6.08		
PASE scores[b]								
Lowest quartile	487	7.07	–0.27 (–0.37, –0.17)	0.000*	504	5.94	–0.22 (–0.31, –0.13)	0.000*
Second quartile	516	7.16	–0.18 (–0.28, –0.08)	0.011*	446	5.99	–0.18 (–0.27, –0.08)	0.001*
Third quartile	500	7.22	–0.13 (–0.23, –0.02)	0.032*	557	6.12	–0.04 (–0.13, 0.05)	n.s.
Highest quartile	497	7.34			493	6.16		
COPD								
Yes	232	6.90	–0.32 (–0.49, –0.20)	0.000*	101	5.89	–0.16 (–0.31, –0.02)	0.025*
No	1,768	7.23			1,899	6.06		
ABI								
< or = 0.9	95	6.89	–0.31 (–0.48, –0.14)	0.022*	180	5.94	–0.12 (–0.23, –0.01)	n.s.
> 0.9	1,904	7.21			1,819	6.06		
BMI								
<18.5	115	5.89	–1.28 (–1.47, –1.29)	0.000*	100	5.04	–1.06 (–1.15, –0.97)	0.000*
≥18.5	1,885	7.27			1,900	6.11		
Diabetes								
Yes	293	7.41	0.25 (0.15, 0.35)	0.000*	286	6.16	0.12 (0.04, 0.21)	0.003*
No	1,707	7.16			1,714	6.03		
Hypertension								
Yes	836	7.34	0.25 (0.18, 0.32)	0.000*	871	6.13	0.13 (0.07, 0.19)	0.000*
No	1,164	7.09			1,129	6.00		
Heart disease								
Yes	366	7.30	0.12 (0.03, 0.22)	0.003*	330	6.17	0.14 (0.05, 0.22)	0.001*
No	1,634	7.18			1,670	6.04		

PASE = Physical activity scale of the elderly; ASM = appendicular skeletal muscle mass; CI = confidence interval, COPD = chronic obstructive airway diseases; ABI = ankle-brachial index; BMI = body mass index; n.s. = not significant.

[a] Comparisons were done by analysis of covariance, adjusted to age.

[b] p values are comparisons to never smokers and highest quartile in PASE scores respectively.

* $p < 0.05$.

slightly lower than that in White women but much lower than that in Black women [4, 5, 18].

We found that current but not past history of cigarette smoking might be a risk factor of sarcopenia among older Asians. The relationship was particularly strong in men. Lau et al. [7] had reported a suggestive effect of smoking on sarcopenia in Chinese women but that did not reach statistical significance. Using a much larger co-

Table 3. Comparison of physical performance measures across tertiles of height-adjusted appendicular skeletal muscle mass

	Men, kg/m^2			Women, kg/m^2		
	high >7.52	intermediate 6.83–7.52	low <6.83	high >6.33	intermediate 5.69–6.33	low <5.69
Grip strength, kg	33.52 (0.25)	31.43 (0.23)	28.66 (0.24)	21.39 (0.17)	20.40 (0.16)	18.98 (0.14)
p	–	0.000*	0.000*	–	0.000*	0.000*
Five chair-stands test, s	12.33 (0.14)	12.75 (0.16)	12.87 (0.16)	13.57 (0.22)	13.50 (0.21)	13.18 (0.16)
p	–	0.197	0.409	–	0.580	0.023*
Six-meter walk speed, m/s	1.05 (0.01)	1.02 (0.01)	0.99 (0.01)	0.90 (0.01)	0.93 (0.01)	0.92 (0.01)
p	–	0.355	0.141	–	0.003*	0.002*
Step length, m	0.58 (0.00)	0.58 (0.00)	0.57 (0.00)	0.49 (0.00)	0.49 (0.00)	0.50 (0.00)
p	–	0.918	0.616	–	0.040*	0.000*

Comparisons used the highest tertile height-adjusted ASM group as reference group by analysis of covariance, adjusted to age. Figures expressed are mean (standard error). CI = Confidence interval; ASM = appendicular skeletal muscle mass.

* $p < 0.05$.

Table 4. Comparison of psychosocial well-being scores across tertiles of height-adjusted appendicular skeletal muscle mass

	Men, kg/m^2			Women, kg/m^2		
	high >7.52	intermediate 6.83–7.52	low <6.83	high >6.33	intermediate 5.69–6.33	low <5.69
SF-12 physical subscore	51.45 (0.26)	50.56 (0.29)	49.57 (0.32)	46.60 (0.34)	46.51 (0.33)	46.67 (0.35)
p	–	0.033*	0.000*	–	0.844	0.879
SF-12 mental subscore	56.00 (0.25)	55.73 (0.27)	55.75 (0.26)	55.09 (0.31)	55.30 (0.29)	54.75 (0.31)
p	–	0.473	0.500	–	0.608	0.424
GDS score	2.85 (0.10)	2.92 (0.11)	3.14 (0.11)	2.96 (0.12)	2.99 (0.11)	3.11 (0.11)
p	–	0.601	0.054	–	0.832	0.318

Comparisons used the highest tertile height-adjusted ASM group as reference group by analysis of variance. Figures expressed as mean (standard error). CI = Confidence interval; ASM = appendicular skeletal muscle mass; SF-12 = Short Form 12 quality of life score; GDS = Geriatric Depression Scale.

* $p < 0.05$.

hort, we were able to establish that association. Whether smoking is indeed a risk factor needs to be determined by a prospective study.

Regular load-bearing exercise and daily walks were not associated with higher muscle mass both in Lau et al.'s [7] and our study respectively. However, the PASE score, a more detailed record on time and physical exertion involved in recreational, household and social/voluntary work in a week did review a highly significant relationship between physical inactivity and low appendicular muscle mass. Past studies have shown that progressive resistive exercise could increase muscle size and strength [19, 20] while endurance training alone might not [21]. On the other hand, findings of a longitudinal study suggested that leisure time physical activities were not likely to be able to prevent sarcopenia [22]. Being cross-sectional, our results could not establish a causal relationship between these activities and sarcopenia. Prospective interventional studies will be required to determine the intensity and type of exercise

or activities most useful to counteract age-related muscle loss.

Underweight was strongly associated with sarcopenia, which reaffirmed the findings of Lau et al. [7]. In addition, we found that COPD and atherosclerosis were also associated with lower muscle mass. The chronic activation of inflammatory cytokines in COPD [23, 24] might have contributed to muscle wastage, as inflammatory cytokines such as tumor necrosis factor, interleukin-1 and 6 and oxidative stress have been shown to be important catabolic factors [25–27]. Disuse muscle atrophy due to restricted exercise tolerance in COPD could be another mechanism. Atherosclerosis was associated with low muscle mass in our study and the effect was likely to be mediated through cytokines such as low insulin-like growth factor I [28], an important modulator of muscle mass and function.

We found that among Chinese, sarcopenia in older women was less associated with poor physical performance than in older men. In contrast to women, men performed similarly in most physical function tests across all tertiles of muscle mass. Previous groups [17, 29, 30] had reported that in non-Asian older women, high body fat rather than low muscle mass might be more important in predicting functional limitations, while Janssen et al. [3] were able to find association between sarcopenia and poor function in both men and women. On the other hand, this sex difference in the effect of sarcopenia on physical performance could also be related to the method of adjustment for body size. As reported by Newman et al. [4], among his female subjects, the association of sarcopenia and lower physical functions was apparent only in the residuals method but not in the height-adjustment method. The inverse relationship between lower limb muscle performance and appendicular muscle mass among women suggested that factors other than age and muscle mass were in place. The search for these factors in women could be important as weight-bearing activities contribute heavily to ambulation and independence in activities of daily living.

In our cohort, grip strength alone among all physical performance tests was strongly associated with appendicular muscle mass in both genders, suggesting that this simple test could serve as a convenient surrogate marker of muscle mass in future epidemiology studies among community-dwelling older Asians.

To the best of our knowledge, this was the largest body composition study in older Asians using DXA measurements. Following the study of Lau et al. [7], this study provided further information regarding sarcopenia among Asians utilizing a much larger cohort and included more variables such as a detailed physical activity record, several physical performance measures that reflected upper and lower limb strength, and quality of life measurements.

We must however draw attention to the limitations of our results. Firstly, being cross-sectional, the results could not be used to establish cause-effect relationship between the associated factors and sarcopenia. Secondly, our subjects were independently living volunteers who were interested in participating in research and therefore were likely to represent only the healthier and more educated amongst the general older population. Finally, our physical performance tests were carried out under test conditions and might not directly translate into functional impairment and disability in daily living, which would be more meaningful outcomes. Nevertheless, our findings suggested possible risk factors of sarcopenia in older Chinese men and women, and provided physical performance data for which future studies in Asians could be based on.

Conclusion

Older age, cigarette smoking, COPD, underweight, atherosclerosis and physical inactivity were associated with sarcopenia in older Chinese men and women. Muscle mass was strongly associated with poorer upper limb physical performance in both men and women. Men with lower muscle mass in addition had poorer physical well-being. Longitudinal studies would be required to answer how these findings would be translated into clinically important outcomes such as falls, institutionalization and mortality.

Acknowledgements

This study is jointly supported by the Hong Kong Research Grant Council and grant 5R01 AR049439-02 from the National Institute of Health. The authors would like to thank Mr. Jason Leung for his advice in statistical analysis.

References

1 Baumgartner RN, Koehler KM, Gallagher D, et al: Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755–763.
2 Melton LJ III, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM, Riggs BL: Epidemiology of sarcopenia. J Am Geriatr Soc 2000;48:625–630.
3 Janssen I, Heymsfield SB, Ross R: Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–890.
4 Newman AB, Kuplelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB: Sarcopenia: alternative definitions and associations with lower extremity function. J Am Geriatr Soc 2003;51:1602–1609.
5 Rolland Y, Lauwers-Cances V, Cournot M, Nourhashemi F, Reynish W, Riviere D, Vellas B, Grandjean H: Sarcopenia, calf circumference, and physical function of elderly women: a cross-sectional study. J Am Geriatr Soc 2003;51:1120–1124.
6 Iannuzzi-Sucich M, Prestwood KM, Kenny AM: Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol Med Sci 2002; 57:M772–M777.
7 Lau EMC, Lynn HSH, Woo JW, Kwok TCY, Melton LJ III: Prevalence of and risk factors for sarcopenia in elderly Chinese men and women. J Gerontol Med Sci 2005;60:M213–M216.
8 Fried LP, Tangen CM, Walston J, et al: Frailty in older adult: evidence for a phenotype. J Geront Med Sci A 2001;56A:M146–M156.
9 Cesari M, Leeuwenburgh C, Lauretani F, et al: Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr 2006;83:1142–1148.
10 WHO Expert Consultation: Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163.
11 Goldstein M, Siegel J, Boyer R: Predicting changes in perceived self-reported health status. Am J Publ Health 1984;74:611–614.
12 Washburn RA, Smith KW, Jette AM, Janny CA: The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153–162.
13 Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al: Development and validation of a geriatric depression screening scale. J Psychiatr Res 1983;17:37–49.
14 Ware JE, Kosinski M, Keloler SD: SF-36 Health Survey: Manual and Interpretational Guide. Boston, The Health Institute, New England Medical Center, 1994.
15 Kim J, Wang ZM, Heymsfield SB, Baumgartner RN, Gallagher D: Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 2002;76:378–383.
16 Heymsfield SB, Smith R, Aulet M, et al: Appendicular skeletal muscle mass: measurement by dual-energy X-ray absorptiometry. Am J Clin Nutr 1990;52:214–218.
17 Davison KK, Ford ES, Cogswell ME, Dietz WH: Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. J Am Geriatr Soc 2002;50: 1802–1809.
18 Kanis JA, Johnell O, Oden A, et al: Smoking and fracture risk: a meta-analysis. Osteoporos Int 2005;16:155–162.
19 Charette SL, McEvoy L, Pyka G, et al: Muscle hypertrophy response to resistance training in older women. J Appl Physiol 1991;70: 1912–1916.
20 Frontera WR, Meredith CN, O'Reilly KP, Evans WJ: Strength training and determinants of $VO_{2\,max}$ in older men. J Appl Physiol 1990; 68:329–333.
21 Klittgaard H, Mantoni M, Schiaffino S, et al: Function, morphology and protein expression of ageing skeletal muscle: a cross-sectional study of elderly men with different training backgrounds. Acta Physiol Scand 1990;140:41–54.
22 Raguso CA, Kyle U, Kossovsky MP, et al: A three-year longitudinal study on body composition changes in the elderly: role of physical exercise. Clin Nutr 2006;25:573–580.
23 Di Francia M, Barbier D, Mege JL, et al: Tumor necrosis factor-α levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;150:1453–1455.
24 De Godoy I, Donahoe M, Calhoun WJ, et al: Elevated TNF-α production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med 1996;153: 633–637.
25 Dinarello CA: Biological basis for interleukin-1 in disease. Blood. 1996;87:2095–2147.
26 Boots AW, Haenen GRMM, Bast A: Oxidant metabolism in chronic obstructive pulmonary disease. Eur Respir J 2003;22(suppl 46):14s–27s.
27 Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS: Sarcopenia. J Lab Clin Med 2001;137:231–243.
28 Ceda GP, Dall'Aglio E, Maggio M, et al: Clinical implications of the reduced activity of the GH-IGF-I axis in older men. J Endocrinol Invest 2005;28(suppl):96–100.
29 Zoico E, Di Francesco V, Guralnik JM, et al: Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. Int J Obes Relat Metab Disord 2004;28:234–241.
30 Lebrun CE, van der Schouw YT, de Jong FH, Grobbee DE, Lamberts SW: Fat mass rather than muscle strength is the major determinant of physical function and disability in postmenopausal women younger than 75 years of age. Menopause 2006;13:474–481.

DOI: 10.1111/j.1464-5491.2010.03118.x

Original Article: Pathophysiology

The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults

J. S. W. Lee*†‡, T. W. Auyeung§¶, J. Leung**, T. Kwok*, P. C. Leung** and J. Woo*

*Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, †Department of Medicine and Geriatrics, Shatin Hospital, ‡CADENZA Project, A Jockey Club Initiative for Seniors, §Department of Medicine and Geriatrics, Pok Oi Hospital, ¶The S. H. Ho Centre of Geriatrics and Gerontology and **Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong, Hong Kong, China

Accepted 25 August 2010

Abstract

Aims Diabetes mellitus may be associated with excessive lean mass loss. Other diabetes-related conditions may also play a role. We assessed body composition changes associated with diabetes in older adults with adjustment for diabetes-related co-morbidities.

Methods Three thousand, one hundred and fifty-three community-living adults aged ≥ 65 years were examined for lifestyle factors, diabetes-related medical conditions and body composition by dual energy X-ray absorptiometry at baseline and 4 years later. Body composition changes were compared between participants with diabetes and those without diabetes. Multivariate linear regression was used to examine the relationship between appendicular lean mass loss and confounders.

Results Appendicular lean mass loss in men with diabetes was two times that of men without diabetes (−1.5% in 'no diabetes' vs. −3.0% in 'diabetes') and in women with diabetes was 1.8 times that of those without diabetes (−1.9% in 'no diabetes' vs. −3.4% in 'diabetes') over 4 years. Men with diabetes also had higher total body mass loss and higher total body fat loss than men without diabetes. Women with diabetes had higher total body mass loss but total body fat loss was similar. After adjusting for age, body mass index, diabetes-related conditions, lifestyle factors and total body mass loss, diabetes remained an independent predictor of appendicular lean mass loss in both men and women.

Conclusion Diabetes was associated with higher body mass loss and higher appendicular lean mass loss in older adults. In men, diabetes was also associated with total body fat loss.

Diabet. Med. 27, 1366–1371 (2010)

Keywords diabetes, elderly, muscles, sarcopaenia

Introduction

Diabetes mellitus becomes more prevalent with ageing [1–5] and is associated with significant disability in older adults [6–9]. With ageing, fat increases while muscle decreases [10], resulting in sarcopaenia, an important component of frailty [11–13]. Diabetes was associated with higher fat mass and lower muscle mass in older adults in a cross-sectional study in a Western population [14]. In the Chinese population, however, diabetes was associated with higher muscle mass [15], yet its association with disability remained similar [16,17]. There is a variety of mechanisms by which diabetes can act synergistically with ageing to accelerate muscle loss [13], but longitudinal studies on how diabetes affected body composition and muscle loss were few. Only one cohort has reported longitudinal data in muscle loss among older adults with diabetes at 3 years [18] and 6 years [19]. In these reports, diabetes was associated with more appendicular muscle loss over time in older White and Black adults.

Diabetes commonly coexists with hypertension, heart disease, stroke, atherosclerosis and obesity. These conditions could predispose to sarcopaenia directly or they might have done so through their association with diabetes [13,20]. Identification of the independent risk factors of sarcopaenia may facilitate early intervention to sarcopaenia-associated frailty.

We examined the effect of diabetes on muscle loss and concurrent body composition changes over 4 years and studied whether this effect of diabetes is independent of other diabetes-related conditions in a large cohort of well-functioning older adults. We hypothesized that diabetes was an independent risk

Correspondence to: Jenny S. W. Lee, Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong. E-mail: jennylee@cuhk.edu.hk

factor for muscle loss in older people, irrespective of the effect of other diseases commonly coexisting with diabetes.

Subjects and methods

Between August 2001 and December 2003, 4000 community-dwelling ethnic Chinese men and women aged 65 years or over were recruited by notices in elderly social centres and housing estates to attend a health check in the School of Public Health of The Chinese University of Hong Kong. We excluded those who (i) were unable to walk independently, (ii) had had bilateral hip replacements, (iii) were not competent to give informed consent and (iv) had medical conditions which made it unlikely that they would survive the follow-up period of 4 years (in the judgment of the study physicians). The sample was stratified to have equal numbers in three age groups: 65–69, 70–74 and 75 years or above. The study was approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong.

The Questionnaire

A questionnaire containing information regarding demographics, lifestyle, physical activity level and medical history was administered by trained interviewers. Smokers were classified by 'having ever smoked more than five packs of cigarettes in the past', 'smoking currently' or 'never smoked'.

Physical activity level was assessed using the Physical Activity Scale of the Elderly [21], which measured the number of hours per day spent in leisure, household and occupational physical activities over the previous 7 days. Activity weights for items were based on the amount of energy spent and each item score was calculated by multiplying the weight with activity frequency. A summary score reflected the daily physical activity level.

Medical diagnoses

Medical diagnoses were based on the subjects' report of their physician's diagnoses, supplemented by medications brought to the interviewers. Diabetes was defined by either self-report (ever being told by a physician that the patient had diabetes) or being on hypoglycaemic agents, which were brought to the study centre for confirmation. Stroke, heart disease and hypertension were defined by self-reporting. Heart disease included coronary heart disease, heart failure and myocardial infarction. Self-report diseases have been recognized as a valid method for collecting medical diagnoses in large-scale studies [22,23]. Low ankle-brachial index was defined as the ankle–brachial index (the ratio of the systolic blood pressure of the posterior tibial artery to that of the brachial artery) being < 0.9 [24].

Physical measurements

Body weight was measured, with subjects wearing a light dressing gown, using the Physician Balance Beam Scale (Health-O-Meter, Arlington Heights, IL, USA). Height was measured using the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Blood pressure was measured on both sides at the arm and at the posterior tibial artery. The lower ankle–brachial index measurement of the two was used for analysis. Hip circumference (the maximum circumference around the buttocks posteriorly and the symphysis pubis anteriorly) and waist circumference (the narrowest circumference around the trunk between the rib cage and the pelvis) were measured with a flexible measuring tape to the nearest millimeter. Waist–hip ratio was taken to be high if > 0.9 in men and > 0.85 in women [25].

Body composition

We measured total body mass, body fat and lean mass by dual-energy X-ray absorptiometry using a Hologic QDR 4500W densitometer (Hologic Delphi, software version 11.2; Hologic Inc, Bedford, USA) at baseline and 4 years later. Appendicular lean mass was calculated by the sum of lean mass measured in the four limbs, with the operator adjusting the cut lines of the limbs according to specific anatomical landmarks as described by Heymsfield *et al*. [26]. In delineating the trunk for measurement of the trunk fat, a line was drawn just below the chin to separate the head from the trunk. Another line was drawn between the head of the humerus and the scapula through the glenoid fossa to separate the arm from the trunk, and another passed through the femoral necks and just below the ischium to separate the pelvis from the leg. The Hologic Body composition step phantom was scanned daily to ensure proper calibration for fat and non-fat compartments. The maximum coefficient of variation for fat and lean mass is 1.47% and 0.84%, respectively.

Statistical methods

Data analysis was performed using statistical package SAS, version 9.1 (SAS Institute, Inc., Cary, NC, USA). As body composition differs with gender, all statistical tests were carried out separately for men and women. Characteristics of subjects with diabetes and those without were compared. Two-samples independent *t*-tests were used for continuous variables and χ^2-tests for categorical variables. Body composition changes at 4 years were compared by using analysis of covariance (ANCOVA), adjusting for age. Multivariate linear regressions were used to examine the relationship between appendicular lean mass loss and diabetes, adjusting for age, physical activity, smoker status, BMI and diabetes-related conditions (low ankle–brachial index, hypertension, heart disease and stroke) and total body mass loss, in different models. All tests were two-sided and a *P*-value of < 0.05 was taken as statistically significant.

Results

Four thousand participants had a baseline dual-energy X-ray absorptiometry measurement and 3153 (74.95%) returned for the 4th-year dual-energy X-ray absorptiometry measurements. Among those who did not return, 248 (6.2%) had died and 599

(15.0%) defaulted. Those who did not return were older, had lower physical activity, lower total body mass, lower appendicular lean mass and were more likely to have an ankle–brachial index measurement < 0.9 at baseline. Women who did not return were more likely to have high waist–hip ratio and men who did not return were more likely to be current smokers and have a history of stroke. A similar proportion of participants with diabetes did and did not return for the 4th-year measurement.

At baseline, adults with diabetes were more likely to have hypertension, heart disease, low ankle–brachial index and high waist–hip ratio (Table 1). In both men and women, there was no difference in physical activity scores among those with or without diabetes. Among the 3153 subjects with both baseline and 4th-year dual-energy X-ray absorptiometry measurements, 442 (14.0%) had diabetes. Both men and women with diabetes had higher total body lean mass and total lean mass % (total lean mass/total body mass) than those without diabetes, but participants with diabetes had lower appendicular lean mass to total body lean mass ratios.

Changes in body composition over time are presented in Table 2. Participants both with and without diabetes had significant loss of total body mass and appendicular lean mass after 4 years, irrespective of gender ($P < 0.001$). Appendicular lean mass loss per year in our male participants was 69.5 g/year (without diabetes) vs. 150.3 g/year (with diabetes) and in our female participants was 64.5 g/year (without diabetes) vs. 118.8 g/year (with diabetes). Those with diabetes had higher total body mass loss than those without diabetes (−2.3 vs. −0.9% in men, $P < 0.001$; −2.4 vs. −1.2% in women, $p = 0.005$). Participants both with diabetes and without diabetes lost total body lean mass, trunk lean mass and appendicular lean mass over time, but those with diabetes had higher loss than those without. Men without diabetes lost appendicular lean mass at a rate of 1.5% over 4 years, while women without diabetes lost appendicular lean mass at a rate of 1.9% over the same period. The difference in lean mass loss was more marked in the limbs (−3.0 vs. −1.5% in men, $P < 0.001$; −3.4 vs. −1.9% in women, $P < 0.001$) than in the trunk (−2.7 vs. −1.9% in men, $P = 0.003$; −2.5 vs. −1.9% in women, $P = 0.034$).

Multivariate analyses

Table 3 shows the relationship of appendicular lean mass loss over time in relation to diabetes, adjusted for age, physical activity, smoking status, BMI, total body mass change and diabetes-related conditions. The appendicular lean mass loss in

Table 1 Comparison of baseline characteristics between subjects with diabetes (DM) and without diabetes (no DM)

	Men			Women		
	No DM (n = 1344)	DM (n = 222)	P-value	No DM (n = 1367)	DM (n = 220)	P-value
	Mean (SD)/ frequency (%)	Mean (SD)/ frequency (%)	P-value of t-test/χ^2-test	Mean (SD)/ frequency (%)	Mean (SD)/ frequency (%)	P-value of t-test/χ^2-test
Age	71.7 (4.7)	72.0 (4.6)	0.439	72.0 (5.1)	72.4 (4.9)	0.235
PASE score	100.7 (50.1)	100.1 (54.5)	0.864	86.8 (33.6)	88.1 (32.1)	0.601
Body mass index (kg/m^2)	23.3 (3.1)	24.7 (2.8)	< 0.001	23.9 (3.4)	24.3 (3.3)	0.104
Total body mass (kg)	61.4 (9.1)	64.9 (8.2)	< 0.001	54.4 (8.4)	55.6 (8.5)	0.052
Total body fat mass (kg)	15.1 (4.6)	16.6 (4.3)	< 0.001	19.2 (5.1)	19.0 (5.1)	0.629
Total body lean mass (kg)	44.2 (5.3)	46.1 (4.8)	< 0.001	33.8 (4.0)	35.1 (4.3)	< 0.001
Trunk fat mass (kg)	8.5 (3.0)	9.9 (2.8)	< 0.001	9.9 (2.9)	10.2 (2.7)	0.141
Trunk lean mass (kg)	21.6 (2.7)	22.7 (2.5)	< 0.001	17.0 (2.1)	17.9 (2.3)	< 0.001
Appendicular fat mass (kg)	5.7 (1.8)	5.9 (1.8)	0.171	8.5 (2.5)	8.0 (2.7)	0.007
Appendicular lean mass (kg)	19.3 (2.6)	19.9 (2.3)	< 0.001	13.8 (1.9)	14.3 (2.0)	0.002
Total lean mass/total body mass (%)	71.3 (4.1)	72.5 (4.7)	0.001	62.6 (5.0)	63.6 (5.0)	0.005
Appendicular lean mass/total body lean mass (%)	43.5 (1.5)	43.2 (1.5)	0.003	40.9 (1.6)	40.5 (1.7)	0.004
Smoker status			0.364			0.434
Never smokers	506 (37.7%)	86 (38.7%)		1249 (91.4%)	199 (90.5%)	
Ex-smokers	686 (51.0%)	118 (53.2%)		94 (6.9%)	19 (8.6%)	
Current smokers	152 (11.3%)	18 (8.1%)		24 (1.8%)	2 (0.9%)	
Hypertension	499 (37.1%)	148 (66.7%)	< 0.001	540 (39.5%)	154 (70.0%)	< 0.001
Stroke	50 (3.7%)	21 (9.5%)	< 0.001	46 (3.4%)	8 (3.6%)	0.837
Heart disease	222 (16.5%)	53 (23.9%)	0.008	209 (15.3%)	48 (21.8%)	0.015
ABI < 0.9	40 (3.0%)	7 (3.2%)	0.888	101 (7.4%)	24 (10.9%)	0.073
High gender-specific waist–hip ratio	839 (62.4%)	174 (78.4%)	< 0.001	1086 (79.5%)	195 (88.6%)	0.001

ABI, ankle–brachial index; PASE, Physical Activity Scale for the Elderly.

Table 2 Comparison of body composition changes over 4 years between subjects with diabetes (DM) and without diabetes (no DM)

Body composition changes at 4 years	Men						Women					
	No DM (n = 1344)		DM (n = 222)		Difference		No DM (n = 1367)		DM (n = 220)		Difference	
	Mean (SD)	%*	Mean (SD)	%*	Mean (SE)	%*	*P*-value[a]	Mean (SD)	%*	Mean (SD)	%*	Mean (SE)	%*	*P*-value¶
Total body mass (g)	−576 (2977)§	−0.9	−1482 (3147)§	−2.3	−887 (216)	−1.3	< 0.001	−670 (2923)§	−1.2	−1297 (2882)§	−2.4	−597 (211)	−1.1	0.005
Total body fat mass (g)	107 (2130)	0.7	−269 (1997)	−1.6	−370 (153)	−2.3	0.016	−70 (2155)	−0.4	−332 (2109)†	−1.8	−241 (155)	−1.4	0.120
Total body lean mass (g)	−709 (1540)§	−1.6	−1,251 (1912)§	−2.7	−530 (115)	−1.1	< 0.001	−606 (1311)§	−1.8	−957 (1313)§	−2.8	−343 (95)	−1.0	< 0.001
Trunk fat mass (g)	−22 (1381)	−0.3	−291 (1318)‡	−3.0	−264 (99)	−2.7	0.008	−107 (1304)‡	−1.1	−262 (1286)§	−2.6	−143 (94)	−1.5	0.128
Trunk lean mass (g)	−398 (913)§	−1.9	−604 (1083)§	−2.7	−200 (68)	−0.8	0.003	−324 (757)§	−1.9	−443 (743)§	−2.5	−116 (55)	−0.6	0.034
Appendicular fat mass (g)	137 (830)§	2.4	35 (771)	0.6	−101 (60)	−1.8	0.089	43 (926)	0.5	−58 (952)	−0.7	−93 (67)	−1.2	0.168
Appendicular lean Mass (g)	−278 (836)§	−1.5	−601 (1030)§	−3.0	−315 (62)	−1.6	< 0.001	−258 (683)§	−1.9	−475 (694)§	−3.4	−212 (50)	−1.5	< 0.001

*% change from baseline; †P < 0.05; ‡P < 0.01; §P < 0.001, age adjusted P-value compared with baseline.
¶P-value of ANCOVA, age adjusted for DM vs. no DM within gender .

Table 3 Multivariate linear regression models showing relationship between appendicular lean mass (ALM) % change over time and diabetes, adjusted for age, physical activity, smoking status, BMI, total body mass change and diabetes-related conditions

	ALM % change over 4 years (SE)	
	Men (n = 1566)	Women (n = 1587)
Diabetes (vs. no diabetes)		
Model 1	−1.380 (0.326)‡	−1.387 (0.360)‡
Model 2	−0.846 (0.256)†	−0.962 (0.289)‡
Model 3	−0.783 (0.256)†	−0.951 (0.289)†

*P < 0.05; †P < 0.01; ‡P < 0.001.
Model 1: adjusted for age, Physical Activity Scale of the Elderly (PASE) score, smoker status (never, ex- and current), low ankle–brachial index, stroke, hypertension, heart disease, BMI
Model 2: additionally adjusted for total body mass % change over 4 years.
Model 3: additionally adjusted for PASE score change over 4 years.

men and women with diabetes was higher than those without diabetes by 1.380 and 1.387%, respectively. The difference was attenuated after additional adjustment for total body mass loss over the same period in model 2, but association between diabetes and appendicular lean mass loss remained significant. Having diabetes was associated with an additional 0.85% of appendicular lean mass loss in men and 0.96% loss in women. Total body mass loss over time was strongly associated with appendicular lean mass loss in men and women irrespective of diabetes status [2.664% (0.086%) per additional 5 kg total body mass loss in men, P <0.001; 2.635% (0.089%) in women, P < 0.001]. There was no significant interaction effect between age and diabetes (P > 0.30) on appendicular lean mass change, in either men or women. Further adjustment for changes in the Physical Activity Scale of the Elderly over four years (model 3) showed that the effect of diabetes was only slightly attenuated. The change in the physical activity score was significant in the multivariate model only in men but not in women.

Discussion

Our results suggest that diabetes is associated with increased lean mass loss and, in particular, appendicular lean mass loss in older adults over a period of 4 years. This concurs with the findings of Park *et al.* [18,19], in which a similar association was found in White and Black older adults. Diabetes was associated with a higher prevalence of disability and a more rapid decline in functions [9,23]. As appendicular lean mass was associated with poorer physical function in old age [10,27], it is possible that higher appendicular lean mass loss in diabetes contributes partly to this phenomenon.

There was a loss of total body mass in participants both with and without diabetes over time. The magnitude of body mass loss was higher among our participants with diabetes. Diabetes-

associated weight loss has been previously reported [28] and was found to be associated with adverse health outcomes. Low body mass and weight loss have also been reported as risk factors for mortality, disability and institutionalization in old age [28–30]. Our results suggest that diabetes is associated with excessive loss of weight through excessive loss of both body fat and lean mass, especially in men.

In our cohort, diabetes was consistently associated with appendicular lean mass loss in both men and women, independent of the diabetes-related conditions studied (low ankle–brachial index, high BMI, heart disease, stroke and hypertension). The average appendicular lean mass loss difference between participants with diabetes and those without diabetes was 1.6% per 4 years (0.40% per year) in men and 1.5% per 4 years (0.38% per year) in women. This difference was comparable with or slightly greater than that reported in White and Black populations [18], which averaged approximately 1% per 3 years (0.33% per year), with men and women considered together. Absolute appendicular lean mass loss in our male participants was 69.5 g/year (without diabetes) vs. 150.3 g/year (with diabetes) and in our female participants was 64.5 g/year (without diabetes) vs. 118.8 g/year (diabetes). In term of absolute weight, this loss was lower than that in White and Black populations, as estimated from the report by Park *et al*. (193.3 g/year without diabetes vs. 246.7 g/year with diabetes, with men and women taken together) [18], but their baseline total body mass and appendicular lean mass were much higher than in our results. Unfortunately, as no separate data for men and women and White and Black populations were available, the effect of diabetes on appendicular lean mass in different ethnic groups in each of the genders could not be directly compared at present. As lean mass, especially appendicular lean mass, is associated with activities of daily living [27], and Asians have a greater increase in diabetes prevalence in comparison with other populations [2], the impact of diabetes on appendicular lean mass loss may lead to a higher diabetes-related healthcare burden in Asian populations.

In our cohort, the absolute amount of total lean mass, appendicular lean mass and total lean mass % were higher in participants with diabetes, but the relative proportion of lean mass in the limbs (appendicular lean mass/total lean mass) was lower in participants with diabetes. A higher lean mass in diabetes was also found in White and Black populations [18]. Increased fat infiltration of muscles in diabetes [13] might account for the higher total lean mass when measured by dual-energy X-ray absorptiometry, which could not distinguish between muscle and muscle infiltrated by fat. Whether diabetes causes higher fat infiltration in trunk lean mass (e.g. internal organs) when compared with appendicular lean mass could not be answered using dual-energy X-ray absorptiometry measurements.

There were multiple possible mechanisms of more rapid loss of appendicular lean mass observed in older adults with diabetes, most of which involved alterations in protein synthesis and protein breakdown in muscles. Lower bioavailable testosterone and insulin-like growth factor 1 in older men with diabetes might contribute to lower protein synthesis, while higher pro-inflammaory cytokines and higher angiotension II levels might contribute to increased muscle breakdown, resulting in loss of muscle mass [13,20].

While physical activities had been associated with muscle mass in older populations [31], physical activities as reflected by the Physical Activity Scale of the Elderly score used in this study only mildly attenuated the association between appendicular lean mass loss and diabetes, and only in men. This score captures all activities, including activities of daily living, such as shopping, walking and doing home chores, and was not used exclusively for resistive or aerobic exercise. This might have limited its association with the decline in muscle mass.

Our study had several limitations. We had no data regarding control or the duration of diabetes. The diagnoses relied on self-report, although this had been recognized as a valid method for collecting medical diagnoses in large studies [22,23]. Weight loss could not be classified as intentional or unintentional. We were unable to demonstrate causality between diabetes and the observed weight and muscle losses. A higher than expected proportion of participants did not return for the 4th-year assessment, which might have biased our results towards healthier older adults. The cohort consisted of community-dwelling and well-functioning older adults; hence, the results should not be generalized to those who are more frail.

Conclusion

Diabetes was associated with higher body mass loss and appendicular lean mass loss in older Chinese adults. In men, diabetes was also associated with higher total body fat loss. Diabetes-associated muscle loss may contribute to diabetes-related frailty in older adults.

Competing interests

Nothing to declare.

Acknowledgement

The authors are grateful to Professor Robert Kane for his valuable suggestions to improve this manuscript. The study was supported jointly by a Hong Kong Research Grant Council Grant (CUHK4101/02M) and a National Institute of Health Grant (5R01 R049439-02).

References

1 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047–1053.

2 McBean AM, Li S, Gilbertson DT, Collins AJ. Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethic groups: whites, blacks, Hispanics, and Asians. *Diabetes Care* 2004; **27**: 2317–2324.

3 Choi BD, Shi F. Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. *Diabetologia* 2001; **44**: 1221–1231.
4 Woo J, Swaminathan R, Cockram C, Pang CP, Mak YT, Au SY *et al.* The prevalence of diabetes mellitus and an assessment of methods of detection among a community of elderly Chinese in Hong Kong. *Diabetologia* 1987; **30**: 863–868.
5 Wong KC, Wang Z. Prevalence of type 2 diabetes mellitus in Chinese populations in mainland China, Hong Kong and Taiwan. *Diabetes Res Clin Prac* 2006; **73**: 126–134.
6 Gregg EW, Mangione CM, Cauley JA, Thompson TJ, Schwartz AV, Ensrud KE *et al.*, for the Study of Osteoporotic Fractures Research Group Diabetes and incidence of functional disability in older women. *Diabetes Care* 2002; **25**: 61–67.
7 Volpato S, Ferrucci L, Blaum C, Ostir G, Cappola A, Fried LP *et al.* Progression of lower-extremity disability in older women with diabetes. The Women's Health and Aging Study. *Diabetes Care* 2002; **26**: 70–75.
8 Maty SC, Fried LP, Volpato S, Williamson J, Brancati FL, Blaum CS. Patterns of disability related to diabetes mellitus in older women. *J Gerontol A Biol Sci Med Sci* 2004; **59A**: 148–153.
9 Maggi S, Noale M, Gallina P, Marzari C, Bianchi D, Limongi F *et al.* Physical disability among older Italians with diabetes. The ILSA Study. *Diabetologia* 2004; **47**: 1957–1962.
10 Fantin F, Francesco VD, Fontana G, Zivelonghi A, Bissoli L, Zoico E *et al.* Longitudinal body composition changes in old men and women: interrelationships with worsening disability. *J Geront A Biol Sci Med Sci* 2007; **62A**: 1375–1381.
11 Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–763.
12 Roubenhoff R. Sarcopenia: effects on body composition and function. *J Gerontol A Biol Sci Med Sci* 2003; **58A**: 1012–1017.
13 Morley JE. Diabetes, sarcopenia, and frailty. *Clin Geriatr Med* 2008; **24**: 455–469.
14 Pedersen M, Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, Eldrup E *et al.* Circulating levels of TNF-α and IL-6—relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type 2 diabetes. *Mech Ageing Dev* 2003; **124**: 495–502.
15 Lee JSW, Auyeung TW, Kwok T, Lau EMC, Leung PC, Woo J. Associated factors and health impact of sarcopenia in older Chinese men and women: a cross-sectional study. *Gerontology* 2007; **53**: 404–410.
16 Woo J, Ho SC, Yu LM, Lau J, Yuen YK. Impact of chronic diseases on functional limitations in elderly Chinese aged 70 years and over: a cross-sectional and longitudinal survey. *J Gerontol A Biol Sci Med Sci* 1998; **53**: M102–M106.
17 Chou KL, Chi I. Functional disability related to diabetes mellitus in older Hong Kong Chinese adults. *Gerontology* 2005; **51**: 334–339.
18 Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C *et al.*, for the Health, Aging and Body Composition Study. Accelerated loss of skeletal muscle strength in older adults with Type 2 diabetes. *Diabetes Care* 2007; **30**: 1507–1512.
19 Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, DeRekeneire N *et al.*, for the Health, Aging, and Body Composition Study. Excessive loss of skeletal muscle mass in older adults with Type 2 diabetes. *Diabetes Care* 2009; **32**: 1993–1997.
20 Rolland Y, Czerwinski S, Abellan Van Kan C, Morley JE, Cesari M, Onder G *et al.* Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging* 2008; **12**: 433–450.
21 Washburn RA, Smith KW, Jette AM, Janny CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993; **46**: 153–162.
22 Bourdel-Marchasson I, Dubroca B, Manciet G, Decamps A, Emeriau JP, Dartigues JF. Prevalence of diabetes and effect on quality of life in older French living in the community: the PAQUID Epidemiological Survey. *J Am Geriatr Soc* 1997; **45**: 295–301.
23 McGuire LC, Ford ES, Ajani UA. The impact of cognitive functioning on mortality and the development of functional disability in older adults with diabetes: the second longitudinal study on aging. *BMC Geriatrics* 2006; **6**: 8–14.
24 Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. *J Clin Epidemiol* 1991; **44**: 15–20.
25 Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
26 Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J *et al.* Appendicular skeletal muscle mass: measurement by dual-energy X-ray absorptiometry. *Am J Clin Nutr* 1990; **52**: 214–218.
27 Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002; **50**: 889–896.
28 Wedick NM, Barrett-Connor E, Knoke JD, Wingard DL. The relationship between weight loss and all-cause mortality in older men and women with and without diabetes mellitus: the Rancho Bernardo Study. *J Am Geriatr Soc* 2002; **50**: 1810–1815.
29 Alibhai SM, Greenwood C, Payette H. An approach to the management of unintentional weight loss in elderly people. *CMAJ* 2005; **172**: 773–780.
30 Auyeung TW, Lee JSW, Leung J, Kwok T, Leung PC, Woo J. Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4000 older adults using DXA. *J Gerontol A Biol Sci Med Sci* 2010; **65A**: 99–104.
31 Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev* 1999; **107**: 123–136.

Age and Ageing 2006; **35:** 246–251
doi:10.1093/ageing/afj056
Published electronically 23 February 2006

Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study

Jenny SW Lee[1], Timothy Kwok[1], PC Leung[2], Jean Woo[3]

[1]Department of Medicine and Therapeutics, School of Medicine, The Chinese University of Hong Kong, 9/F Clinical Science Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR
[2]Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong, 3/F, School of Public Health, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR
[3]Department of Community and Family Medicine, School of Public Health, The Chinese University of Hong Kong, School of Public Health, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR

Address correspondence to: Jenny S.W. Lee, Tel: (+852) 2636 7779, Fax: (+852) 2635 1037. Email: jleesw_2000@yahoo.com

Abstract

Background: previous studies have confirmed the contribution of various medications towards falls in the older population. Recently questions were raised as to whether the chronic illnesses or drug use was more important.
Objective: we attempt to test the hypothesis that underlying medical illnesses are the cause of falls rather than medications.
Design: cross-sectional.
Setting: urban community in Hong Kong.
Subjects: 4,000 ambulatory community-dwelling men and women aged 65 years or over.
Methods: demographic data, fall history in the previous 12 months, medical diagnoses, current medications and self-rated health were recorded. Body measurements and neuromuscular function tests were performed. Medical diagnoses and their corresponding medications were tested simultaneously in a multivariate model.
Results: 789 (19.7%) subjects reported at least one fall and 235 (5.9%) experienced two or more falls. After adjustment for age and sex, medications associated with any falls were aspirin, diabetic drugs, nitrates, NSAIDs, and paracetamol, and those associated with recurrent falls were calcium channel blockers, diabetic drugs, nitrates, NSAIDs, aspirin and statins. Only anti-diabetics and nitrate showed moderate and borderline significance in multivariate analyses for recurrent and any falls respectively (OR 2.9, $P = 0.01$; OR 1.5, $P = 0.027$). Other medications failed to show significant relationship with falls, while eye diseases, heart diseases and musculoskeletal pain showed variable associations.
Conclusion: The apparent association between many medications and falls was mediated through the underlying medical diagnoses and neuromuscular impairment. Anti-diabetics agents were associated with falls.

Keywords: *falls, 65 and over, medications, diseases, elderly, co-morbidities*

Introduction

About 18–32% of community dwelling older persons fall each year, resulting in significant mortality, morbidity, fear of falling and restrictions in physical activities [1–8]. Medications, in particular antihypertensives and sedatives, have often been cited as one of the major causes for these falls [3, 4, 7, 9, 10]. Other associated risk factors found were physical disabilities, poor vision, cognitive impairment, and presence of certain conditions such as depression, stroke and cardiovascular diseases [1, 2, 5, 6, 10]. Few studies, however, have attempted to compare the relative importance of medications and their indications in causing falls. We attempt to test the hypothesis that underlying medical illnesses are the cause of falls rather than the medications among functionally independent community-dwelling older individuals.

Methods

A total of 4,000 community-dwelling men and women aged 65 years or over were invited to attend a health check carried out in the School of Public Health of The Chinese University of Hong Kong between August 2001 and December 2003. Invitation was by placing recruitment notices in community centres for the elderly and in housing estates. Talks were given at these centres explaining the purpose, procedures and investigations to be carried out. Only volunteers who could walk independently either with or without aids were included. Those with a history of bilateral hip fractures were excluded. The example was stratified so that approximately 33% were in each of the age groups: 65–69, 70–74 and 75 and over. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All subjects gave written consent prior to data collection.

A questionnaire containing information regarding demographics, socioeconomic status, smoking habit, alcohol intake, self-rated health, daily physical activity level, cognitive function, history of falls in the past 12 months, medical history and current medications was administered by research assistants trained in both data collection and specific physical measurements used in the health check.

The presence or absence of diseases was based on the subjects' report of diagnoses as told by their doctors, and counter-checked by their medications. Subjects brought all their current medications to the centre for inspection and ascertainment on the day of the health check. Self-rated health was graded by each subject on a scale of 1–5, with 1 = excellent and 5 = poor. Physical activity level was assessed using the Physical Activity Scale of the Elderly (PASE). This is a 12-item scale measuring the average number of hours per day spent in leisure, household and occupational physical activities over the previous 7-day period. The activity weight for each item was determined based on the amount of energy expended, and each item score was calculated by multiplying the activity weight by activity daily frequency. A summary score of all the items reflect the daily physical activity level [11]. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [12].

The following physical measurements were performed for each subject: height, weight and stride length in a usual-paced 6-m walk. Body weight was measured, with subjects wearing a light gown, by the Physician Balance Beam Scale (Healthometer, IL, USA). Height was measured by the Holtain Harpenden stadiometre (Holtain Ltd, Crosswell, UK). Stride length was calculated by dividing the distance with the number of steps taken during the 6-m walk.

A fall was defined as any unexpected loss of balance resulting in coming to rest on the ground or floor. Recurrent fallers were defined as those subjects with two or more falls in the past year.

Statistical methods

Statistical analysis was performed using SPSS version 11.5. Multiple logistic regression analysis was used to calculate age and sex adjusted odds ratios for all variables. Variables with $P<0.05$ were chosen to be entered into the final model for each of the significant medications. Fallers (fell at least once) were compared with non-fallers, and recurrent fallers (fell at least twice) were compared with those with one or no falls. A P value of <0.05 was taken as statistically significant. Significance was stratified into three levels in the final models.

Results

Baseline characteristics of 4,000 subjects were listed in Table 1.

Falls

Among 4,000 older men and women, 789 (19.7%) reported having at least one fall in the previous 12 months. Among those, 235 (5.9% of 4,000) had more than one fall.

Association between falls and medications

Table 2 summarizes the age- and sex-adjusted odds ratios of various medications in relation to falls and recurrent falls. Use of aspirin, calcium channel blockers, anti-diabetics (including sulphonylureas, biguanide and insulin), nitrates, non-steroidal anti-inflammatory drugs (NSAIDs) and statins was associated with an increased risk of recurrent falls. Aspirin, anti-diabetics, nitrates, NSAIDs and paracetamol use was associated with increased risk of any number of falls. Psychotropic drugs including benzodiazepines, antidepressants and antipsychotics were not significantly associated with either any or recurrent falls.

Table 3 summarizes the age- and sex-adjusted odds ratios of other factors that may contribute to falls and recurrent

Table 1. Baseline characteristics of 4,000 community-dwelling men and women

Characteristics	*N*	Mean ± SD or percentage
Age (years)	4,000	72.49 ± 5.18
Female sex (%)	2,000	50%
Education level		
No education	856	21.4%
Primary education	2,007	50.2%
Secondary education or above	1,137	28.4%
Living with someone	3,454	86.4%
Walks unaided	3,994	99.9%
Takes daily walks	2,458	61.5%
Current smoker	275	6.9%
Self-rated health		
Excellent or good	1,889	47.2%
Fair	1,815	45.4%
Poor or very poor	296	7.4%
MMSE score		
<18	131	3.3%
18–24	1,197	29.9%
>24	2,672	66.8%
PASE score (0–400)	4,000	91.39 ± 42.93
BMI	4,000	23.69 ± 3.30
Number of medications		
0	1,803	45.1%
1–4	2,106	52.7%
5–7	91	2.3%

SD = standard deviation, MMSE = Mini-Mental State Examination, PASE = Physical Activity Scale of the Elderly, BMI = body mass index.

Table 2. Age-sex adjusted associations between medications and falls in previous 12 months among 4,000 community dwelling older persons age 65 or over

		Any falls (n=789)			Recurrent falls (n=235)[a]		
Medications	N (%)	OR	95% CI	P value	OR	95% CI	P value
ACEI	453 (11.3)	0.984	0.764, 1.268	0.903	1.183	0.784, 1.786	0.423
Aspirin	448 (11.2)	1.386	1.096, 1,752	0.006*	1.636	1.135, 2.360	0.008*
Beta-blocker	645 (16.1)	1.135	0.922, 1.397	0.232	1.313	0.941, 1.833	0.109
CCB	719 (18.0)	0.998	0.815, 1.224	0.988	1.477	1.083, 2.016	0.014*
Anti-diabetics	430 (10.8)	1.292	1.017, 1.641	0.036*	1.852	1.301, 2.636	0.001*
Nitrate	255 (6.4)	1.849	1.393, 2.456	0.000*	2.040	1.330, 3.131	0.001*
NSAID	173 (4.3)	1.461	1.030, 2.072	0.034*	1.955	1.185, 3.227	0.009*
Paracetamol	83 (2.1)	1.628	1.002, 2.645	0.049*	1.173	0.503, 2.738	0.711
Statin	236 (5.9)	1.194	0.870, 1.638	0.272	1.673	1.052, 2.661	0.030*
Psychotropics	49 (1.2)	1.382	0.726, 2.630	0.324	0.955	0.293, 3.108	0.938
Diuretics	381 (9.5)	1.047	0.808, 1.358	0.728	0.794	0.499, 1.264	0.331

OR = odds ratio, CI = confidence interval, ACEI = angiotensin converting enzyme inhibitors, CCB = Calcium channel blocker, NSAID = non-steroidal anti-inflammatory agent, psychotropics = benzodiazepines, antidepressants, antipsychotics, diuretics = thiazide, loop and potassium sparing diuretics.
*P<0.05.
[a]Comparisons are between subjects with no or 1 fall and those with ≥2 falls.

Table 3. Age-sex adjusted associations between medical diagnoses, cognitive function, social factors, physical activity, neuromuscular functions and falls in previous 12 months among 4,000 community dwelling older persons age 65 or over

		Any falls (n = 789)			Recurrent falls (n = 235)[a]		
Risk factors	N (%)	OR	95% CI	P value	OR	95% CI	P value
Medical diagnoses							
Stroke	175 (4.4)	1.641	1.159, 2.324	0.005*	1.178	0.627, 2,213	0.611
Parkinson's disease	16 (0.4)	1.623	0.518, 5.086	0.406	3.022	0.669, 13.643	0.151
COPD	333 (8.3)	0.927	0.686, 1.251	0.619	1.290	0.806, 2.065	0.289
Diabetes	579 (14.5)	1.274	1.030, 1.575	0.026*	1.424	1.013, 2.001	0.042*
Any eye disease (glaucoma, cataract)	1,646 (41.2)	1.293	1.098, 1.524	0.002*	1.536	1.165, 2.026	0.002*
Any heart disease (MI, angina, CHF)	696 (17.4)	1.636	1.350, 1.982	0.000*	1.896	1.401, 2.565	0.000*
Any lower musculoskeletal pain (LBP, hip, knee pain)	2,317 (57.9)	1.349	1.141, 1.594	0.000*	1.661	1.230, 2.242	0.001*
Cognitive function							
MMSE score (0–30)	4,000 (100)	1.022	0.998, 1.046	0.068	0.989	0.953, 1.026	0.549
Sociodemographic factors							
Living with someone	4,000 (100)	0.840	0.673, 1.047	0.121	0.760	0.539, 1.070	0.115
Average drinks / week in past year among drinkers	522 (13.1)	1.015	0.990, 1.042	0.239	0.862	0.706, 1.054	0.148
Smoke years in ever smokers	1,466 (36.7)	0.997	0.992, 1.002	0.221	1.000	0.992, 1.009	0.930
Current smoker	275 (6.9)	0.744	0.515, 1.073	0.114	1.109	0.591, 2.081	0.747
Physical activities, self-rated health and number of medications							
PASE score (0–400)	4,000 (100)	1.000	0.998, 1.002	0.801	0.999	0.995, 1.003	0.572
Self-rated health (1–5, 1=best, 5=worst)	4,000 (100)	1.196	1.078, 1.326	0.001*	1.266	1.063, 1.509	0.008*
Number of medications (per each additional drug)	4,000 (100)	1.085	1.025, 1.149	0.005*	1.197	1.095, 1.309	0.000*
Physical Measurements							
BMI	4,000 (100)	1.010	0.987, 1.035	0.389	1.023	0.984, 1.065	0.251
Average stride length (per 0.1 m increment)	4,000 (100)	0.795	0.715, 0.883	0.000*	0.707	0.595, 0.830	0.000*

OR = odds ratio, CI = confidence interval, COPD = chronic obstructive pulmonary diseases, MI = myocardial infarction, CHF = congestive heart failure, LBP = low back pain, MMSE = Mini-Mental State Examination, PASE = Physical Activity Scale for the Elderly, BMI = body mass index.
*P<0.05.
[a]Comparisons are between subjects with no or 1 fall and those with ≥2 falls.

falls, including medical diagnoses, cognitive function, social factors, physical activity score, self-rated health and physical measurements. Factors significantly associated with recurrent falls include the following: diabetes, eye diseases (cataract and/or glaucoma), heart diseases (history of myocardial infarction, angina and congestive heart failure), lower body musculoskeletal pain (low back pain, hip and knee pain), self-rated health and average stride length. The same variables, apart from the addition of a history of stroke, were associated with any falls in the previous year.

Table 4. Final model: association between medications, significant age-sex adjusted risk factors and history of *any* falls in the previous 12 months

	OR (95% CI) *P* value				
Risk factors	Aspirin	Anti-diabetics	Nitrates	NSAIDs	Statin
Medication	1.022 (0.753, 1.387) *P* = 0.890	1.169 (0.755, 1.809) *P* = 0.484	1.489 (1.046, 2.120) *P* = 0.027[c]	1.417 (0.980, 2.048) *P* = 0.064	1.392 (0.844, 2.297) *P* = 0.196
Age (per year increase)	0.997 (0.981, 1.014) *P* = 0.741	0.997 (0.981, 1.014) *P* = 0.747	0.996 (0.980, 1.013) *P* = 0.677	0.997 (0.981, 1.014) *P* = 0.754	0.997 (0.981, 1.014) *P* = 0.743
Female sex	1.413 (1.176, 1.697) *P* = 0.000[a]	1.411 (1.175, 1.696) *P* = 0.000[a]	1.413 (1.176, 1.698) *P* = 0.000[a]	1.419 (1.181, 1.706) *P* = 0.000[a]	1.418 (1.180, 1.704) *P* = 0.000[a]
Any eye disease	1.207 (1.044, 1.396) *P* = 0.011[c]	1.206 (1.043, 1.395) *P* = 0.012[c]	1.215 (1.051, 1.405) *P* = 0.009[b]	1.207 (1.043, 1.395) *P* = 0.011[c]	1.205 (1.042, 1.393) *P* = 0.012[c]
Any heart disease	1.558 (1.246, 1.948) *P* = 0.000[a]	1.579 (1.270, 1.961) *P* = 0.000[a]	1.440 (1.143, 1.814) *P* = 0.002[a]	1.604 (1.291, 1.993) *P* = 0.000[a]	1.569 (1.264, 1.946) *P* = 0.000[a]
Lower musculoskeletal pain	1.230 (1.036, 1.461) *P* = 0.018[c]	1.233 (1.039, 1.465) *P* = 0.017[c]	1.228 (1.034, 1.458) *P* = 0.019[c]	1.217 (1.025, 1.446) *P* = 0.025[c]	1.221 (1.028, 1.450) *P* = 0.023[c]
Diabetes	1.208 (0.954, 1.528) *P* = 0.116	1.086 (0.744, 1.585) *P* = 0.668	1.235 (0.975, 1.563) *P* = 0.080	1.241 (0.980, 1.573) *P* = 0.073	1.220 (0.964, 1.544) *P* = 0.097
History of stroke	1.493 (1.030, 2.163) *P* = 0.034[c]	1.517 (1.059, 2.172) *P* = 0.023[c]	1.509 (1.054, 2.161) *P* = 0.025[c]	1.523 (1.064, 2.180) *P* = 0.021[c]	1.518 (1.061, 2.173) *P* = 0.023[c]
Self-rated health (per score increase)	1.094 (0.982, 1.219) *P* = 0.104	1.094 (0.982, 1.219) *P* = 0.105	1.093 (0.981, 1.218) *P* = 0.107	1.092 (0.980, 1.217) *P* = 0.110	1.092 (0.980, 1.217) *P* = 0.110
Stride length (per 0.1 m increase)	0.842 (0.755, 0.938) 0.002[a]	0.842 (0.756, 0.938) *P* = 0.002[a]	0.839 (0.753, 0.935) *P* = 0.001[a]	0.847 (0.760, 0.944) *P* = 0.003[a]	0.844 (0.758, 0.941) *P* = 0.002[a]
Number of medications (per each additional drug)	0.967 (0.894, 1.045) *P* = 0.397	0.963 (0.895, 1.036) *P* = 0.309	0.940 (0.871, 1.014) *P* = 0.112	0.953 (0.886, 1.025) *P* = 0.199	0.962 (0.896, 1.034) *P* = 0.292

OR = odds ratio, CI = confidence interval, NSAID = non-steroidal anti-inflammatory agent.
[a] $P<0.005$.
[b] $P<0.01$.
[c] $P<0.05$.

Tables 4 summarizes the multivariate models demonstrating the association between each medication and falls with adjustment to significant non-drug factors. Female sex, heart diseases and shorter stride length were highly associated with falls history ($P<0.005$). Eye disease was moderately associated with falls in the nitrates model ($P = 0.009$), while lower body musculoskeletal pain, previous stroke and eye disease were slightly associated with falls in all medication models. The only medication with any significant association with any falls was nitrate, showing borderline significance (OR 1.489, $P = 0.027$).

Table 5 summarizes multivariate models on recurrent falls. Female sex and shorter stride length were again strongly associated with recurrent falls. Eye disease was moderately associated while heart diseases and lower musculoskeletal pain showed a slight association. Among medications, only anti-diabetics showed a moderate association (OR 2.9, $P = 0.01$).

Discussion

Previous studies have demonstrated the relationship between falls and various types of medications. Few had addressed the possible confounding effect of the underlying medical illnesses. When we studied medications together with their indications and other significant non-drug risk factors, we found that most of the medications failed to demonstrate association with falls. This suggests that underlying medical illnesses and non-drug factors, rather than medications, were responsible for falls in functionally independent community-dwelling older persons.

We found shorter stride length to be a good indicator of falls. It is a measurement of balance, gait and muscular power. Changes in stride length have been associated with reductions in falls after fall intervention [13]. It is easy to measure, requires no special equipment and can be done in virtually any setting. Its value as a falls risk assessment tool is worthy of further examination.

Female sex has often been associated with increased falls [1, 5, 9, 14]. This association persisted after adjustment for all the other significant factors for falls in our study including stride length, a surrogate for neuromuscular function and stature, and remained as the strongest predictor. Whether it is due to recall bias difference between the two genders as suggested previously [15], or there are other gender specific risk factors yet unknown will need to be answered in a prospective study.

Increase in age was not associated with increased falls amongst our subjects after adjustment for underlying medical illnesses, medications, visual impairment and stride length. The relative high physical independence and good health of our cohort may have contributed to this finding. In a frailer population, the effect of age on falls could have been more prominent.

Our study had shown that heart diseases were associated with falls, while medications used in these diseases were not.

Table 5. Final model: association between medications, significant age-sex adjusted risk factors and history of *recurrent* falls in the previous 12 months

Risk factors	OR (95% CI) *P* value					
	Aspirin	Ca channel blockers	Anti-diabetics	Nitrates	NSAIDs	Paracetamol
Medication	1.013 (0.635, 1.617) *P* = 0.957	1.218 (0.847, 1.750) *P* = 0.288	2.909 (1.287, 6.575) *P* = 0.010[b]	1.214 (0.711, 2.073) *P* = 0.477	1.595 (0.938, 2.713) *P* = 0.085	1.173 (0.689, 1.995) *P* = 0.557
Age (per year increase)	1.008 (0.981, 1.036) *P* = 0.553	1.008 (0.981, 1.036) *P* = 0.573	1.008 (0.981, 1.036) *P* = 0.559	1.008 (0.981, 1.036) *P* = 0.581	1.009 (0.981, 1.036) *P* = 0.540	1.009 (0.982, 1.037) *P* = 0.532
Female sex	1.660 (1.207, 2.285) *P* = 0.002[a]	1.648 (1.197, 2.268) *P* = 0.002[a]	1.638 (1.190, 2.253) *P* = 0.002[a]	1.661 (1.207, 2.286) *P* = 0.002[a]	1.673 (1.216, 2.303) *P* = 0.002[a]	1.649 (1.197, 2.271) *P* = 0.002[a]
Any eye disease	1.398 (1.102, 1.774) *P* = 0.006[b]	1.396 (1.100, 1.772) *P* = 0.006[b]	1.393 (1.097, 1.769) *P* = 0.007[b]	1.402 (1.105, 1.780) *P* = 0.005[b]	1.395 (1.099, 1.771) *P* = 0.006[b]	1.398 (1.101, 1.774) *P* = 0.006[b]
Any heart disease	1.514 (1.063, 2.156) *P* = 0.022[c]	1.553 (1.100, 2.192) *P* = 0.012[c]	1.600 (1.133, 2.259) *P* = 0.008[b]	1.453 (1.007, 2.096) *P* = 0.046[c]	1.577 (1.117, 2.227) *P* = 0.010[c]	1.508 (1.068, 2.127) *P* = 0.019[c]
Lower musculoskeletal pain	1.466 (1.078, 1.993) *P* = 0.015[c]	1.469 (1.080, 1.997) *P* = 0.014[c]	1.491 (1.096, 2.027) *P* = 0.011[c]	1.462 (1.075, 1.988) *P* = 0.015[c]	1.440 (1.058, 1.960) *P* = 0.020[c]	1.469 (1.080, 1.997) *P* = 0.014[c]
Diabetes	1.141 (0.782, 1.665) *P* = 0.493	1.151 (0.790, 1.677) *P* = 0.464	0.508 (0.235, 1.097) *P* = 0.085	1.153 (0.791, 1.680) *P* = 0.460	1.193 (0.816, 1.744) *P* = 0.362	1.153 (0.791, 1.682) *P* = 0.459
Self-rated health (per score increase)	1.085 (0.904, 1.303) *P* = 0.380	1.082 (0.901, 1.299) *P* = 0.399	1.086 (0.904, 1.304) *P* = 0.377	1.085 (0.904, 1.303) *P* = 0.383	1.083 (0.902, 1.300) *P* = 0.392	1.087 (0.905, 1.305) *P* = 0.372
Stride length (per 0.1 m increase)	0.771 (0.646, 0.920) *P* = 0.004[a]	0.768 (0.643, 0.917) *P* = 0.004[a]	0.770 (0.646, 0.919) *P* = 0.004[a]	0.770 (0.645, 0.919) *P* = 0.004[a]	0.781 (0.654, 0.932) *P* = 0.006	0.769 (0.645, 0.919) *P* = 0.004[a]
Number of medications (per each additional drug)	1.076 (0.950, 1.218) *P* = 0.252	1.044 (0.922, 1.183) *P* = 0.495	1.038 (0.925, 1.165) *P* = 0.528	1.061 (0.943, 1.194) *P* = 0.326	1.053 (0.940, 1.180) *P* = 0.373	1.062 (0.942, 1.198) *P* = 0.325

OR = odds ratio, CI = confidence interval, Ca channel blocker = calcium channel blocker, NSAID = non-steroidal anti-inflammatory agent.
[a] $P<0.005$.
[b] $P<0.01$.
[c] $P<0.05$.

Subjects with cardiovascular diseases are more prone to cerebral white matter disease, which has been found to be related to gait and balance impairments and falls in high-functioning older persons [16, 17].

Anti-diabetic medications were found to be related to recurrent falls, but being diabetic was not. Diabetes on treatment had been found to be an independent risk factor of falls [18, 19], though the association was less robust among those on oral agents when compared with insulin-treated diabetics [20]. Our cohort contained a significant proportion of diabetic subjects not on drug treatment (25.7%), allowing direct comparison between those with and without anti-diabetics. Our findings suggest that being on anti-diabetics or having diabetes requiring drug control could be a risk factor for falls. More advanced diabetes or hypoglycaemic side effects of drugs could be the cause of falls among older diabetics.

Limitations

We were unable to find any correlation between the use of psychotropic medications and falls. This could be explained by the fact that very few of our subjects (3.5%) were on these agents and the prevalence of these medications was much lower among our subjects than in western studies [4, 10]. Adverse effect of medications could also have been masked by our cohort being relatively healthy and mobile.

Being retrospective in nature, our results were subject to recall bias [15, 21]. We also had difficulties in determining whether a specific medication was actually being taken around the time of falls, especially if it was a take-as-required medication or one that had been newly prescribed sometime within the previous 12 months.

Conclusion

The association between medications and falls appears to be due to the underlying diseases and non-drug factors rather than due to the medications themselves. Female sex, shorter stride length and heart diseases are strong risk factors for falls. Anti-diabetic drugs are strongly associated with falls. How these factors affect falls and why females and those with heart diseases are more prone to falls will be the topics for further prospective studies.

Key points

- Chronic medical conditions were often more important than medications in causing falls in high-functioning community-dwelling older individuals.
- Cardiovascular disease, lower back and leg pain were all more associated with falls than medications used for these conditions.
- Diabetic drugs are associated with falls after adjustment for other chronic medications, short stride length and visual impairments.

Acknowledgements

The study was jointly funded by the Research Grant Council of Hong Kong and by grant 5R01 AR049439-02 from the National Institute of Health.

Declaration of conflicts of interest

None.

References

1. Prudham D, Evans JG. Factors associated with falls in the elderly: a community study. Age Ageing 1981; 10: 141–146.
2. Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. Age ageing 1981; 10: 264–70.
3. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Eng J Med 1988; 319: 1701–7.
4. Cumming RG, Miller JP, Kelsey JL *et al.* Medications and multiple falls in elderly people: The St Louis OASIS Study. Age Ageing 1991; 20: 455–61.
5. O'Loughlin Robitaille Y, Boivin J-F, Suissa S. Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. Am J Epidemiol 1993; 137: 342–54.
6. Lord SR, Sambrook PN, Gilbert C *et al.* Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. Med J Aust 1994; 160: 684–91.
7. Ho SC, Woo J, Chan SSG, Yuen YK, Sham Aprille. Risk factors for falls in the Chinese elderly population. J Gerontol Med Sci 1996; 51A: M195–8.
8. Chu LW, Chi I, Chiu AYY. Incidence and predictors of falls in the Chinese elderly. Ann Acad Med Singapore 2005; 34: 60–72.
9. Koski K, Luukinen H, Laippala P, Kivela S-L. Physiological factors and medications as predictors of injurious falls by elderly people: A prospective population-based study. Age Ageing 1996; 25: 29–38.
10. Lawlor DA, Patel R, Ebrahim S. Association between falls in elderly women and chronic disease and drug use: cross sectional study. Br Med J 2003; 327: 712–7.
11. Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): Development and evaluation. J Clin Epidemiol 1993; 46: 153–62.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
13. Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT Trial? Frailty and Injuries Cooperative Studies of Intervention Techniques. Am J Epidemiol 1996; 144: 389–99.
14. Tinetti ME, Speechley M. Prevention of falls among the elderly. N Eng J Med 1989; 320: 1055–9.
15. Cumming RG, Klineberg RJ. A study of the reproducibility of long-term recall in the elderly. Epidemiology 1994; 5: 116–9.
16. Starr JM, Leaper SA, Murray AD, *et al.* Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. J Neurol Neurosurg Psych 2003; 74: 94–8.
17. Whitman GT, Tang Y, Lin A, Baloh TW. A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. Neurology 2001; 57: 990–4.
18. Maurer MS, Burcham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. J Gerontol Med Sci 2005; 60: 1157–62.
19. Hanlon JT, Landerman LR, Fillenbaum GG, Studenski S. Falls in African American and White Community-Dwelling Elderly Residents. J Gerontol Med Sci 2002; 57A: M473–M8.
20. Schwartz AV, Hillier TA, Sellmeyer DE *et al.* Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002; 25: 1749–54.
21. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc 1988; 36: 613–6.

Received 24 October 2005; accepted in revised form 18 January 2006

JAMDA 15 (2014) 342–348

JAMDA

journal homepage: www.jamda.com

Original Study

Obesity Can Benefit Survival—A 9-Year Prospective Study in 1614 Chinese Nursing Home Residents

Jenny S.W. Lee MSc, FRCP [a,b,*], Tung-Wai Auyeung MPH, FRCP [a,*], Patsy P.H. Chau PhD [c], Elsie Hui MSc, FRCP [d], Felix Chan FHKAM, FRCP [e], Iris Chi DSW [f], Jean Woo MD [a,b]

[a] *The S. H. Ho Center for Gerontology and Geriatrics, The Chinese University of Hong Kong, Hong Kong SAR, China*
[b] *Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China*
[c] *School of Nursing, The University of Hong Kong, Hong Kong SAR, China*
[d] *Department of Medicine and Geriatrics, Shatin Hospital, Hong Kong SAR, China*
[e] *Department of Medicine, Fung Yiu King Hospital, Hong Kong SAR, China*
[f] *School of Social Work, University of Southern California, Los Angeles, CA*

Keywords:
Mortality
nursing home
body mass index
weight
obesity
underweight
elderly
nutrition

A B S T R A C T

Objective: Weight loss has been considered predictive of early mortality in nursing home residents. Lower body mass index, irrespective of weight loss, has also been considered detrimental for survival in community-dwelling older persons. We examined which of the 2 is more important for survival in nursing home residents and at what body mass index (BMI) cut-offs survival benefits are gained or lost.
Design: Prospective study.
Setting: Nursing homes.
Participants: One thousand six-hundred fourteen nursing home residents.
Measurement: Minimum Data Set at baseline and mortality status assessed at 6 months, 1, 2, 4, and 9 years later. Relationship between mortality and significant weight loss ($\geq$5% over 30 days or $\geq$10% over 180 days), and BMI, was studied by Cox regression with both variables in the same model, adjusted for age, sex, medical conditions (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus), tube-feeding, 25% food left uneaten, swallowing problem, and the activities of daily living hierarchy scale.
Results: One thousand six-hundred fourteen residents (69.5% female) with mean age 83.7 $\pm$ 8.4 years and mean BMI 21.7 $\pm$ 4.8 were studied. Mortality rates were 6.3% (6-month), 14.3% (1-year), 27.1% (2-year), 47.3% (4-year), and 78.1% (9-year). Significant weight loss was not associated with higher mortality at all follow-up durations, whereas higher BMI was significantly protective: mortality reduction per 1 unit increase in BMI were 9% at 6 months, 10% at 1 year, 9% at 2 years, 7% at 4 years, and 5% at 9 years, all at $P < .001$. Having $\geq$25% of food left uneaten (51.2% of participants) had no relationship to survival at all follow-up durations. At 9 years, compared with those with BMI $< 18.5 kg/m^2$, the normal weight (BMI 18.5–22.9 kg/m^2, Asia Pacific cut-off), overweight (BMI 23–25 kg/m^2, Asia Pacific cut-off) and obese (BMI $> 25 kg/m^2$, Asia Pacific cut-off) had significantly lower mortality (hazard ratio 0.65, 0.62, and 0.47, respectively, all $P < .001$).
Conclusions: Significant weight loss as defined by the Minimum Data Set was not associated with short- or long-term survival in Chinese nursing home residents. BMI, however, is predictive of short- and long-term survival irrespective of weight loss in this population. Low BMI, detectable at a single point of time, may be another readily available alternative trigger point for possible interventions in reducing mortality risk. Obese residents had the lowest mortality compared with those with normal weight.

Weight loss has been considered predictive of early mortality in nursing home residents. Studies in nursing home residents have demonstrated that significant weight loss, defined as >5% over 1–6 months,[1–3] was highly predictive of mortality, in particular short-term mortality over 6–12 months.[4,5] Because regular body weight measurement is a common routine in many long-term care facilities across the world, this change could be readily captured for the necessary medical attention if unexpected, or advance care

The survey was funded by the SK Yee Memorial Fund. The authors declare no conflicts of interest.
* Address correspondence to Jenny S.W. Lee, MSc, FRCP, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China or Tung-Wai Auyeung, MPH, FRCP, Department of Medicine and Geriatrics, Pok Oi Hospital, Yuen Long, Hong Kong SAR, China.
E-mail addresses: jennylee@cuhk.edu.hk (J.S.W. Lee), auyeungtw@cuhk.edu.hk (T.-W. Auyeung).

1525-8610/$ - see front matter © 2014 - American Medical Directors Association, Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jamda.2013.12.081

planning if the resident is deemed to be approaching the end of life.

On the other hand, lower body mass index (BMI), irrespective of weight loss, has also been considered detrimental for survival in both nursing home residents and community-living older adults.[5,6] Weight change is sometimes difficult to monitor because it requires multiple weightings at regular intervals, hence, both time and manpower consuming. In some long-term care facilities, a single BMI may be the only readily available index of nutritional status. Recently, authors have reported that the BMI may be used to predict 5-year mortality in nursing home residents.[7,8] In view of this, a single BMI measurement might be as good as weight changes as a predictor of mortality for nursing home residents.

Both BMI and weight loss are documented in the Minimum Data Set (MDS). We, therefore, attempt to compare these parameters as mortality predictors in nursing home residents and to examine whether their relative importance may change over a wide range of observation periods. It had been noted that compared with Caucasians, Asians have higher metabolic risks at the same BMI, having higher body fat and central fat, higher fasting blood sugar, and lower high density lipoprotein levels.[9–11] Owing to these differences, BMI among Asians was categorized according to the World Health Organization (WHO) Asia Pacific cut-offs in 2000: <18.5 kg/m^2 (underweight), 18.5–23 kg/m^2 (normal weight), 23.1–25 kg/m^2 (overweight), and >25 kg/m^2 (obese).[12] In this study, we also examined whether the Asia-Pacific BMI cut-offs might be associated with mortality outcomes in Chinese nursing home residents.

Methods

Ten private and 4 subsidized homes with at least 100 residents were randomly selected from among the 533 private nursing homes and 130 subsidized nursing homes in Hong Kong in 2001. The ratio of private and subsidized homes was chosen to reflect the excess of private homes. Of the 1914 residents in these residential care facilities, 1820 of them were successfully assessed between December 2001 and August 2002, using the Chinese version of the Minimum Data Set—Residential Assessment Instrument (MDS-RAI) version 2.0,[13–15] with a response rate of 95%. Reasons for unsuccessful assessments of the remaining 94 residents included hospitalization, moved to other facilities, and home leave during the period of study. Of the 1914 residents, the data of 1614 were included in this analysis: 4 were excluded due to invalid Hong Kong identity numbers and, therefore, untraceable mortality status; 202 were excluded due to missing or erroneous data on their body weight or height. Among those included in this analysis, 546 (33.8%) resided in subsidized homes, whereas 1068 (66.2%) were from private homes.

The MDS-RAI

The MDS-RAI captures detailed information on each resident including demographic information, medical diagnoses and medications, physical and cognitive functional status, and their dietary, nutrition, and behavioral patterns. Data were collected by 2 trained research assistants. Medical and social information was collected from the residents or from a proxy if the former were too frail to be interviewed. Proxies included personal care workers, other front-line nursing staff, family members, or close friends. The participant's file at the facilities was also consulted for background social and medical history. Participants' daily routines were confirmed with care home staff to ensure reliability and validity of the information gathered.

Weight Loss and BMI

Weight loss of $>5\%$ over 30 days or $\geq 10\%$ over 180 days was extracted from the original MDS variable with the exact description. BMI was calculated from the body height and weight variables in the dataset.

Mortality

Residents were assessed by the MDS at baseline and mortality status was ascertained as at December 31, 2010, giving a follow-up of 9 years from baseline assessment. The exact date of death was ascertained by the death registry kept by the Hong Kong Special Administrative Region government, and death was identified using the Hong Kong Identity Card number, which is unique to every Hong Kong resident.

Covariates

Covariates were chosen because of their probable relationship to mortality in nursing home residents.[3,5] Age, sex, tube-feeding, presence of swallowing problems, having 25% food left uneaten, and medical conditions were obtained directly from variables available in the MDS. The medical conditions included in the analyses were dementia (Alzheimer's disease or dementia other than Alzheimer's), cancer, renal failure, heart disease (atherosclerotic heart disease or congestive heart failure), diabetes mellitus, and a history of hip fracture. Functional level in activities of daily living (ADLs) was categorized by the MDS ADL Self-Performance Hierarchy (MDS ADL) scale, which described the actual performance level of each resident across a spectrum of activities of daily living.

Multiple MDS items concerning ADL and dependency levels in performing those activities were used to formulate a score that ranged from 0 (independent) to 6 (total dependence) according to the methods described by Morris et al.[16] The functional level in ADLs has been found to be a significant predictor in nursing home residents in previous studies.[17]

Statistical Analysis

Relationship between mortality and significant weight loss ($\geq 5\%$ over 30 days or $\geq 10\%$ over 180 days), and BMI, was studied by Cox regression with both variables in the same model, adjusted for age, sex, medical conditions (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus), tube-feeding, 25% food left uneaten, swallowing problem, and the level of functional impairment as represented by the category on the ADL hierarchy scale. In model 1, BMI was used as a continuous variable, whereas in model 2, BMI was used as an ordinal variable according to the Asia Pacific cut-off values described above,[12] with the underweight group as reference. To study whether the association between BMI and weight loss would vary according to the duration of survival, in each model, separate Cox regressions were performed with the dependent variable being the survival time censored at different time points: 182 days (6 months), 1, 2, 4, and 9 years after the date of the MDS assessment. Statistical analysis was conducted using the SPSS software version 16.0 (SPSS Inc, Chicago, IL). A P value of $<.05$ was taken as statistically significant.

Results

Of the 1614 residents, 69.5% were female. The mean age was 83.7 ± 8.4 years. Approximately one-half (49.4%) of the residents were mildly impaired in ADLs as defined by the MDS-ADL scale, whereas 36.1% were severely impaired. The mean BMI was 21.7 ± 4.8; one-quarter of the residents were underweight (BMI < 18.5 kg/m^2) and another one-quarter approximately were obese (BMI > 25 kg/m^2). Overall, 36.7% of

Table 1
Baseline Characteristics of Nursing Home Residents (n = 1614)

Characteristic	Total, N (%)	Dead at 9 Years, n (%)	Alive at 9 Years, n (%)	*P* Value*
Age, years (mean, SD)	83.7 (8.4)	84.8 (7.9)	79.8 (8.9)	<.001‡
Female	1122 (69.5)	865 (68.6)	257 (72.8)	.129
Activities of daily living hierarchy scale				
Mildly impaired (0,1,2)	797 (49.4)	556 (44.1)	241 (68.3)	<.001‡
Moderately impaired (3,4)	234 (14.5)	196 (15.5)	38 (10.8)	
Severely impaired (5,6)	583 (36.1)	509 (40.4)	74 (21.0)	
Nutrition and feeding				
BMI (kg/m^2)				
<18.5	421 (26.1)	381 (30.2)	40 (11.3)	<.001‡
18.5–22.9	601 (37.2)	471 (37.4)	130 (36.8)	
23.0–25.0	211 (13.1)	165 (13.1)	46 (13.0)	
>25	381 (23.6)	244 (19.3)	137 (38.8)	
Tube feeding	90 (5.6)	83 (6.6)	7 (2.0)	.001‡
Swallowing problems	65 (4.0)	59 (4.7)	6 (1.7)	.012†
25% food left uneaten after each meal	826 (51.2)	643 (51.0)	183 (51.8)	.778
Weight loss of ≥5% over 30 days or ≥10% over 180 days	24 (1.5)	21 (1.7)	3 (0.8)	.263
Medical conditions				
Number of medical conditions present				<.001‡
0	651 (40.3)	472 (37.4)	179 (50.7)	
1	700 (43.4)	570 (45.2)	130 (36.8)	
2	231 (14.3)	191 (15.1)	40 (11.3)	
3	30 (1.9)	26 (2.1)	4 (1.1)	
4	2 (0.1)	2 (0.2)	0 (0.0)	
Dementia	491 (30.4)	426 (33.8)	65 (18.4)	<.001‡
Cancer	70 (4.3)	58 (4.6)	12 (3.4)	.328
Renal failure	44 (2.7)	38 (3.0)	6 (1.7)	.180
Heart disease	171 (10.6)	150 (11.9)	21 (5.9)	.001‡
Diabetes	362 (22.4)	271 (21.5)	91 (25.8)	.088
Hip fracture	122 (7.6)	95 (7.5)	27 (7.6)	.942
Polypharmacy (≥4 drugs)	857 (53.1)	664 (52.7)	193 (54.7)	.502

BMI, body mass index; SD, standard deviation.
*P value for the difference between those who were dead and alive at 9 years.
†P value <.05.
‡P value <.001.

the participants were either overweight or obese. One-half of them had left 25% of their food uneaten at meals, and 1.5% were recorded to have significant weight loss (≥5% over previous 30 days or ≥10% over previous 180 days). In terms of medical diagnoses, 30% suffered from dementia, 22% suffered from diabetes mellitus, 11% had heart diseases, 7.6% had hip fracture, and 4% had a diagnosis of cancer. Polypharmacy (>4 drugs) was found in 53% (Table 1). Compared with residents who were alive by the end of the 9 years, residents deceased by then were older, more impaired in ADLs, more likely to be underweight, on tube-feeding, and had swallowing problems. They also had more of the studied medical conditions and were more likely to be suffering from dementia and heart disease at baseline (Table 1).

The number (%) of residents with significant weight loss among the different BMI categories were 9 (2.1%) out of 421 underweight residents, 11 (1.8%) out of 601 normal weight residents, 1 (0.5%) out of 211 overweight residents, and 3 (0.8%) out of 381 obese residents. The proportions of those with weight loss among the different BMI categories were not statistically significant (χ^2 test, $P > .05$).

Mortality rates at different time points from the baseline assessment were 6.3% at 6 months, 14.3% at 1 year, 27.1% at 2 years, 47.3% at 4 years, and 78.1% at 9 years. At 9 years, the mortality rates among those who were underweight, normal weight, overweight, and obese were 90.5%, 78.4%, 78.2%, and 64.0%, respectively. Figure 1 shows the survival curves of residents in the four BMI categories over 9 years,

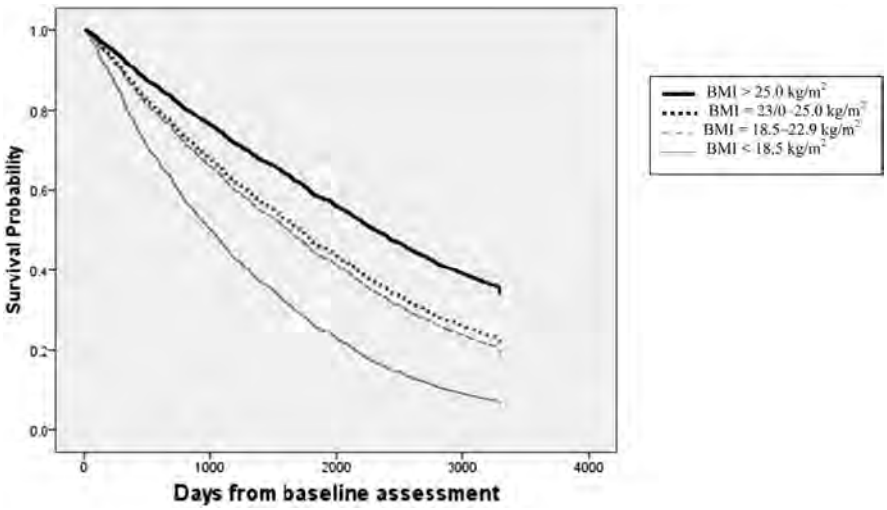


Fig. 1. Survival curves according to baseline BMI categories. BMI, body mass index.

Table 2
Likelihood of Death at Different Time Points by Cox Regression, in Relation to Different BMI and Significant Weight Loss

	6 Months		1 Year		2 Years		4 Years		9 Years	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1										
Significant weight loss	0.00 (0.00, 0.00)	.958	1.12 (0.49, 2.57)	.788	1.00 (0.53, 1.91)	.991	1.16 (0.69, 1.94)	.586	1.16 (0.75, 1.79)	.507
BMI (per kg/m^2 increment)	**0.91 (0.86, 0.95)**	**<.001**	**0.90 (0.87, 0.93)**	**<.001**	**0.91 (0.89, 0.93)**	**<.001**	**0.93 (0.91, 0.95)**	**<.001**	**0.95 (0.93, 0.96)**	**<.001**
Model 2										
Significant weight loss	0.00 (0.00, 0.00)	.956	1.19 (0.52, 2.72)	.680	1.08 (0.57, 2.04)	.818	1.20 (0.71, 2.00)	.51	1.17 (0.76, 1.81)	.482
BMI (kg/m^2)										
<18.5	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
18.5–22.9	**0.50 (0.31, 0.80)**	**.004**	**0.63 (0.47, 0.85)**	**.002**	**0.63 (0.51, 0.78)**	**<.001**	**0.64 (0.54, 0.76)**	**<.001**	**0.65 (0.57, 0.75)**	**<.001**
23–25	**0.36 (0.17, 0.78)**	**.009**	**0.39 (0.24, 0.64)**	**<.001**	**0.44 (0.31, 0.62)**	**<.001**	**0.51 (0.40, 0.66)**	**<.001**	**0.62 (0.52, 0.75)**	**<.001**
>25	**0.43 (0.23, 0.79)**	**.006**	**0.34 (0.22, 0.53)**	**<.001**	**0.37 (0.27, 0.50)**	**<.001**	**0.42 (0.34, 0.52)**	**<.001**	**0.47 (0.39, 0.55)**	**<.001**

BMI, body mass index; CI, confidence interval; HR, hazard ratio.
Bold numbers are statistically significant.
Significant weight loss = loss ≥5% over 30 days or ≥10% over 180 days.
Adjusted for age, sex, medical conditions (cancer, renal failure, heart disease, dementia, hip fracture, diabetes mellitus), tube-feeding, left 25% food uneaten, swallowing problem, and the activities of daily living hierarchy scale.

using univariate analysis. Those in the obese category had the highest survival rate, whereas those in the underweight category, the lowest survival rate.

Table 2 describes the 2 Cox regression models used to examine the relationship between both significant weight loss and BMI, and mortality, with different periods of observation. Both significant weight loss and BMI were entered at the same time into the models, with adjustment for other factors which might be related to mortality. The survival benefit of the higher BMI tended to be more prominent with longer duration of observation.

In model 1, BMI was used as a continuous variable. Significant weight loss was not associated with higher mortality at all time points, whereas each unit of increase in BMI significantly reduced the risk of mortality between 5% and 10% at various time points (Table 2, model 1).

In model 2, BMI was entered as a categorized variable, and mortality risk was presented for each BMI category, compared with the underweight (BMI < 18.5 kg/m^2) group. Significant weight loss was again not associated with higher mortality risk. Higher BMI were associated with lower risk compared with the underweight group: at 6 months those had normal weight, were overweight and obese had 50% to 64% lower mortality risk; at 1 year, 37% to 66% lower risk, at 2 years, 37% to 63% lower risk, at 4 years, 36% to 58% lower risk, and at 9 years, 35% to 53% lower risk (Table 2, model 2).

Discussion

We found that short-, intermediate-, and long-term mortality up to 9 years were lower in nursing home residents with higher BMI, compared with those with BMI < 18.5. The mortality risks were lowest in those within the obesity range BMI (by Asia Pacific cut-off). In addition, the survival benefit of the obese group became more significant over the other BMI groups with longer periods of observation. At 9 years, compared with those with normal weight (BMI 18.5–22.9 kg/m^2 using Asia Pacific cut-off), those who were obese (BMI > 25 kg/m^2) had significantly lower mortality (hazard ratio = 0.71, 95% confidence interval = 0.61–0.84), whereas those who were underweight (BMI < 18.5 kg/m^2) had significantly higher mortality (hazard ratio = 1.53, 95% confidence interval = 1.33–1.76). This survival benefit of the obese had been reported in certain Western nursing home populations[8,18] as well as in a Chinese long-term care facility population.[19] However, studies varied in their definition of the obese, with BMI values ranging from >25 kg/m^2 in the Chinese study to >28 or 30 kg/m^2 in Western populations. Studies among Asian nursing home populations were scarce, and only one studied mortality according to the Asia Pacific BMI cut-offs.[19] Our results supported the idea that among Asian nursing home residents, being overweight or obese were beneficial to survival.

The survival benefits of the overweight and obese older adults in this study also echoed similar findings reported among community-living older persons reported in the recent decade or so, among Western as well as Asian populations.[6,20–25] Although it was not always consistently protective, BMI within the overweight range (23–24.9 kg/m^2) and obesity range (>25 kg/m^2) among Asians often had the lowest mortality rate in community-living cohorts (Table 3).[21,24–26] Among studies not demonstrating this effect, being overweight or obese was at least not harmful toward all-cause mortality,[21,26–28] unless perhaps only among the very obese according to the Asian cut-offs (BMI ≥ 30 or 32 kg/m^2).[23,24] Comparing with that of community-living older people, the survival benefit of adiposity in nursing home residents seemed even more pronounced, showing that the lowest mortality was found in the obese group instead of in the overweight group as in community cohorts. Since similar findings had been reported in white nursing home cohorts with higher mean BMI (mean BMI 23.1–25.4 kg/m^2 vs 21.7 kg/m^2 in our cohort) and with a lower percentage of underweight individuals (8.5%–11% in other cohort vs 26% in our cohort),[7,8,29] it appears that the survival benefit of adiposity remains valid across different ethnic groups and different BMI ranges.

We found that mortality risk was reduced by 5% to 10% over various periods per each BMI unit increment (Table 2). In older people, though fat proportion increases with age, higher BMI might also be the result of higher muscle mass,[30,31] which may contribute to functional benefits and better survival. Fat, being an energy reserve during periods of poor intake in stress or illness, is often given as a possible explanation for the obesity paradox observed in community-living older people. This function of fat may become even more important in long-term care settings where poor intake because of physiological changes in aging such as earlier satiety, slower gastric emptying, and lower levels of orexigenic hormones (eg, ghrelin) are common.[32]

We found that BMI was more useful as a survival predictor than weight loss in our study. Although the latter had been found to be a good short-term mortality predictor in many nursing home settings, it may have lost its sensitivity as a mortality predictor in populations where a significant proportion was already underweight at baseline, such as in our cohort. It has been suggested that the relationship of low BMI and higher mortality would be lost if body cell mass as measured by bioimpedance was adjusted for.[33] This earlier study was, however, conducted in a nursing home cohort with a higher mean BMI than our current cohort. It is possible that in those with a very low BMI, the percentage of weight loss as a trigger for higher mortality could be lower than 5% in a month or 10% over 6 months.

Table 3
Studies Showing Association Between BMI and Mortality in Nursing Home Residents and Community-Living Older Adults in Asia and Elsewhere

	N	Follow-Up Duration	Mortality	BMI Cut-Offs Used (kg/m^2)	Findings (HRs for Mortality)	
Nursing Home Cohorts						
Italian nursing home residents (Volpato 2004)[33]	344	3.5 years	All-cause	BMI tertiles (mean ± SD)		
				19.3 ± 1.8	1.00 (reference)	
				23.6 ± 1.0	0.72 (0.49–1.06)	
				29.3 ± 3.0	0.94 (0.61–1.43)	
Existing US nursing home residents, >88% white (Grabowski 2005)[18]	5899	1 year	All-cause	<19 (thin)	**1.40 (1.11–1.77)**	
				19–28 (normal)	1.00 (reference)	
				>28 (obese)	**0.75 (0.57, 0.98)**	
Chinese long-term care facility residents (Lin 2010)[19]	354	5 years	All-cause	WHO Asia:		
				<18.5	1.00 (Reference)	
				18.5–22.9	0.75 (0.53–1.07)	
				22.9–25	**0.54 (0.32–0.92)**	
				>25	**0.60 (0.38–0.95)**	
Singaporean nursing home residents, 97% Chinese (Chan 2010)[38]	158	2 years	All-cause	<18.5	**2.71 (1.12–6.58)**	
				≥18.5	1.00 (reference)	
White nursing home residents in Germany (Kaiser 2010)[29]	200	1 year	All-cause	<20 (low)	**3.4 (1.6–7.0)**	
				>20–30 (normal)	1.0 (reference)	
				>30 (high)	0.5 (0.2–1.3)	
Israel nursing home residents (Kimyagarow 2010)[39]	82	1 year	All-cause	<22 (low)	1.45 (0.61–4.94)	
				22–27 (normal)	0.97 (0.36–2.47) (Reference)	
				>27 (high)	0.89 (0.22–1.85)	
Italian nursing home residents (Cereda 2011)[7]	519	5.7 years	All-cause	BMI tertiles		
				≤21	**1.53 (1.13–2.06)**	
				21–25	1.04 (0.77–1.40)	
				≥25	1.00 (reference)	
Italian nursing home residents (Veronese 2012)[8]	181	5 years	All-cause	<20	1.44 (0.95–3.60)	
				20–24.9	1.00 (reference)	
				25–29.9	0.90 (0.61–1.71)	
				≥30	**0.43 (0.20–0.70)**	
Community Cohorts						
US Combined NHANES I, II and III data, age ≥70 (Flegal 2005)[27]	36,859 (all ages)	20 years	All-cause	<18.5	**1.69 (1.38–2.07)**	
				18.5 to <25	1.00 (reference)	
				25 to <30	0.91 (0.83–1.01)	
				30 to <35	1.03 (0.91–1.17)	
				≥35	1.17 (0.94–1.47)	
Korean men and women (age 30–95) (Jee 2006)[24]	1,213,829	Up to 12 years	All-cause		Men	Women
				<18.5	**1.51 (1.45–1.57)**	**1.25 (1.18–1.33)**
				18.5–19.9	**1.28 (1.24–1.32)**	**1.17 (1.11–1.23)**
				20.0–21.4	**1.21 (1.18–1.25)**	1.02 (0.98–1.07)
				21.5–22.9	**1.12 (1.09–1.15)**	1.02 (0.97–1.06)
				23.0–24.9	1.00 (reference)	1.00 (reference)
				25.0–26.4	**0.95 (0.92–0.98)**	0.96 (0.92–1.01)
				26.5–27.9	**0.95 (0.91–0.99)**	0.97 (0.92–1.03)
				28.0–29.9	0.97 (0.92–1.03)	1.03 (0.96–1.09)
				30.0–31.9	1.09 (0.98–1.21)	1.07 (0.97–1.18)
				≥32.0	**1.82 (1.54–2.16)**	1.11 (0.99–1.26)
Japanese community 80-year-old cohort (Takata 2007)[25]	1282	4 years	All-cause		HR using two different reference groups:	
				<18.5	1.00 (reference)	**1.94 (1.00–3.76)**
				18.5–24.9	0.52 (0.27–1.00)	1.00 (reference)
				>25	**0.25 (0.10–0.60)**	**0.48 (0.24–0.96)**

Japanese community older adults (Tamakoshi 2010)[23]	26,747	11.2 years	All-cause			Men	Women
				<16.0		**1.78 (1.45–2.20)**	**2.55 (2.13–3.05)**
				16.0–16.9		1.66 (1.41–1.96)	1.47 (1.22–1.77)
				17.0–18.4		**1.16 (1.06–1.28)**	**1.42 (1.26–1.59)**
				18.5–19.9		**1.12 (1.04–1.22)**	**1.22 (1.11–1.35)**
				20.0–22.9		1.00 (reference)	1.00 (reference)
				23.0–24.9		0.94 (0.87–1.02)	0.96 (0.88–1.06)
				25.0–27.4		0.92 (0.83–1.01)	1.01 (0.92–1.12)
				27.3–29.9		0.89 (0.73–1.07)	0.98 (0.84–1.14)
				≥30.0		0.93 (0.67–1.29)	**1.24 (1.01–1.52)**
Japanese community living cohort, age ≥65 (Nagai 2010)[26]	7274 men, 8477 women	12 years	All-cause	BMI		Men	Women
				<18.5		**1.48 (1.23–1.78)**	**1.45 (1.15–1.83)**
				18.5–20.9		1.09 (0.96–1.25)	1.17 (0.97–1.40)
				21.0–22.9		0.98 (0.87–1.11)	0.96 (0.81–1.15)
				23.0–24.9		1.00 (reference)	1.00 (reference)
				25.0–27.4		0.88 (0.76–1.03)	1.04 (0.86–1.25)
				27.5–29.9		0.91 (0.71–1.17)	1.07 (0.83–1.37)
				≥30.0		1.22 (0.83–1.79)	1.24 (0.92–1.68)
Chinese men and women, age ≥65 (Auyeung 2010)[21]	4000	5.3 years	All-cause	BMI quintiles		HR (unadjusted)	
				Men	Women	Men	Women
				<21.0	<21.1	**1.96 (1.33–2.90)**	1.55 (0.72–3.30)
				21.0–22.7	21.1–23.0	1.09 (0.71–1.69)	1.00 (reference)
				22.8–24.2	23.0–24.6	1.21 (0.79–1.85)	1.54 (0.72–3.29)
				24.2–25.9	24.6–26.7	1.00 (reference)	1.44 (0.67–3.10)
				>25.9	>26.7	1.04 (0.67–1.61)	1.54 (0.72–3.29)
Chinese hypertensive patients, age ≥60 (Wang 2013)[28]	9186	3.7 years	All-cause			(reference = overall study population)	
				<18.0		**1.87 (1.39, 2.51)**	
				18–19.9		1.02 (0.80, 1.30)	
				20–21.9		1.07 (0.88, 1.29)	
				22–23.9		0.96 (0.80, 1.15)	
				24–25.9		0.82 (0.67, 1.01)	
				26–27.9		0.81 (0.63, 1.04)	
				28–29.9		0.92 (0.66, 1.28)	
				≥30		0.83 (0.51, 1.35)	

BMI, body mass index; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; WHO, World Health Organization.
Bold numbers are statistically significant.

Prediction of mortality among long-term care residents is important for individual prognosis as well as for planning of long-term care services. Recently, physical performance measures such as gait speed[34] and handgrip strength[35] were found to be useful in both community and long-term care settings in very old adults. These functional tests, together with BMI measurements, may be able to provide quick and simple prognostication of survival in the nursing home population.

This study was subjected to some limitations. BMI may not reflect the amount of body fat accurately in older people due to sarcopenic obesity. Waist circumference may be a more accurate measure but is rarely available in the nursing home setting.[36,37] The waist circumference with the lowest mortality risk, as validated in a study with body composition data, was in the overweight range among community-living older men,[20] but this has never been tested among nursing home residents who are likely to be older and more frail. Studies with body composition data in nursing home setting may be able to delineate whether body fat or muscle contributed more to the survival benefit. Higher BMI would reflect high muscle mass in addition to fat mass and functionality might be a confounder for lower mortality.[29] Although our data did not include physical performance measures, the use of the MDS ADL scale categories might have compensated partially for this deficit. Data of 94 residents not successfully assessed were not captured, thus, it was not possible to comment on any patterns distinguishing this group. We did not have major laboratory data or blood pressure measurements which might be important in mortality prediction, nor did we have data at intermediate evaluations, data on mininutritional assessment or global frailty.

Conclusions

Significant weight loss as defined by the MDS was not associated with short- or long-term survival in Chinese nursing home residents. Higher BMI, however, was beneficial to short- and long-term survival irrespective of weight loss in this population. Low BMI, detectable at a single point of time, may be another readily available alternative trigger for nutritional interventions. Obesity may be beneficial to survival among Asian nursing home residents.

Acknowledgments

The authors thank Ms Kathy Chow for her assistance in data management.

The data collection was approved by the ethics committees of the Hospital Authority of Hong Kong, and the ethics committee of the Chinese University of Hong Kong. Informed written consent was signed by all participating residents Etic or by family members if the residents were not mentally capable.

References

1. Wang SY, Fukagawa N, Hossain M, Ooi WL. Longitudinal weight changes, length of survival, and energy requirements of long-term care residents with dementia. J Am Geriatr Soc 1997;45:1189–1195.
2. Ryan C, Bryant E, Eleazer P, et al. Unintentional weight loss in long term care: Predictor of mortality in the elderly. South Med J 1995;88:721–724.
3. Kiely DK, Flacker JM. Resident characteristics associated with mortality in long-term care nursing homes: Is there a gender difference? J Am Med Dir Assoc 2000;1:8–13.
4. Sullivan DH, Morley JE, Johnson LE, et al. The GAIN (Geriatric Anorexia Nutrition) registry: The impact of appetite and weight on mortality in a long term care population. J Nutr Health Aging 2002;6:275–281.
5. Flacker JM, Kiely DK. Mortality-related factors and 1-year survival in nursing home residents. J Am Geriatr Soc 2003;51:213–221.
6. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in men and women aged 70 to 75. J Am Geriatr Soc 2010;58:234–241.
7. Cereda E, Pedrolli C, Zagami A, et al. Body mass index and mortality in institutionalized elderly. J Am Med Dir Assoc 2011;12:174–178.
8. Veronese N, De Rui M, Toffanello ED, et al. Body mass index as a predictor of all-cause mortality in nursing home residents during a 5-year follow-up. J Am Med Dir Assoc 2013;14:53–57.
9. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163.
10. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev 2002;3:141–146.
11. Wang D, Li Y, Lee SG, et al. Ethnic differences in body composition and obesity related risk factors: Study in Chinese and white males living in China. PLoS One 2011;6:e19835.
12. World Health Organization Western Pacific Region International Association for the Study of Obesity and the International Obesity Task Force. The Asia-Pacific perspective: Redefining obesity and its treatment. Australia: Health Communications Australia Pty Limited; 2000.
13. Morris JN, Hawes C, Fries BE, et al. Designing the national resident assessment instrument for nursing facilities. Gerontologist 1990;30:293–307.
14. Morris JN, Nonemaker S, Murphy K, et al. A commitment to change: Revision of HCFA's RAI. J Am Geriatr Soc 1997;45:1011–1016.
15. Chou KL, Chi I, Leung ACT, et al. Validation of minimum dataset for nursing homes for Hong Kong Chinese elders. Clin Gerontol 2001;23:43–54.
16. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. J Gerontol Med Sci 1999;54A:M546–M553.
17. Lee JSW, Chau PPH, Hui E, et al. Survival prediction in nursing home residents using the Minimum Data Set subscales: ADL Self-Performance Hierarchy, Cognitive Performance and the Changes in Health, End-stage disease and Symptoms and Signs scales. Eur J Public Health 2009;19:308–312.
18. Grabowski DC, Campbell CM, Ellis JE. Obesity and mortality in elderly nursing home residents. J Gerontol A Biol Sci Med Sci 2005;60:1184–1189.
19. Lin W-Y, Albu J, Liu C-S, et al. Larger body mass index and waist are associated with lower mortality in the Chinese long term care facility residents. J Am Geriatr Soc 2010;58:2092–2098.
20. Lee JS, Auyeung TW, Kwok T, et al. Survival benefit of abdominal adiposity: A 6-year follow-up study with dual X-ray absorptiometry in 3978 older adults. Age 2012;34:597–608.
21. Auyeung TW, Lee JS, Leung J, et al. Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4000 older adults using DXA. J Gerontol A Biol Sci Med Sci 2010;65:99–104.
22. Janssen I. Morbidity and mortality risk associated with an overweight BMI in older men and women. Obesity (Silver Spring) 2007;15:1827–1840.
23. Tamakoshi A, Yatsuya H, Lin Y, JACC Study Group, et al. BMI and all-cause mortality among Japanese older adults: Findings from the Japan collaborative cohort study. Obesity (Silver Spring) 2010;18:362–369.
24. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. N Engl J Med 2006;355:779–787.
25. Takata Y, Ansai T, Soh I, et al. Association between body mass index and mortality in an 80-year-old population. J Am Geriatr Soc 2007;55:913–917.
26. Nagai M, Kuriyama S, Kakizaki M, et al. Effect of age on the association between body mass index and all-cause mortality: The Ohsaki cohort study. J Epidemiol 2010;20:398–407.
27. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. J Am Med Assoc 2005;293:1861–1867.
28. Wang Y, Wang Y, Qain Y, et al. Association of body mass index with cause specific deaths in Chinese elderly hypertensive patients: Minhang community study. PLoS One 2013;8:e71223.
29. Kaiser R, Winning K, Uter W, et al. Functionality and mortality in obese nursing home residents: An example of 'risk factor paradox'? J Am Med Dir Assoc 2010;11:428–435.
30. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci 2002;57:M772–M777.
31. Lee JS, Auyeung TW, Kwok T, et al. Associated factors and health impact of sarcopenia in older Chinese men and women: A cross-sectional study. Gerontology 2007;53:404–410.
32. Morley JE. Anorexia of aging: A true geriatric syndrome. J Nutr Health Aging 2012;16:422–425.
33. Volpato S, Romagnoni F, Soattin L, et al. Body mass index, body cell mass, and 4-year all-cause mortality risk in older nursing home residents. J Am Geriatr Soc 2004;52:886–891.
34. Toots A, Rosendahl E, Lundin-Olsson L, et al. Usual gait speed independently predicts mortality in very old people: A population-based study. J Am Med Dir Assoc 2013;14:529.e1–529.e6.
35. Ling CH, Taekema D, de Craen AJ, et al. Handgrip strength and mortality in the oldest old population: The Leiden 85-plus study. CMAJ 2010;182:429–435.
36. Woo J, Ho SC, Yu ALM, Sham A. Is waist circumference a useful measure in predicting health outcomes in the elderly? Int J Obes 2002;26:1349–1355.
37. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359:2105–2120.
38. Chan M, Lim YP, Ernest A, Tan TL. Nutritional assessment in an Asian nursing home and its association with mortality. J Nutr Health Aging 2010;14:23–28.
39. Kimyagarov S, Klid R, Levenkrohn S, et al. Body mass index (BMI), body composition and mortality of nursing home elderly residents. Arch Gerontol Geriatr 2010;51:227–230.

The Journal of Nutrition, Health & Aging©
Volume 15, Number 10, 2011

PHYSICAL FRAILTY IN OLDER ADULTS IS ASSOCIATED WITH METABOLIC AND ATHEROSCLEROTIC RISK FACTORS AND COGNITIVE IMPAIRMENT INDEPENDENT OF MUSCLE MASS

J.S.W. LEE[1,2], T.-W. AUYEUNG[3], J. LEUNG[4], T. KWOK[1], P.-C. LEUNG[4], J. WOO[1,3]

1. Division of Geriatrics, Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China; 2. Department of Medicine and Geriatrics, Shatin Hospital, Hong Kong SAR, China; 3. The S H Ho Centre of Gerontology and Geriatrics, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China; 4. Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong, Hong Kong SAR, China. Corresponding Author: Jenny SW Lee, Division of Geriatrics, Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, Email: jennylee@cuhk.edu.hk, Tel: (852) 2636 7688, Fax: (852) 2635 1037

Abstract: *Objective:* Metabolic and atherosclerotic diseases are known risk factors for disability in old age, and can result in sarcopenia as well as cognitive impairment, which are both components of frailty syndrome. As muscle loss increases with ageing, it is unclear whether muscle loss per se, or the diseases themselves, are the underlying cause of physical frailty in those suffering from these diseases. We tested the hypothesis that metabolic and atherosclerotic diseases and cognitive impairment are associated with physical frailty independent of muscle loss in old age, and further examined their impact on the relationship between physical frailty and mortality. *Design:* Prospective. *Setting:* Community. *Participants:* 4000 community dwelling Chinese elderly ≥65 years. *Measurements:* Diabetes, hypertension, stroke, heart disease, cognitive impairment, smoking, physical activity, waist hip ratio (WHR) and ankle-brachial index (ABI)) were recorded. Physical frailty measurements (grip-strength, chair-stands, stride length and 6-metre walks) were summarized into a composite frailty score (0-20), 0 being the most frail) according to quartiles of performance. Appendicular muscle mass (ASM) was measured using dual X-ray absorptiometry. Relationships between the score and covariates were analyzed. Cox regression was used to study the impact of metabolic and atnerosclerotic risk factors on the relationship between physical frailty and 6-year mortality. *Results:* After adjustment for ASM, all metabolic diseases and indexes, and cognitive impairment were significantly associated with the composite physical frailty score in univariate analysis. In multivariate analysis, cognitive impairment, high WHR, diabetes, stroke and heart disease were all independently associated with higher physical frailty with adjustment for age, physical activity level and ASM. Hypertension was associated with physical frailty in men but not in women. In Cox regression, increased physical frailty was associated with higher 6-year mortality. The impact of metabolic and atherosclerotic risk factors was however only modest after adjustment for age and cognitive function. *Conclusion:* Metabolic and atherosclerotic diseases and high WHR, was associated with physical frailty, independent of their adverse effect on cognitive function and muscle mass.

Key words: Metabolic, atherosclerotic, frailty, physical, function.

Introduction

Older people who suffer from metabolic diseases, such as diabetes, heart diseases, or obesity, are more disabled or frail. (1-5) Precisely why those suffering from metabolic diseases are frailer required a detailed examination of the effect of these conditions on the other components of frailty, such as physical performance. It has been reported that these diseases are associated with lower muscle mass (6, 7), and the resulted sarcopenia and sarcopenic obesity then cause disability (8, 9). While sarcopenia is a component of the frailty syndrome (10), individual metabolic diseases have rarely been considered as a component. Traditionally, health outcomes of metabolic diseases and obesity have mainly focused on cerebro-or cardiovascular events or mortality.

We and others have reported that obesity was associated with more instrumental activities of daily living (IADL) limitations, pre-frailty or frailty (2, 4, 11). Many have also reported on how diabetes, coronary heart diseases, hypertension or peripheral artery disease were associated with disability in older adults (12-15). While muscle strength have also been reported to be adversely affected by cognitive impairment (16) and sarcopenia (17, 18), whether metabolic diseases caused frailty or disability via sarcopenia or cognitive impairment or they have a mechanism on their own is worth studying.

We examined whether metabolic conditions, cardiovascular disease, generalized atherosclerosis as reflected by low ankle-brachial index (ABI), and obesity reflected by WHR have impact on physical frailty among high functioning elderly, in addition to the loss of muscle mass and cognitive impairment. We also examine how metabolic and atherosclerotic risk factors affect the impact of physical frailty on the outcome of mortality.

Methods

Four thousand Chinese men and women older than the age of 65 were invited to participate in a health check at The Chinese University of Hong Kong from August 2001 to December 2003. We excluded those who (1) were unable to

Received November 2nd, 2010
Accepted for publication January 14, 2011

walk independently; (2) had had bilateral hip replacements; (3) were not competent to give informed consent, and (4) had medical conditions (in the judgment of the study physicians) which made it unlikely that they would survive the follow-up period of 4 years. The procedure included a detailed health questionnaire, brief physical / cognitive assessments, a battery of physical performance tests, and a body composition assessment by dual-energy X-ray absorptiometry (DXA). The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Questionnaire and physical / cognitive assessments

Demographic data such as age, smoker status, and medical conditions were recorded. The presence of diabetes, hypertension, heart disease, and a history of stroke was defined as having ever been informed of the diagnoses by the participant's physician. Heart disease includes coronary heart disease, heart failure and myocardial infarction. Physical activity was recorded by the Physical Activity Scale for the Elderly (PASE) score (19). Cognitive impairment was defined by having a Community Screening Instrument of Dementia (CSI-D) cognitive score. 28.40 (20, 21).

The ankle-brachial index (ABI) was the ratio of the systolic blood pressure measured at the posterior tibial and at the brachial artery. An ABI < 0.9 was defined as low and reflects a state of generalized atherosclerosis (22). The waist-hip ratio (WHR) was defined as the ratio between the waist (the narrowest circumference around the trunk midway between the lower rib cage and the pelvis) and the hip (the largest circumference around the buttocks posteriorly and the symphysis pubis anteriorly). WHR was taken to be high if > 0.9 in men and >0.85 in women (23).

Physical frailty tests

A battery of 5 physical performance tests was conducted for each participant: time taken for 5 chair-stands, grip strength (average of both hands), time taken for "normal and narrow (within 20 cm width)" a 6-metre walk, and the stride length (6 metres divided by the number of steps taken during the walk). The performance was summarized into a composite physical frailty score (0-20), 0 being the most frail) according to quartiles of performance. Weakness or low grip strength, and slowness or slow walking speed had been included as two of the five frailty characteristics defined by Fried at al. (10).

Body composition assessment

Body composition was measured by Dual-energy X-ray Absorptiometry (DXA) using a Hologic QDR 2000 densitometer (Hologic Delphi, software version 11.2). ASM was calculated by the summation of muscle mass measured in the four limbs, with the operator adjusting the cut lines of the limbs according to specific anatomical landmarks as described by Heymsfield et al. (24). The Hologic Body composition step phantom was scanned daily to ensure proper calibration for fat and non-fat compartments. The maximum coefficient of variation for lean mass is 0.84%.

Mortality Status

Mortality status was ascertained by annual death registry search in the Death Registry of the Hong Kong Government. The data used in this study was obtained last from February 28, 2009.

Statistical Methods

Data analysis was performed using SPSS version 16.0, done separately for men and women. Cox regression analysis was used to examine the relationship between 6-year mortality and the composite physical performance score. Age, physical activity, smoker status, the presence of cognitive impairment and metabolic conditions were subjected to multiple linear regression analysis to study their effect on the composite physical performance score. All tests were 2-sided and a p value of <0.05 was taken as statistically significant.

Results

Among the 2000 men and 2000 women assessed, the mean age was 72.3 years for men and 72.5 years for women. The prevalence of diabetes, hypertension and heart disease were similar among men and women. Compared with women, men had significantly more strokes (5.5% vs. 3.3%, p = 0.001) but lower prevalence of low ankle-brachial index (4.8% vs. 9.0%, p<0.001) and high waist-hip ratio (64.9% vs. 81.5%, p<0.001). Men were more likely to be smokers, had higher education level and higher physical activity scores (Table 1).

In both men and women, all metabolic conditions examined (diabetes, hypertension, heart disease, stroke, low ABI and high WHR) were significantly associated with the composite physical frailty score, both before and after adjustment for appendicular skeletal mass (Table 2).

In multivariate linear regression analysis, the relationship between various metabolic conditions and the composite physical performance score was studied with adjustment for age, cognitive impairment, appendicular skeletal mass and physical activities. Diabetes, hypertension, heart disease, stroke and high WHR were all associated with lower composite physical frailty scores in men, independent of the effect of cognitive impairment and muscle mass, while low ABI was not related. In women, diabetes, heart disease, stroke and high WHR was associated with lower physical performance, while both hypertension and low ABI were not related (Table 3).

After a mean follow-up period of 72.0 ± 12.7 months, 271(13.5%) men and 90(4.5%) women had died. Lower physical performance score was associated with higher mortality after 6 years of follow-up, in both men and women, with exclusion of early deaths that occurred within the first twelve months after the physical assessment. Adjustment for age and cognitive function attenuated the relationship but it remained significant, particularly in men. Further adjustment for metabolic and atherosclerotic risk factors resulted in a small

reduction in the detrimental effect of physical frailty in men (HR reduced from 1.103 to 1.098), but not in women (HR increased from 1.058 to 1.061) (Table 4).

Table 1
Comparison of baseline characteristics between men and women

	Men (n = 2000)	Women (n = 2000)	p-value
Age (year)	72.3 ± 5.0	72.5 ± 5.3	NS
Body Weight (kg)	62.4 ± 9.3	54.5 ± 8.4	< 0.001
Body Mass Index	23.4 ± 3.1	23.9 ± 3.4	< 0.001
<18.5	5.8	5.0	
18.5 – 23.0	38.0	35.6	
23.0 – 24.9	26.2	23.8	
25 – 29.9	28.1	31.4	
30 or above	2.0	4.3	
Current Smokers	11.9%	1.9%	< 0.001
Years of Education			< 0.001
0 years	5.2%	37.7%	
1-6 years	55.2%	45.2%	
7-12 years	26.1%	11.3%	
> 12 years	13.6%	6.0%	
PASE Score	97.2 ± 50.2	85.3 ± 33.1	< 0.001
CSI-D cognitive score $\leq$ 28.40	4.9%	25.3%	< 0.001
MMSE score	26.9 ± 2.7	24.2 ± 3.9	< 0.001
Appendicular Skeletal Mass (kg)	19.1 ± 2.6	13.8 ± 1.9	< 0.001
Diabetes Mellitus	14.7%	14.3%	NS
Hypertension	41.8%	43.6%	NS
Stroke	5.5%	3.3%	0.001
Heart disease	18.3%	16.5%	NS
ABI < 0.9	4.8%	9.0%	< 0.001
High gender-specific waist-hip ratio	64.9%	81.5%	< 0.001
Composite physical performance score	12.2 ± 4.1	12.2 ± 4.3	NS

Values are expressed as mean ± standard deviation or percentage; CSI-D= Community Screening Instrument of Dementia; MMSE = Mini-mental Status Examination; PASE = Physical Activity Scale for the elderly; ABI = ankle-brachial index; Statistical comparison by unpaired student-t test for continuous variables and Chi-square test for categorical variables; NS = not significant

Discussion

Frailty is described by a variety of measures. Some included mainly physical performances (25), others included limitations in activities of daily living (26), or a combination of impairment in fitness and function (27). Our results suggested that poorer physical performance in the 5 tests used was related to higher risk of death after 6 years, confirming the findings of others that physical frailty was associated with higher mortality (25), not only in women, but also in men.

However, not all frailty criteria included individual medical conditions, and even those that did, include only the number of medical conditions plus the above (28, 29). Apart from being the components of a measure of biological age (30) and putting older individuals at risk of cognitive dysfunction (31), our result suggest that metabolic conditions themselves are associated with physical frailty independent of sarcopenia and cognitive impairment in old age, and that they might contribute to frailty on their own accord.

Our results suggested that among all the metabolic conditions, high waist-hip ratio has the highest impact on physical frailty, independent of the other commonly co-existing disorders. This is accordance with the results of others that adiposity, though associated with longer survival (32, 33), might give rise to increased physical frailty or disability (2, 4, 11). It is therefore important to identify the intersecting point in adiposity which is best for both survival and function.

Low ABI ceased to be significant in the multivariate model, after adjustment for diabetes, cardiovascular diseases and general factors such as age, physical activities, cognitive impairment and smoking. Although peripheral artery disease has been found to be associated with disability, its effect was largely explained by the presence of diabetes, diabetic neuropathy, and diabetes-related cardiovascular diseases (13). On the other hand, low ABI at our cut-off may not reflect atherosclerosis severe enough to affect our physical frailty measurements.

The exact mechanisms for how each metabolic condition was linked to physical frailty were not known. Most proposed underlying mechanisms for explaining physical frailty due to individual conditions also involved other commonly co-existing metabolic conditions: for example, stroke and heart disease partially explained the relationship between diabetes and disability (12), and diabetes, heart disease and peripheral artery disease partially explained the relationship between obesity and frailty (2). Increased rate of sarcopenia might be a cause for diabetes-related physical frailty (7), while increased inflammation (34) and cytokines (35) might also be underlying mechanisms shared by diabetes, obesity and atherosclerosis. Oxidative stress might be yet another possible underlying mechanism linking metabolic conditions to physical frailty (36). Higher oxidative stress associated with metabolic and atherosclerotic conditions (37, 38) had been implicated in the decline of muscle mass (sarcopenia) and muscle strength via oxidative protein damage, thus compromising physical performance. The tests used in this physical performance score were not strenuous thus should not be particularly affected by cardiopulmonary function. The slowness or weakness detected could be signs of reduced physical reserve that is reflected even in mild everyday activities such as getting up from a chair, walking, and gripping.

It is worth noting that physical activity as reflected by the PASE score was associated with better physical performance in both men and women, even after adjustment for all the metabolic conditions and relevant covariates. Physical activities in the PASE included basic and instrumental activities of daily living, hobbies or leisure activities, in addition to exercise. The message is thus clear that any physical activity, not just formal exercise, might be able to retard physical frailty in old age.

In survival analysis, metabolic and atherosclerotic risk factors slightly attenuated the impact of physical frailty on mortality in men, but not in women. This could be due to the higher prevalence of smoking among men, which caused a higher background load of vascular dysfunction, thus making

Table 2

Univariate analysis of composite physical performance score, unadjusted and after adjustment for appendicular skeletal muscle mass

Covariates	Mean ± SD/ %	Unit	Mean difference per unit change of covariates (95% CI) unadjusted	p value	adjusted for ASM	p value
Men						
Cognitive impairment	4.9%	Yes/ no	-0.16 (-3.74, -2.12)	<0.001	-0.14 (-3.33, -1.75)	< 0.001
Age (year)	72.3 ± 5.0	5	-2.15 (-1.90, -1.55)	< 0.001	-1.95 (-1.75, -1.35)	< 0.001
PASE score	97.2 ± 50.2	50.2	10.49 (0.50, 1.00)	< 0.001	9.54 (0.50, 1.00)	< 0.001
Diabetes	14.7%	Yes/ no	-3.08 (-1.29, -0.29)	0.002	-0.09 (-1.54, -0.56)	< 0.001
Hypertension	41.8%	Yes/ no	-0.12 (-1.31, -0.60)	< 0.001	-0.14 (-1.53, -0.83)	< 0.001
Heart Disease	18.3%	Yes/ no	-0.08 (-1.42, -0.40)	< 0.001	-0.09 (-1.57, -0.57)	< 0.001
Stroke	5.5%	Yes/ no	-0.11 (-2.81, -1.25)	< 0.001	_0.12 (-2.82, -1.30)	<0.001
ABI < 0.9	4.8%	Yes/ no	-0.11 (-3.00, -1.33)	< 0.001	-0.93 (-2.59, -0.966)	< 0.001
High Waist – Hip Ratio	64.8%	Yes/ no	-0.06 (-0.84, -0.10)	0.013	-0.12 (-1.37, -0.63)	< 0.001
Current smoker	11.9%	Yes/ no	0.01 (-0.41, 0.69)	NS	0.03 (-0.18, 0.89)	NS
Women						
Cognitive impairment	25.3%	Yes/ no	-0.21 (-2.50, -1.66)	< 0.001	-0.21 (-2.46, -1.62)	<0.001
Age (year)	72.5 ± 5.3	5.3	-2.12 (-1.86, -1.48)	< 0.001	-2.01 (-1.80, -1.43)	< 0.001
PASE score	85.3 ± 33.1	33.1	8.28 (0.99, 1.32)	< 0.001	7.61 (0.66, 1.32)	< 0.001
Diabetes	14.3%	Yes/ no	-0.08 (-1.55, -0.48)	< 0.001	-0.09 (-1.65, -0.60)	< 0.001
Hypertension	43.6%	Yes/ no	-0.03 (-0.66, 0.09)	NS	-0.05 (-0.77, -0.02)	0.038
Heart Disease	16.5%	Yes/ no	-0.08 (-1.55, -0.42)	0.001	-0.08 (-1.63, -0.51)	< 0.001
Stroke	3.3%	Yes/ no	-0.06 (-2.53, -0.44)	0.005	-0.06 (-2.41, -0.34)	0.009
ABI < 0.9	9.0%	Yes/ no	-0.11 (-2.22, -0.92)	< 0.001	-0.09 (-2.05, -0.76)	< 0.001
High Waist – Hip Ratio	81.5%	Yes/ no	-0.08 (-2.12, -1.17)	< 0.001	-0.18 (-2.44, -1.49)	< 0.001
Current smoker	1.9%	Yes/ no	0.01 (-1.23, 1.55)	NS	0.02 (-0.90, 1.85)	NS

PASE = Physical Activity Scale for the Elderly; ABI = ankle-branchial index; BMI = body mass index; ASM = Appendicular skeletal mass; CI = Confidence interval; NS = not significant

Table 3

Multivariate analysis of composite physical performance score with adjustment for metabolic factors, cognitive impairment, and appendicular skeletal muscle mass

Covariates	Mean ± SD/ %	Unit	Mean difference per unit change (95% CI)	p value
Male				
ASM (kg)	19.1 ± 2.6	2.6	0.43 (0.49, 0.83)	< 0.001
Cognitive impairment	4.9%	Yes/ no	-0.07 (-2.05, -0.60)	< 0.001
Age (year)	72.3 ± 5.0	5.0	-1.72 (-1.55, -1.23)	< 0.001
PASE score	97.2 ± 50.2	50.2	5.82 (0.30, 0.60)	< 0.001
Metabolic/ artherosclerotic conditions				
Diabetes	14.7%	Yes/ no	-0.04 (-0.90, -0.00)	0.049
Hypertension	41.8%	Yes/ no	-0.05 (-0.78, -0.12)	0.008
Heart Disease	18.3%	Yes/ no	-0.05 (-1.05, -0.14)	0.010
Stroke	5.5%	Yes/ no	-0.08 (-2.20, -0.81)	< 0.001
ABI < 0.9	4.8%	Yes/ no	-0.03 (-1.31, 0.17)	NS
High Waist – Hip Ratio	64.8%	Yes/no	-0.09 (-1.08, -0.40)	< 0.001
Female				
ASM (kg)	13.8 ± 1.9	1.9	0.17 (0.20, 0.55)	< 0.001
Cognitive impairment	25.3%	Yes/ no	-0.12 (-1.54, -0.75)	< 0.001
Age (year)	72.5 ± 5.3	5.3	-1.57 (-1.44, -1.07)	< 0.001
PASE score	85.3 ± 33.1	33.1	4.30 (0.36, 0.73)	< 0.001
Metabolic/ artherosclerotic conditions				
Diabetes	14.3%	Yes/ no	-0.05 (-1.15, -0.17)	0.009
Hypertension	43.6%	Yes/ no	0.02 (-0.20, 0.51)	NS
Heart Disease	16.5%	Yes/ no	-0.05 (-1.20, -0.17)	0.009
Stroke	3.3%	Yes/ no	-0.05 (-2.07, -0.20)	0.018
ABI < 0.9	9.0%	Yes/ no	-0.01 (-0.70, 0.49)	NS
High Waist – Hip Ratio	81.5%	Yes/no	-0.11 (-1.64, -0.76)	< 0.001

PASE = Physical Activity Scale for the Elderly; ABI = ankle-branchial index; BMI = body mass index; ASM = Appendicular skeletal mass; CI = Confidence interval; NS = not significant.

Table 4
Change of impact of composite physical performance score on 6-year mortality by Cox regression analysis per 1 point decrease in physical performance score

	Change of unadjusted HR (95% CI)	p value	age-adjusted HR (95% CI)	p value	additional adjustment for cognitive status HR (95% CI)	p value	additional adjustment for metabolic & atherosclerotic risk factors	p value
Men								
Excluded early deaths up to 12 months from baseline	1.160 (1.124,1.196)	<0.001	1.108 (1.070, 1.146)	<0.001	1.103 (1.067, 1.142)	<0.001	1.098 (1.060, 1.137)	<0.001
Women								
Excluded early deaths up to 12 months from baseline	1.097 (1.043, 1.154)	<0.001	1.063 (1.008, 1.123)	0.025	1.058 (1.002, 1.117)	0.042	1.061 (1.005, 1.122)	0.032

Metabolic and atherosclerotic risk factors included diabetes, hypertension, stroke, heart disease, ABI < 0.9 and high gender-specific waist hip ratio.

the presence of metabolic and atherosclerotic risk factors more hazardous. The lack of effect of these risk factors in women might be attributed to the lower background vascular dysfunction due to fewer smokers, or that death in older women were not as strongly associated with vascular risks as in men. In frailty criterion, genders are usually not considered. However, in view of this difference in vascular risks or impact on mortality, perhaps some consideration should be given to gender, when mortality prediction is concerned.

There were several limitations. Our study design was cross-sectional, hence the results can only demonstrate associations between these conditions and physical frailty, but not causal relationships. Our cohort consisted of relatively healthy and mobile individuals, thus the results may not applied to those who were more infirmed. The medical diagnoses was based on self-report, although this might be affected by recall bias, it had been recognized as a valid method for collecting medical diagnoses in large studies (9, 25). Although a quarter of the female participants were categorized as possibly cognitively impaired, 37% of them had no formal education, which might have affected the cognitive assessment result.

Further prospective studies are warranted to examine the effect of these metabolic conditions on frailty, or indeed, whether any of these conditions have strong enough impact on frailty that it may worth a place in the frailty criterion. The addition of some metabolic conditions to the current frailty criteria may help to identify those who are at risk of frailty and thus allow early interventions. As it is unlikely that physical frailty can result in metabolic conditions, it would be prudent to conclude that the latter contribute significantly to the former. However, when mortality prediction was considered as an outcome of physical frailty, these conditions exerted only very modest additional impact. We conclude therefore that metabolic conditions contributed significantly to physical frailty, but not to the impact of physical frailty on mortality.

Conclusion

Metabolic and artherosclerotic diseases and high WHR, were associated with physical frailty, independent of their adverse effect on cognitive function and muscle mass.

Acknowledgement: Hong Kong Research Grant Council Grant (CUHK4101/02M) and The S H Ho Centre of Gerontology and Geriatrics, at The Chinese University of Hong Kong.

References

1. Miller DK, Lui LYL, Perry III HM, Kaiser FE, Morley JE. Reported and measured physical functioning in older inner-city diabetic African Americans. J Gerontol 1999;54A:M230-M236.
2. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. J Am Geriatr Soc 2005;53(6):927-934.
3. Al Snih S, Ottenbacher KJ, Markides KS, Kuo Y-F, Eschbach K, Goodwin JS. The effect of obesity on disability vs mortality in older Americans. Arch Intern Med 2007;167:774-780.
4. Woo J, Leung J, Kwok T. BMI, body composition, and physical functioning in older adults. Obesity 2007; 15:1886-1894.
5. Hubbard RE, Andrew MK, Fallah N, Rockwood K. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. Diabet Med 2010; 27, 603–606.
6. Park SW, Goodpaster BH, Lee JS, et al. for the Health, Aging, and Body Composition Study. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care 2009;32:1993-1997.
7. Lee JSW, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults. Diab Med 2010; 27:1366–1371. DOI: 10.1111/j.1464-5491.2010.03118.x
8. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755-763.
9. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (Sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889-896.
10. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
11. Houston DK, Stevens J, Cai J. Abdominal fat distribution and functional limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. Int J Obes 2005;29(12):1457-1463.
12. Gregg EW, Mangione CM, Cauley JA, Thompson TJ, Schwartz AV, Ensrud KE, Nevitt MC; Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. Diabetes Care 2002;25(1):61-67.
13. Dolan NC, Liu K, Criqui MH, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. Diabetes Care 2002;25(1):113-120.
14. Hajjar I, Lackland DT, Cupples LA, Lipsitz LA. Association between concurrent and remote blood pressure and disability in older adults. Hypertension. 2007;50(6):1026-

1032.
15. Pinsky JL, Jette AM, Branch LG, Kannel WB, Feinleib M. The Framingham Disability Study: relationship of various coronary heart disease manifestations to disability in older persons living in the community. Am J Public Health 1990; 80(11):1363–1367.
16. Auyeung TW, Kwok T, Lee J, Leung PC, Leung J, Woo J. Functional decline in cognitive impairment--the relationship between physical and cognitive function. Neuroepidemiology 2008;31(3):167-173.
17. Zoico E, Di Francesco V, Guralnik JM , et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. Int J Obes 2004; 28: 234–241.
18. Rolland Y, Czerwinski S, Abellan van Kan G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008;12:433-450.
19. Washburn RA, Smith KW, Jette AM, Janny CA: The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993; 46: 153–162.
20. Chan TS, Lam LC, Chiu HF, Prince M. Validity and applicability of the Chinese version of Community Screening Instrument for Dementia. Dement Geriatr Cogn Disord, 2003;15:10–18.
21. Prince M, Acosta D, Chiu H, et al. 10/66 Dementia Research Group Dementia diagnosis in developing countries: a cross cultural validation study. Lancet 2003;361:909–917.
22. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. J Clin Epidemiol 1991;44:15-20.
23. Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Report of a WHO consultation. Diab Med 1998;15:539-553.
24. Heymsfield SB, Smith R, Aulet M, et al: Appendicular skeletal muscle mass: measurement by dual-energy X-ray absorptiometry. Am J Clin Nutr 1990; 52: 214–218.
25. Rolland Y, Lauwers-CancesV, Cesari M, Vellas B, Pahor M, Grandjean H. Physical performance measures as predictors of mortality in a cohort of community-dwelling older French women. Eur J Epidemiol 2006;21:113-122.
26. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet 1999; 535:205-206.
27. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, andabdominal obesity in older people. J Gerontol A Biol Sci Med Sci 2010; 65(4): 377-381.
28. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12(1):29-37.
29. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. J Am Med Dir Assoc 2008;9:71–72.
30. Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. J Gerontol A Biol Sci Med Sci 2005;60(8):1046-1051.
31. Sinclair A, Viljoen A. The metabolic syndrome in older persons. Clin Geriatr Med 2010;26:261-274.
32. Auyeung TW, Lee JS, Leung J, Kwok T, Leung PC, Woo J. Survival in older men may benefit from being slightly overweight and centrally obese--a 5-year follow-up study in 4,000 older adults using DXA. J Gerontol A Biol Sci Med Sci 2010;65(1):99-104.
33. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in men and women aged 70 to 75. J Am Geriatr Soc 2010;58(2):234-241.
34. Barzilay JI, Blaum C, Moore T, et al. Insulin resistance and inflammation as precursors of frailty. The Cardiovascular Health Study. Arch Intern Med 2007;167:635-641.
35. Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999;47(6):639-646.
36. Semba RD, Ferrucci L, Sun K, et al. Oxidative stress and severe walking disability among older women. Am J Med 2007;120(12):1084 – 1089.
37. Kedziora-Kornatowska K, Czuczejko J, Pawluk H, et al. The markers of oxidative stress and activity of the antioxidant system in the blood of elderly patients with essential arterial hypertension. Cell Mol Biol Lett 2004;9(4A):635-641.
38. Helmersson J, Vessby B, Larsson A, Basu S. Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. Circulation 2004;109(14):1729-1734.

Survival benefit of abdominal adiposity: a 6-year follow-up study with Dual X-ray absorptiometry in 3,978 older adults

Jenny Shun Wah Lee, Tung Wai Auyeung, Timothy Kwok, Martin Li, Jason Leung & Jean Woo

AGE
The Official Journal of the American Aging Association

ISSN 0161-9152

AGE
DOI 10.1007/s11357-011-9272-y

Springer

AGE
DOI 10.1007/s11357-011-9272-y

Survival benefit of abdominal adiposity: a 6-year follow-up study with Dual X-ray absorptiometry in 3,978 older adults

Jenny Shun Wah Lee · Tung Wai Auyeung · Timothy Kwok · Martin Li · Jason Leung · Jean Woo

Received: 14 December 2010 / Accepted: 18 May 2011

Abstract In contrast to that in the middle-aged, higher body mass index (BMI) in older people is associated with higher survival rates. Yet, BMI makes no distinction between fat elsewhere and abdominal fat, the latter being metabolically more harmful. We hypothesized that overall adiposity might be protective in old age, but that central fat might offset that benefit and remained harmful as in the middle-aged. Three thousand nine hundred seventy-eight Chinese elderly ≥65 years had demographics, medical conditions, physical activity, and body composition by DXA recorded at baseline. Overall adiposity was measured as whole body fat%, and abdominal adiposity as waist circumference, waist–hip ratio, and relative abdominal fat (RAF) (relative abdominal fat = abdominal fat according to anatomical landmarks/whole body fat). Deaths within 1 year from baseline were excluded from analysis. All-cause and cardiovascular mortality were analyzed using Cox regression, adjusted for covariates. The lowest quintile of adiposity measurements was used for comparison. After a mean follow-up of 72.3 months, 13.7% men and 4.5% women had died. In men, the highest two quintiles of whole body fat % and the upper four quintiles of RAF were associated with significantly lower all-cause mortality, and adjusted hazard ratio (95% CI) in ascending quintiles of RAF compared with the lowest quintile was 0.62 (0.43–0.89), 0.58 (0.4–0.85), 0.52 (0.36–0.77), and 0.67 (0.47–0.96). No relationship was found between abdominal adiposity and cardiovascular mortality in both genders. Higher whole body fat % as well as higher proportion of abdominal fat was associated with lower all-cause mortality in men. No such relation was found in women.

Keywords Central adiposity · Obesity · Elderly · Mortality

J. S. W. Lee · T. Kwok · M. Li · J. Woo
Division of Geriatrics,
Department of Medicine and Therapeutics,
The Chinese University of Hong Kong,
Hong Kong, China

J. S. W. Lee
e-mail: jennylee@cuhk.edu.hk

J. S. W. Lee · T. W. Auyeung (✉) · J. Woo
The S H Ho Centre for Gerontology and Geriatrics,
The Chinese University of Hong Kong,
Hong Kong, China
e-mail: auyeungtw@cuhk.edu.hk

T. W. Auyeung
Department of Medicine and Geriatrics, Pok Oi Hospital,
Hong Kong, China

J. Leung
The Jockey Club Centre of Osteoporosis Care and Control,
The Chinese University of Hong Kong,
Hong Kong, China

J. S. W. Lee
Department of Medicine and Geriatrics, Shatin Hospital,
33 A Kung Kok Street, Shatin,
Hong Kong, China

Published online: 11 June 2011

Introduction

Higher body mass index (BMI) in older people is associated with higher survival rates, in contrast to middle-aged people (Adams et al. 2006; Al Snih et al. 2007; Reis et al. 2009; Auyeung et al. 2010; Janssen 2007; Tamakoshi et al. 2010). This has led to the postulation that obesity might be less harmful or even protective in old age (Al Snih et al. 2007; Reis et al. 2009; Auyeung et al. 2010; Lea et al. 2009). Yet, BMI is a measure of overall adiposity, which makes no distinction between fat elsewhere and abdominal fat, the latter being metabolically more harmful (Lapidus et al. 1994; Chang et al. 2000; Snijder et al. 2006). Some have demonstrated that overall adiposity and abdominal adiposity act in different directions regarding the risk of metabolic diseases such as diabetes or cardiovascular diseases (Lapidus et al. 1994; Lafortuna et al. 2006). The effect of higher central adiposity on survival in older adults however was controversial (Reis et al. 2009; Auyeung et al. 2010; Visscher et al. 2001; Woo et al. 2002; Lindqvist et al. 2006). Many have reported that central adiposity was more related to cardiovascular diseases and health risk, independent of BMI (Zamboni et al. 2005), and that peripheral fat such as that in the hips was independently protective (Lissner et al. 2001).

Previous studies have often used waist circumference and the waist–hip ratio (WHR) as a measurement of abdominal adiposity. However, the relationship between mortality, and waist circumference and WHR is controversial among the older population (Reis et al. 2009; Visscher et al. 2001; Woo et al. 2002; Price et al. 2006; Pischon et al. 2008; Jacobs et al. 2010). While some found a more linear relationship between WHR and mortality (Lindqvist et al. 2006; Price et al. 2006; Zhang et al. 2007), others were more in favor of the waist circumference (Visscher et al. 2001; Woo et al. 2002; Pischon et al. 2008; Jacobs et al. 2010). Dual-energy X-ray absorptiometry (DXA) can provide both accurate measurements of overall and regional adiposity (Snijder et al. 2006) and thus may help to elucidate the relationship between different measurements of abdominal fat, fat distribution, and mortality.

Trunk adiposity includes the breasts in women and in obese men. This might have led to overestimation of central or abdominal adiposity (Auyeung et al. 2010) when it is used as a measurement of the latter, confounding the true effect of abdominal obesity on health outcomes. This might also have obscured the relationship between abdominal adiposity and mortality, particularly in women. In the present study, we used DXA-measured abdominal adiposity, delineated according to specific anatomical landmarks, to examine its effect on survival. We hypothesized that overall adiposity might be protective in old age, but that abdominal adiposity might offset that benefit and remain harmful as in middle-aged people. To study that effect, we examined the relationship between how abdominal adiposity, as a proportion of overall adiposity measured by DXA, as waist circumference or as WHR, affects mortality in a cohort of older adults.

Methods

Four thousand community-living Chinese men and women aged 65 years or over were recruited for a cohort study on osteoporosis and general health in Hong Kong between August 2001 and December 2003. Recruitment was by notices in senior social centers and housing estates as a large proportion of the elderly population resides in housing estates and attends senior social centers. Talks were given to explain the purpose, procedures, and investigations to be carried out. We excluded those who (1) were unable to walk independently; (2) had had bilateral hip replacements; (3) were not competent to give informed consent; and (4) had medical conditions (in the judgment of the study physicians) which made it unlikely that they would survive the follow-up period of 4 years for the osteoporosis study. The sample was stratified so that approximately 33% were in each of the age groups: 65–69, 70–74, and 75 or above. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants gave written consent to allow their personal, psychosocial, and physical data thus obtained to be used for research purposes, prior to undergoing a health check in the School of Public Health in the Chinese University of Hong Kong.

The questionnaire

A questionnaire containing information regarding demographics, lifestyle, physical activity level, and medical history was administered by trained inter-

viewers. Smokers were classified by having ever smoked more than five packs of cigarettes in the past, smoking currently, or never smoked. Physical activity level was assessed using the Physical Activity Scale of the Elderly (PASE) (Washburn et al. 1993), which measured the hours spent per day in leisure, household, and occupational physical activities over the previous 7 days. A summary score reflected the daily physical activity level. Cognitive function was measured by the Mini-Mental State Examination (MMSE), a cognitive test including items on time and place orientation, registration and delayed recall, calculation and concentration, language, and praxis. The maximum score was 30 (Folstein et al. 1975). The cut-off for suspected cognitive impairment for the Hong Kong population was set at 18 for those with no formal education, and 22 for those with elementary education (Chiu et al. 1994). Socioeconomic status was recorded using the social economic status ladder—Hong Kong. Participants were asked to mark their position on the picture of a ladder with ten rungs, with the explanation that the top rung represented people with the most money, most education, and the most respected jobs, and the bottom rung represented the other end of the spectrum. The ladder represented the individual's perception of his/her own status in the community with respect to income, education, and occupation. This subjective measure of socioeconomic status has been associated with health outcomes in various populations including that of Hong Kong (Adler et al. 2000; Cheng et al. 2002; Singh-Manoux et al. 2005).

Medical diagnoses and medications

Medical diagnoses were based on the subjects' report of their physician's diagnoses, supplemented by medications brought to the interviewers. Diabetes, heart disease, and cancer were defined by self-reporting (ever being told to have the condition by a physician). Heart disease included coronary heart disease, heart failure, and myocardial infarction. Self-report diseases have been recognized as a valid method for collecting medical diagnosis in large-scale studies (Bourdel-Marchasson et al. 1997; McGuire et al. 2006). The number of medications was taken as the total number of medications the participants was taking at the time of the assessment and which they brought to the place of the assessment.

Physical measurements

Body weight was measured, with subjects wearing a light dressing gown, by the Physician Balance Beam Scale (Health-O-Meter, Arlington Heights, IL, USA). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Waist circumferences (the circumference around the trunk midway between the rib cage and the pelvis) and hip circumferences (the maximum circumference around the buttock posteriorly and the pubis symphysis anteriorly) were measured with a flexible measuring tape. Only one measurement was taken. Four staff were involved in the measurement of the waist and the hip. The inter-rater reliability intra-class correlation using 15 subjects was 0.985 and 0.879 for waist and hip, respectively. Body weight at age 25 was obtained by recall of the subjects. Weight change since age 25 was calculated by the formula: body weight at the physical assessment minus recalled weight at age 25.

Body composition

We measured body fat by DXA using Hologic Delphi W4500 (Hologic Delphi, auto whole body version 12.4, Hologic Inc, Bedford, Massachusetts, USA) at baseline. The upper border of the abdominal region was defined by a horizontal line drawn through the lower one third of the vertical height between the left midpoint acromion and the external end of left iliac crest. The lower border of the abdominal region was defined by a horizontal line through the external ends of the iliac crests. The method was adopted from that of Bertin et al. (2000). The abdominal height was reduced to the lower one third instead of the lower half as in the report by Bertin et al. because the latter method would have included the lungs and heart due to the smaller body size in the Chinese population. We were not able to use the method of measuring abdominal fat as defined by the region between the L1 and L4 vertebrae because many subjects had scoliosis and low bone mass, making the delineation of the upper or lower borders of these vertebrae difficult from a whole-body DXA scan. The relative abdominal fat (RAF) was calculated as the proportion of abdominal fat within whole body fat (RAF = abdominal fat/whole body fat × 100%). The Hologic

Body composition step phantom was scanned daily to ensure proper calibration for fat and nonfat compartments. The maximum coefficient of variation for fat is 1.47%.

Follow-up procedure and mortality data

Follow-up was done every 4-monthly by phone then every 2-yearly by a mailed reminder for a follow-up body check appointment until the end of 4 years (a total of three follow-up visits) or death, whichever occurred earlier. Phone reminders were given again close to the appointment dates, and defaulters were given a second appointment to enhance attendance rates. Mortality status was confirmed by annual reports from the death registry in the Department of Health in Hong Kong. Cardiovascular causes of death were identified by the cause of death reported on the death certificate, and classified according to the International Classification of Disease (ICD) version 10 codes as those ranging from 100 to 199.

Statistical methods

Data analysis was performed by using SPSS version 17.0 (IBM Corp, Somers, NY, USA). As body composition differs with gender, all statistical tests were done separately for men and women. Characteristics of decedents and survivors were compared. Unpaired *t* tests were used for continuous variables and chi-square tests for categorical variables. Crude mortality was plotted against quintiles of different adiposity measurements. All-cause and cardiovascular mortality as on February 28, 2009 were analyzed using Cox regression, adjusted for covariates that were relevant to mortality in older individuals (age, physical activity, smoker status, history of cancer, diabetes, heart disease, measures of socioecomonic status and medications. To adjust for the effect of lifelong obesity, recalled weight change since early adulthood at 25 years of age was further adjusted for. The lowest quintile of all adiposity measures was used as the comparison group. Early deaths within 12 months of the baseline assessment were excluded to avoid bias due to reverse causality. All tests were two-sided, and a p value of <0.05 was taken as statistically significant.

Results

After a mean follow-up of 72.3±11.7 months (median 74.4 months), 286 (14.3%) men and 97 (4.9%) women had died. Those who died within the first year after the baseline visit were excluded from the analysis (15 men and 7 women) to eliminate bias in body fat changes close to the time of death (reverse causality). Decedents in both men ($n=271$) and women ($n=90$) were older, had lower MMSE scores, and were more likely to have a past history of cancer at baseline. In men, those who died also had lower physical activity scores and were more likely to have diabetes (Table 1).

Men who survived had higher BMI, higher whole body fat %, and higher relative abdominal fat. There was no difference in the waist circumference and waist–hip ratio between the survivors and the decedents (Table 1). In women, no difference in any of the adiposity measurements was observed between survivors and decedents.

Figure 1 (or Table 6) showed the crude mortality rates of both men and women across the quintiles of four obesity measures (whole body fat % for general adiposity, waist circumference, WHR, and relative abdominal fat for abdominal adiposity). Higher quintiles of both whole body fat % and RAF were associated with lower crude mortality in men (whole body fat %, p for trend <0.01; relative abdominal fat, p for trend <0.05). Waist circumference and WHR had a U-shaped relationship with mortality with the lowest rate at the third quintile and second quintile, respectively. None of the obesity measures bore any significant relationship with mortality in women.

Table 2 shows the hazard ratios (HR) of all-cause and cardiovascular mortality according to quintiles of whole body fat %, relative abdominal fat, waist circumference, and WHR. In men, each of the four upper quintiles of RAF was associated with a significantly lower HR for all-cause mortality after adjustment for age, physical activity, history of cancer, diabetes, heart disease and smoker status. Only the highest two quintiles of whole body fat % showed similar protective effect. The p for trend was significant for the HRs of all-cause mortality across quintiles of whole body fat % (p for trend <0.001) and relative abdominal fat (p for trend $=0.011$) in men, indicating a tendency for those with higher fatness to have lower mortality, after adjustment for age,

Table 1 Characteristics of decedents and survivors

	Men		Women	
	Decedents (n=271)	Survivors (n=1,714)	Decedents (n=90)	Survivors (n=1,903)
Age	75. (5.4)	71.9 (4.8)*	74.9 (6.2)	72.5 (5.3)*
Physical activity score	84.0 (45.2)	99.5 (50.8)*	85.2 (33.2)	85.4 (33.2)
Smoker status (%)**[a]				
Never	24.7	37.9	77.8	91.1
Ex-smoker	60.9	50.5	16.7	7.2
Current smoker	14.4	11.6	5.6	1.7
Number of medications[b]	1 (0–7)	1 (0–7)*	1 (0–6)	1 (0–7)
Social economic status ladder—Hong Kong	4.2 (2.0)	4.5 (1.8)*	4.5 (2.0)	4.6 (1.9)
MMSE	26.2 (3.7)	27.1 (2.6)*	23.3 (4.1)	24.3 (3.9)*
Diabetes (%)[a]	21.8	13.4*	15.6	14.2
Heart disease (%)[a]	20.7	17.8	15.6	16.6
History of cancer (%)[a]	6.6	3.9*	8.9	4.3*
Adiposity measurements				
BMI	22.8 (3.5)	23.6 (3.0)*	24.0 (4.1)	23.9 (3.4)
Whole body fat %	23.6 (5.3)	24.5 (4.9)*	33.8 (7.0)	34.6 (5.2)
Waist (cm)	87.1 (13.0)	87.4 (8.9)	87.1 (10.2)	85.6 (9.4)
Waist–hip ratio	0.93 (0.07)	0.92 (0.07)	0.93 (0.09)	0.92 (0.08)
Relative abdominal fat (%)	14.7 (2.7)	15.2 (2.4)*	14.0 (2.1)	14.0 (2.0)

MMSE Mini-Mental State Examination score, *BMI* body mass index

Numbers are expressed as mean (SD) unless stated otherwise. All comparisons were by t test unless stated otherwise

*p<0.05; **p for trend <0.05

[a] Comparison by chi-square test

[b] Number expressed as median (range)

physical activity, smoker status, history of cancer, diabetes, and heart disease. Waist circumference and WHR quintiles however were not related to all-cause mortality. No relationship between these measures of obesity and all-cause of mortality was found in women, nor was there any relationship found between

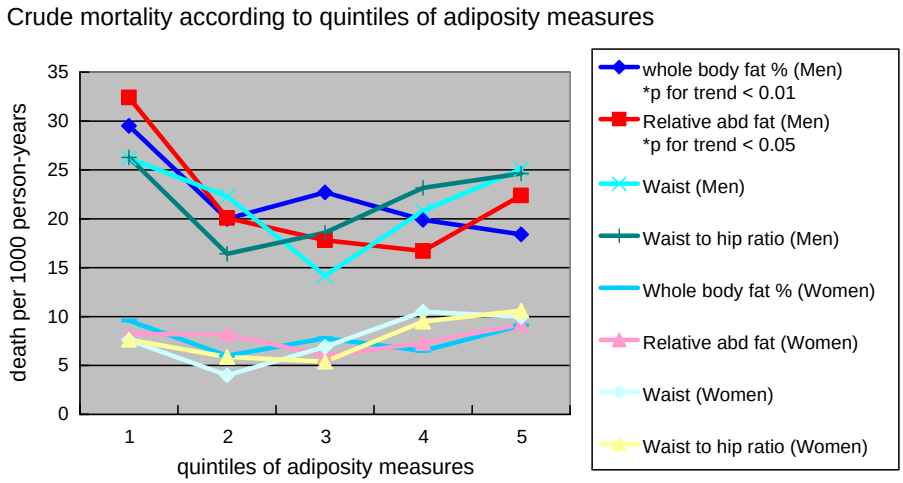


Fig. 1 Relationship between crude mortality rate and quintiles of adiposity measurements in older men and women

Table 2 Hazard ratios of all-cause and cardiovascular mortality according to adiposity measurement quintiles

Quintile	Whole body fat %			Relative abdominal fat			Waist circumference			Waist–hip ratio		
	n	All-cause mortality	Cardiovascular mortality	*n*	All-cause mortality	Cardiovascular mortality	*n*	All-cause mortality	Cardiovascular mortality	*n*	All-cause mortality	Cardiovascular mortality
Men												
1st	373	1.00	1.00	396	1.00	1.00	407	1.00	1.00	396	1.00	1.00
2nd	396	0.72 (0.50, 1.04)	1.33 (0.57, 3.09)	397	0.62 (0.43, 0.89)**	0.82 (0.37, 1.80)	402	0.85 (0.59, 1.21)	0.97 (0.38, 2.44)	395	0.68 (0.46, 1.00)	1.25 (0.54, 2.91)
3rd	336	0.81 (0.56, 1.18)	1.48 (0.61, 3.45)	399	0.58 (0.40, 0.85)**	0.72 (0.32, 1.66)	371	0.58 (0.38, 0.88)*	1.82 (0.80, 4.16)	399	0.78 (0.53, 1.14)	1.02 (0.42, 2.48)
4th	352	0.63 (0.43, 0.92)*	0.91 (0.37, 2.26)	396	0.52 (0.36, 0.77)**	0.58 (0.25, 1.38)	406	0.83 (0.57, 1.19)	1.40 (0.59, 3.30)	395	0.92 (0.64, 1.33)	1.27 (0.55, 2.93)
5th	528	0.54 (0.38, 0.78)**	1.09 (0.49, 2.43)	397	0.67 (0.47, 0.96)*	1.31 (0.64, 2.68)	398	0.87 (0.60, 1.25)	1.54 (0.67, 3.53)	400	0.86 (0.60, 1.23)	1.56 (0.71, 3.42)
p value for trend		<0.001	0.692		0.011	0.443		0.196	0.296		0.811	0.417
Women												
1st	396	1.00	1.00	398	1.00	1.00	387	1.00	1.00	404	1.00	1.00
2nd	399	0.72 (0.37, 1.42)	0.48 (0.09, 2.50)	398	1.10 (0.58, 2.09)	0.45 (0.09, 2.33)	384	0.55 (0.24, 1.23)	0.79 (0.13, 4.77)	378	0.76 (0.37, 1.55)	0.77 (0.17, 3.46)
3rd	399	1.05 (0.56, 1.98)	0.57 (0.11, 3.05)	400	0.75 (0.38, 1.50)	0.22 (0.03, 1.92)	426	1.00 (0.51, 1.97)	1.52 (0.33, 6.93)	416	0.74 (0.36, 1.52)	0.83 (0.19, 3.73)
4th	399	0.83 (0.43, 1.62)	1.04 (0.27, 3.98)	400	0.94 (0.49, 1.82)	0.66 (0.16, 2.78)	361	1.44 (0.76, 2.71)	2.06 (0.49, 8.70)	398	1.12 (0.60, 2.10)	0.67 (0.15, 3.03)
5th	400	1.22 (0.66, 2.25)	0.55 (0.10, 2.91)	397	1.20 (0.65, 2.24)	0.93 (0.25, 3.50)	434	1.31 (0.70, 2.44)	0.33 (0.03, 3.14)	396	1.18 (0.63, 2.21)	0.42 (0.07, 2.32)
p value for trend		0.896	0.504		0.783	0.831		0.096	0.700		0.124	0.549

By Cox regression, adjusted for age, physical activity, smoker status, history of cancer, diabetes, and heart disease

*$p<0.05$; **$p<0.01$

any of the three abdominal adiposity measurements and cardiovascular mortality in both genders.

In men, there was a mean increase in weight since age 25 among decedents (4.78±10.13 kg) and survivors (7.26±9.02 kg), $p<0.000$, 95% CI 1.17 to 3.81. Among decedents, the weight gain from age 25 of those died within the first year of follow-up was not different from those who survived beyond the first year: 3.23±11.99 kg vs. 4.78±10.13 kg, $p>0.05$, 95% CI −7.07 to 3.99. Further adjustment for weight change since the age of 25 slightly attenuated the protective effect of the highest two quintiles of whole body fat % and the second to fourth quintiles of relative abdominal fat %, but the relationship remained significant. The highest quintile in relative abdominal fat % ceased to be protective after this adjustment (Table 3).

The relationship between all-cause mortality and quintiles of fat measurements remained essentially unchanged after further adjustment of the model in Table 2 for the number of medications and self-rank socioeconomic status (Table 4). The p for trend for relative abdominal fat became more significant with the adjustment (p for trend increased from 0.011 to 0.005).

The relative abdominal fat quintile with the lowest adjusted HR for all-cause mortality was the fourth quintile. Common obesity measurements of the five quintiles in relative abdominal fat (men) were shown for clinical reference (Table 5). The corresponding waist circumference in the fourth quintile of relative abdominal fat was 90.53 cm, the BMI 24.6, the waist–hip ratio 0.94, and whole body fat % 26.4%.

Discussion

We found that higher abdominal fat proportion was associated with lower all-cause mortality in older men. Mortality did not increase with increase in abdominal obesity in older men. This finding is in line with that of previous authors (Reis et al. 2009; Auyeung et al. 2010) which showed higher waist circumference or waist–hip ratio conferred survival benefits, but in contrary with those of others (Lindqvist et al. 2006; Price et al. 2006; Pischon et al. 2008; Jacobs et al. 2010). Waist circumference does not take into consideration the distribution of fat, as it only measures the waist; a large waist circumference could imply central fat accumulation, overall fatness, or a large body size. The waist–hip ratio does not take into account the loss of gluteal muscles with aging, to the effect that a stable waist circumference with a decreasing hip circumference due to gluteal muscle loss would result in an increasing waist–hip ratio. On the other hand, DXA-measured abdominal fat describes more accurately fat distribution and hence may be more suitable to address the question on the effect of central fat versus peripheral fat. We and others have shown that adiposity (Adams et al. 2006; Flicker et al. 2010) and truncal adiposity (Auyeung et al. 2010) may be beneficial for survival in old age, even for those with history of cardiovascular disease (Lea et al. 2009). Our present results showed that in contrary to findings in middle-aged adults, higher proportion of abdominal fat may also be beneficial for survival in men older than 65 years of age.

With adjustment, both whole body fat % and relative abdominal fat still maintained a linear trend

Table 3 Hazard ratios of all-cause mortality according to adiposity measurement quintiles in men, further adjusted for weight changes since age 25, in addition to age, physical activity, smoker status, history of cancer, diabetes, and heart disease

Quintile	Whole body fat %		Relative abdominal fat		Waist circumference		Waist–hip ratio	
	n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
1st	373	1.00	396	1.00	407	1.00	396	1.00
2nd	396	0.73 (0.50, 1.08)	397	0.65 (0.44, 0.95)*	402	0.94 (0.65, 1.38)	395	0.74 (0.49, 1.11)
3rd	336	0.86 (0.57, 1.29)	399	0.62 (0.41, 0.92)*	371	0.69 (0.44, 1.07)	399	0.87 (0.58, 1.31)
4th	352	0.65 (0.42, 1.00)*	396	0.59 (0.39, 0.89)*	406	1.11 (0.73, 1.68)	395	1.13 (0.77, 1.67)
5th	528	0.58 (0.38, 0.90)*	397	0.74 (0.49, 1.11)	398	1.16 (0.73, 1.85)	400	1.01 (0.68, 1.51)
p value for trend	0.010		0.175		0.772		0.379	

*$p<0.05$

Table 4 Hazard ratios of all-cause mortality according to adiposity measurement quintiles in men, further adjusted for number of medications and self-rated socioeconomic status, in addition to age, physical activity, smoker status, history of cancer, diabetes, and heart disease

Quintile	Whole body fat %		Relative abdominal fat	
	n	HR (95% CI)	*n*	HR (95% CI)
1st	373	1.00	396	1.00
2nd	396	0.77 (0.53, 1.11)	397	0.65 (0.45, 0.92)*
3rd	336	0.86 (0.60, 1.25)	399	0.59 (0.41, 0.86)*
4th	352	0.65 (0.44, 0.96)*	396	0.51 (0.35, 0.75)*
5th	528	0.51 (0.35, 0.73)*	397	0.63 (0.43, 0.90)*
p value for trend	<0.001		0.005	

*$p<0.05$

with all-cause mortality (Table 2, p for trend <0.001 and equals to 0.011, respectively). This highlights the need to review current nutrition guidelines for older adults that advocate weight control or reduction. In fact, the negative impact of obesity should be reviewed when the individual reaches the age of 65. The waist circumference cutoffs for metabolic risks in midlife may not be applicable to old age, when overall mortality within a shorter life expectancy is considered.

As quintiles of relative abdominal fat showed a reverse relationship with all-cause mortality in older men (Table 6), we further described the phenotype of the men having the amount of relative abdominal fat associated with lowest mortality. According to the WHO classification of BMI (World Health Organization Western Pacific Region 2000; Ko et al. 2005), and criteria for metabolic syndrome in Asian populations, these men were in a group at risk of metabolic diseases: mean waist 90.53 cm (>90 cm cutoff for obesity), mean BMI 24.6 (>23.5, in overweight range), mean waist–hip ratio 0.94 (>0.9 for obesity), and mean whole body fat 26.38% (≥25%, in high body fat range). According to the BMI and the waist circumference, these men should be considered to have moderate metabolic risk, yet our results showed that instead of having adverse effects, older men having these markers of obesity have a lower HR for mortality. Obesity criteria have been mostly developed using younger adult data. Heim et al. have shown that waist circumference cutoff for disability outcomes could be higher in older adults (Heim et al. 2010).

The relationship between obesity and mortality may be altered by age or by frailty (Kopple 2005). In older, healthy individuals without chronic diseases, the risk of obesity may remain similar to that in middle-aged adults (Adams et al. 2006; Schooling et al. 2006). However, the level of fitness might modulate the mortality risk of obesity. In fact, among those within the same strata of low, moderate, or high cardiorespiratory fitness, overweight and obese men consistently had lower mortality than normal weight men, in groups of middle-aged and older male veterans (McAuley et al. 2010, 2009). This is consistent with our results which showed that beyond the age of 65, in a cohort of high functioning older men and women, obesity operated in a different

Table 5 Clinical anthropometric measurements of men according to quintiles of relative abdominal fat

Quintiles of relative abdominal fat	Waist (cm)		Body mass index		Waist–hip ratio		Whole body fat %	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1st	407	77.2 (7.5)	393	20.2 (2.6)	396	0.87 (0.06)	373	18.9 (4.9)
2nd	402	86.3 (6.5)	398	22.9 (2.3)	395	0.91 (0.05)	396	22.9 (2.3)
3rd	371	88.8 (9.1)	398	23.9 (2.4)	399	0.93 (0.05)	336	25.4 (3.6)
4th[a]	406	90.5 (6.8)	398	24.6 (2.6)	395	0.94 (0.06)	352	26.4 (3.6)
5th	398	94.6 (7.3)	398	25.7 (2.8)	400	0.97 (0.06)	528	27.3 (3.7)

Numbers are expressed as mean (SD)

[a] The fourth quintile of relative abdominal fat had the lowest all-cause mortality

Table 6 Relationship between crude mortality rate and quintiles of adiposity measurements in older men and women

Quintiles	Death per 1,000 person-years				
	1st	2nd	3rd	4th	5th
Men					
Whole body fat %*	29.5	20.0	22.7	19.9	18.4
Relative abdominal fat**	32.4	20.1	17.8	16.7	22.4
Waist	26.2	22.3	14.2	20.8	25.1
Waist to hip ratio	26.3	16.4	18.6	23.2	24.6
Women					
Whole body fat %	9.6	6.0	7.8	6.5	9.1
Relative abdominal fat	8.2	8.2	6.0	7.3	9.2
Waist	7.6	4.0	6.9	10.5	10.0
Waist to hip ratio	7.6	5.9	5.4	9.5	10.6

*p for trend <0.01; **p for trend <0.05

direction regarding longevity than in midlife. Possible explanations are that in older or frail individuals, infections and acute illnesses become significant causes of death, and those with greater fat or energy reserve tend to survive acute illnesses better. Indeed, weight loss in old age might be a marker of risk of mortality (Newman et al. 2001). In contrary, those with end-stage chronic diseases tend to be more cachexic; therefore, those with more adiposity should be the ones with less severe chronic diseases. In old age, therefore, the more fat an elderly individual, the better the survival, and thus, overweight or obese people might rank high regarding life expectation. It is important to note however that despite significant trends for linearity showing the higher the fat, the better the survival, those in the highest quintile of relative abdominal adiposity in our cohort had a mean BMI of 25.7, which was at the lower end of the obesity range for Asians, and had a mean whole body fat % of 27.3% only. The fatness–survival relationship might be different for those in the upper end of the obesity range.

Another possible explanation for the negative relationship between fat mass and all-cause mortality in the older population could be that traditional cardiovascular risk predictors such as those used in the Framingham risk score (systolic blood pressure, total and high density lipoprotein cholesterol, diabetes mellitus, smoking, and electrocardiogram-based left ventricular hypertrophy) and the International Diabetes Federation (IDF) criteria (high waist circumference, high blood pressure, high blood sugar or diabetes, high triglyceride, and low high density lipoprotein) (Alberti et al. 2005) were less predictive of cardiovascular risks in the elderly (de Ruijter et al. 2009; Motta et al. 2009).

Lifelong weight trajectories might have a role in modifying the effects of obesity in old age. In a cohort of healthy men, those who were overweight in midlife but had normal weight in late life had the highest mortality (Strandberg et al. 2009). We did not have the weight in midlife; therefore, we attempted to use the recalled weight change since the age of 25 to estimate the weight trajectories of our subjects, and adjusted for that in our model to assess the relationship between different obesity measurements and mortality. Although recalled weight changes did not differ between survivors and decedents, we did find that it attenuated the protective effect of obesity in late life. Nevertheless, the obesity paradox remained robust in our model: higher overall fatness (whole body fat %) and abdominal adiposity (relative abdominal fat) remained protective against mortality. More importantly, all adiposity measurements, both general and abdominal, did not affect cardiovascular mortality, even with adjustment for recalled weight change in adulthood.

The lack of associations in women might be explained by the small numbers of deaths during follow-up, or that mortality in older women might genuinely be independent of central adiposity. Our previous report using trunk fat did not observe any relationship between that and mortality in women, which could have been due to the inclusion of breast fat (Auyeung et al. 2010). Using a more defined abdominal region in the present study, we confirmed the absence of relationship even with the exclusion of breast fat. It has been reported that women have twice as much subcutaneous fat than men, but their amount of intra-abdominal fat and liver fat is similar. However, as only liver fat, but not subcutaneous or intra-abdominal fat is independently associated with markers on insulin resistance, the same amount of general abdominal fat and whole body fat % as measured by DXA would have implied different levels of insulin resistance or cardiovascular risks in men and women. This might be one of the explanations for the gender differences seen in the associations between fat measures and mortality in our cohort (Westerbacka et al. 2004).

Since the number of cardiovascular death outcomes was small, this might account for the difference in results between all-cause mortality and cardiovascular deaths (lack of association with the latter). A longer follow-up duration with more cardiovascular deaths is needed to demonstrate more clearly whether it is a genuine lack of association or that fat may even be protective towards cardiovascular deaths in the elderly.

There are limitations in this study. DXA could not differentiate between abdominal subcutaneous fat from visceral fat in contrast to CT measurements. Nevertheless, trunk fat as determined by DXA was found to correlate well with insulin resistance and dyslipidemia, and survival (Auyeung et al. 2010; Hamdy et al. 2006). Only one measurement of the waist and hip was taken. We used a novel method of defining abdominal adiposity as it was difficult to delineate margins of the vertebral bodies in older participants due to scoliosis and low bone mass. Our results may reflect the phenomenon of selective survival in which only middle-aged persons more resistive to the hazard of central adiposity survived into old age and were thus included in the present study. Those with serious complications of abdominal obesity or its related metabolic disorders might have premature death prior to age 65 or have become too disabled to be included in our cohort. Our cohort is from a population with relatively little morbid obesity; therefore, findings should not be generalized into populations with a high proportion of obesity. Our cohort is more educated and more physically active than the general elderly population in Hong Kong; therefore, the results might not be generalized to those who are institutionalized or frailer, or with lower education level. Caution should be exercised in the interpretation of lifelong weight trajectory using just weights at two points in time. Someone who was overweight both at age 25 and when baseline measures were taken would have a weight change of zero, while another person who had normal weight or was underweight at both these time points could have the same weight change value. In addition, our result could not take into account the weight fluctuations in between these time points. Using recalled weight at age 25 may be prone to bias, and the accuracy depends on age, sex, lapsed time, current body mass index, and cognitive function (Perry et al. 1995; Stevens et al. 1990). The number of cardiovascular deaths was small, especially among women; therefore, the power of analysis in demonstrating a genuine lack of relationship between fatness and cardiovascular deaths, or even whether fat might be protective as in all-cause mortality, might be limited. A longer follow-up period with higher number of cardiovascular deaths might be able to provide a more definitive answer. Nevertheless, the all-cause mortality in women did not show any association with any of the four adiposity measurements.

Conclusion

Higher abdominal adiposity in addition to whole body fat might be beneficial for survival in older men. Waist circumference, whole body fat %, and body mass index cutoffs corresponding to the quintile of abdominal adiposity with the lowest mortality were higher than those recommended for middle-aged adults.

Acknowledgments This study was funded by the Hong Kong Research Grant Council Grant (CUHK4101/02M). We thank The S H Ho Centre for Gerontology and Geriatrics, Faculty of Medicine, The Chinese University of Hong Kong for personnel support in data collection.

References

Adams KF, Schatzkin A, Harris TB et al (2006) Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Eng J Med 355:763–778

Adler NE, Epil ES, Castellazzo G, Ickovics JR (2000) Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 19:586–592

Al Snih S, Ottenbacher KJ, Markides KS, Kuo Y-F, Eschbach K, Goodwin JS (2007) The effect of obesity on disability vs mortality in older Americans. Arch Intern Med 167:774–780

Alberti KGMM, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group (2005) The metabolic syndrome—a new world-wide definition. Lancet 366:1059–1062

Auyeung TW, Lee JS, Leung J, Kwok T, Leung PC, Woo J (2010) Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4,000 older adults using DXA. J Gerontol A Biol Sci Med Sci 65:99–104

Bertin E, Marcus C, Ruiz JC, Eschard JP, Leutenegger M (2000) Measurement of visceral adipose tissue by DXA combined with anthropometry in obese humans. Int J Obes Relat Metab Disord 24:263–270

Bourdel-Marchasson I, Dubroca B, Manciet G, Decamps A, Emeriau JP, Dartigues JF (1997) Prevalence of diabetes

and effect on quality of life in older French living in the community: the PAQUID Epidemiological Survey. J Am Geriatr Soc 45:295–301

Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH (2000) Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. In J Obes Relat Metab Disord 24:1699–1704

Cheng YH, Chi I, Boey KW, Ko LS, Chou KL (2002) Self-rated economic condition and the health of elderly persons in Hong Kong. Soc Sci Med 55:1415–1424

Chiu HFK, Lee HC, Chung WS, Kwong PK (1994) Reliability and validity of the Cantonese version of the Mini-Mental State Examination—a preliminary study. J Hong Kong Coll Psych 4(SP2):25–28

de Ruijter W, Westendorp RG, Assendelft WJ, den Elzen WP, de Craen AJ, le Cessie S, Gussekloo J (2009) Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ 338:a3083. doi:10.1136/bmj.a3083

Flicker L, McCaul KA, Hankey GJ et al (2010) Body mass index and survival in men and women aged 70 to 75. J Am Geriatr Soc 58:234–241

Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Research 12:189–198

Hamdy O, Porramatikul S, Al-Ozairi E (2006) Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diab Rev 2:367–373

Heim N, Snijder MB, Heymans MW, Deeg DJH, Seidell JC, Visser M (2010) Exploring cut-off values for large waist circumference in older adults: a new methodological approach. J Nutr Health Aging 14:272–277

Jacobs EJ, Newton CC, Wang Y et al (2010) Waist circumference and all-cause mortality in a large US cohort. Arch Intern Med 170:1293–1301

Janssen I (2007) Morbidity and mortality risk associated with an overweight BMI in older men and women. Obesity (Silver Spring) 15:1827–1840

Ko GTC, Cockram CS, Chow CC, Yeung V, Chan WB, So WY, Chan NN, Chan JCN (2005) High prevalence of metabolic syndrome in Hong Kong Chinese—comparison of three diagnostic criteria. Diab Res Clin Prac 69:160–168

Kopple JD (2005) The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. Am J Clin Nutr 81:1257–1266

Lafortuna CL, Agosti F, Proietti M, Adorni F, Sartorio A (2006) The combined effect of adiposity, fat distribution and age on cardiovascular risk factors and motor disability in a cohort of obese women (aged 18–83). J Endocrinol Invest 29:905–912

Lapidus L, Bengtsson C, Björntorp P (1994) The quantitative relationship between "the metabolic syndrome" and abdominal obesity in women. Obes Res 2:372–377

Lea JP, Crenshaw DO, Onufrak SJ, Newsome BB, McClellan WM (2009) Obesity, end-stage renal disease, and survival in an elderly cohort with cardiovascular disease. Obesity (Silver Spring) 17:2216–2222

Lindqvist P, Andersson K, Sundh V, Lissner L, Björkelund C, Bengtsson C (2006) Concurrent and separate effects of body mass index and waist-to-hip ratio on 24-year mortality in the Population Study of Women in Gothenburg: evidence of age-dependency. Eur J Epidemiol 21:789–794

Lissner L, Björkelund C, Heitmann BL, Seidell JC, Bengtsson C (2001) Larger hip circumference independently predicts health and longevity in a Swedish female cohort. Obes Res 9:644–646

McAuley P, Pittsley J, Myers J, Abella J, Froelicher VF (2009) Fitness and fatness as mortality predictors in healthy older men: the Veterans Exercise Testing Study. J Gerontol A Biol Sci Med Sci 64A:695–699

McAuley PA, Kokkinos PF, Oliveira RB, Emerson BT, Myers JN (2010) Obesity paradox and cardiorespiratory fitness in 12,417 male veterans aged 40 to 70 years. Mayo Clinic Proceedings 85:115–121

McGuire LC, Ford ES, Ajani UA (2006) The impact of cognitive functioning on mortality and the development of functional disability in older adults with diabetes: the second longitudinal study on aging. BMC Geriatrics 6:8–14

Motta M, Bennati E, Cardillo E, Passamonte M, Ferlito L, Malaguarnera M (2009) The metabolic syndrome (MS) in the elderly: considerations on the diagnostic criteria of the International Diabetes Federation (IDF) and some proposed modifications. Arch Gerontol Geriatr 48:380–384

Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP, Cardiovascular Study Research Group (2001) Weight change in old age and its association with mortality. J Am Geriatr Soc 49:1309–1318

Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF (1995) The validity of self-reports of past body weights by U.S. adults. Epidemiology 6:61–66

Pischon T, Boeing H, Hoffmann K et al (2008) General and abdominal adiposity and risk of death in Europe. N Engl J Med 359:2105–2120

Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE (2006) Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. Am J Clin Nutr 84:449–460

Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL (2009) Comparison of overall obesity and body fat distribution in predicting risk of mortality. Obesity 17:1232–1239

Schooling CM, Lam TH, Li ZB et al (2006) Obesity, physical activity and mortality in a prospective Chinese elderly cohort. Arch Intern Med 166:1498–1504

Singh-Manoux A, Marmot MG, Adler NE (2005) Does subjective social status predict health and change in health status better than objective status? Psychosom Med 67:855–861

Snijder MB, van Dam RM, Visser M, Seidell JC (2006) What aspects of body fat are particularly hazardous and how do we measure them? Int J Epidemiol 35:83–92

Stevens J, Keil JE, Waid LR, Gazes PC (1990) Accuracy of current, 4-year, and 28-year self-reported body weight in an elderly population. Am J Epidemiol 132:1156–1163

Strandberg TE, Strandberg AY, Salomaa VV et al (2009) Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. Eur Heart J 30:1720–1727

Tamakoshi A, Yatsuya H, Lin Y, JACC Study Group et al (2010) BMI and all-cause mortality among Japanese older adults: findings from the Japan collaborative cohort study. Obesity (Silver Spring) 18:362–369

Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC (2001) A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. Int J Obes Relat Metab Disord 25:1730–1735

Washburn RA, Smith KW, Jette AM, Janny CA (1993) The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 46:153–162

Westerbacka J, Cornér A, Tiikkainen M, Tamminen M, Vehkavaara S, Häkkinen A-M (2004) Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. Diabetologia 47:1360–1369

Woo J, Ho SC, Yu ALM, Sham A (2002) Is waist circumference a useful measure in predicting health outcomes in the elderly? Int J Obes 26:1349–1355

World Health Organization Western Pacific Region (2000) International Association for the Study of Obesity and the International Obesity Task Force. The Asia-Pacific perspective: redefining obesity and its treatment. Health Communications Australia Pty Limited, Australia

Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, Fantin F, Bissoli L, Bosello O (2005) Health consequences of obesity in the elderly: a review of four unresolved questions. Int J Obes 29:1011–1029

Zhang X, Shu XO, Yang G et al (2007) Abdominal adiposity and mortality in Chinese women. Arch Intern Med 167:886–892

JAMDA 15 (2014) 281–286

JAMDA

journal homepage: www.jamda.com

Original Study

Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors

Jenny S.W. Lee MSc, FRCP [a,b,c,*], Tung-Wai Auyeung MPH, FRCP [c], Jason Leung MSc [d], Timothy Kwok MD [a,c], Jean Woo MD [a,c]

[a] Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China
[b] Department of Medicine and Geriatrics, Shatin Hospital, Hong Kong, Hong Kong SAR, China
[c] The S.H. Ho Centre for Gerontology and Geriatrics, The Chinese University of Hong Kong, Hong Kong SAR, China
[d] The Jockey Club Centre of Osteoporosis Care and Control, The Chinese University of Hong Kong, Hong Kong SAR, China

Keywords:
Frailty
transition
older adults
elderly
fluctuation

A B S T R A C T

Background: Frailty renders older individuals more prone to adverse health outcomes. Little has been reported about the transitions between the different frailty states. We attempted to examine the rate of these transitions and their associated factors.
Methods: We recruited 3018 Chinese community-living adults 65 years or older. Frailty status was classified according to the Fried criteria in 2 visits 2 years apart. Demographic data, medical conditions, hospitalizations, and cognition were recorded. Rates of transitions and associated factors were studied.
Results: At baseline, 850 (48.7%) men and 884 (52.6%) women were prefrail. Among these, 23.4% men and 26.6% women improved after 2 years; 11.1% of men and 6.6% of women worsened. More men than women ($P < .001$) deteriorated into frailty. Hospitalizations, older age, previous stroke, lower cognition, and osteoarthritis were risk factors for decline among prefrail participants. Having diabetes was associated with 50% lower chance of improvement in women. Among the robust, older age and previous cancer, hospitalizations, chronic lung diseases, and stroke were risk factors for worsening. Higher socioeconomic status was protective. Previous stroke reduced the chance of improvement by 78% in frail men. Only younger age was associated with improvement in frail women.
Conclusion: Women were less likely to decline in frailty status than men. Hospitalizations, older age, previous stroke, lower cognitive function, diabetes, and osteoarthritis were associated with worsening or less improvement. Older age, previous cancer, hospitalizations, lung diseases, and stroke were risk factors for worsening in the robust and higher socioeconomic status was protective.

Frailty is the state of lack of reserve, which renders the older individual more prone to adverse health outcomes, such as hospitalizations, institutionalization, and death.[1–5] The prevalence of frailty in different populations has been widely studied.[6–9] However, although frailty has been recognized to be a dynamic state, relatively few studies had focused on the natural history of persons in the different frailty states.[10,11] In particular, relatively little has been said about the reversibility of the prefrail state without any interventions.[12–14] Both studies on transitions between frailty states were conducted in North America.[12,13] Data from other populations are scarce.

Taking the analogy of mild cognitive impairment and dementia as an example, it is well recognized that not all those in the intermediate state of mild cognitive impairment will deteriorate into dementia: some will remain the same for years whereas some may even revert back to normal cognitive function.[15] In the clinical setting, understanding who is more likely to deteriorate and who may remain stable or even revert back to the robust state will allow clinicians to focus on those at the highest risk for early interventions. In the public health setting, understanding the natural history of the prefrail state will allow better future health care planning because the future may not be as gloomy as it seems, for not all will decline. In the clinical trials setting, the proportions of subjects who will naturally remain in the prefrail state or spontaneously improve back into the robust state will have to be taken into consideration, before any intervention can be said to be useful in stabilizing or reducing frailty.

With these 3 perspectives in mind, we examined the natural history of transitions between frailty states in a cohort of community-living older Chinese people. We also attempted to

This study was funded by The Jockey Club Charities Trust; the S.H. Ho Centre for Gerontology and Geriatrics, Faculty of Medicine, The Chinese University of Hong Kong; and the Hong Kong Research Grant Council (CUHK 4101/01M).
The authors declare no conflicts of interest.
* Address correspondence to Jenny S.W. Lee, 9/F, Department of Medicine & Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Sha Tin, Hong Kong SAR.
E-mail address: jennylee@cuhk.edu.hk (J.S.W. Lee).

1525-8610/$ - see front matter © 2014 - American Medical Directors Association, Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jamda.2013.12.002

identify demographic or clinical characteristics that may be associated with these transitions.

Materials and Methods

Between 2001 and 2003, 4000 older men and women aged 65 years or older were recruited by public notices and talks held in social centers for the aged and in public housing estates in Hong Kong. The cohort consisted of equal numbers of men and women, and equal numbers of individuals aged 65 to 69 years, 70 to 74 years, and 75 years and older. These individuals were invited to attend a health check, which included a structured questionnaire and a physical assessment. Participants were excluded if they (1) were unable to walk independently, (2) had a history of bilateral hip fractures, and (3) were not competent to sign informed consent. All participants signed a written informed consent. The study was approved by the Ethics Review Committee of the Chinese University of Hong Kong and the Hong Kong Hospital Authority. A second interview and assessment was conducted between 2003 and 2005 (baseline visit for this analysis), during which 3427 participations returned. A third interview and assessment was conducted between 2005 and 2007 (follow-up visit for this analysis), during which 3153 participants returned.

Questionnaire

The questionnaire contained demographic information, including age, gender, cognitive function, self-assessed socioeconomic status, physical activity levels, mood symptoms, and smoking habits. Cognitive function was assessed by the Mini-Mental State Examination (MMSE).[16] Socioeconomic status was assessed by asking the participants to mark their self-perceived position on a ladder with 10 rungs, with the lowest and highest rungs representing the lowest and highest socioeconomic status in society. Physical activity level was scored by the Physical Activity Scale for the Elderly (PASE), which included exercise, household, social, and leisure activities in the past week, on a scale of 0 to 400.[17] Mood symptoms were assessed by the Geriatric Depression Scale, with a score of 8 or higher out of 15 indicative of depressed mood.[18] Smoking habits were categorized as never smoked, ex-smoker, and current smoker.

Medical Diagnoses and Hospitalizations

Participants were asked whether they had ever been told by a physician that they had diabetes, heart disease (ischemic heart disease, congestive heart failure, angina), hip fracture, stroke, chronic obstructive pulmonary diseases (COPD), cancer, or osteoarthritis. Medical diagnoses were cross-checked in the computerized medical system database of the Hong Kong Hospital Authority. Diagnoses were counted as present if reported by the participant or recorded in the medical database of that participant. The number of all-cause hospitalizations between the 2 visits was obtained from the Hong Kong Hospital Authority records, which covered more than 93% of the hospitalizations in the Hong Kong population.[19]

Frailty Status

Frailty status at both baseline and follow-up visits was categorized into 3 groups: robust, prefrail, and frail, based on the Fried frailty criteria.[1] The 5 components of the Fried criteria are as follows: (1) low physical activity (defined as the lowest quintile of the Physical Activity Scale for the Elderly score), (2) fatigue (defined as answering "No" to the question: "Do you feel full of energy?" in the Geriatric Depression Scale), (3) shrinkage (significant weight loss of $\geq$5% between the first visit and the year 2 visit, 2 years apart), (4) weakness (defined as the lowest quintile in gender-specific grip strength), and (5) slowness (defined as the lowest quintile of gender-specific walking speed). Robust was defined as having none of these features, prefrailty as having 1 to 2 features, and frailty as having three or more of these features. The lowest quintile cutoff values for grip strength, walking speed, and physical activity in the baseline assessment was also used as the cutoff values in the follow-up assessment.

Physical Assessment

Grip strength (the average of the maximum strength of both hands) was measured using a dynamometer (Jamar Hand dynamometer 5030 J1; Sammons Preston, Inc, Bolingbrook, IL), and walking speed was measured by the time taken for a 6-meter walk. Body weight change was calculated from the body weight measured at the baseline, 2-year, and 4-year visits, with the participants wearing a light dressing gown without shoes, by the Physician Balance Beam Scale (Health-o-Meter, Arlington Heights, IL). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Body mass index (BMI) was categorized into underweight ($<$18.5), normal weight (18.5–23.0), overweight (23.0–25.0), and obese ($\geq$25.0), according to the World Health Organization Asia Pacific criteria.[20]

Statistical Analysis

The change in frailty status between the baseline and follow-up visits was used as the outcome. The number and proportions of participants in the robust, prefrail, and frail categories at both visits were reported according to gender. The numbers of those in each frailty category who had remained stable, improved, or declined after 2 years with respect to their frailty status were also listed. Comparison of the gender, age, and baseline frailty status of those who did or did not return for the follow-up visit was made. Continuous variables were compared using the Student *t* test and categorical variables by the chi-square test.

Age-adjusted logistic regression for each possibly related covariate, and multiple stepwise logistic regressions were used to identify significant factors associated with changes in frailty status. As others have reported that baseline frailty status significantly influenced the probability of transitions and the directions of transitions between frailty states,[12] regressions were done separately for frailty groups as categorized at baseline (robust, prefrail, and frail). Directions of change examined included (1) prefrail to frail, (2) prefrail to robust, (3) robust to prefrail or frail, and (4) frail to prefrail or robust. Because women and men had different prevalence of frailty and might have different rates and associated factors for these transitions, separate models were performed for the genders. Covariates included age, smoking, BMI, MMSE, socioeconomic status, and medical conditions (diabetes, heart disease, COPD, osteoarthritis, history of hip fracture, stroke, or cancer), and number of hospitalization in the intervening years between the 2 visits. The latter was categorized into none, 1 to 2, 3 to 4, and 5 or more episodes. Analysis was performed using the statistical package SAS version 9.1 (SAS Institute, Inc, Cary, NC). All tests were 2-sided and significance level was set at *P* less than .05.

Missing Data

Participants with missing data that rendered it impossible to classify their frailty state and baseline and at the follow-up visits were excluded from analysis.

Results

A total of 1519 men (87.0% of 1745 at baseline) and 1499 women (89.1% of 1682 at baseline) attended both visits with complete frailty

Table 1
Characteristics of Subjects Who Did or Did Not Return for Follow-Up Visit (Deceased or Defaulted)

	Men		Women	
	Did Not Return, n = 226	Returned, n = 1519	Did Not Return, n = 183	Returned, n = 1499
Age, mean (SD)	76.6 (5.4)	73.5 (4.7)*	76.4 (5.8)	73.8 (5.0)*
MMSE, mean (SD)	26.3 (3.3)	27.3 (2.5)*	23.3 (4.2)	24.6 (3.8)*
SES ladder HK, mean (SD)	4.3 (2.0)	4.5 (1.8)	4.6 (2.2)	4.6 (1.9)
Smoking, n (%)		*		
Never	56 (24.8)	574 (37.8)	161 (88.0)	1371 (91.5)
Past	141 (62.4)	802 (52.8)	20 (10.9)	107 (7.1)
Current	29 (12.8)	143 (9.4)	2 (1.1)	21 (1.4)
BMI, n (%)				
Underweight (<18.5)	18 (7.9)	81 (5.3)	9 (4.9)	73 (4.8)
Normal (18.5 to <23)	91 (40.3)	576 (37.9)	73 (39.9)	548 (36.6)
Overweight (23–24.9)	64 (28.3)	419 (27.6)	45 (24.6)	354 (23.7)
Obese (25 or above)	53 (23.5)	442 (29.1)	56 (30.6)	522 (34.9)
Diabetes, n (%)	39 (17.3)	215 (14.2)	24 (13.1)	211 (14.1)
Heart disease, n (%)	49 (21.7)	289 (19.0)	37 (20.2)	251 (16.7)
COPD, n (%)	41 (18.1)	157 (10.3)*	13 (7.1)	79 (5.3)
Osteoarthritis, n (%)	16 (7.1)	99 (6.5)	26 (14.2)	162 (10.8)
Hip fracture, n (%)	3 (1.3)	4 (0.3)*	3 (1.6)	18 (1.2)
Stroke, n (%)	15 (6.6)	79 (5.2)	4 (2.2)	52 (3.5)
Cancer, n (%)	24 (10.6)	89 (5.9)*	12 (6.6)	75 (5.0)
Hospital admission since baseline till death or follow-up visit, n (%)		*		*
0	69 (30.5)	978 (64.4)	90 (49.2)	1033 (69.0)
1–2	77 (34.1)	390 (25.7)	51 (27.9)	377 (25.2)
3–4	37 (16.4)	99 (6.5)	24 (13.1)	66 (4.4)
5 or above	43 (19.0)	52 (3.4)	18 (9.8)	22 (1.4)
Frailty – baseline, n (%)		*		*
Robust	53 (23.5)	736 (48.5)	47 (25.7)	586 (39.1)
Prefrail	131 (58.0)	719 (47.3)	95 (51.9)	789 (52.6)
Frail	42 (18.5)	64 (4.2)	41 (22.5)	124 (8.3)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HK, Hong Kong; MMSE, Mini-Mental State Examination score; SES, socioeconomic status.
*$P < .05$ of t test for continuous variables and chi-square for categorical variables.

data. Table 1 compares the characteristics of participants who did or did not return (either deceased or defaulted) for the follow-up visit. Those who did not return for the follow-up were older, had lower MMSE scores, had more hospitalizations after the baseline visit, and were more likely to be frail at baseline. Men who did not return for the follow-up visit were also more likely to be past or current smokers and to have a history of COPD, hip fracture, or cancer.

Table 2 shows the change in status between baseline and follow-up. At baseline, 48.7% of men and 52.5% of women were in the prefrail group, and 6.0% men and 9.8% women were frail. By the end of 2 years, 66 (3.7%) men and 20 (1.1%) women had died. Mortality increased significantly with increasing frailty at baseline for both men and women (both $P < .001$). Default rate also increased with baseline frailty (both $P < .001$). There was no difference between the percentage of defaulters and the deceased across the different frailty states ($P < .05$). At the follow-up visit, slightly more than half of those in the prefrail state at baseline had remained in the same state, whereas 11.1% of men and 6.6% of women worsened into frailty, and a quarter of both genders recovered into the robust state. Only 4.5% of prefrail men and 1.2% of prefrail women had died. Among the frail at baseline, one-quarter had remained frail and about half had recovered into the prefrail state, but 15.1% of men and 4.2% of women had died. Among the robust, two-thirds had remained robust, whereas one-third had worsened into the prefrail state, and very few had declined into frailty or died. Men tended to worsen into frailty more than women.

Table 2
Status at Follow-Up, Including Deaths and No Follow-Up

Frailty Status—Baseline	Status—Follow-Up at 2 y, n (%)					
	Robust	Prefrail	Frail	Deceased	Defaulted	Total
Male	657	727	135	66	160	1745
Robust	456 (57.8)	266 (33.7)	14 (1.8)	12 (1.5)	41 (5.2)	789
Prefrail	199 (23.4)	426 (50.1)	94 (11.1)	38 (4.5)	93 (10.9)	850
Frail	2 (1.9)	35 (33.0)	27 (25.5)	16 (15.1)	26 (24.5)	106
Female	622	773	104	20	163	1682
Robust	381 (60.2)	199 (31.4)	6 (1.0)	2 (0.3)	45 (7.1)	633
Prefrail	235 (26.6)	496 (56.1)	58 (6.6)	11 (1.2)	84 (9.5)	884
Frail	6 (3.6)	78 (47.3)	40 (24.2)	7 (4.2)	34 (20.6)	165

P value: male: <.0001, female: <.0001.

Age-Adjusted Models

Table 3 shows the age-adjusted odds ratios (ORs) of factors possibly associated with directions of change in frailty status after 2 years. Different factors were associated with the transitions in frailty states among men and women. Among prefrail men, having normal and overweight BMI was protective against worsening, whereas hospitalizations and having previous stroke was associated with worsening or less improvement. Among prefrail women, having osteoarthritis, hospitalizations, and a history of stroke were associated with higher chance of worsening, whereas having diabetes and heart disease was associated with less improvement.

Among robust men, a history of cancer and 5 or more hospitalizations during the 2 years between visits were associated with worsening. In robust women, having COPD or a history of stroke was associated with worsening, whereas higher socioeconomic status was protective.

Among frail men, a history of stroke lowered the chance of any improvement by 82%. In frail women, having 5 or more hospitalizations in the intervening years reduced the chance of any improvement by 97%.

Multivariate Models

Table 4 shows the stepwise multiple logistic regression models of the 4 different directions of change in frailty status. Older age was consistently associated with either higher risk of decline or lower

Table 3
Age-Adjusted Odds Ratio of Possible Associated Factors for Transitions in Frailty Status After 2 Years

	Male				Female			
	Prefrail Worsening	Prefrail Improvement	Robust Worsening	Frail Improvement	Prefrail Worsening	Prefrail Improvement	Robust Worsening	Frail Improvement
MMSE, per 1 score increase	0.98 (0.90-1.06)	1.10 (1.02-1.18)*	0.99 (0.92-1.06)	0.90 (0.74-1.09)	0.96 (0.90-1.03)	1.02 (0.98-1.07)	0.98 (0.94-1.04)	0.96 (0.88-1.05)
SES ladder HK, per 1 unit increase	0.96 (0.85-1.08)	1.02 (0.92-1.12)	0.97 (0.89-1.05)	1.05 (0.78-1.40)	0.94 (0.81-1.09)	1.03 (0.94-1.13)	0.89 (0.81-0.98)*	0.84 (0.67-1.04)
Smoking								
Non	1	1	1	1	1	1	1	1
Past	0.75 (0.46-1.24)	1.01 (0.70-1.46)	0.95 (0.69-1.32)	0.57 (0.18-1.82)	1.75 (0.79-3.89)	0.99 (0.52-1.88)	1.36 (0.66-2.80)	0.58 (0.18-1.89)
Current	1.53 (0.73-3.23)	0.63 (0.33-1.21)	1.29 (0.75-2.23)	0.21 (0.02-1.80)	3.07 (0.63-14.80)	2.44 (0.76-7.83)	0.26 (0.03-2.15)	—
BMI								
Underweight (<18.5)	1	1	1	1	1	1	1	1
Normal (18.5 to <23)	0.47 (0.23-0.99)*	1.24 (0.59-2.61)	1.25 (0.42-3.76)	0.27 (0.04-1.60)	0.86 (0.32-2.31)	0.84 (0.42-1.65)	0.93 (0.32-2.75)	1.25 (0.22-7.09)
Overweight (23–24.9)	0.36 (0.16-0.81)*	1.45 (0.68-3.08)	1.18 (0.39-3.59)	0.78 (0.09-6.45)	0.72 (0.26-2.00)	0.92 (0.46-1.86)	0.57 (0.19-1.75)	1.01 (0.17-6.05)
Obese (25 or above)	0.65 (0.31-1.38)	1.26 (0.59-2.70)	1.77 (0.59-5.35)	0.26 (0.04-1.75)	0.57 (0.20-1.62)	0.73 (0.37-1.45)	0.93 (0.32-2.75)	0.65 (0.11-3.77)
Diabetes	0.86 (0.45-1.62)	0.84 (0.52-1.35)	1.54 (0.97-2.42)	0.43 (0.12-1.62)	1.35 (0.67-2.71)	0.50 (0.31-0.82)†	0.99 (0.58-1.69)	0.63 (0.23-1.77)
Heart disease	1.13 (0.66-1.93)	1.08 (0.71-1.65)	1.14 (0.76-1.71)	1.12 (0.35-3.60)	1.10 (0.55-2.20)	0.64 (0.42-0.99)*	1.61 (1.00-2.57)	0.84 (0.31-2.22)
COPD	1.69 (0.92-3.09)	0.70 (0.39-1.28)	0.61 (0.34-1.11)	1.15 (0.33-4.06)	1.11 (0.37-3.29)	0.84 (0.44-1.63)	2.66 (1.10-6.44)*	2.05 (0.35-12.05)
Osteoarthritis	1.03 (0.42-2.55)	1.08 (0.55-2.11)	1.29 (0.70-2.37)	0.35 (0.05-2.46)	2.11 (1.01-4.44)*	1.11 (0.67-1.84)	0.99 (0.58-1.69)	0.76 (0.22-2.56)
Hip fracture	—	—	—	—	0.95 (0.12-7.83)	0.62 (0.13-3.00)	—	0.70 (0.11-4.61)
Stroke	1.79 (0.84-3.82)	0.40 (0.17-0.92)*	1.53 (0.74-3.15)	0.18 (0.04-0.84)*	2.81 (1.01-7.77)*	0.49 (0.20-1.23)	3.86 (1.42-10.50)†	0.35 (0.10-1.27)
Cancer	0.75 (0.30-1.88)	1.07 (0.48-2.37)	2.03 (1.03-4.00)*	2.20 (0.44-11.02)	0.98 (0.29-3.33)	1.39 (0.71-2.70)	0.79 (0.32-1.95)	2.25 (0.42-12.12)
Hospital admission								
0	1	1	1	1	1	1	1	1
1–2	1.71 (1.02-2.88)*	0.66 (0.43-1.02)	1.24 (0.87-1.76)	1.17 (0.37-3.72)	2.62 (1.46-4.73)†	0.71 (0.49-1.02)	1.36 (0.89-2.05)	0.41 (0.16-1.03)
3–4	2.50 (1.23-5.10)*	1.06 (0.57-1.96)	0.88 (0.40-1.92)	0.65 (0.12-3.66)	4.07 (1.59-10.42)†	0.24 (0.08-0.68)†	6.32 (1.99-20.09)†	0.31 (0.07-1.27)
5 or above	5.33 (2.16-13.15)‡	0.50 (0.16-1.51)	3.04 (1.24-7.44)*	1.30 (0.11-15.24)	2.73 (0.32-23.37)	0.18 (0.02-1.48)	3.09 (0.51-18.85)	0.03 (0.004-0.33)†

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HK, Hong Kong; MMSE, Mini-Mental State Examination score; SES, socioeconomic status; —, unable to estimate.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table 4
Multiple Stepwise Logistic Regressions: Factors Significantly Associated With Transitions in Frailty Status Over 2 Years

	Male				Female			
	Prefrail Worsening	Prefrail Improvement	Robust Worsening	Frail Improvement	Prefrail Worsening	Prefrail Improvement	Robust Worsening	Frail Improvement
Age, per 1-year increase	1.13 (1.08-1.18)	0.86 (0.82-0.90)	1.12 (1.07-1.16)	*	1.14 (1.08-1.21)	0.91 (0.88-0.94)	1.08 (1.03-1.12)	0.90 (0.83-0.97)
Hospital admission								
0	1.0				1.0	1.0	1.0	
1–2	1.70 (1.01-2.85)				2.51 (1.35-4.68)	0.78 (0.53-1.15)	1.48 (0.95-2.30)	
3–4	2.28 (1.10-4.74)				5.12 (1.90-13.76)	0.20 (0.06-0.67)	6.36 (1.95-20.74)	
5 or above	5.08 (1.98-13.08)				—	0.28 (0.03-2.26)	3.87 (0.62-24.14)	
Stroke		0.40 (0.17-0.92)		0.22 (0.05-0.93)	3.11 (1.05-9.18)		3.53 (1.24-10.09)	
MMSE, per 1-unit increase		1.09 (1.01-1.18)			0.91 (0.84-0.99)			
Cancer			2.02 (1.03-4.00)					
Osteoarthritis					2.28 (1.04-5.02)			
Diabetes						0.48 (0.29-0.80)		
SES ladder, per 1-unit increase							0.89 (0.81-0.99)	
COPD							3.49 (1.38-8.78)	

COPD, chronic obstructive pulmonary disease; MMSE, Mini-Mental State Examination score; SES, socioeconomic status; —, unable to estimate.
*Blank cells indicate that the variable is not included in the model.

chance of improvement, except in the improvement of frail men. Among the prefrail, higher MMSE score was protective, whereas a history of stroke reduced the chance of improvement by 60% in men and increased the likelihood of decline by threefold in women. In addition, having diabetes reduced the chance of improvement by 50% in prefrail women. Having 3 or 4 hospitalizations within the intervening 2 years also significantly reduced the chance of improvement. Any hospitalization increased the risk of worsening up to 5 times in both prefrail men and women. Additional factors associated with decline in prefrail women included a history of osteoarthritis.

In robust men, having a history of cancer increased the risk of worsening by 2 times. In robust women, hospitalizations, COPD, or stroke were risk factors for decline. In frail men, a history of stroke reduced the chance of improvement by 78%. We were not able to find any significant factors associated with improvement in frail women in our model, apart from younger age.

Discussion

This is the first study to report frailty transitions among Asian individuals. We found that a quarter of prefrail men and women recovered into the robust state after 2 years, with only 11% of men and 7% women of progressing into frailty. The large proportion of prefrail persons remaining stable within a period of 2 years suggested that there may be a window during which interventions can be applied to reduce the decline rate or to improve the recovery rate.

Men and women in our cohort had different transition rates: prefrail men tended to progress into frailty more than women (11.1% vs 6.6%). An earlier study in a Western cohort did not find men to be at higher risk of decline.[13] This will have to be further confirmed by other studies, but it may imply that the effect of frailty interventions might have different efficacy in men and women and that the same interventions may be less or more helpful in men.

Our results confirmed the findings of Gill et al[21] that hospitalizations reduce the chance of recovery from the frailer states. In fact, hospitalizations also significantly and consistently increased the likelihood of worsening in not only the prefrail, but also the robust state. The detrimental effect of hospitalizations was more consistent in women than in men. It is not clear what may be the underlying mechanism of this gender disparity.

Our study is the first to report the effects of various medical comorbidities on frailty state changes in men and women separately. Among medical comorbidities studied, stroke was the most consistent harmful factor in both genders. It reduced the chance of improvement in men and increased worsening in women. Having previous stroke increased the risk of worsening in both the prefrail and robust states by 3 times. Cognitive impairment was detrimental in both prefrail men and women. Cognitive impairment has recently been linked to physical frailty[22–25] and interventions that help to maintain or improve cognitive function in the prefrail might have a role in reducing decline or improving recovery in this group. We also confirmed the findings of Espinoza et al[13] that diabetes is a harmful condition in the prefrail. Diabetes predisposes older individuals to more rapid muscle loss[26,27] and functional decline,[28] and metabolic risk factors are associated with poorer physical performance[29]; therefore, this finding is not surprising. Unfortunately we had no information on diabetes complications and therefore were not able to analyze whether uncomplicated diabetes might have the same effect on frailty transitions as complicated diabetes.

Overall, we found more significant factors associated with the change in frailty status in women. Although some were shared by both genders (age, hospitalizations, stroke, and cognitive impairment), some were apparent only among women. The identification of the different risk factors for the 2 sexes will allow us to select a high-risk group for earlier intervention. It is also possible that better management of these risk factors may further increase the recovery rate of the prefrail, or reduce their decline. Enhancing rehabilitation after hospitalizations may be very important to reduce deterioration in the prefrail and even the robust.

Limitation

Our cohort was not randomly selected, but it was likely a representative sample of community-living independent older people, as evidenced by comparable prevalence of frailty when compared with other cohorts.[1,9] Hospitalizations may be a result of frailty rather than a cause of the decline in frailty state. As we did not study the details of the individual hospitalizations, it was also uncertain whether they could be preventable. Our data might have an underrepresentation of the most frail, as those who defaulted the follow-up visit had significantly more hospitalizations. We did not have information on diabetic complications, which limited our ability to examine whether better controlled or less complicated diabetes would have less effect on frailty transitions. We defined frailty according to the Fried criteria,

which had been commented to be difficult to adopt by primary care or in clinical practice. However, we hope our study may serve as a starting point for looking at how individual medical conditions may affect the improvement or worsening of frailty in the future.

Conclusion

Women were less likely to decline in frailty status than men. Hospitalizations, older age, previous stroke, lower cognitive function, diabetes, and osteoarthritis were associated with worsening or less improvement in frailty status. Older age, previous cancer, hospitalizations, lung diseases, and stroke were risk factors for worsening in robust individuals, and higher socioeconomic status was protective.

References

1. Fried LP, Tangen CM, Walston J, et al. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
2. Morley JE, Perry HM, Miller DK. Editorial: Something about frailty. J Gerontol A Biol Sci Med Sci 2001;57:M698–M704.
3. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc 2010;58:681–687.
4. Hubbard RE, Rockwood K. Frailty in older women. Maturitas 2011;69:203–207.
5. Romero-Ortuno R, Kenny RA. The frailty index in Europeans: Association with age and mortality. Age Ageing 2012;41:684–689.
6. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009;64:675–681.
7. Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr 2010;50:S43–S47.
8. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC Geriatr 2010;10:57.
9. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. J Am Geriatr Soc 2012;60:1487–1492.
10. Abellan van Kan G, Rolland Y, Bergman H, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12:29–37.
11. Ahmed N, Mandel R, Fain MJ. Frailty: An emerging geriatric syndrome. Am J Med 2007;120:748–753.
12. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med 2006;166:418–423.
13. Espinoza SE, Jung I, Hazuda H. Frailty transitions in the San Antonio Longitudinal Study of Aging. J Am Geriatr Soc 2012;60:652–660.
14. Fallah N, Mitnitski A, Searle SD, et al. Transitions in frailty status in older adults in relation to mobility: A multistate modeling approach employing a deficit count. J Am Geriatr Soc 2011;59:524–529.
15. DeCarli C. Mild cognitive impairment: Prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2003;2:15–21.
16. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
17. Washburn RA, Smith KW, Jette AM, Janny CA. The Physical Activity Scale for the Elderly (PASE): Development and evaluation. J Clin Epidemiol 1993;46:153–162.
18. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982;17:37–49.
19. Yip PSF, Law CK. Assessment of the future resources and needs for hospitalization in Hong Kong SAR. Int J Health Plann Manage 2002;17:113–122.
20. World Health Organization. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Australia: Health Communications Australia Pty Limited; 2000.
21. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. J Gerontol A Biol Sci Med Sci 2011;66:1238–1243.
22. Houles M, Canevelli M, Van Kan GA, et al. Frailty and cognition. J Frailty Aging 2012;1:56–63.
23. Malmstrom TK, Morley JE. Frailty and cognition: Linking two common syndromes in older persons. J Nutr Health Aging 2013;17:723–725.
24. Auyeung TW, Kwok T, Lee J, et al. Functional decline in cognitive impairment—the relationship between physical and cognitive function. Neuroepidemiology 2008;31:167–173.
25. Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. J Nutr Health Aging 2011;15:690–694.
26. Park SW, Goodpaster BH, Lee JS, et al, for the Health, Aging, and Body Composition Study. Excessive loss of skeletal muscle mass in older adults with Type 2 diabetes. Diabetes Care 2009;32:1993–1997.
27. Lee J, Auyeung TW, Kwok T, et al. The effect of diabetes mellitus on age-associated lean mass loss in 3153 older adults. Diabet Med 2010;27:1366–1371.
28. Gregg EW, Mangione CM, Cauley JA, et al. Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. Diabetes Care 2002;25:61–67.
29. Lee J, Auyeung TW, Leung J, et al. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. J Nutr Health Aging 2011;15:857–862.