FRAILTY AND OBESITY IN AGEING MEN

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Contents

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Abstract

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Background & Aim: Frailty is a syndrome characterised by multisystem physiological dysfunction, making older adults vulnerable to stressors. Frailty is often considered as a wasting disorder however there is increasing evidence that many overweight and obese people are also frail. The broad aim of the thesis was to explore whether anthropometric indicators of adiposity and obesity are linked with an increased susceptibility to frailty in middle aged and older European men.

Methods: 3,369 men aged 40-79 years were recruited from population registers in eight European centres for participation in the European Male Ageing Study (EMAS) a prospective study of male ageing. Subjects were invited by letter to attend for an interviewer-assisted questionnaire, functional assessments and anthropometric measurements including height (m), weight (Kg), waist (cm) and hip circumference (cm), from which body mass index (BMI) (Kg/m^2), and waist hip ratio (WHR) were calculated. Subjects were assessed again after a median of 4.5 years, using the same study instruments. They were asked also about occurrence of falls in the past year. Frailty was assessed using adaptations (because of availability of data) of two established methods, the frailty phenotype (FP) and the Frail Scale (FS), both comprising 5 domains, and also a Frailty Index (FI) a ratio based on observed over a range of potential deficits. Incident frailty was defined as the new occurrence of frailty in those who were not frail at baseline.

Results: 3369 men, mean age 60yrs contributed data to this analysis. Using data from the study the prevalence of frailty at baseline was 2.6% using the FP method and 2.7% using the FS and the mean Frailty Index was 0.13 (IQR=0.05-0.18). The prevalence of frailty increased with age. Those who were frail, using either definition had a significantly increased waist circumference (WC) and also WHR. The FI was higher and also correlated with these anthropometric measures. During follow-up there were 193 deaths. Compared to those who were not frail at baseline those who were frail had an increased risk of mortality and also were more likely to experience falls. Of those who were not frail at baseline and who completed the follow-up assessments the incidence of frailty ranged from 2.1% to 3.5% depending on the definition. Mean Frailty Index increased from 0.12 to 0.13, in men who returned at follow-up. An increase in baseline adiposity measures WC & WHR was significantly associated with frailty incidence, at follow-up using both (FP & FS) models, while there was no association with BMI and % body fat. An increase in all baseline adiposity measure was significantly associated with frailty incidence defined by the FI and also a change in the Frailty Index.

Conclusion: Frailty models adapted to EMAS predicted adverse outcomes. Obesity was associated with frailty and predicted frailty incidence at follow-up. Interventions to combat obesity in the elderly may help in preventing and reducing the occurrence of frailty.

Declaration

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List of Abbreviations

ADT	Androgen deprivation therapy
AL	Allostatic Load
ANOVA	Analysis of variance
BAT	Brown Adipose Tissue
BDI	Beck's Depression Inventory
BMI	Body Mass Index
CES-D	Center for Epidemiological Studies Depression Scale
CSHA	Canadian Study of Health and Aging
CGA	Comprehensive Geriatric Assessment
CHS	Cardiovascular Health Study
CHAMP	Concord Health and Ageing in Men
CI	Confidence Interval
CMV	Cytomegalovirus
CRP	C-Reactive Protein
CSBA	Conselice Study of Brain Ageing
CTRM	Camden Topographical Recognition Memory Test
DEXA	Dual-Energy X-ray Absorptiometry
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate DHEAS
DNA	Deoxyribo Nucleic Acid
DSST	Digit-Symbol Substitution test
EA	European American
EE	Energy Expenditure
ED	Emergency Department
ELSA	English Longitudinal Study of Ageing
EMAS	European Male Ageing Study
ESR	Erythrocyte Sedimentation Rate
ESPEN-SIG	The European Society for Clinical Nutrition and Metabolism Special Interest Groups
EWGSOP	European Working Group on Sarcopenia in Older People
FI	Frailty Index
FL	Frail Lean
FO	Frail Obese
FP	Frailty Phenotype
FS	FRAIL Scale
FSH	Follicle Stimulating Hormone
GAP	Geriatric Advisory Panel
GH	Growth Hormone
GP	General Practitioner
H-EPESE	Hispanic Established Population for the Epidemiological Study of the Elderly
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRV	Heart Rate Variability
HIMS	Health in Men study
HN	Healthy Non-obese
HRS	Health and Retirement Study
HS	Hubbard Scale
IAQ	Interview Assisted Questionnaire
ICD	International Classification of Diseases
IR	Insulin Resistance
InCHIANTI	Invecchiare in Chianti, aging in the Chianti area
IL-6	Interleukin-6
IGF-1	Insulin - like Growth Factor-1
LOH	Late Onset Hypogonadism
LOWESS	Locally Weighted Scatter plot Smoothing technique
LH	Luteinising Hormone
MA	Mexican American

MetS	Metabolic Syndrome
MMAS	Massachusetts Male Aging Study
MrOS	Osteoporotic fractures in Men's Study
MSSA	MacArthur Study of Successful Aging
NPHS	National Population and Health Survey
OR	Odds Ratio
PASE	Physical Activity Scale for the Elderly
PPT	Physical Performance Test
PQ	Postal Questionnaire
pQCT	Peripheral quantitative computerized tomography
PTH	Parathyroid Hormone
ROCF	Rey-Osterrieth Complex Figure
RRR	Relative Risk Ratio
SALSA	San Antonio Longitudinal Study of Aging
SARM	Selective Androgen Receptor Modulator
SENECA	Survey in Europe on Nutrition and the Elderly; a Concerted Action
SES	Socio-economic status
SF-36	Short Form 36
SHARE	Survey of Health, Aging and Retirement in Europe
SHBG	Sex Hormone Binding Globulin
SNP	Single Nucleotide Polymorphisms
SOF	Study of Osteoporotic Fractures
T	Testosterone
TNF-α	Tumour necrosis factor-alpha
WBC	White Blood Cell
WHAS	Women's Health and Aging Study
WHO	World Health Organisation
WC	Waist Circumference
WHR	Waist Hip Ratio

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Chapter 1 Introduction

1.1 Summary

Frailty is a widely recognised clinical syndrome of ageing which is linked with a variety of adverse health outcomes. This chapter outlines definitions which have been used to define frailty and the approaches and models that have been developed to operationalize the definition of frailty. The outcomes of frailty using different models are considered, followed by a review of the determinants of frailty and the role in particular of obesity.

1.1.1 Demographic changes

The last 50 years has seen a demographic shift towards a more elderly population in most developed nations due in part to an increase in life expectancy, a decrease in fertility rate, improved healthcare systems and socioeconomic status. In 2006 over half a billion people worldwide were aged 65 and older [1], with this number set to rise substantially. It is believed in Europe alone there will be a 30% rise in the proportion of the population over the age of 65 years by 2060 [2]. Because of these demographic changes the number of people with diseases and conditions related to ageing are set to increase substantially, presenting challenges to public health and policy makers. As a result, an increasingly important priority for many countries is to ensure that health risks among older people are minimized and the quality of life they lead improved, with the aim of maintaining health and independence.

1.1.2 Frailty – Definition

Frailty is one of the common adverse health outcomes associated with increasing age. Geriatricians have used the term frailty for many years and identify frail individuals as being at increased risk of institutionalization, disability, falls and death. However, even though clinicians can easily recognise this condition, there is no current, clear definition of frailty or official International Classification of Diseases (ICD) designation for the syndrome [3, 4]. Defining frailty is important in beginning to understand its causes and characterisation of its consequences with the ultimate aim of targeting interventions to prevent or delay adverse outcomes associated with it [5]. A number of definitions have been suggested: Stamford and colleagues defined frailty in 1972 as a term synonymous with institutionalisation [6]. Broklehurst in 1985 considered a dynamic model of frailty with assets and deficits; frail individuals were defined as those in whom deficits outweighed the assets [7]. In 1988, Woodhouse and colleagues [8] defined the frail

elderly as individuals, over 65 years of age, dependent on others for activities of daily living, and often in institutional care. In 1995, Brown and colleagues defined frailty as a state which "occurs when there is diminished ability to carry out the important practical and social activities of daily living [9]". They also suggested that frailty was not a dichotomous state, rather a continuum (frailty – robustness). Over time, there has been gradual convergence and agreement on the broad components of a frailty definition. Gobbens *et al* [10] in a review to identify the most appropriate definition of frailty for identifying frail community dwelling older adults suggested the following: "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes". A recent consensus conference concluded frailty to be "a clinical state where an individual is vulnerable to increased risk of adverse outcomes when exposed to stressors" [11].

1.1.3 Frailty and Ageing

Research on ageing is complex, as every aspect of the organism changes with age [12]. Leonard Hayflick, an established bio-gerontologist, describes 'aging as an artefact of civilization' [13], as we have learned ways to increase our chances of survival and consequently face this concept. Biological ageing is only observed in humans and the animals we keep as pets or as domesticated animals, it doesn't occur to the same degree in the wild [13]. Ageing in itself is a complicated process with many definitions and theories. As with the definitions of ageing, theories of ageing are numerous in the literature. They can be divided into biological theories and non-biological theories. In 1990, a review by Medvedev identified over 300 theories of ageing [14]. This large variety of data on the observations of ageing has led to the development of an encyclopedia on ageing known as the *Macmillan Encyclopedia of Aging* [15]. Details of some of the key biomedical theories of ageing are summarised in Table 1.1.

Theories of ageing	Definition
Programmed Cell theory	Ageing is programmed to limit population size and free the resources for the younger generation
Mutation Accumulation Theory	As people grow older they accumulate late acting mutations, which increases mortality
Antagonostic pleiotropy theory	Genes that increase fitness in younger life may be harmful in later life
Free Radical theory	Ageing is a result of free radicals in cells that will ultimately result in damage to the body's cells and tissues of the body resulting in ageing symptoms
Somatic Mutation Theory	Life expectancy and number of mutations are inversely related to each other. Experiments showing accelerated somatic mutations show organisms to have shorter life spans.
Cross-linkage Theory	With age new cross links are formed in cells that could alter the formation of proteins and the structures are altered irreversibly causing malfunction in cells, which causes dysfunction in the tissues and organs made by the cells.
Waste Accumulation Theory	Accumulation of inert substances such as lipofuscins which are usually by products of cellular metabolism can interfere with cell function and cause ageing.
Wear and Tear theory	The metabolic energy resources of a cell are limited and this determines the life span of an organism. The popular concept of calorie restriction to extend lifespan arose from this concept.
Autoimmune Theory	The immune system is no longer able to distinguish foreign proteins from the body's self-proteins, resulting in antibodies being produced to attack self-proteins which then attack and destroy the body's immune cells.
Reliability theory	A theory about systems failure. This explains the age-related failure of kinetics in a given system and reliability of its components. It states that even non-ageing elements of a system accumulate damage with age if they are redundant in elements which cannot be replaced. Hence, ageing is a direct result of system redundancy.

Table 1.1 Biomedical theories of Ageing

One of the earliest theories of ageing was put forward by August Weismann in 1882 and considered the concept of ageing and death as programmed [16]. Weismann stated that it was important for such a program to exist through natural selection that would favour the elimination of the old to provide more resources to the young. This theory has been argued to have many flaws. The major drawback of this theory is that in the natural world living beings rarely die of old age. Another popular concept was the mutation accumulation theory of ageing suggested by Peter Medawar [16], where ageing is considered to be a result of natural selection. Any mutations in a young person would not be selected, as they would probably not live long enough to pass the mutant genes to the next generation, whereas there is increased chance of genetic diseases increasing with age resulting in an accumulation of mutations and ultimately death. George Williams [17] proposed a theory of ageing known as the theory of antagonistic pleiotropy in which he suggested that genes which would be advantageous during the reproductive period of an individual would play a reverse role during their old age. For example, any mutations causing an overproduction of sex hormones would result in an increased sex drive, hence resulting in more offspring, but in old age may cause prostate cancer or ovarian cancer. Gavrilov and Gavrilovae [18] suggested a general theory of ageing and longevity known as 'The reliability theory of ageing and longevity'. This is a general theory about ageing caused by a loss of redundancy in system components and the ultimate failure of these systems.

There remains debate among researchers and clinicians as to whether frailty is synonymous with ageing. As people get older their needs tend to increase both 'socially' and 'medically', and in this perspective frailty was put forward as a better way to study the health needs of the aged [19] and to maintain a good quality of life. Frailty is a separate entity by itself which might be prevented, treated or delayed, whereas ageing is not a condition in itself it but is part of the biology of a person and an inevitable part of the lifespan of an individual. Age is a predictor of frailty but not the main cause of it [20]. Frailty has been found to be a better predictor of mortality than chronological age [21]. Schuurmans *et al* [22], carried out a study to identify whether frailty or chronological age is a better indicator for geriatric interventions. They measured frailty using the Groningen Frailty Indicator. This scores a loss of functioning in four

aspects of an individuals' functioning: physical, cognitive, social and psychological. A score of four or more was considered as moderately frail. They compared the associations of chronological age and frailty status with a decrease in self-management activities. The results showed frailty to be a better predictor of decline in self-management activities than chronological age. Geriatricians in clinical practice can identify the difference between the 'frail' and sometimes known as the 'biologically old', and chronologically old individuals [23]. The ability of the operational definitions of frailty to measure the parameters needed for a successful ageing process is key to distinguishing frailty from ageing. Ageing is universal, but the rate at which each individual ages is not constant. Frailty may be able to capture these differences in the process of ageing and provide a measure of biological functional age [24].

1.2 Assessment of Frailty

Given the lack of consensus concerning the definition of frailty, it is perhaps not surprising that there are no universally agreed criteria for the assessment or classification of frailty. A number of frailty models have been developed and operational classification criteria proposed. The most widely used are the Fried Phenotype and the Frailty Index [11]. Recently the FRAIL scale [11] has been also promoted as a clinical screening tool in assessing frailty which to some extent captures elements of both the Frailty Phenotype and the Frailty Index. These models are outlined below.

1.2.1 Fried's Phenotype

One of the most commonly used criteria is the 'Frailty Phenotype' (FP) [5]. Developed by Fried and colleagues [5] the criteria are based on a model of frailty which comprises five domains; sarcopenia, weakness, exhaustion, slowness and low activity. Based on data from a large population survey these were assessed as: weight loss in the last year (sarcopenia), decreased grip strength measured by a dynamometer (weakness), exhaustion, measured by a modified Centre for Epidemiological Studies Depression scale, slowness time to walk 15 feet adjusted by height and gender (slowness) and low activity, measured by the Minnesota Leisure Time Activity Questionnaire. The data used to develop the criteria were derived from the Cardiovascular Health Study (CHS), an observational study of community dwelling men and women 65 years and older from four U.S communities in the period of 1989 to 1990 [25]. Thresholds for each of the criteria were defined from the cohort itself as shown in Table 1.2 below.

Characteristics of Frailty	Cardiovascular Health Study Measure
Sarcopenia: Weight loss (unintentional)	Baseline: >10 lbs. lost unintentionally in prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance/Exhaustion	"Exhaustion" (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week

Table 1.2 Operationalizing a frailty Phenotype model from the CHS study data. Reproduced from [5]

Fried and colleagues defined a "Frailty Phenotype" as those with three or more of the criteria as 'frail', those with one or two criteria as pre-frail and those with none as robust. Using this definition of frailty, they were able to show that frailty increased with age and was more common in women than in men [5]. Data from the study supported the hypothesis that frailty caused disability and was associated with a range of adverse outcomes including falls, hospitalisations and mortality. The phenotypic definition was subsequently validated in an independent data set, the Women's Health and Aging Study (WHAS) [26]. The results from both the CHS and WHAS confirmed that the phenotypic criteria were able to predict disability and mortality independent of disease and other measures [5, 26]. Investigators in other studies have adapted the individual criteria used by Fried based on the information available in their own cohort. Cawthon *et al* [27], in a study of older community dwelling men, used a measure of body fat and size instead of weight loss to define sarcopenia, and found that frail men were more likely to be older, have lower physical function, poorer cognitive function, poor self-rated health, more likely to fall and have increased mortality.

The phenotypic criteria have been used in many other studies internationally, though most (as discussed) have used a modified version of the component criteria depending on the data available within individual cohorts [28-32]. These studies have validated the phenotypic model by its ability to predict adverse outcomes in older adults. For example, Avila-Funes *et al* [28], studied frailty in an elderly French community to predict adverse outcomes including disability, mortality and an increase in hospitalization. In this study, sarcopenia was defined as present if participants reported weight loss or if they had a body mass index (BMI) less than 21 kg/m^2. Slowness was defined as the slowest quintile on time to walk 6 meters, adjusted for

gender and height. 'Weakness' was defined if participants answered 'yes' to the question "do you have any difficulty rising from a chair". Individuals who answered that they did not partake in any leisure activities such as walking, were defined having low activity. Using these data frailty was associated with incident disability and hospitalization, although, interestingly was not significantly associated with mortality after adjustment for confounders [28].

The criteria have also been used in different populations including a large cohort of middle-aged and older community dwelling Europeans in 10 countries, the Survey of Health, Aging and Retirement in Europe (SHARE) [29]. In this study the prevalence of frailty was higher in those living in countries in the south of Europe compared to the north. Furthermore frailty was linked to an increased rate of mortality [33] and adverse health outcomes [34]. Chang *et al* [35], using data from a Taiwanese cohort aged 65 years and over, reported an association between frailty and lower quality of life. Another study among Mexican-American men and women aged 70 and over, also operationalized the Frailty Phenotype model proposed by Fried (Hispanic Established Populations for Epidemiologic Study of the Elderly) [36]. This was a home based interview survey and the measure of frailty was a modified version of Fried's criteria. The modified scale had range of 0 to 4 that included weight loss, exhaustion, walking speed, and grip strength. The results showed that muscle strength was an important predictor of frailty. It also showed disability, comorbidity, and frailty were more frequent among women than men and that disability appeared to be the best predictor of frailty for in men and women. Another recent analysis [37], on this population also showed that frailty assessed by the FP predicted falls in older Mexican Americans. Attempts have been made to simplify the criteria for use in a clinical setting. In the Study of Osteoporotic Fractures (SOF), a SOF Frailty Phenotype was developed by Ensrud *et al* [3]. In the SOF FP, the criteria used were weight loss, weakness assessed as the ability to stand up from a chair without using arms and, reduced energy level. Individuals with two or more criteria were considered frail, those having a single criterion were considered pre-frail and those who had none were considered robust. The SOF FP was compared to Fried's CHS Frailty Phenotype for prediction for falls, fractures and mortality in a cohort of 6701 community dwelling women aged 69 years and over and also men aged >67 years in the Osteoporotic fractures in Men's Study (MrOS) [38]. The results showed concordance between both measurements of frailty in assessing frailty status and for predicting adverse outcomes. In

another study [39] of older adults aged over 70 years based in Boston, the FP and the SOF models were compared, with both models predicting adverse outcomes.

Although the FP is the most widely used tool to assess frailty, there are several limitations which need to be considered. These include i) the need for relatively detailed measurements requiring specific instruments which may be time consuming and costly in large surveys and not easy to operationalize in clinical settings, ii) the need for population specific cut-points for the individual frailty criteria iii) the absence of any comorbid disorders that are important components of the frailty syndrome, iv) the fact that there is likely to be some overlap between some of the domains, for example slow walking speed and weakness, v) the threshold for the criteria are based on data from within the cohort studied limiting generalizability, vi) it is primarily a measure of physical frailty and lacks other important contributors of frailty including mental health and cognition [40].

1.2.2 Rockwood Frailty Scale

In 1999, Rockwood et al [41] described an operational classification of frailty which classified community dwelling elders into one of four levels from fitness to frail. The classification was based on the Geriatric Status Scale [42]. The four levels of classification are described below:

0 "Those who walk without help perform basic activities of daily living, continent of bowel and bladder and not cognitively impaired;"

1. "bladder incontinence only"
2. "one (two if incontinent)" or more of needing assistance with mobility or activities of daily living , has cognitive impairment and no dementia, or has bowel or bladder incontinence.
3. "two (three if incontinent)" or more of totally dependent for transfers or one or more activities of daily life, incontinent of bowel and bladder, and diagnosis of dementia".

The dataset used to develop the classification was the Canadian Study of Health and Aging (CSHA), phase 1, a study on health related problems in individuals aged 65 and over. It was validated by predicting mortality and institutionalization in the cohort and showed a significant trend of an increasing level of frailty with an increase in institutionalization [41] .

1.2.3 Frailty Index

The Frailty scale was further developed by Rockwood and colleagues[43] to achieve a new approach in the assessment of frailty. The Frailty Index (FI) which he developed after the

Frailty scale is now a widely used method for the assessment of frailty. It differs from the FP in that it is a continuous scale. The idea underlying the development of the FI is that the more health disorders or deficits a person accumulates, the higher the risk of frailty and associated adverse outcomes. The rate of accumulation of deficits differs between individuals and separate individuals will not necessarily accumulate similar deficits [44]. The FI was derived from the dynamic model of frailty shown in Figure 1.1 proposed by Rockwood *et al* [23]. This model is a balance between assets, such as health, positive attitude towards life, good socioeconomic status, etc. and deficits, including ill health, chronic diseases, disability, comorbidity, etc. People who have more assets than deficits are considered as robust and in those with a significant number of deficits are considered frail. The dynamic model suggests that depending on the number of assets present and the number of deficits accumulated an addition of a single deficit increases the probability of creating an imbalance, hence instability in the individual.

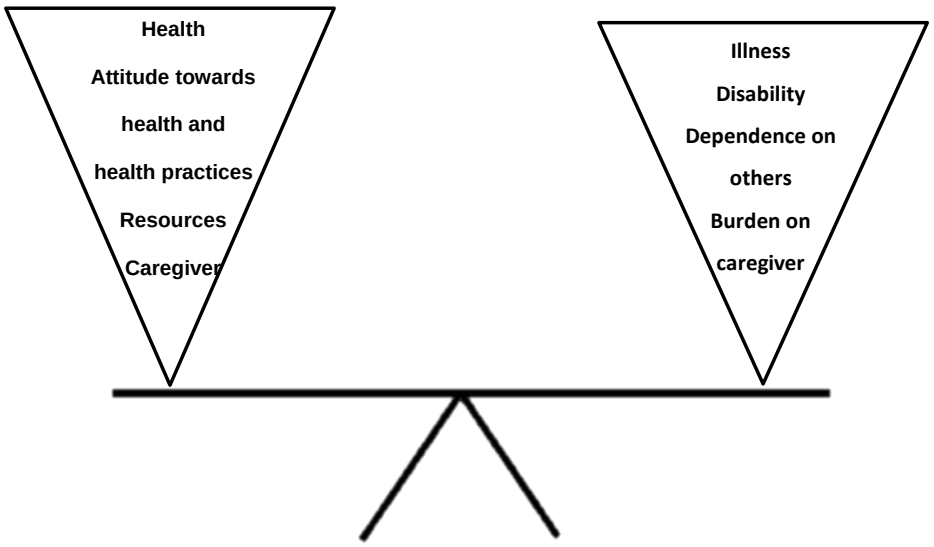


Figure 1.1 Dynamic model of frailty in elderly people, in which the balance between assets (left) and deficits (right) determines whether a person can maintain a disabled free life in the community. Adapted from [23]**.**

In practice the FI may include a range of deficits which are easily accessible from health surveys or clinical data. These data consist mainly of laboratory measurements, clinical evaluations, and self-reported health outcomes obtained by questionnaires such as the Mini-

Mental State Examination, etc. In the FI the deficits are summed together, i.e. if the deficit is present a score of 1 is given, when absent 0 and a fraction when present to a limited extent. The greater the number of variables added the better the index. Binary, continuous and ordinal variables can be considered by recoding 0 when the deficit is absent, 1 when present and a 0.5 for an intermediate response. It is then divided by the total number of deficits assessed to give a ratio or index, e.g. for an assessment which has 40 items, if the individual has 10 deficits the Frailty Index is calculated as 10/40=0.25. It has been suggested that a minimum of 20 deficits may be considered although considering 50 or more deficits gives a better FI. After 70 deficits any further addition of deficits thought to have little effect on the performance of the FI [45].

The FI has been validated by its ability to predict death, with the risk of death increasing exponentially with number of deficits [46]. Interestingly, the FI shows a consistent maximum limit, i.e., the upper limit does not exceed a FI of around 0.67 (at about 2/3 of the deficits that are considered). For example, in the case where 60 deficits are considered the maximum number of deficits a person is able to acquire is 40 and not 60 [44]. Those approaching this number of deficits are clearly at high risk of death. This accords with the reliability theory of ageing [47] in which an individual is considered as a complex machine in which if one part fails another part would compensate, thus redundancy is built up in the system. The theory states that once redundancy is exhausted, the system fails and is not able to accumulate any more deficits.

Other investigators have used the index approach. Jones *et al* [48], also used a FI based on the Comprehensive Geriatric Assessment Scale, with 10 variables to develop the FI which predicted a range of adverse outcomes including mortality and institutionalization. Searle *et al* [49], used data from the Yale Precipitating Events Project, a longitudinal cohort study to introduce a standard procedure for creating a FI. A total of 754 nondisabled, English speaking, community dwelling participants, aged 70 years and more based in New Haven CT were included in the study. To be included as a variable as part of the FI the variable needed to satisfy five criteria: it had to be related to health status (could not include grey hair, wrinkles, etc. which are age related), it should increase with age, the deficit should not appear too early in a person's life, the deficits should cover a range of systems and not be concentrated on one domain, and if the index is to be used continuously in the same set of people, the variables used to make it up should not differ in subsequent waves of measurement. The FI has been

used and validated in a number of other populations [50, 51]. Mitnitski *et al* [52], validated the FI in seven populations and clinical studies from four developed countries, using data from national health surveys. In calculating the FI, a total of 40 variables were considered, with similar results seen across the different countries, despite quite marked differences in study design and in the variables used in the different datasets. In a further study, (CHAS) 20 deficits were used to develop the FI. In a Canadian study, the National Population and Health Survey (NPHS), Song *et a*l [53] developed a FI which increased with age and in which increasing FI was associated with an increased risk of mortality. Kulminski *et al* [54] developed a FI in a longitudinal analysis using data from the National Long Term Care Survey of aged individuals in the USA, using 32 deficits to calculate their index. Their results showed a nonlinear relationship between frailty and age, with the rate of increase in the mean FI slowest at younger ages, increasing more rapidly with advancing age, and then decelerating when an individual reaches extreme old age. In contrast to findings from the other studies frailty was independent of gender in younger and extremely old individuals, a possible explanation being a higher proportion of disabled people in the population. For other age groups it followed similar trend of females being more likely to be frail than males. The results suggested a strong impact of gender on frailty dynamics and confirmed the importance of studying men and women separately. It also confirmed that women tend to cope with increasing frailty better than men do. This may be because women accumulate deficits for a longer period prior to death whereas men tend to have an increase in the number of deficits accumulated just before the event of death [55-57].
An FI was also developed using 40 deficits in a European setting using the SHARE data set, where the operationalized FI exhibited similar properties to that in other cohorts, i.e., a gamma distribution, positive association with increasing with age, and higher values were associated with an increased mortality across all age groups [58].

Kulmiski *et al* [59], used the Cardiovascular Health Study (CHS) data to compare the FI with the FP to determine which of the two approaches better predicted mortality, while Rockwood *et al* [60] compared the FI and the FP in the Canadian Survey of Health and Aging (CSHA). In the CSHA study, cut-points were used to categorise the FI into robust, pre-frail and frail similar to the FP. Individuals with a FI ≤0.2 were considered as robust, pre-frail individuals scored between 0.2< FI ≤0.35 and frail individuals scored ≥0.35. The two models correlated moderately and frail individuals were at a higher risk of mortality, however, frailty was defined.

Overall, though the FI was a better predictor of mortality in the CHS study as it underestimated death in 134 individuals (out of a total of 1073 frail individuals) whereas when frailty was defined using the FP it underestimated death for 720 frail individuals. Studies using the FI have used other cut-points including a FI >0.25 to classify an individual as frail [60], while in the Canadian National Population Health Survey, a cut-point of >0.21 was used to classify individuals as frail and a FI ≥0.45 as most frail [61]. In the same study, Song *et al* [53], used 36 deficits to construct an FI and defined the cut-points as robust (FI ≤0.08, i.e. having 3 or less of 36 deficits), frail (FI ≥0.25,9 or more deficits out of 36) and pre-frail as 4-8 deficits out of 36 or having a FI between 0.08 and 0.25.

1.2.4 FRAIL Scale

In 2008, the Geriatric Advisory Panel [6] of the International Academy of Nutrition Health and Aging suggested that frailty is a pre-disability state and that a screening assessment tool should include a combination of the physical criteria used by Fried, and also the occurrence of comorbidity. Furthermore, any screening assessment tool used should be easy to apply in a clinical setting. The criteria suggested included; Fatigue, Resistance (ability to climb stairs), Ambulation (ability to walk a given distance), number of Illnesses and Loss of weight. Such a scale was operationalized by Hyde *et al* [62], in a longitudinal study, (the Health in Men study) in Australia. Data used were from the 3638 men who participated in wave 2. Fatigue, Resistance and Ambulation were defined as present or absent based on responses given in the short form 36 (SF-36) questionnaire, a health related quality of life questionnaire. Deficits (comorbidities) were present if the participant had more than 5 illnesses from a given set of comorbidities. Loss of weight was defined as a weight loss of 5% or more between Wave 1 and 2. Men with 3 or more of these criteria were considered 'frail', while those with 2 criteria were considered to be 'pre-frail and one or fewer 'robust'. The results showed that frailty, defined using the FRAIL scale (FS) independently predicted mortality after adjustment for body mass index, smoking and comorbidity, and was also associated with disability. Morley *et al* [63], recently operationalized and validated a FS to assesses frailty in a population of community dwelling middle-aged African Americans. All 5 components of the FS were scored based on the responses from self-reported questionnaire. The study showed that in participants without any functional impairment/dependency, frailty and pre-frailty were associated with significantly increased mortality and disability after 9 years.

1.2.5 Other assessment tools

Other frailty models have been developed though they are less commonly used. These are summarised briefly below:

1.2.5.1 Seven Point Clinical Frailty Scale

Many frailty definitions have not found widespread application in clinical practice because of the length of time needed to carry out the assessment or not having the necessary equipment to measure the criteria needed. In an attempt to address this, Rockwood *et al* [64], developed another measure of frailty known as the seven point clinical frailty scale, based on clinical assessment. The cohort used for assessment was participants in the second wave of the Canadian Study of Health and Aging (CSHA) [65, 66]; participants from the initial data set without dementia were included. The scale was based on a clinical judgement, with a range from 1 to 7 where 1=very fit, 2=well, without active disease; 3=well, with treated comorbid disease; 4=apparently vulnerable; 5=mildly frail; 6=moderately frail and 7=completely dependent or in a critical health condition. Individuals with a higher score on the 7-point frailty scale were older, more likely to be female, had more pre-existing disease, and impaired cognition and mobility. One of the disadvantages of the approach, however, is that it requires an experienced geriatrician to conduct the examination. This would not be ideal when applying the scale to a general clinical setting. The scale was used by Hubbard *et al* [67], in CSHA to show that a clinical scale of frailty was better at predicting the risk of mortality than age, sex, presence of diabetes or a count of comorbidities. The scale has also been used recently in a study comparing frailty models where it was referred as the Hubbard Scale [68].

1.2.5.2 Edmonton's frail Scale

Rolfson *et al* [69, 70], introduced the Edmonton Frail Scale which classified individuals into five categories covering ten domains based on areas such as cognition, medical illness and quality of life as shown in Table 1.3. The categories were robust (0-4), apparently vulnerable (5-6), mildly frail (7-8), 9-10 moderately frail (9-10), severely frail (11-17). This was proposed as an easy screening tool to assess frailty which could be administered by individuals without specialist training. This validity and reliability of the Edmonton Frail scale was tested in a sample of patients who were referred for a Comprehensive Geriatric Assessment (CGA) [69]. The CGA, though requires specialists in geriatric medicine to administer the test. The results of both tests

(Edmonton Frail Scale and the CGA) were compared and showed significant correlation. This tool has now been developed as a web based app to be used on an iPad or iPhone.

The Edmonton Frail Scale:				**Score: ___/17**
Frailty domain	**Item**	**0 point**	**1 point**	**2 points**
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health status	In the past year, how many times have you been admitted to a hospital?	0	1–2	⩾2
	In general, how would you describe your health?	'Excellent', 'Very good', 'Good'	'Fair'	'Poor'
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0–1	2–4	5–8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis?	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down'	0–10 s	11–20 s	One of >20 s patient unwilling, or requires assistance
Totals	Final score is the sum of column totals			

Table 1.3 The Edmonton Frail Scale Reproduced from [69]

1.2.5.3 Strawbridge's Model of Frailty

Most of the frailty models proposed concentrate on the physical aspects of the individual. According to Bergman *et al* [71], in addition to Fried's five criteria they should also include cognitive decline and depressive symptoms as core components of frailty. In addition, observational studies suggest associations between several lifestyle factors, including exercise, nutrition, education, socioeconomic status, and the onset of frailty. The model proposed by Strawbridge *et al* includes these aspects of frailty [72]. Frailty, according to this model is defined as a deficiency in two or more domains involving physical, nutritive, cognitive and sensory capabilities. The data used were from the Alameda County Study, a longitudinal study of health and mortality in community dwelling individuals aged 65 years and over. Frailty was assessed using 16 variables capturing the four domains mentioned above. Physical Functioning was assessed using four items; sudden loss of balance, weakness in arms, weakness in legs, and dizziness when standing up quickly. Nutrition was assessed using two items; loss of appetite and unexplained weight loss. Cognition was assessed using four items; difficulty paying attention, trouble finding the right word, difficulty remembering things, and forgetting where you put something. Sensory capabilities were assessed using six items; reading a newspaper, recognizing a friend across the street, reading signs at night, hearing over the phone, hearing a normal conversation, and hearing conversation in a noisy room. The domains on physical function, nutrition and cognition were scored as 1 (rarely or never had the problem in the last 12 months), 2 (sometimes had the problem), 3 (often had the problem) and 4 (very often had the problem). The sensory items were scored as 1 (having no difficulty), 2 (have a little difficulty), 3 (have some difficulty) and 4 (have a great deal of difficulty). A score of three or more on any one item, in any domain, was considered as a problem in that domain. Based on the data the prevalence of frailty increased with age and was more common in men than women. The higher prevalence of frailty seen in men was suggested to be due to the inclusion of cognition and hearing loss as components of the frailty model.

1.2.5.4 Prognostic Score of Frailty

Ravaglia *et al* [73] developed a multisystem model of frailty using criteria which included socio-demographic, lifestyle, comorbidity and sensory problems, physical function, disability, nutrition, mood and cognitive status variables. The study population was the Conselice Study of Brain Ageing (CSBA) an Italian cohort of men and women aged 65 years and over. Seventeen

mortality predictors were identified from six domains covering lifestyle, socio-demographic, medical status, physical function, nutrition, mood and cognitive status, (see in Table 1.4). Results from multivariate analyses suggested a prognostic frailty score including nine variables (* in the table) which significantly predicted adverse outcomes. Frailty was identified as the presence of three or more of the nine features. The score was found to be associated with adverse outcomes (mortality, institutionalisation, disability and hospital admission) of frailty [74], although it has not been validated in other population studies.

Mortality Predictors considered
Demographic - * age ≥80, *gender males, Education ≤3 years and living alone
Lifestyle - Current or former smoking, *Physical inactivity
Medical - With ≥2 chronic medical conditions + *Daily use of ≥3 drugs and *blindness or deafness
Nutritional status - * Calf circumference <31 cm, Body mass index <25 kg/m^2
Functional status - Activities of daily living (Any difficulty),* Instrumental activities of daily living (Any difficulty), *Gait and balance test score ≤24
Mood and cognition - Mini mental state examination >24, Geriatric depression scale ≥10, *Pessimism about one's own health- Yes

Table 1.4 Development of a prognostic frailty score.

Adapted from [73] *The nine variables selected to develop the prognostic frailty score

1.2.5.5 Others

Paw *et al* [75], used data collected from participants of the SENECA (Survey in Europe on Nutrition and the Elderly; a Concerted Action) study and used weight loss and inactivity as criteria for identifying frail individuals. Gill *et al* [76], identified frail individuals in his study as those who required more than 10 seconds to walk a 10-foot path and back (gait speed) and those who were unable to stand up from a chair with their arms folded. Syddall *et al* [77], suggested that grip strength could be used as a single marker of frailty for people of similar age. Puts *et al* [78], used a static and dynamic definition of frailty to predict the decline in physical functioning. This study used a performance test as well as self-reported questionnaires, to capture different aspects of physical functioning. In addition, nine frailty markers were used, body weight, peak expiratory flow, cognitive functioning, vision capacity, hearing capacity, incontinence, and sense of mastery, depressive symptoms and physical activity. An individual with three or more markers was considered frail. Cesari *et al* [79], concluded from their study that aged individuals with a gait speed of less than 1m/s are at increased risk of adverse outcomes.

1.2.6 Comparative studies

A number of comparative studies looking at the performance of the different frailty models have been published [3, 38, 60, 74, 80-85]. Cigolle *et al* [86], compared the prevalence of frailty using Fried's phenotypic measure, Rockwood's Frailty Index and Strawbridge's model in adults aged 65 and over in the Health and Retirement Study (HRS). The HRS results showed that only 3.1% were frail according to all three models and those who were identified as frail by the different models varied in socio-demographic characteristics and the presence of chronic comorbidities. Van Iersel *et al* [87], compared the prevalence of frailty using the Fried model, Rockwood's frail scale, low handgrip strength and gait velocity less than 1.0m/s in 125 (72 women) patients admitted to an acute geriatric ward with a mean age of 77.3 ± 7.4 years. The prevalence of frailty varied from 36% (grip strength), 48% (Rockwood Frail scale) to 62.4% (Fried) and 88.8% (gait velocity). Another recent study [68] compared the ability of four frailty models, i.e., an adapted Frailty Phenotype, a FS, the Hubbard Scale (HS) and the FI, to predict mortality and limitation in physical activity in 4000 men aged >65 years in Hong Kong. The study showed that all four models predicted the adverse outcomes. Studies comparing the frailty models suggest that while there is a lack of consensus on a definition of frailty most tools used to assess frailty can be used with a certain degree of effectiveness, especially in predicting adverse outcomes [82]. Different frailty models, however, do not necessarily identify the same individuals as frail. Further, different groups of older adults are identified at risk of adverse outcomes according to the theoretical construct of the frailty model. This suggests/reinforces that multiple pathways are present in developing the frailty syndrome, and instead of using a single frailty model, different models should be explored to identify multiple steps/stages at which interventions can be targeted to prevent or delay the frailty process in the elderly [86].

1.3 Pathophysiology of Frailty

The pathophysiology of frailty is unknown. Lipsitz [88] used chaos theory to define frailty, suggesting that frailty occurs "when the responses of an organism lose complexity in resting dynamics and maladaptive responses to perturbations". To expand on this theory is to say that as people get older they may have more deficits as a result of chronic comorbidities, environmental, lifestyle and genetic factors which may lead to problems in physiological systems such as the endocrine, nervous and cardiovascular systems. These problems may cause a reduction in the complex interactions across multiple systems which are needed to

maintain homeostatic balance. This imbalance in homeostatic reserve due to a decrease in function across complex biological systems may cause an inability in older adults to respond to stressors resulting in the frailty syndrome [89]. Chaves *et al*, used cross-sectional data from the WHAS 1 to explore the association of frailty, assessed by a FP model, and the loss of complexity in physiological systems assessed by Heart Rate Variability (HRV) indices. The results showed that lower HRV was associated with frailty, suggesting the frailty syndrome to be a result of homeostatic imbalance [90]. Bortz [91] has suggested that frailty is a result of early disease in multiple systems leading to impaired muscle strength, mobility, balance, and endurance. While according to Campbell and Buchner [92] frailty arises from a decline in the reserve of multiple systems, which places the frail older person 'at risk' of disability or death with minor stresses. Frailty is usually associated with increased comorbid conditions but there are instances when frailty is present in the absence of any identified comorbidity [93]. Lupien *et al* [94], defined successful ageing as getting old with a minimum number of diseases. A study by Drey *et al* on the frailty syndrome in general practitioner care showed that osteoarthritis and chronic heart failure were the two most frequent diseases occurring in frail older adults [95].

It is recognised that the immune system becomes less efficient as people grow older, a process that has been referred as 'immunosenescence'. This may result in the elderly being at an elevated risk of comorbidities such as cardiovascular disease, dementia, depression, cancers, diabetes related infectious diseases and autoimmune disorders [96], which may in turn mediate pathways in the development of the frailty syndrome through chronic inflammation [91, 97, 98]. Due to the multidimensional nature of the frailty syndrome, it has been suggested that there are many potential activators which may initiate the cycle of frailty. It may also be possible that there are different states of frailty for, e.g., a dynamic state as well as a static state, a wasting state, and also a state which exists together with obesity [99].

As discussed earlier, the pathophysiology of frailty is thought to be the result of changes or failures in multiple inter-related systems [93, 100, 101]. Changes in the levels of hormones and cytokines are also major factors involved in the pathophysiology of frailty [102]. To understand the biological mechanism of frailty we need to pinpoint the processes whereby problems arise in multiple systems, which in turn result in a reduction of homeostatic reserve leading to a vulnerable state in the elderly where they are no longer able to respond to stressors resulting in frailty. The systems integrally associated with the frailty syndrome are the brain,

skeletal muscle, endocrine and immune systems [101]. Studies have explored the association of the frailty syndrome with dysregulation in these systems and identified biomarkers which are discussed in detail in the next section.

1.3.1 Genetics

Changes which take place during ageing are a result of both genetic and environmental factors influenced by epigenetic mechanisms [12, 100]. A few studies have looked at genetic determinants of frailty [103-105], although to date the results have been somewhat disappointing. Shortening of telomere length is associated with poor health and ageing, with Cawthon *et al* showing that shorter telomere length was associated with increased mortality in adults aged over 60 years [106]. A study on a Chinese population [103] explored whether telomere length could explain the biology of the frailty syndrome, where frailty was assessed using the FI with 47 deficits. The results showed that females were frailer than men, however, they had longer mean telomere lengths than males and there was no correlation between telomere length and the FI in either gender. Data from the WHAS I and II studies were used to examine whether genes associated with inflammation and muscle maintenance were also associated with frailty. Frailty was assessed using the FP model, the results showed no significant associations between the Single Nucleotide Polymorphisms (SNP) related to these systems and frailty [105]. However, the data provided some evidence that proteins involved in the apoptosis and transcription regulated pathways may play a role in the development of frailty [105]. It has been suggested that mitochondrial dysfunction plays a role in cellular ageing [107], and Collerton *et al* [104] used the Newcastle 85+ study to explore whether genetic variation in mitochondrial DNA(Deoxyribonucleic acid) was associated with frailty assessing this using both a FP and FI. The authors found no association however between mitochondrial DNA (Mitochondrial haplo-group H,V,J,T,U,K,W,X,I,M) and either frailty or mortality.

It has been noted that developing animal and cellular models to study specific biological pathways related to frailty would be one of the key aims for future research. Walston *et al* used the interleukin 10 (IL-10) homozygous deletion mouse as a model of frailty as it was likely to develop similar characteristics to that of a frail individual [108]. A control, the C57BL/6J mouse was also used in this experiment. Physical measurements, observations and blood analyses were carried out on both the IL-10 and control mice. The results showed that the IL-10 (frail), mice models had more hair loss and lost more muscle strength with increasing age compared to

mice used as controls. The IL-10 mice additionally showed increased levels of IL-6, suggesting that this mouse model may be a useful model to study frailty as well as chronic inflammation in ageing. Parks *et al* developed an FI with 31 deficits in the C57BL/6 mice model. The results suggested that the aged animals of both sexes had a significantly higher FI. FI in the mice also reached a maximum limit of 0.73 similar to humans (maximum limit was 0.7) [109] In a recent study Feridooni *et al* [110], developed an FI on the C57BL/6J mice aged 343-430 days. A clinical assessment was used on the mice to record 30 deficits which were used to construct the FI. The results showed that even between mice of the same age there was quite a difference in their health status. It was hoped that the FI tool developed for the mouse model could be used in clinical trials to reduce frailty

1.3.2 Inflammation

Frailty, as assessed by both an adapted FP model and the FI, has been associated with high levels of inflammation [111, 112]. Inflammation was assessed by measuring levels of inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (Il-6) [113], Factor VIII and fibrinogen [114]. Increased levels of CRP have been shown to predict frailty incidence in the CHS [115]. Researchers have found that frail older adults have higher levels of IL-6, lower levels of haemoglobin and hematocrit than robust older adults in community-dwelling adults aged 74 and over in Baltimore [116]. Frailty has also been independently associated with white blood cell (WBC) counts and IL-6 levels [117]. This was further confirmed by a study by Leng *et al* [118], which suggested WBC count and IGF-1(Insulin –like growth factor 1) levels (low and high levels of WBC and IGF-1 suggesting a U shaped association) were both associated with an adapted FP model, showing evidence for a complex immune-endocrine dysregulation in frailty. The research of Puts *et al* [119], on serum blood markers and frailty suggested that individuals with increased levels of CRP were at an increased likelihood of becoming frail in a 3 year period. An important point to note is that most of these observational studies were carried out using female cohorts. Cytomegalovirus (CMV) infection was shown to be associated with the frailty syndrome in the WHAS I and II study and inflammation was shown to increase the effect of the infection on frailty [120]. Young adults are often infected with CMV and this is known to cause functional decline in later life. A longitudinal observational study by Wang *et al* [121] on community dwelling, older women showed that those with higher CMV Immunoglobulin G (IgG) antibody concentrations were at an increased risk of being frail and had an increased risk of

death. A recent study by Chang *et al* [122], showed an association between specific combinations of diseases linked to inflammation such as diabetes, anaemia, cardiovascular disease and chronic kidney disease, and frailty. A longitudinal study with a 5 year follow-up period by Aleman et al [123] in older adults (aged 60-84 years) free of sarcopenia showed a significant association between higher IL-6 and CRP and loss of skeletal muscle mass. Higher levels of WBC counts, neutrophils, monocytes, lymphocytes and ESR (Erythrocyte Sedimentation Rate) predicted frailty status after 10 years in the Hertfordshire Ageing Study on participants aged 65 to 70 years [124].

1.3.3 Hormonal factors

1.3.3.1 Sex hormones

It has been suggested that low testosterone (T) levels play a role in the development of frailty in older individuals [102, 125]. Results from the Massachusetts Male Aging Study (MMAS) failed to show an association between free or total T and frailty (assessed using a FP model) cross-sectionally, however, increased levels of sex hormone binding globulin (SHBG) were associated with frailty [126]. In the MrOS study [127], low bioavailable T was associated with frailty status cross-sectionally and predicted incident frailty, although the strength of the association was attenuated after adjustment for confounders. Tajar *et al* [128], using the EMAS cross-sectional data, showed that low total T and free T were associated with frailty. The results also showed that higher levels of luteinising hormone (LH), follicle stimulating hormone (FSH) and SHBG, and lower levels of Dehydroepiandrosterone sulphate (DHEAS) were associated with frailty status assessed by the FI. These results from EMAS suggest that increased frailty indicated by a higher FI was associated with primary testicular dysfunction as shown by increased levels of LH.

Longitudinal studies [62, 129] have shown an association between androgens, oestrogens, LH and the development of frailty. T has been shown to be associated with many aspects of frailty. For example, data has shown that men with low free T had a 57% greater risk of developing mobility limitation and a 68% higher risk of decline in mobility functions [130]. T may play a role in muscle function and growth [131], and erythropoiesis [132]. A decline in T has been linked with a decline in bone mineral density [133], hip fractures [134] and lower physical strength [135]. T replacement therapy has been suggested to improve quality of life and ameliorate many of the factors involved in frailty [136]. Srinivas-Shankar *et al* [137] was the first

to design a clinical trial specifically to study the effect of T on pre-frail and frail elderly men. The frailty criteria were measured by an adapted FP model. Their results showed that pre-frail and frail elderly men with low T or borderline T showed an increase in lean body mass, muscle strength and improvement in quality of life when treated with T replacement. In relation to oestrogen, low levels of oestradiol have been shown to be associated with increased frailty in women aged 65 to 79 years in the Toleda Study for Healthy Ageing [138]. In a cross-sectional study on American men aged over 60 years, total T, and total and free oestradiol were not associated with frailty, while low free T and increased SHBG were associated with frailty status, though adjusting for BMI and smoking attenuated this relationship [139]

1.3.3.2 Dehydroepiandrosterone (DHEA)

DHEA and Dehydroepiandrosterone sulphate(DHEAS) are produced in the adrenal cortex as precursors of sex hormones [140]. It has been suggested that DHEAS could be used as biomarker of ageing because it declines to about 80-90% in the third decade of the life and there is a gender difference where higher levels are seen in men than in women [141]. Sanders *et al* [141], found evidence of an association between DHEA and increased age in women and that it was a better predictor of cognitive decline than physical performance. DHEA has been shown to be associated with frailty [142], though interventional trials have not shown any improvement of function when subjects are given the hormone [143, 144]. Results from the longitudinal data of the study showed no cross-sectional association between low DHEAS and frailty (assessed by the SOF frailty index) in either gender, however, robust men with low DHEAS were more likely to become frail in 4 years [145]. Lower levels of DHEAS also predicted frailty status after 10 years in 254 community dwelling adults aged 65 to 70 years in the Hertfordshire Ageing Study [124].

1.3.3.3 Growth hormone (GH)

Growth hormone levels reach a maximum during puberty and thereafter decline with age [140]. The GH/IGF-1(Insulin like Growth Factor-1) axis has been found to be associated with muscle mass, strength and function, though the associations are poorly understood [146, 147]. Studies on the association of growth hormone and frailty are limited. Cappola *et al*, explored the effect of multiple hormonal deficiencies on frailty syndrome in the WHAS I and II. IGF-1 was one of the hormones considered and the results suggested that frail individuals were more likely to be deficient in IGF1, although the association was not significant (Odds Ratio

[OR] 1.82, confidence interval [CI] (0.81-4.08) [148]. Further, growth hormone replacement therapies have failed to show significant improvement in aged individuals and has been known to cause many side effects [149]

1.3.3.4 Metabolic Hormones

Frailty has been associated with factors linked with metabolic syndrome (MetS) such as Diabetes Mellitus, hypertension, cardiovascular disease, congestive heart failure, atherosclerotic vascular disease and obesity [114, 150]. Most of the studies exploring frailty status and MetS components have been based on the CHS and WHAS I and II where frailty has been measured using the FP model. Cross sectional studies have shown an association of insulin resistance, hyperglycaemia [151] and components of the metabolic syndrome (MetS) [114]. Results from the WHAS I and II showed that hyperglycaemia assessed by increased glycosylated haemoglobin (HbA1c) levels predicted frailty incidence and limitation of lower extremity body function [152]. Barzilay *et al* used the data from the CHS to explore whether components of the MetS and insulin resistance (IR) assessed by the IR-HOMA process predicted frailty incidence. Metabolic syndrome was defined as being present if 3 or more of the following criteria were present: triglycerides level ≥1.7mmol/L; high density lipoprotein cholesterol (<1mmol/L for men and <1.3mmol/L); blood pressure of 130/85mm/Hg or treated for hypertension; fasting glucose level ≥6.1mmol/L; waist circumference >102cm for men and 88cm for women. The results showed that IR and CRP predicted frailty incidence, however, in this case, MetS failed to show any significant association with frailty incidence. Another study on frail patients from a geriatric unit showed that IR was associated only with frail subjects who were centrally obese with increased abdominal fat mass [153]. A possible mechanism linking frailty to the metabolic diseases is suggested to be through sarcopenia which is a major component of the frailty syndrome. However, results from a Chinese cohort of older adults showed that physical frailty, assessed by 5 physical function tests, was associated with diabetes, heart disease, stroke and high WHR independent of cognitive function and muscle mass, suggesting that metabolic diseases and any link to frailty are independent of the role of muscle mass and sarcopenia [154]

1.3.3.5 Low vitamin D

Puts *et al*, reported an association between low serum 25(OH) D levels and frailty [119]. Hirani *et al* [155] in the Concord Health and Ageing in Men (CHAMP) cohort study showed an

association between 25hydroxyvitamin D and 1,25dihydroxyvitamin D and frailty. Of the frailty components there was significant association with weakness, exhaustion, slowness and low activity. Vitamin D deficiency was also shown to have significant associations with other health problems and adverse effects related to the frailty syndrome such as osteoporosis, myopathy [156], disability [157, 158], sarcopenia [159, 160], risk of institutionalisation [161] and falls [162]. Vitamin D deficiency has been shown also to have a strong association with an adapted FP in community dwelling older adults in Northern Taiwanese community [163] in a cross-sectional analysis. In the European Male Ageing Study (EMAS), frailty assessed using both the FP and FI showed an association with low levels of serum 25 (OH) Vitamin D and higher levels of para-thyroid hormone in a cross-sectional analysis [128]. Other cross-sectional studies have also shown an association of frailty status with low vitamin D levels [164, 165]. Ensrud *et al*, showed that low vitamin D levels were associated with prevalent frailty (FP model) but baseline low levels of vitamin D did not predict frailty status at follow-up in men in the MrOS.[166]. However, when they explored the association of low vitamin D levels and frailty status in women in the SOF study they found a "U" shaped relationship with low levels and higher levels of Vitamin D associated with prevalent frailty status and low levels of vitamin D predicted frailty incidence. It was suggested this association of higher levels of vitamin D in frail older women may possibly due to vitamin D supplementation taken by frail women [167]. In the HIMS study, low vitamin D levels showed an association with frailty, assessed using a FRAIL scale, cross-sectionally as well as predicted frailty incidence after 5 years [168]. In the InCHIANTI ((Invecchiare in Chianti, aging in the Chianti area) study [169], transition in frailty (an adapted FP model) states and vitamin D levels were explored. The results showed that individuals in the pre-frail state with low levels of vitamin D were more likely to become frail or die, suggesting perhaps that vitamin-D could be used as an intervention to prevent further deterioration in frailty status.

1.3.3.6 Allostatic load and multiple hormone dysfunctions

Another model which had been proposed to understand the biology of the frailty syndrome is a theory based on allostatic load (AL). This theory suggests that a degree of wear and tear processes occur in multiple systems as a result of responding to external and internal stress resulting in biological imbalance in the individual. When the degree of wear and tear reaches a maximum limit the person is at an increased risk of adverse outcomes [170]. Allostatic load consists of a summary score of 10 biomarkers across multiple systems [171]

which has been used as an example of multiple system dysregulation. Studies have shown an association of allostatic load to an increased risk of frailty, where frailty was assessed using the FP [172, 173]. Cappola *et al* [148], in a study of aged women, showed that pre-frail and frail individuals had more hormonal deficiencies than robust individuals.

In intervention studies single hormonal replacement in older patients to match the levels in young adults had led to disappointing results. This is likely due to the fact that individual hormones do not work independently but by interacting in multiple hormonal axes [174]. This theory was further explored by Fried *et al* [175], who showed that the number of abnormal physiological systems was related nonlinearly to frailty, and suggested when the physiological dysregulation reaches a thresh hold, frailty would be clinically obvious. Although studies have shown an association between number of biomarkers and frailty status suggesting many potential pathways, there appears to be no single pathophysiological mechanism explaining the biology of the frailty syndrome [117].

1.3.4 Micronutrients

There is some evidence that micronutrient deficiency may play a role in causing frailty. Malnutrition is a common problem in the aged, due to difficulty with swallowing, loss of appetite due to changes in taste and smell and also reduced income in older adults [102]. In a study conducted in older women a decrease in serum micronutrient concentration in particular serum carotenoids was observed with change in frailty status from pre-frail to frail, when frailty status was assessed using the FP model [176]. The results also suggested a significant association between deficiencies in vitamin B12, α-carotene and 25-hydroxy vitamin D (25(OH) D) and frailty in older women. This was further verified in a longitudinal study conducted by Semba *et al* [177], which showed that micronutrient deficiencies increased the risk of being frail and could be used to predict frailty. The result remained constant even after eliminating unintentional weight loss from the frailty criteria.

1.3.5 Sarcopenia

Loss of muscle mass which occurs with ageing has been suggested to play a key role in the development of the frailty syndrome [5]. Irwin Rosenberg in 1989 used the term sarcopenia to describe age related loss of muscle mass, which is the (the term being derived from the Greek word for “sarx”=flesh and “penia”=loss) [178]. The interrelationship, however between loss of muscle mass and loss of muscle strength (dynapenia) is not very clear [179]. Hence,

recent definitions of sarcopenia have included a measure of muscle mass and also a measure of muscle strength. Three definitions of sarcopenia have been proposed, of which The European Working Group on Sarcopenia in Older People (EWGSOP) is probably the most widely used. In this definition, sarcopenia is defined as a reduction in muscle mass (below a fixed threshold) together with either reduced muscle strength or low physical performance [180]. Another group proposed that a working definition of sarcopenia should be considered in individuals who are bedridden, those who are unable to rise independently from a chair, or those who have a gait speed less than 1m/s. Individuals identified in this way should undergo further body composition assessment using dual energy x-ray absorptiometry to assess sarcopenia [181]. The European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG) suggested the diagnosis of sarcopenia to be the presence of low muscle mass and low muscle strength assessed by walking speed [182]. The prevalence of sarcopenia varies widely in the literature depending on the population studied and the different methods used to assess muscle mass, strength and physical performance [181, 183]. Prevalence of sarcopenia using the EWGSOP definition varied from 1-33% in different populations; prevalence was higher in older people and in those who were more ill [183]. The causes of sarcopenia are multifactorial with lack of physical activity a major cause [184]. Sarcopenia has been associated with an increased risk of mortality [185, 186], falls [187] and disability [188]. Another concept which has gained extensive attention in recent years is the co-existence of low muscle mass together with high fat mass which results in reduced muscle strength. This has been termed as sarcopenic obesity [189-193]. Although sarcopenia may play an important role in the development of the frailty syndrome they are not the same condition [194]. Although most frail individuals may show symptoms of sarcopenia and individuals with sarcopenia may be frail, the concept of the frailty syndrome is multidimensional and is not restricted to physical symptoms as it may also include cognitive, psychological, social and environmental factors [195].

1.4 Epidemiology of Frailty

1.4.1 Prevalence

The prevalence of frailty varies depending on the criteria used to classify frailty [83, 196, 197]. In the CHS the prevalence of frailty in community-dwelling older adults living in United States was 6.9% [5]. In a cohort of community dwelling older adults living in St. Petersburg, Russia, the prevalence of frailty ranged from 21% using the FP and 44% using the Put's frailty

model [83]. In the SHARE cohort a study across 10 European countries, frailty prevalence overall was 4.1% [29]. In a recent systematic review, which used cross-sectional data across 21 studies in 61,500 participants aged over 65 years, the frailty prevalence ranged from 4.0-5.9%[196, 197].

1.4.2 Influence of age and gender

Almost all of these studies have shown that frailty prevalence increases with age [100, 196, 198] and the majority have shown that females have a higher prevalence of frailty than men, although men tend to have a shorter period of frailty and die sooner whereas in females there tends to be a steady decline and longer period of frailty before death [57]. These gender differences may be because women have lower lean mass compared to males which might contribute to sarcopenia being more common or to an effect of survival as women tend to live longer than men. It is rare for those who are frail to improve and become fit. Individuals who are frail are more likely to decline and ultimately face adverse outcomes [199].

1.4.3 Influence of race and ethnicity

The prevalence of frailty varies in different population groups [200]. It is not clear whether this variation observed are due to the difference in socio-economic status across ethnic groups or due to cultural or other differences across ethnic groups which may exhibit higher prevalence of certain comorbidities such as diabetes, etc. When Hirsch *et al* [201], used the CHS data and phenotype definition of frailty, showed that frailty was more common among the older African Americans than Caucasians. Some of the population differences in frailty prevalence may be due to methodological factors. Espinoza *et al* [202], showed that frailty transitions or worsening of frailty status was similar in both Mexican American (MA) and European American (EA) older adults. In a previous study [203] on the same cohort, the results suggested when frailty was assessed using an adapted FP on the entire cohort (MA and EA) frailty prevalence was higher in MA older adults. If however ethnic specific criteria were used to define frailty characteristics there were no differences in frailty status. A higher prevalence of frailty was noted in southern European countries than in northern Europe in the SHARE cohort [204].

1.4.4 Influence of socioeconomic status

Szanton *et al* [205], used data collected from the WHAS I and II to determine the effects of low socioeconomic status on frailty independent of smoking, illness, insurance status and

race. Frailty was measured using the FP model [5]. Education and income were used as modes of measuring social economic status. The results showed that there was a significant association between socioeconomic status and frailty even after adjusting for confounders including age, race, illness, insurance status and smoking status. The limitations of the study were the cross sectional design and the fact that the cohort comprised only women. Lang *et al* [206], used the ELSA data to show that individuals aged 65 years and over who were poorer and lived in deprived neighbourhoods had a higher FI. Other studies which reported the relationship between frailty and socioeconomic status include the CHS by Fried *et al* [5]. In this study frailty was higher in people with lower socio economic status and people who had poorer health. In the three city study [28] frail individuals were more likely to be older, female, have more health problems, live alone and have a low income. The SHARE study also showed a strong association between frailty and education as well as a link to social inequalities and lower income [207], and survival of frail individuals was higher in higher income countries. Analysis carried out on the Hertfordshire Cohort Study [208] with 482 participants, showed an association between lack of emotional and physical support in close relationships at baseline and the risk of developing frailty after a mean of 4.4 years in women. No association was seen in men. In a population study in North-East Spain on older adults aged >74 years, a social frailty phenotype (defined if 2 or more of the following were present: *living alone,*Lack of contact with family or friends, *lack of a person to help with activities of daily living, *infrequent contact with family, *infrequent contact with friends, *absence of a confidant, *lack of support for daily living during the past 3 months) was only significantly increased in widowers and making them to be socially disadvantaged and vulnerable [209]. Gu *et al* [50] used the Frailty Index to measure frailty in the Chinese population and showed that there was an inverse association between frailty and exercise and being a part of religious group. There was only a weak association of frailty with education, occupation and being married and being close to offspring.

1.4.5 Outcomes of frailty

The most common outcomes associated with frailty are mortality, disability, falls, hospitalization, use of health care services, decreased quality of life, decline in physical function and institutionalisation [210]. A systematic review on the association of frailty with survival in 24 studies on community-dwelling adults aged 65 and over showed that frailty was associated with mortality, the average mortality risk when compared to non-frail individuals, using a FP definition

was 50% and a FI definition 15% [197]. In another systematic review which identified 27 frailty instruments, mortality varied by the frailty instrument used. For the FP hazard ratio/odds ratio for mortality risk for frailty compared to non-frail varied from 1.2 to 6.0 and for the FI it varied from 1.6 to 10.5 [4].

1.5 Lifestyle determinants of frailty

A number of factors have been linked with the occurrence of frailty either cross-sectionally or prospectively. A better knowledge of the factors linked with frailty is important and may help in determining who is at risk of developing frailty and also may aid the development of targeted interventions and population strategies to reduce the occurrence of frailty and its adverse consequences.

1.5.1 Smoking

Hubbard *et al* [211], looked at data from the Canadian Study of Health and Aging (CSHA) a longitudinal study of over 9,000 community dwelling older adults to explore the effects of smoking on frailty status, (assessed using the FI) [43]. Smoking status was assessed using a self-assessed risk factor questionnaire. Heavy smokers had a higher FI compared to light smokers and non-smokers. Excluding those with health problems related to smoking, smokers still had a higher FI than non-smokers supporting the view that smoking leads to general ill health and contributes to frailty. Results from the Beijing Longitudinal Study of Aging showed that men who were smokers were frailer (mean FI=0.17) compared to men who were non-smokers (mean FI=0.13). Such an effect was not observed in women, although women who smoked had similar survival rates to male non-smokers. Also a 34% increase in the FI was reported over the 15 year follow-up period and the FI was higher in those who smoked at baseline [212]. Studies have shown that smoking causes increased inflammation [213], decrease in muscle strength and lower physical function [214], all of which are major contributors for the onset of frailty and a potential mechanism by which smoking confers apparent increased susceptibility**.**

1.5.2 Physical Activity

Physical inactivity has been linked to frailty in studies [72, 215, 216] and also the hours spent on leisure time physical activity in mid-life predicted frailty and pre-frailty in the Helsinki Business Men (HBM) study [217]. Studies have shown a link between low physical activity and components of frailty especially the development of sarcopenia [185]. In a population of

institutionalised older adults aged >=70 years, sarcopenia was less prevalent in those who took part in leisure activity for one hour or more/day. Rockwood *et al* [198] used the Geriatric Status Scale (measures cognitive and functional items of an individual) to assess frailty in the CSHA to show that fitness and frailty in a continuous scale. Exploring the association between low physical activity and frailty status is complicated especially when it is a component of the frailty model in the case of FP. One mechanism suggested to link low physical activity to frailty is that acute events such as stroke or myocardial infarction reduce physical capacity leading to a decrease in physical capacity, and further decline. It has also been suggested that an increase in physical activity can delay or prevent ill health by increasing baseline fitness levels, prevent chronic conditions, improve recovery after an acute event and slow the rate of physical decline which occurs with ageing [218].

1.5.3 Obesity

The prevalence of obesity is increasing across all age groups [219] and is considered a growing threat to health in older people [220, 221]. There are more than 1 billion overweight adults across the world, and of those 300 million are obese [222]. Studies have shown that overweight and obese individuals are living longer due to improved medical care but their disability free years are fewer than those of normal weight [223]. Obese older adults will probably have similar life expectancies to their normal weight peers due to advances in medicine and treatment for obesity related conditions, but these individuals will experience additional healthcare costs, increasing the burden on public health care systems [224, 225].
Obesity has become a major public health concern in recent times, in part due to an increasing tendency to a sedentary lifestyle and also the increasing availability of cheap high fat food. Obesity is likely to be due to a combination of genetic and environmental factors [226]. There is also increasing evidence of a relationship between obesity and socioeconomic status [227].

In 1989, Sobal and Stunkard reviewed 144 published studies on the relationship between obesity and socioeconomic status (SES) in developing and developed countries. In developed countries they found that women of lower SES were more likely to be obese though the relationship between obesity and SES among men and children was not consistent. However, in developing countries individuals (men, women and children) of higher SES were more likely to be obese [228]. The most recent review looking at the association of obesity and SES was carried out by Dr. Lindsay McLaren in 2007 [229]. Her findings suggested that women

of lower SES in developing countries were more likely to be obese; however, this relationship was not as strong as that seen in earlier reviews. McLaren suggests that a possible explanation for this difference may be that although women in higher SES groups would prefer to be thin, they may find it difficult to maintain their weight in the present obesogenic environment. The relationship between SES and obesity in men was similar to previous findings and was inconsistent.

A recent Korean Study showed a significant association between higher obesity and unemployment [230]. In a study using the SHARE cohort to explore the prevalence of obesity and health related conditions in Europeans aged 50 years and older, the difference in the prevalence of obesity across the different countries could not be explained by socio-demographic differences [219].

1.6 Obesity and Frailty

Obesity can be defined as an increase or the excess fat mass for a given body weight and is associated with an increased risk of comorbidities [231], and also associated with difficulties with daily living activities and lower quality of life [232, 233]. The WHO defines obesity as having a body mass index (BMI=weight of an individual/height^2) of ≥30 kg/m^2. In population studies, obesity is linked with a variety of adverse health outcomes, including diabetes, cardiovascular disease and osteoarthritis. However, obesity in older adults has been shown also in some studies to be protective [234] against adverse life events including the risk of osteoporosis, falls and mortality [234-236]. A reduced risk of mortality in the obese elderly does not imply, however, that obesity is not harmful in the aged. Possible reasons include the fact that BMI may not be an accurate measure of excess adiposity in the elderly [237], or due to a survival effect, those who are obese for a long period might have shorter life expectancy hence do not reach old age and those who were obese and survived might have inherited genes of longer life expectancy [238].

Traditionally, geriatricians were more concerned about unintentional loss of weight in older adults aged over 80 years living in nursing homes, as these elders were more likely to have problems consuming food due to swallowing, lack of teeth, comorbidities, assistance with feeding and other health problems [239]. Increasingly, however there are reports of overweight and obesity in older adults even in nursing homes [240]. Age related body composition changes are not simply a result of excess calorie consumption and reduced energy expenditure they also

include changes due to hormones related to metabolism, neuromuscular, pro-inflammatory cytokines, oxidative stress, mitochondrial dysfunction, apoptosis pathways, genetics and also dietary changes [223, 241]. In addition, there are body composition changes which occur during ageing including a decrease in lean mass and increase in distribution of fat mass especially in the region of the abdomen and a decrease in subcutaneous fat [242]. There is good evidence that the distribution of adipose tissue in the body impacts on outcomes. Abdominal obesity for example, specifically, is a risk factor for many comorbid conditions including high blood pressure, diabetes, stroke, obstructive sleep apnea, urinary incontinence, cancers and coronary artery disease [243, 244].

An association between obese older adults and frailty is not widely recognised because as discussed previously frailty considered to be a wasting syndrome and the image of a frail individual is that of being thin, weak and exhausted. However, overweight and obese individuals also face loss of muscle mass with age [245] with fat replacing muscle mass with age [246] hence the problem arises of the fat frail. It has been suggested the fat frail be the most common phenotype of frailty in the future [246]. Obesity and frailty are closely related, as they are both multifactorial conditions and share similar outcomes such as loss of physical function [247, 248], and are associated with increased inflammatory markers such as CRP and IL-6 (9) and also linked with lower anabolic hormones [249] and decreased growth hormone [250]. A decrease in lean mass together with an increase in fat mass in the elderly may result in physiological changes resulting in frailty [251]. Also, muscle quality and strength reduces with fatty infiltration of muscle, which occurs with ageing [252]. An ageing individual with a higher body composition is more likely to have loss of physical function leading to disability [253] and frailty. Both frailty and obesity have been linked to similar comorbid conditions. Studies have shown an association of frailty with cardiovascular diseases [97] metabolic syndrome, insulin resistance [115] and hyperglycaemia [152], conditions linked also with obesity. Goulet *et al* [153], studied 54 elderly participants who were grouped into Healthy Non-obese (HN), Frail Lean (FL) and Frail Obese (FO) and found that Insulin Resistance (IR) was only significantly associated with FO, and this association was attenuated after adjustment for abdominal fat suggesting it to be the main factor in developing IR. FL did not show any difference in IR compared to the HN. The obese elderly also have problems with ADL, chronic pain and poorer quality of life [254, 255] which are in turn associated with frailty [256, 257]. Wu *et al* [258], showed in a cross-sectional

study in older community dwelling adults and those visiting hospital clinics, that frailty status assessed using the FP was positively associated with increased age, depression, waist-hip-ratio, CRP levels and oxidative stress, and negatively associated with lower serum albumin levels. They suggested that oxidative stress may play a role in the development of frailty through increased adiposity and inflammation.

Epidemiologic studies have suggested that obesity is associated with frailty. Hubbard *et al* [259] used data from the English Longitudinal Study of Ageing (ELSA) to show that cross-sectionally individuals with both high and low BMI, as well as high waist circumference, had an increased prevalence of frailty assessed by both an FI and the FP model. Blaum *et al* [150] used data from the WHAS I and II studies to show that frailty is associated with high BMI independent of comorbidities and inflammation. They also demonstrated that overweight individuals were more likely to be pre-frail. Women in the underweight (<18.5 kg/m^2) category were excluded from the study. The relationship between obesity and frailty is however, complex as it is likely that being overweight tends to make people less physically active and have poor health, hence confounding the relationship and making it unclear whether frailty or being obese causes the problems with health and therefore making it unclear, hence prospective data are needed. Shah *et al* [260], found in older adults with Human Immunodeficiency Virus (HIV) that central obesity, especially truncal fat mass, and high BMI are associated with the frailty syndrome. Cesari *et al* [251] used the data from the InCHIANTI study to examine the association of frailty with skeletal muscle mass among 923 participants aged 65 to102. Peripheral quantitative computerized tomography (pQCT) scans were used to measure muscle and fat, and an adapted FP model was used to assess frailty. The results showed that frail individuals had increased fat mass and lower muscle density and muscle mass. This association remained even after adjustment for the inflammatory markers IL-6, CRP and Tumour necrosis factor-alpha (TNF-α).In addition, of the frailty components, walking speed and physical activity were more strongly related to changes in body composition. This study suggests that fat infiltration into muscle may contribute in developing frailty. The main limitation of the above study was its cross sectional design for which cause and effect cannot be determined as for this longitudinal data is required.

Villareal *et al* [261], studied 156 community dwelling elderly subjects to determine the association between body composition, physical activity and quality of life. They were able to

identify obesity as the major cause of physical frailty. In addition, they also found that frailty in these obese older adults may be possibly due to decreased and poorer quality muscle mass. There have been contradictory data from studies, suggesting that obesity or excess fat in older adults may be beneficial, i.e., an increased bone mineral density in obese individuals helps reduce risk of fractures from osteoporosis and general fractures as the excess fat provides some protection. Studies have also shown that in a period of less energy/starvation/reduced nutrient intake in an individual, those with excess fat lose less lean mass initially [234]. However, the data collected by Villareal *et al*, suggests that even though there is less muscle loss associated with ageing for the obese elderly, this extra muscle mass is not sufficient to maintain efficient physical function [261]. This study [261] has also shown that the obese elderly had poorer quality of life determined by the SF-36 questionnaire. A case-control study [262] on frailty in men on androgen deprivation therapy (ADT) used a modified FP model where the weight loss criterion was redefined as weight gain, indicated by having a BMI >30, as it was found that the weight loss component of the frailty syndrome does not apply to this cohort as men on ART gain weight and are more likely to be obese frail.

Sarcopenic obesity is the term used to describe the process of lean muscle mass loss and the increase or maintenance of fat mass [193]. While this occurs with ageing, until recently, importance was only given to loss in muscle mass. It is increasingly evident that the composition of the muscle is also of equal importance, as fat infiltration into muscle may cause low muscle quality and strength which in turn causes a decline in physical function [246]. A few longitudinal studies have looked at the association between obesity and frailty. Being obese or overweight in midlife predicted frailty after 26 years in the Helsinki Business men study [263] and obesity also predicted frailty status after 22 years in the mini- Finland health survey [264], after adjustment for confounders. In both studies, obesity was assessed using WHO cut-points defined by BMI. However, BMI has been suggested not to be an accurate measure in the elderly due to its inability to differentiate lean mass versus fat and due to age related changes in body composition, such as loss of lean mass, bone, height and rise in fat mass [265]. In the Women's Health Initiative study, Woods *et al* showed that underweight, overweight and obese women were at higher risk of frailty and pre-frailty compared to those of normal weight after 3 years [266]. Here too BMI was used to assess body composition. In all three studies mentioned above frailty were assessed using adapted FP models.

1.7 Summary

Frailty is an important clinical and public health problem and is linked with an increased risk of falls, institutionalisation and mortality. There remains a lack of agreement on a standard definition and operational classification for frailty. A number of classification criteria have been proposed, though there are few data comparing these methods in prospective studies particularly among men. The mechanism or cause of frailty remains unknown, though it is likely to be a result of multiple dysregulations across multiple systems. A number of factors have been linked with frailty, though relatively little is known about the impact of lifestyle factors on the new occurrence of frailty. Obesity has been linked with frailty, and although it is uncertain whether this is a causal association such data are important, as the prevalence of obesity is increasing. Furthermore, most studies have focused on BMI only, which may not be an optimum marker of adiposity in older adults.

The broad aim of the work described in this thesis was to determine the incidence of frailty among middle-aged and older European men, and the impact of measures of adiposity (BMI, WC, WHR and body fat) on the development frailty.

Chapter 2 Aims and Objectives

2.1 Broad Aim

The broad aim of this thesis is to determine the incidence of frailty among middle-aged and older European men and the impact of measures of adiposity on the development frailty.

2.2 Specific objectives

The specific objectives are to:

- Adapt and validate classification criteria for a 'FRAIL scale', based on a combination of the Fried Phenotype definition and the presence of comorbidities, in a community-based sample of middle-aged and older men.
- Determine how the FRAIL scale compares with other frailty definitions operationalised in the European Male Ageing Study (EMAS), including the Fried Phenotype and Frailty Index definitions with respect to the occurrence of frailty.
- Determine whether frailty defined using the FRAIL scale and other frailty definitions operationalised in EMAS predicts the development of adverse outcomes, including mortality, falls and health care utilisation.
- Determine the cross-sectional association between frailty status and anthropometric measurements of adiposity, including body mass index, waist circumference, waist hip ratio and percentage body fat.
- Determine, using different frailty models, the incidence of frailty in a cohort sample of middle aged and older men.
- Determine whether baseline measures of adiposity, including body mass index, waist hip ratio, percentage body fat and waist circumference, predict the incidence of frailty.

Chapter 3 Methods

3.1 Summary

Subjects who contributed data to the analysis presented in this thesis were recruited for participation in the European Male Ageing Study (EMAS). The design and methods of the EMAS study, including the baseline and follow-up phases, are described in the first part of the chapter. A description of the methods which were used to develop the Frailty Index and Frailty Phenotype in EMAS are described in the second section. The chapter concludes with a summary of what is covered in subsequent chapters and also the specific role of the candidate in achieving the aims and objectives of the thesis.

3.2 Design

The EMAS is a multicentre, population based prospective study looking at symptoms and biological correlates of ageing, in men aged 40 to 79 years, and was funded by the European Commission fifth framework Programme, 'Quality of life and Management of living resources'. There were two phases, a cross sectional phase which took place during 2003-2005 and a follow-up phase which took place during 2007-2009. Ethical approval for the study was obtained at each of the participating centre according to local requirements and regulations and written informed consent was obtained from all participants [267].

3.3 Setting

The eight European centres who took part in the study were selected based on their research background and interests in male health, as the major aim of this study was to investigate the symptoms of male ageing. They were: Florence (Italy), Manchester (UK), Szeged (Hungary), Leuven (Belgium), Łódź (Poland), Malmö (Sweden), Tartu (Estonia) and Santiago (Spain), as shown in Figure 3.1.

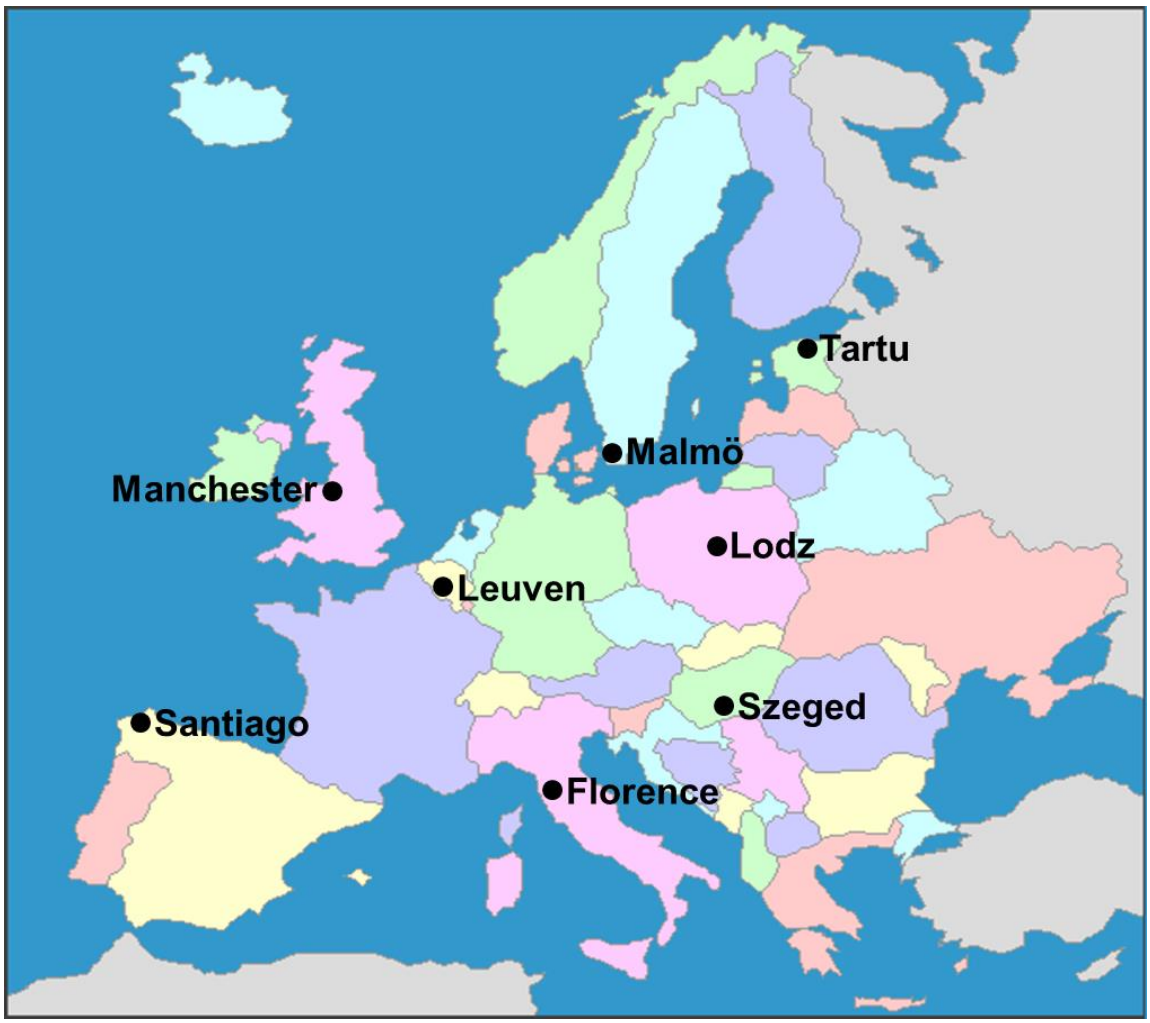


Figure 3.1 European Male Ageing Study Centres

3.4 Recruitment

Each of the eight centres was asked to recruit 100 men in each of four age groups (40-49 years, 50-59 years, 60-69 years and 70-79 years) from a population based register. The population registers used are summarised in Table 3.1. Stratified random sampling was used to identify subjects within each age group from the sampling frames. Those who were identified as possible subjects were contacted by mail. This included an information pack about the study, a short postal questionnaire (PQ) and an invitation to attend for a screening visit. Those who agreed to participate were invited to attend a local clinic for further questionnaires, assessment of cognitive and physical function, anthropometric measurements and a fasting blood sample. A detailed description of the instruments is provided in Appendix 1. Those who did not respond were sent a further letter of invitation. In total 8,416 men were invited to participate of whom 4,993 replied. 3963 men returned the postal questionnaire of which 3,369 participated in the full study. After adjusting for those who died or moved (in centres in which it was possible to identify these) the overall response rate was 41%. Response rate varied by centre, (Table 3.1) [267].

Centre	**Register**	**Participation rate [a] (%)**
Florence	Primary care	61.5
Leuven	Electoral	38.6
Łódź	City registers	52.4
Malmö	Population	46.9
Manchester	Primary care	38.8
Santiago	National register	37.9
Szeged	Electoral	24.1
Tartu	Primary care	59.2

Table 3.1 Sampling Frame and baseline participation rate by centre [268]**.**

[a] Adjusted participation rate after excluding those who died or moved house

3.4.1 Non-responders

For participants who did not respond after two contact attempts, a sub-sample of 361 subjects were invited to take part in a brief telephone survey. The survey included questions from the PQ relating to health status, education, physical activity and smoking status. Compared to the participants, the men who responded to the telephone survey were more likely to be current smokers and to have had a lower number of years in education.

3.5 Baseline Assessments

3.5.1 Postal Questionnaire (PQ)

The PQ included questions about general health; lifestyle was collected including, smoking status, frequency of alcohol consumption, and level of physical activity. Information was also obtained about comorbidities subjects were currently being treated for, including a history of cancer or stroke and any fractures since the age of 25 years.

3.5.2 Interview-assisted Questionnaire (IAQ)

Subjects who agreed for further assessment were asked to complete an interviewer-assisted questionnaire that included several validated instruments. The Short Form 36 (SF-36) questionnaire [269] was used as a measure of health-related quality of life and symptoms of depression were assessed using the Becks Depression Inventory (BDI) [270]. Additional instruments included the Adverse Life Events Scale [271], the Physical Activity Scale for the Elderly (PASE) [272], and the International Prostate Symptom Score [273] to assess lower urinary tract symptoms. An optional sexual function questionnaire [274] was also included. Following completion of the interviewer-assisted questionnaire all current prescribed and non-prescribed drugs were recorded and verified by inspection of the drugs brought in by the subject. Any history of previous surgery was also recorded. A detailed description of the questionnaire is provided in Appendix 1.

3.5.2 Physical and Cognitive performance

3.5.2.1 Physical Performance Tests

Physical function was assessed using Reuben's Physical Performance Test (PPT) [275] and gait and balance measured by the Tinetti [276] test for balance and postural stability. As part of the Reuben's PPT the time taken to complete a 50 foot walk was measured. A component of the Tinetti test was the sit to stand test, which is a timed test measuring the ability of the subjects to rise from a chair unaided without using their arms. Subjects were asked to repeat this five times.

Cognitive function was assessed by three neuropsychological tests which were chosen to be language neutral. These were, in the order they were administered, the Rey-Osterrieth Complex Figure (ROCF) [277] test, the Camden Topographical Recognition Memory test

(CTRM) [278] and the Digit-Symbol Substitution test [279] (DSST). These tests measure visual perceptual abilities and memory, the recognition component of visual memory and speed of processing information, respectively. The ROCF involves the subject being shown a design and asked to copy this diagram. The time the subject takes to do this is recorded. Then after 30 minutes, they are asked to recall what they originally drew and redraw the image from memory without any cues. The CTRM is a test of visual recall which involves the presentation of 30 colour photographs of urban scenes, each for 3 seconds, followed by a three-way forced recognition component (30). The DSST is a coding test with subjects asked to make as many correctly coded digit letter substitutions as possible over a one-minute period.

3.5.2.2 Anthropometry

Height was measured to the nearest 0.1 cm using a calibrated Seca Leicester Stadiometer. Measurements were repeated twice and the highest reading recorded. Body weight was measured to the nearest 0.1 kg using a calibrated SECA model electronic scale. Body mass index was calculated as weight in kg divided by height in m^2. Further measurements of body circumferences were carried out using anthropometric tape. All measurements were made on the LEFT side of the body, repeated three times and the median recorded. Waist circumference was measured between the tips of the lowest ribs and the tips of the hipbones. Hip circumference was measured as the widest part of the hips. Mid-calf circumference was measured as the area between the top of the knees and the malleolus. The mid upper arm was initially identified as midway between the top of the arm and the tip of the elbow, and the anthropometric tape placed horizontally to measure the mid upper arm circumference. Skin fold thickness was measured with callipers from Holtain (UK). Skin fold thicknesses were obtained from the biceps, triceps, and sub scapular and supra iliac regions. Three readings were taken and the median of these readings recorded.

3.5.2.3 Other assessments

Dual-Energy X-ray Absorptiometry (DEXA) scans were performed in a subset of 800 men in Leuven and Manchester. Assessment permitted ascertainment of lean and fat mass. Resting pulse and blood pressure were recorded in all subjects once on the non-dominant side of the subject using an Omron 5001 (Omron Healthcare (UK) Ltd).

3.5.2.4 Blood samples and processing

Fasting blood samples were obtained from the subjects before 10 am, either at the clinic or at the subject's home. Samples were stored at 0-4ºC prior to processing and subsequently at -80ºC for long-term storage. Samples were forwarded to three laboratories for specific analyses Florence (Italy) (reproductive hormones), Santiago (Spain) (metabolic hormones) and Manchester (genetic analysis). General laboratory tests, including full blood count, profile, glucose, lipids and prostate-specific antigen were carried out in the local clinics of each centre.

3.6 Follow-up (2007-9)

Participants were contacted for a follow-up assessment approximately 4 years after their initial EMAS visit (median 4.3 years, range 3.0-5.7 years). The instruments used were identical to those at baseline were used, though additional exposures were assessed: (changes are summarised in Appendix 1).

3.7 Attrition

During the 4 year follow-up there were 193 deaths. Of the 3176 surviving men invited to the follow-up, 2736 participated, 106 (3%) were unable to attend due to poor health or were now living in some form of institutional care, leaving 334 (10%) who were lost to follow-up. The follow-up rates varied by centre and were highest in Malmö (94.4%) and lowest in Tartu (77.2%). The overall follow-up rate adjusted for mortality was 86.2%, (Table 3.2). Similar, response rates have been reported in other [280, 281] longitudinal multicentre studies in Europe.

Centre	Baseline cohort n (%)	Died n (%)	Non responders ∫ (unable to participate)	Lost to follow-up n (%)	Retained n (%)	Follow-up rate [a] (%)
Florence	433	16 (3.7)	25 (5.8)	38 (8.8)	354 (81.8)	84.9
Leuven	451	17 (3.8)	14 (3.1)	31 (6.9)	389 (86.3)	89.6
Łódź	408	50 (12.3)	9 (2.2)	38 (9.3)	311 (76.2)	86.9
Malmö	409	13 (3.2)	4 (1.0)	18 (4.4)	374 (91.4)	94.4
Manchester	396	16 (4.0)	7 (1.8)	45 (11.4)	328 (82.8)	86.3
Santiago	406	22 (5.4)	10 (2.5)	58 (14.3)	316 (77.8)	82.3
Szeged	431	32 (7.4)	15 (3.5)	33 (7.7)	351 (81.4)	88.0
Tartu	435	27 (6.2)	22 (5.1)	71 (16.3)	315 (72.4)	77.2
Total	3369	193 (5.7)	106 (3.2)	332 (9.9)	2738 (81.3)	86.2

Table 3.2 Follow-up rates: by centre [268]**.**

[a] Participation rate adjusted for mortality

∫ Non responders reported they were unable to take part due to poor health or living in an institution

3.8 Follow-up assessments

The follow-up assessments were similar to the baseline assessments, with a number of modifications and additions. In contrast to the baseline survey, the information on the age at which the subject left education and their occupation were not included. A question was also asked on how many falls the subject had had in the past 12 months. Additional questions were also asked to assess hearing loss and the number of visits to a doctor.

3.9 Development of the frailty models in EMAS.

This section describes the development of the frailty models in EMAS [282, 283].

3.9.1 Frailty Phenotype

The Frailty Phenotype (FP) proposed by Linda Fried is the most commonly used model to measure frailty in the literature. This was originally developed and validated in the Cardiovascular Health Study (CHS) [5] and has been modified in different data sets to assess frailty [26, 28]. As variables used in the original FP operational definition were not available in the EMAS data set, equivalent measures were identified and the EMAS FP model developed using these. As outlined in the introduction this comprised five criteria. These criteria and cut-points are presented in Table 3.3.

3.9.2. Frailty Phenotype in EMAS

The development of the EMAS FP was undertaken as part of a doctoral thesis by Matthew O'Connell [282]. The EMAS variables used to derive the criteria and the cut-points are shown in Table 3.3. For the sarcopenia criteria, the mid arm muscle circumference was used after subtracting skin fold thickness (mid arm muscle circumference = arm circumference - π triceps skin fold). The cut-point used was the lowest 10% in those aged 65 years and over. The approach was validated using DEXA measurements of lean mass at the upper limb [284]. In relation to weakness, lower limb strength was assessed using the five chair stands test [3, 38, 285]. Again the cut-point was chosen as the lowest 10% from those who were 65 years and over and those who were unable to complete the test were also included. Exhaustion was identified using two questions from the Beck's Depression Inventory on energy and fatigue. The questions used were 'I don't have enough energy to do very much/anything' and 'I am too tired or fatigued to do a lot/most of the things I used to do'. A positive score was given if they answered "all of the time" or "most of the time" to either one of the questions. The PASE score was used as the low activity criteria, with the cut-point as the lowest 20% from those aged 65 years and over. Slowness was measured by the PPT walk (time taken to walk 50 feet), with the cut-point as the slowest 20% stratified by height for those ages 65 years and over.

Other than the sarcopenia and weakness criteria, all others were equivalent measures to those used in the original FP model [27, 113, 126, 199]. The original FP model was on a

population of men and women aged 65-102 years, with cut-points for most criteria set at 20% [5]. The EMAS cut-points were taken from men aged 65 and over and the cut-points in the case of the sarcopenia and low activity was set at 10% to obtain prevalence similar to the other frailty criteria. A comparison of the cut-points of the original criteria and those used in the EMAS cohort are shown in Table 3.3. As with the original FP model, frailty was defined as the presence of 3 or more of these criteria, pre-frail individuals were identified as those with 1-2 criteria, and those having none were considered robust. The adapted EMAS FP model has been validated by its association with increasing age, its ability to predict falls after 2 years, and its relationship with poorer health-related quality of life [257].

Criteria	Cardiovascular Health Study (CHS)	European Male Ageing Study (EMAS)	
		Measure used	*Cut-point*
Sarcopenia	>10 lb. body weight lost unintentionally in past year	Mid upper arm muscle circumference - lowest 10% from ≥ 65 years	mid arm muscle circumference ⩽ 23.7 cm
Weakness	Grip strength - lowest 20% by gender and BMI	5 Chair stands Slowest 10% from ≥ 65/Unable	5 chair stands time ⩾18s or unable
Poor endurance	Exhaustion - self report Center for Epidemiological Studies Depression Scale (CES-D) questions on low energy	Exhaustion - self report	Answered 'All of the time' or 'Most of the time' to the SF36 questions 'How often during the last month did you feel worn out?' or 'How often during the last month did you feel tired?'
Slowness	Walking Time/15 feet - slowest 20% by height.	50 foot walk slowest 20% by height for ≥ 65 years	50 foot walk time ⩾17.2s for height ⩽ 173.5 cm, ⩾16s for height >173.5 cm
Low activity	Kcals/week - lowest 20%. Males <383	PASE score lowest 20% from ≥ 65 years	PASE score ⩽78

Table 3.3 EMAS frailty criteria and the original Cardiovascular Health Study Criteria[5, 282]

3.9.3 Frailty Index in EMAS

Work undertaken in EMAS to develop a Frailty Index (FI) at the baseline phase was carried out in collaboration with Ken Rockwood. The deficits considered included variables from the SF-36 questionnaire, Beck's Depression Inventory, problems related to activities of daily living, the International Prostate Symptom score, morbidities and medication use. Forty-three deficits were considered, (see Table 3.4). To construct the EMAS FI all binary variables were recoded, using the convention that '0' indicated the absence of a deficit and '1' the presence of a deficit. For variables that included a single intermediate response (e.g. 'sometimes' or 'maybe'), an additional value of '0.5' was used [283]. The FI can be presented as either a score or a fraction of the score, i.e. the number of deficits present in the subject divided by the total number of deficits counted. The EMAS FI has been previously shown to be associated with disruptions in hormones of the hypothalamic-pituitary-testicular axis [283]. Frailty status assessed by both frailty models in EMAS were shown to be associated with lower vitamin D [25(OH) D], higher parathyroid hormone [PTH] levels [128] and also with poor sexual function [286].

3.9.4 Follow-up Frailty Index

For the purpose of this thesis, the EMAS FI was modified to include 39 deficits and calculated at both baseline and follow-up. The difference was due to the lack of availability of data for some of the medications diabetic drugs, prostate drugs and heart failure drugs. A further deficit, the presence of cardiovascular disease, was dropped as it duplicated information already provided when subjects reported a heart condition, high blood pressure and/or a stroke. There was relatively little difference in the EMAS FI at baseline when the index was either recalculated as a 39 item index or using the original 43 items (correlation coefficient=0.99).

Origin	Variable	Cut Point
SF36	Rating general health	Excellent/ Very good =0, Good=0.5, Fair/ Poor =1
SF36- Activity Daily Living	Help Feeding yourself	Limited / Limited a little=1, Not Limited=0
	Help Walking in your home	Limited / Limited a little=1, Not Limited=0
	Help Bathing and dressing yourself	Limited / Limited a little=1, Not Limited=0
	Walking 1 km	Limited =1, Limited a little=0.5, Not Limited=0
	Walking more than 1 km	Limited =1, Limited a little=0.5, Not Limited=0
	Climbing one flight of stairs	Limited =1, Limited a little=0.5, Not Limited=0
	Climbing several flights of stairs	Limited =1, Limited a little=0.5, Not Limited=0
	Unable to do moderate activity	Limited =1, Limited a little=0.5, Not Limited=0
	Unable to do vigorous activity	Limited =1, Limited a little=0.5, Not Limited=0
During the past 4 weeks have you had any of the following problems(SF36)	Accomplish less than you would like as a result of your physical health	All/Most of time=1, Sometime=0.5, Little time/ None=0
	Cut down on the amount of time spent on work or other activities as a result of emotional problems	All/Most of time=1, Sometime=0.5, Little time/ None=0
Questions are about how you feel and how things have been with you during the past 4 weeks (SF36)	Full of life	Little time/ None=1, Sometime=0.5, All/Most of time=0
	In the dumps	All/Most of time=1, Sometime=0.5, Little time/ None=0
	Down hearted	All/Most of time=1, Sometime=0.5, Little time/ None=0
	Tired	All/Most of time=1, Sometime=0.5, Little time/ None=0
SF36-During the last six months have you experienced	Serious illness or injury to yourself	Yes=1, No=0
Beck depression inventory BDI	Change in sleep pattern	Less/ Lot more=1, Same/ More=0
	Concentration	Worst/Worse=1, Fair=0.5, Ok=1
International Prostate Symptom Score	Over the past month, how often have you had to	
	Postpone urination	Always,>50%=1, about or less than 50%=0.5, Not at all, <20%=0
	Night urinate	2 or more =1, 0 or 1 =0
Weak Stream	Always,>50%=1, about or less than 50%=0.5, Not at all, <20%=0	

Origin	Variable	Cut Point
Self-reported morbidities		
	Heart condition	Yes=1, No=0
	High blood pressure	Yes=1, No=0
	Bronchitis	Yes=1, No=0
	Asthma	Yes=1, No=0
	Diabetes	Yes=1, No=0
	Liver condition	Yes=1, No=0
	Kidney condition	Yes=1, No=0
	Prostate disorder	Yes=1, No=0
	Thyroid disorder	Yes=1, No=0
	Cancer ever	Yes=1, No=0
	Stroke ever	Yes=1, No=0
		Cut-point corresponds to the lowest (worst performing) 10^{th} centile
Cognition	Copying -Rey-Osterrieth Complex Figure (ROCF)	Score <28, =1, Score >=28, = 0
	Delayed reproduction- Rey-Osterrieth Complex Figure (ROCF)	Score <8, =1, Score >= 8, = 0
	Camden Topographical Recognition Memory (CTRM)	Score <16, =1, Score >= 16, = 0
	Digit-Symbol Substitution (DSST) test	Score <16, =1, Score >= 16, = 0
Physical performance test	Time to walk 15.4 meters	Time >=16.7, =1, Time < 16.7, = 0
Tinetti		Score < 25, =1, Score >= 25, = 0

Table 3.4 The list of health deficit variables included in the EMAS FI (39 deficits)

3.10 Statistical analyses

Both descriptive and analytical statistics were used. Detailed descriptions of the statistical techniques used are outlined in detail in each chapter of this thesis. STATA version 11.0 (StataCorp, College Station, TX, USA) was used for all statistical analyses. Descriptive statistics (mean, standard deviation, median, interquartile range) were used to summarise the data. Analytical statistics were used to explore the association between the subject's characteristics and frailty status. Analysis of Variance (ANOVA) for normally distributed continuous variables and Chi-square tests for categorical variables were used to test differences between the frailty groups.

More advanced modelling techniques were used for the analysis of the association between frailty and various exposures. This included multinomial logistic regressions, multiple linear regressions and logistic regressions. Multinomial logistic regression was used to explore the association between the subject's characteristics such as age, quality of life and adiposity measures and frailty status assessed by the FP and FRAIL Scale (FS). The results were expressed as Relative Risk Ratios (RRR) with 95% Confidence Intervals (CI). Multiple linear regressions were used to assess the relationship between adiposity measures and frailty measured by the FI. Logistic regression was used to explore the relationship between baseline characteristics and frailty incidence. The results were expressed as Odds Ratio (OR) and 95% CI, with frailty incidence as the outcome. For analysis of data on mortality and frailty status, survival curves and Cox proportional hazard models were used and the results expressed as Hazard Ratios (HR) and 95% CI. Ordinal logistic regression was used to assess the association between frailty status and number of falls and number of visits to the doctor. Further details about the statistical methods are included also in the results chapters (Chapters 4 to 8).

3.11 Summary of Chapters 4 to 9

Chapter 4 outlines the development and validation of the FRAIL Scale (FS) in EMAS and the association between frailty assessed by this model with age and life-style factors. This chapter also compares the prevalence of the FS with the other definitions of frailty (FP and FI models). Chapter 5 outlines the results of the analysis looking at the association between the frailty models in EMAS (FP, FI and the FS) and adverse outcomes including mortality, falls and increase use of health care services. Chapter 6 outlines the results of the analysis looking at association between adiposity measures with frailty status (assessed at the baseline survey). Chapter 7 data on the new occurrence of frailty among subjects without frailty at the baseline survey and also change in the FI between baseline and follow-up. The influence of age on the new occurrence of frailty is also presented. Chapter 8 outlines the results of the analysis looking at the influence of baseline adiposity measures on frailty incidence and change in frailty status. Chapter 9 summarises of the main findings and also considers the implications of the results and includes suggestions for future research.

3.12 My role in attaining the aims and objectives in the thesis

Data collection for the EMAS baseline and follow- up phase had been completed before I joined the study. Data cleaning of the baseline phase and much of the development of the FI and the FP had already been completed. My role in the work presented in this thesis was i) assisting in the cleaning of data for the follow-up phase of the study ii) undertaking a literature review focusing particularly on methods of defining frailty and the relationship between frailty and adiposity measures, iii) developing a new definition of frailty within the EMAS – the FRAIL scale iv) defining frailty using three frailty measures (FP,FS and FI) at follow-up (including adapting the baseline FI definition to ensure consistency with the follow-up data) v) undertaking the analysis of the data presented in the thesis (Chapter 4-8).

Chapter 4 Development of the FRAIL Scale for use in the EMAS study

4.1 Summary

This chapter summarises the methods used to construct a model of frailty, the FRAIL Scale (FS) in EMAS. The FS is a frailty model based on a recommendation by the International Academy of Nutrition and Aging and comprises 5 items: Fatigue, Resistance, Ambulation, Illnesses and Loss of Weight. Data from the baseline phase of the EMAS (all based on self-report except for weight loss) were used to develop the EMAS FS. Using the FS, 2.7% of EMAS men were classified as frail and 20.1% as pre-frail. The prevalence of frailty increased with age. Based on the SF-36 questionnaire, both frail and pre-frail men were also more likely to have low physical and mental scores than men classified by the FS as robust. The prevalence of frailty was similar to that observed using the FP definition and there was reasonable agreement between the methods (kappa=0.51). Furthermore, the mean FI was higher in those who were frail than those who were either robust or pre-frail as defined by the FS.

4.2 Background

As outlined in the introduction many models have been proposed to assess frailty [87]. The two most common models are the Frailty phenotype (FP) and the Frailty Index (FI). The former is based primarily on physical components of frailty, while the latter comprises a series of deficits including the occurrence of comorbidities. The FRAIL Scale (FS) was suggested by a Geriatric Advisory Panel (GAP) of the International Academy of Nutrition and Aging [6, 287] to be used as a simple screening tool for frailty and comprising both physical measures (self-reported) of frailty and the occurrence of comorbidities. The Geriatric Advisory Panel stated that the scale should contain the following domains:

Fatigue,

Resistance (ability to climb 1 flight of stairs),

Ambulation (ability to walk 1 block),

Illnesses (greater than 5) and

Loss of Weight (>5%).

Since it has been proposed a number of studies have been reported in which an FS has been used [62, 63, 68, 168].

4.3 Aims

The broad aim of the work described in this chapter was to develop an FS using data from the EMAS study, for classification of frailty based on the GAP recommendations. The specific objectives were i) to operationalize the FS using data from the baseline phase of EMAS, ii) to determine the association between frailty defined by the FS, age and quality of life and, iii) to determine the concordance between the occurrence of frailty defined using the FS and the FP.

4.4 Methods

Details of the EMAS study including recruitment and assessments carried out on participants at baseline are described in the methods chapter (Chapter 3). Detailed descriptions of the development of the EMAS adapted FP and FI criteria are also found in Chapter 3. This chapter describes in detail the construction of the EMAS FS, how it compares with other frailty criteria in terms of defining frailty and an assessment of construct validity including the association with age and quality of life.

4.4.1 Development of the FRAIL Scale in the EMAS

The FS comprises 5 items (as defined by the GAP group):- Fatigue, Resistance, Ambulation, Illnesses and Loss of weight [287]. Individuals with none of the items are considered as robust, those with 1-2 as pre-frail, and those with 3 or more as frail. The items used in the EMAS to develop the FS are outlined below:

a) Fatigue

The items used to assess fatigue were the same as those used in the EMAS FP definition, specifically questions from Beck's Depression Inventory (BDI). The questions considered relate to loss of energy and tiredness or fatigue. Participants scored positive for fatigue if they answered yes to the question, "I do not have enough energy to do very much" or "I do not have enough energy to do anything" or if they answered yes to the question "I am too tired or fatigued to do a lot" or "I am too tired or fatigued to do most of the things I used to do".

b) Resistance

A single item from the SF-36 questionnaire was used to derive this criterion. Resistance was scored positive if participants reported that they were “limited a lot” or “limited a little” in their ability to climb one flight of stairs.

c) Ambulation

A single item from the SF-36 questionnaire was used to derive this criterion. Ambulation was scored positive if participants reported that they were “limited a lot” or “limited a little” in their ability to walk 100 m.

d) Illnesses

Illness was scored positive if participants reported that they were currently being treated for 5 or more out of a total of 16 self-reported illnesses. The illnesses considered were those included in the postal questionnaire and included heart conditions, high blood pressure, pituitary disease, testicular disease, bronchitis, asthma, peptic ulcer, epilepsy, diabetes, kidney conditions, thyroid disorder, ever having had cancer, ever having had a stroke, liver conditions, prostate disease and adrenal disease.

e) Loss of Weight/ Sarcopenia

No data on weight loss was obtained in the baseline survey. The loss of weight criteria was interpreted as meaning Sarcopenia (as in the original Fried phenotype definition). Consequently, the same definition was used as for the EMAS FP, and based on measurements of the arm muscle circumference (arm circumference – π triceps skin fold). This measurement has been previously shown to correlate with lean muscle mass assessed using DEXA [282].

4.4.2 Comparison with other frailty models

Both the FS and FP characterise men as frail, pre-frail or robust. To facilitate comparison with FI, the index was categorised into similar categories – the FI cut points were derived from thresholds based on defining the same proportion of men as frail and pre-frail using the EMAS FS.

4.4.3 Statistical Analysis

Descriptive statistics were used to describe the occurrence of the individual component frailty criteria, the overall prevalence of frailty and pre-frailty, and the influence of age on these

criteria. The mean age and health-related quality of life (including physical and mental component scores from the SF-36) were also determined by frailty group status. Differences between groups (FRAIL Scale Categories) were assessed using chi-squared for categorical variables, and Anova or Kruskall Wallis for continuous data. Multinomial logistic regression models were used to explore the association between age & the SF-36 summary scores (physical and mental) and frailty as defined by the FS. The results were expressed as Relative Risk Ratios (RRR) with 95% Confidence Intervals (CI). Models were adjusted for centre, smoking (current vs. non-smoker) and alcohol consumption (≥5 days/week or <5 days/week). The kappa statistic was used to characterise the agreement between frailty models [288]. Kernel density was used to look at the distribution of FI by frailty status. A Venn diagram was used to look at the overlap in men defined as frail using any of the three frailty models (FI, FS, and FP). ANOVA was used to look at health related quality of life among men defined as frail using different combinations of the models.

4.5 Results

4.5.1 Subjects

A total of 3228 men had data available to allow determination of frailty, using the FS at the baseline survey, (Table 4.1). Men with missing data (n=141) were slightly older and had lower SF-36 (physical & mental) component scores. Missing data varied across centres with Malmö (6.6%) and Tartu (6.9%) having the highest proportion of missing data, (Table 4.2). Analysis was restricted to men with complete frailty (FS) measures.

4.5.2 Prevalence of frailty

Using the derived FS the overall prevalence of frailty in EMAS was 2.7% (n=86) and pre-frailty 20.1% (n=649). In relation to the component criteria, the prevalence of Fatigue was 8.8%, Resistance 11.8%, Ambulation 6.5%, Illnesses 1.9% and Sarcopenia 5.6%, (Table 4.3). The prevalence of these criteria was lowest in the youngest age group and increased significantly with age, (Figure 4.1). The overall prevalence of frailty using the FS increased with age from 0.3% in the 40-49 year age band to 5.9% in those who were aged 70 & over, (Figure 4.2). The prevalence of pre-frailty (1-2 criteria) increased from 10.9% to 32.4% across the same age bands. The prevalence of frailty varied across centres and was highest in Łódź (5.7%) and Tartu (5.4%) and the lowest in Florence (0.5%) (Figure: 4.3). There was variation also in the prevalence of pre-frailty.

4.5.3 Frailty and Health Related Quality of Life

Men who were frail had a lower physical activity (SF-36) and a lower SF-36 mental component score than those who were robust. Frail men were also more likely to be smokers, although their frequency of alcohol consumption was less than those who were robust or pre-frail (all; $p<0.01$), (Table 4.4). Using frailty (FS) status as the dependent variable (robust=base category) and after adjustment for centre, smoking and alcohol consumption, increasing age was associated with being pre-frail (RRR=1.06; 95%CI; 1.05-1.07) and frail (RRR=1.11; 95%CI; 1.08-1.14), (Table 4.5). The RRR indicates the likelihood of being in the outcome category (pre-frail or frail) with reference to the base category (robust). Therefore, for each unit increase in age the odds of being pre-frail compared to being robust increased by 1.06 and the odds of

being frail compared to being robust by 1.11. Frailty and pre-frailty were also significantly associated with reduced SF-36 physical and mental component scores, (Table 4.5).

	Complete data	Missing data	p value
n	3228	141	
Age (years)	59.9 ± 11.0	61.9 ± 11.3	0.03
FI	0.13 ± 0.11	0.13 ± 0.129	0.5
SF-36 Physical component	50.1 ± 8.2	47.2 ± 8.8	0.001
SF-36 Mental component	51.6 ± 9.3	47.5 ± 11.4	0.0003

Table 4.1 Characteristics of men with complete and missing frailty data

Data are Mean ± SD

	Total	Florence	Leuven	Lodz	Malmo	Manchester	Santiago	Szeged	Tartu
Frailty	141 (4.2)	8 (1.9)	13 (2.9)	25 (6.1)	27 (6.6)	16 (4.0)	6 (1.5)	16 (3.7)	30 (6.9)
Fatigue	41 (1.2)	2 (0.5)	4 (0.9)	2 (0.5)	14 (3.4)	0 (0.0)	1 (0.3)	2 (0.5)	16 (3.7)
Resistance	58 (1.7)	1 (0.2)	5 (1.1)	10 (2.5)	16 (3.9)	3 (0.8)	1 (0.3)	6 (1.4)	16 (3.7)
Ambulation	59 (1.8)	1 (0.2)	4 (0.9)	10 (2.5)	18 (4.4)	4 (1.0)	2 (0.5)	5 (1.2)	15 (3.5)
Illnesses	53 (1.6)	5 (1.2)	3 (0.7)	14 (3.4)	5 (1.2)	7 (1.8)	4 (1.0)	9 (2.1)	6 (1.4)
Sarcopenia/Loss of weight	50 (1.5)	0 (0.0)	8 (1.8)	1 (0.3)	14 (3.4)	5 (1.3)	0 (0.0)	1 (0.2)	21 (4.8)

Table 4.2 Missing frailty data, by centre

Data are Count (%)

Frailty Status	Prevalence
Robust	2493 (77.2)
Pre-frail	649 (20.1)
Frail	86 (2.7)
Frailty Criteria	
Fatigue	294 (8.8)
Resistance	392 (11.8)
Ambulation	215 (6.5)
Illnesses >=5	62 (1.9)
Sarcopenia/Weight loss	187 (5.6)

Table 4.3 Prevalence of frailty assessed by EMAS FRAIL Scale

Data are Count (%)

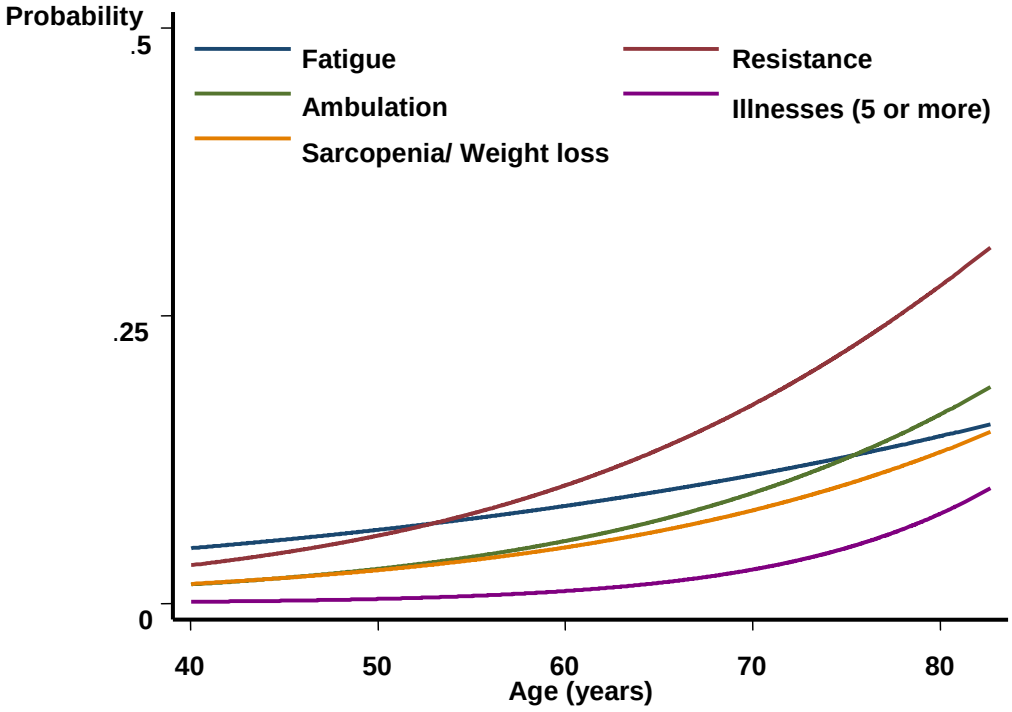


Figure 4.1 Predicted probability of each frailty component with age (years)

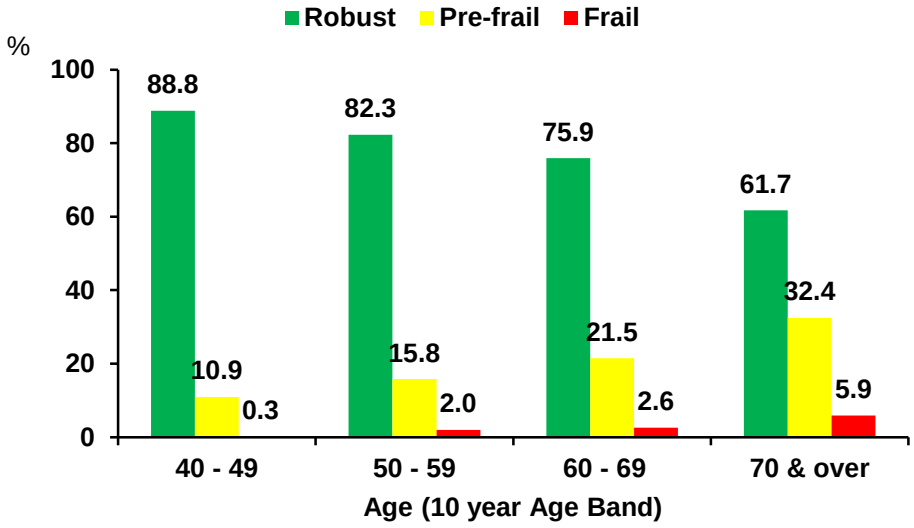


Figure 4.2 Percentage of men who are robust / pre-frail and frail (FRAIL Scale): By 10 year age bands

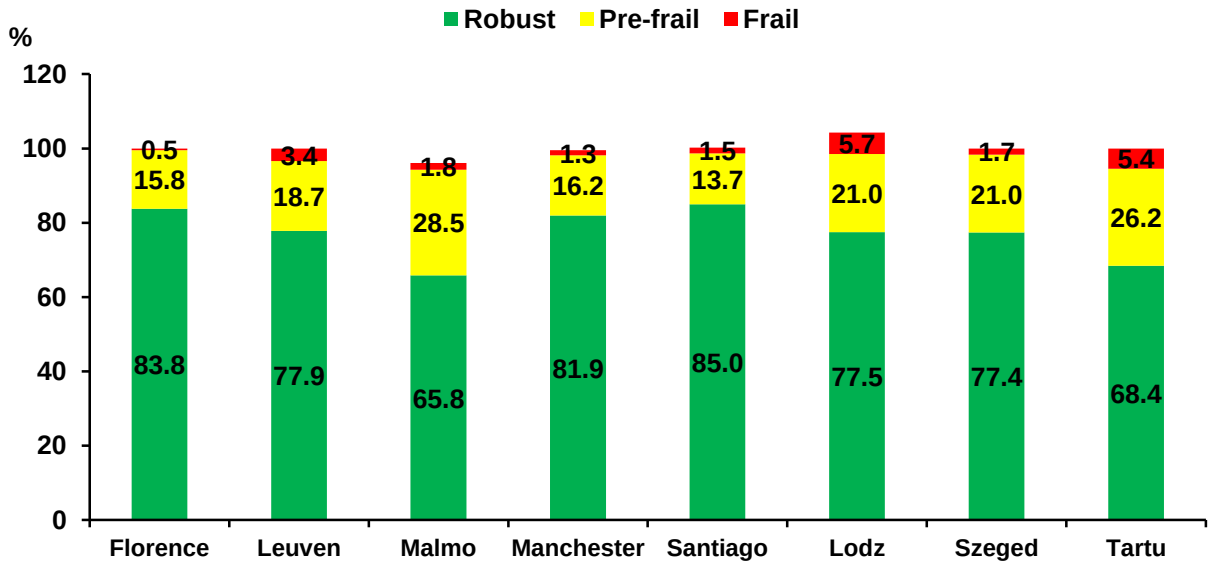


Figure 4.3 Percentage of men who are robust / pre-frail and frail (FRAIL Scale): By centre

	Overall (n=3277)	Robust (n=2493)	Pre-frail (n=649)	Frail (n=86)	p value
			Mean ± SD		
Age at Baseline (years)	59.9 ± 11.0	58.5 ± 10.7	64.4 ± 10.6	68.0 ± 8.9	<0.001˜
Age left Education (years)	20.8 ± 7.6	20.8 ± 7.4	20.9 ± 8.1	21.2 ± 8.4	0.89˜
SF-36 Physical component score	50.1 ± 8.2	52.3 ± 6.0	43.7 ± 9.2	30.9 ± 6.5	<0.001˜
SF-36 Mental component score	51.6 ± 9.3	52.7 ± 8.1	48.9 ± 11.4	40.1 ± 12.8	<0.001˜
			Count (%)		
Smoking status (current)	666 (20.6)	474 (19.0)	166 (25.6)	26 (30.2)	<0.001*
Alcohol Intake (≥5 days/week)	744 (23.2)	599 (24.1)	137 (21.2)	8 (9.5)	0.003*

Table 4.4 Baseline characteristics of EMAS men by Frailty status

˜K-Wallis,* Chi-square tests

	Relative Risk Ratios (95% Confidence Intervals)			
	Unadjusted		Model 1	
	Pre-Frail	Frail	Pre-Frail	Frail
Age(years)[a]	1.05 (1.04 to 1.06)***	1.09 (1.07 to 1.12)***	1.06 (1.05 to 1.07)***	1.11 (1.08 to 1.14)***
SF-36 Physical component score	0.86 (0.85 to 0.87)***	0.71 (0.69 to 0.74)***	0.86 (0.85 to 0.87)***	0.71 (0.68 to 0.74)***
SF-36 Mental component score	0.96 (0.95 to 0.97)***	0.90 (0.88 to 0.92)***	0.96 (0.95 to 0.97)***	0.90 (0.89 to 0.92)***

Table 4.5 Multinomial logistic regression: Frailty status (FS), age and health related quality of life

Multinomial logistic regression models: Model 1 adjusted for age,centre,smoking & alcohol:***p <0.001

[a] Model 1 adjusted only for centre smoking and alcohol

4.5.4 Comparison of frailty models

As discussed the prevalence of frailty was 2.7% using the FS and in these men the prevalence of frailty using FP was 2.6%. The median FI was 0.44 in frail (FS) men, 0.23 in pre-frail and 0.08 in robust men. The mean and median FI increased with an increase in the number of FS criteria (Table 4.6). Figure 4.4 shows the kernel density distribution of the FI by FS frailty status. For the Frailty Index and based on cut-points derived from the FS men, those with an FI above 0.4 were categorised as frail, those with an FI below 0.2 as robust, and those with FI levels between 0.2 and 0.4 as pre-frail. Tables 4.7 and 4.8 show the agreement between the FS & FP and FS & FI models, respectively. Sixty-six percent of men were robust by both the FS and the FP and 69% were classified as robust by the FS and the FI. Very few men [5 (0.2%)] men who were robust by the FS were frail by the FP, and only one individual (0.03%) was robust by the FS and frail by the FI. Cohen's kappa statistic suggested a moderate agreement between the frailty models, i.e., FP and FS kappa = 0.51; FS & FI kappa = 0.47. Figure 4.5, compares the frail men identified by the FS, FP and FI frailty models. Twenty-three (15.7%) men were frail by all three models, 16 (11%) were frail by the FS only, 29 (20%) were frail by the FP only and 33 (23%) were frail by the FI only. This suggests that different groups of men are classified as frail based on the different frailty constructs with only some degree of overlap. Table 4.9 compares the characteristics between the different groups i.e. frail by all models, FP & FS frail, FI & FS frail, FP & FI frail, FP frail, FI frail and FS frail. Men who were frail by all three models had poorer quality of life as indicated by both lower SF-36 physical and mental component scores.

		Frailty Index	
FRAIL Scale	**Mean ± SD**	**Median**	**IQR Range**
Robust	0.10 ± 0.07	0.08	0.04 to 0.13
Pre-frail	0.23 ± 0.12	0.23	0.14 to 0.31
Frail	0.44 ± 0.10	0.44	0.37 to 0.49
No of Criteria			
0	0.10 ± 0.07	0.08	0.04 to 0.13
1	0.20 ± 0.11	0.19	0.12 to 0.27
2	0.32 ± 0.10	0.31	0.26 to 0.39
3	0.42 ± 0.09	0.42	0.36 to 0.49
4	0.50 ± 0.12	0.49	0.43 to 0.60
5 (n=0)	0.00 ± 0.00	0.00	0.00 to 0.00

Table 4.6 Frailty Index by FRAIL Scale

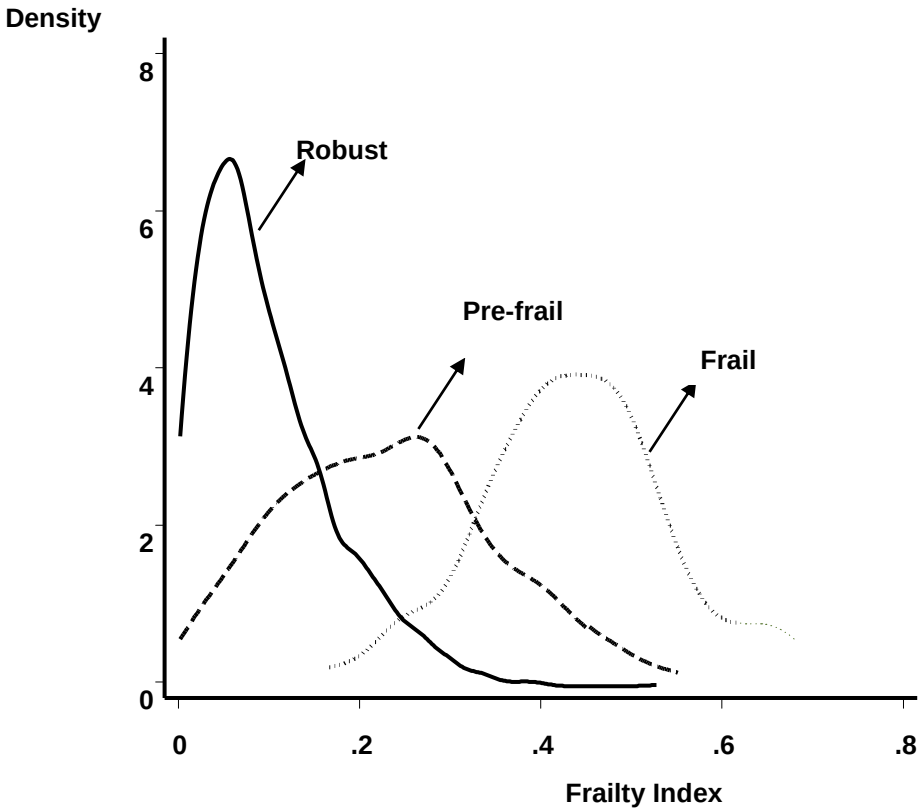


Figure 4.4 Kernel Density distribution of Frailty Index for men classified as robust, pre-frail and frail (using FRAIL Scale).

FS	FP		
	Robust	**Pre-frail**	**Frail**
Robust	1962 (65.8)	357 (11.9)	5 (0.2)
Pre-frail	148 (4.9)	404 (13.5)	37 (1.2)
Frail	0 (0.0)	36 (1.2)	35 (1.2)

Table 4.7 Agreement between frailty models (FS & FP)

Kappa=0.51 p <0.001 (n=2984)

FS	FI		
	Robust	**Pre-frail**	**Frail**
Robust	2240 (69.4)	252 (7.8)	1 (0.03)
Pre-frail	276 (8.6)	321 (9.9)	52 (1.6)
Frail	1 (0.03)	32 (0.99)	53 (1.6)

Table 4.8 Agreement between frailty models (FS & FI)

Kappa=0.47 p <0.001 (n=3228)

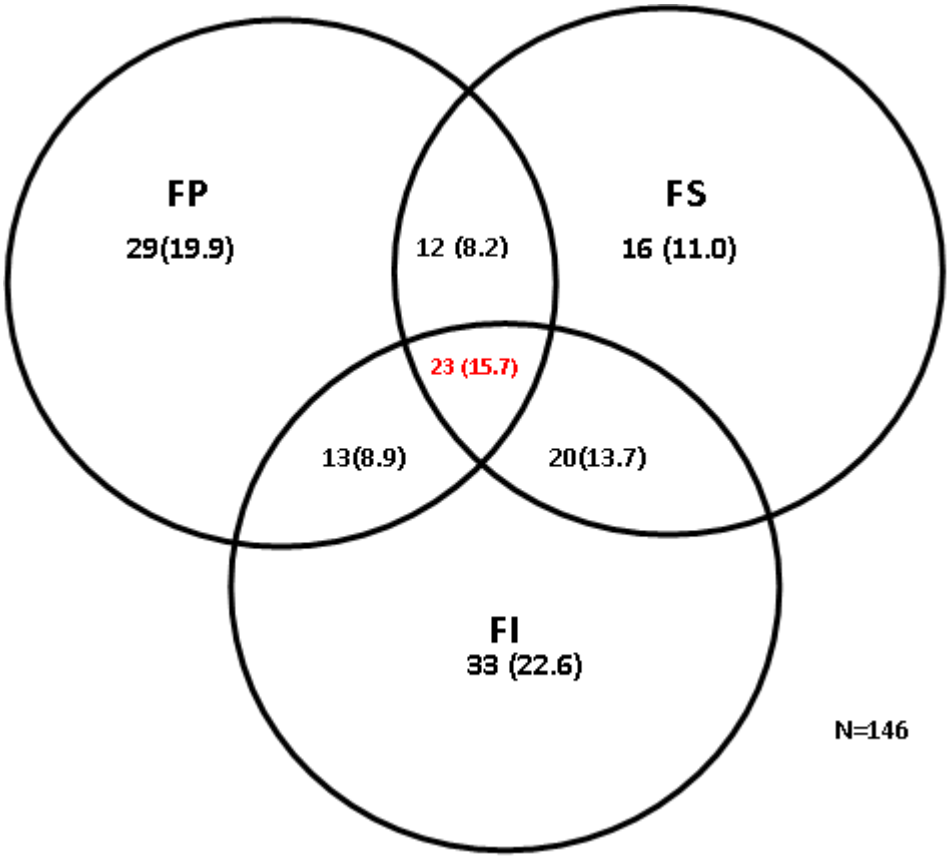


Figure 4.5 Comparison of three frailty models: Venn diagram

Data are number (%) men defined as Frail using at least one definition

	Frail by all models	FP & FS frail	FP & FI frail	FI & FS frail	FP Frail	FI frail	FS frail
Mean ± SD							
Age (years)	66.1 ± 10.6	72.8 ± 6.3	71.1 ± 7.8	69.6 ± 7.3	71.5 ± 6.2	70.9 ± 6.9	66.9 ± 7.6
SF-36 Physical component score*	29.3 ± 5.0	29.2 ± 8.5	33.0 ± 7.6	30.7 ± 7.2	42.2 ± 8.3	33.3 ± 5.5	34.1 ± 6.1
SF-36 Mental component score*	34.8 ± 11.2	53.2 ± 9.4	40.2 ± 13.1	36.9 ± 10.6	47.8 ± 12.5	39.2 ± 10.4	46.3 ± 8.9

Table 4.9 Characteristics of men defined as frail by the different frailty models *p <0.001

4.6 Discussion

The prevalence of frailty using an adapted FS model was similar to that of the other operationalized definitions of frailty used in EMAS. Frailty as defined by the FS model showed convergent validity with the other frailty definitions through its association with age and health-related quality of life. The FS has been developed and validated previously in two other population-based studies. Morley *et al* [63], used data from community dwelling African-Americans to validate the FS model by its ability to predict mortality and poorer health outcomes. The FS has also been utilised in the Health in Men study [168, 289] to assess frailty. It has also been validated in a longitudinal study in 4000 Chinese men and women living in Hong Kong [68]. It has not previously been developed or validated in a European cohort.

The prevalence of frailty using the FS was low (2.7% n=86) in the EMAS cohort and similar to that defined by the FP model (2.6% n=78). A relatively low prevalence of FS frailty (2.7%), was also observed in a study of African American adults (n=998) who were slightly younger (49-65 years) than the EMAS participants [63]. Hyde *et al* [289], used an operational definition of the FS to measure frailty in the Health in Men study, a longitudinal study of 3616 older men aged 70-88 years in Australia. The baseline prevalence of frailty in this population was 15.2% and pre-frailty was 46.2%; the higher proportion of frail and pre-frail men was probably due to the older age of the cohort. As expected the prevalence of frailty increased with age in the EMAS [5, 27, 28, 33, 198, 204, 289]. Of the component FS, the highest prevalence was seen for the Resistance (self-reported difficulty climbing one block of stairs) and the lowest was seen for the Illnesses (having 5 or more comorbidities). However, some of the comorbidities considered in EMAS were relatively uncommon (<1%). The data were also analysed using a more stringent cut-point for the illness criteria (including only relatively common conditions), however, using this approach the prevalence of frailty did not change significantly. The prevalence of the individual criteria of the FS were lower in EMAS than observed in other studies [63], almost certainly reflecting the younger age of the EMAS cohort. All FS criteria increased significantly with age. Frailty measured by the FS was associated with poorer quality of life, as assessed using the SF-36. This association remained significant after

adjustment for age and lifestyle factors. The association of frailty with poorer quality of life has been previously shown in other studies of frailty [290, 291].

There was reasonable agreement between frailty models defined using the FS and FP. Furthermore, the mean FI was higher in those who were frail than those who were robust. Classification of frailty using the FS & FP was concordant in 80% of participants and for the FS & FI was concordant in 81% of the participants, when using the three tier classification of the FI. Despite the convergence and agreement between the three approaches to define frailty, they appear, however, to identify somewhat different people, almost certainly reflecting the different underlying constructs used to define frailty.

The strengths of the EMAS study include its population-based design, large sample size, and use of standardised and validated instruments. However, there are a number of limitations to consider in interpreting the results. The response rate in EMAS was 41%. It is possible that those who took part may have differed from those who were invited but did not take part. Therefore, the absolute prevalence of frailty defined using any of the three models may be an under or overestimate compared to the true prevalence in the sampling frame. This should not, however, tend to affect the results of the main analyses examining the relationship between frailty, age and quality of life, or the comparison with the other frailty models which were based on an internal comparison of responders. Both the FP and the FS were adapted to data available in EMAS, and as such may not necessarily be directly comparable with data from other studies in which other adaptations to the frailty models were used. One of the key differences, though, in both the development of the EMAS FS and the FP, is the weight loss category. No information was available about weight loss and a surrogate marker of loss in lean mass was used instead. Mid upper arm muscle circumference as a marker of loss in lean mass has been shown to predict both decline in function and an increased risk of mortality [292]. Although validated as a marker of sarcopenia in EMAS, caution is again required when comparing the data here with other studies. However, adaptations of modification of criteria are not uncommon in the frailty literature [27, 60, 289] and the advantage of an objective measure of weight loss is less prone to bias due to self-report. As the results were obtained from

predominately European Caucasian men, extrapolating these data to other populations should be done with caution.

4.7 Conclusion

A frailty model based on the FS was developed for use in EMAS. The FS showed convergent validity with age and health related quality of life and by its agreement with other frailty models in EMAS.

Chapter 5 Frailty and Adverse Health Outcomes

5.1 Summary

In this chapter, adverse outcomes linked with the three frailty models developed in EMAS, including mortality, falls and health services utilisation are considered. Subjects in EMAS were reassessed a median of 4.5 years after the baseline survey at which point data on the occurrence of falls and also primary care attendance were obtained by questionnaire. Information on deaths was obtained from a variety of sources. During the follow-up there were 193 deaths, 27% of participants reported a fall in the previous year and 16% reported having visited their General Practitioner (GP) more than once a month since their baseline visit. Frailty was defined (as outlined in Chapters 3 and 4) using the Frailty Phenotype (FP), FRAIL Scale (FS) and Frailty Index (FI). After adjustment for age, centre and lifestyle factors frailty (using all three methods) was associated with an increased mortality (hazard ratios = 4.4 to 4.5). Frailty was also associated with an increased risk of falls (odds ratios = 2.7 to 4.7) and also an increased likelihood of primary care attendance.

5.2 Introduction

Frailty has been shown to be associated with an increased risk of falls, death, disability, institutionalisation, hospitalisation, comorbidity and an increased use of healthcare services [293]. However, most studies have been conducted among older populations in the USA or North America [5, 294]. There are few data which consider adverse outcomes in men, and in a European setting. Furthermore, few studies have directly compared the ability of the most commonly used models of frailty to predict mortality or other adverse outcomes among community-dwelling middle-aged and older people.

5.3 Aims and objectives

The aims of the analyses outlined in this chapter were to determine the ability of the three EMAS frailty models adapted from existing index and phenotypic approaches to predict the occurrence of falls, primary care attendance, and mortality.

5.4 Methods

Detailed methods for the EMAS study, including the baseline and follow-up phases, are summarised in Chapter 3. In this section, further information about ascertainment of the adverse outcomes including falls, primary care attendance and deaths is presented. Also, the statistical methods used to address the analyses of the data are described.

5.4.1 Assessment of falls and primary care visits

At the follow-up survey in 2007-2009, subjects were asked about the occurrence of falls in the past 12 months. The question asked was 'In the past 12 months, how often have you had any falls including a slip or trip in which you lost your balance and landed on the floor, ground or lower level?' (Response set = Never, Once, Twice or more). They were also asked 'How often do you see a doctor?' (Response set = Almost never, only very rarely, about 4 times a year, about once a month, about once a week)

5.4.2 Assessment of mortality

Deaths that occurred during the follow-up period were determined either through direct contact by relatives on receipt of the postal questionnaire or, if this was not returned, by further enquiry made to ascertain the participant's vital status. The enquiry procedure varied between centres and included re-contact by mail or telephone and, where possible, checking death registers. Men who did not reply to the follow-up postal questionnaire or for whom no further information was available were classified as 'lost to follow-up'. Deaths were confirmed by death certificates where possible.

5.4.3 Frailty

Frailty was defined using the approaches as outlined in Chapter 4, i.e. the EMAS FP, FS and the FI. As outlined earlier, for FP and FS subjects were characterised as pre-frail if they satisfied 1-2 criteria and frail if they satisfied 3 or more. FI was defined based on the presence or absence of 39 deficits as discussed previously. In addition to considering the scale as a continuous measure, cut-points were identified based on the prevalence of frailty (as defined by the FS) at baseline to categorise the FI into the three tier classification of robust (FI ≤0.2), pre-frail (FI 0.2-0.4) and frail (FI ≥0.4). The FI is routinely used as a continuous measure and different cut-points are used at time to categorise the FI. To maintain consistency throughout

the thesis, the cut-points based on the prevalence of frailty using the FS were used. Similar approaches to categorise FI had been used in previous studies [53, 60, 61].

5.4.4 Statistical Analysis

Descriptive statistics were used to describe the occurrence of falls, GP visits and deaths. T-tests or Wilcoxon rank-sum tests (for continuous variables) and the Chi-square test (for categorical variables) were used to examine differences in subject characteristics (including quality of life, lifestyle and measures of body fat and comorbidities) between those who took part in the follow-up survey, those who died and those who were lost to follow-up. Participants contributed follow-up time (person-years) from the date of taking part in the baseline survey to the point of last contact, which was either the date of the follow-up assessment or contact, or the date of death. Kaplan Meier survival curves were used to look at the impact of frailty status on mortality. Cox proportional Hazard models were used to analyse the association between frailty status (as defined by the FP, FS or FI) and mortality, with the results presented as hazard ratios (HR) and 95% confidence intervals (CI). For the FP and FS, frailty was categorised in all three models as frail, pre-frail and robust, with the robust category as the referent. The FI was analysed both as a categorical variable (frail / pre-frail / robust) using derived thresholds (see 5.4.2 above), and also as a continuous variable. When used as a continuous variable, to aid interpretation of the HRs the FI (0–1) was multiplied by 10 to derive a possible range of 1–10, thereby defining a practical per unit change in FI equivalent to 0.1 using the original scale. Adjustments were initially made for age and centre and subsequently for other covariates including BMI, smoking (categorised as current, former or never), and frequency of alcohol consumption (categorised as <5 days/week or ≥5 days/week). For analyses involving the FP, adjustments were also made for comorbidities (categorised as none vs. any) as these were not included in the FP definition. The presence of any interaction effects between frailty and age, centre or BMI was also explored.

The association between frailty and falls and also frailty and GP visits, was assessed using ordinal logistic regression where falls were characterised as a three level ordinal outcome (0, 1, ≥2), with adjustments made for age and centre. The number of visits to the GP was categorised into almost never, rarely, about 4 times a year and about once a month or more.

Ordinal logistic regression is an extension of logistic regression, which can be applied to more than two ordered categories of a dependent variable. This model can be applied only to data that meets the proportional odds assumption, i.e. the coefficient which describes differences between each outcome category should be the same, i.e., the model reports only one coefficient or odds ratio. The resulting odds ratio for a given predictor in an ordinal model represents the odds of being in a higher outcome category associated with a unit increase in the value of that variable, in this case more falls or more visits to the GP. Non-violation of the parallel slope assumption of the ordinal logistic models was assessed using the Brant test in Stata. The results were expressed as odds Ratio (OR) and 95% confidence intervals (CI). In the case of falls, adjustments were made initially for age and centre and subsequently for BMI, smoking, and alcohol intake (and for the FP models - comorbidities). For the frequency of primary care attendance adjustments were made only for age and centre, as visits to GP are usually as a direct result of existing comorbidities and conditions related to life-style factors. Analyses were conducted using STATA SE v11.2 (StataCorp, College Station, TX).

5.5 Results

5.5.1 Participant Characteristics

A total of 2736 men completed the follow-up phase of the study. 106 (3%) were unable to attend the survey for various reasons (poor health or said to be in an institution), 334 (10%) were lost to follow-up and there were 193 deaths. The baseline characteristics of those men who participated at follow-up, those who were unable to attend, those who died and those lost to follow-up are presented in Table 5.1. The results showed that those men who died or were unable to attend were significantly older, had a lower PASE score, were more likely to be depressed and had lower quality of life as assessed by the SF-36 physical and mental scores. They were also more likely to be frail compared to those who returned to follow-up. This was true for all frailty models. Those who were lost to follow-up were significantly younger and had a higher baseline PASE score and had a lower frailty index than those who returned to follow-up

5.5.2 Frailty Phenotype (FP) and mortality

Compared to those who took part in the follow-up phase, those who died were much more likely to be frail at baseline (1.5% vs. 12.6% respectively), (Table 5.1). The survival curves for those who were frail, pre-frail and robust at baseline are shown in Figure 5.1, with a significant difference in survival between groups (log rank of $p<0.001$). Using Cox proportional hazards, those who were frail at baseline had a 13 fold increased risk of death and those who were pre-frail at baseline a 3.6 fold increased risk of death, compared to those who were robust (see Table 5.2). These associations were attenuated but remained significant after adjustment for age, centre, BMI, smoking, alcohol and comorbidities, i.e., those who were frail had a 4 fold increased risk of death (HR=4.4; 95% CI 2.6 to 7.7), and those who were pre-frail a 2 fold increased risk of death (HR=1.9; 95%CI 1.3 to 2.7), compared to those who were robust (see Table 5.2). Further adjustment for depression in the model did not substantively change this association (data not shown). Each of the five individual FP components also predicted mortality, (Figure 5.2). Of the individual criteria, however, slowness appeared to be the strongest predictor of death (HR=2.7; 95% CI 1.8 to 3.8). There was no evidence of an interaction between FP and centre or FP and BMI (data not shown). There was however a

significant interaction between FP and age (p=0.02), with a greater HR (after adjustments) for those under 65 years (HR=13.3) compared to those who were 65 years or older (HR=3.2).

5.5.3 Frailty Phenotype (FP), falls and GP visits.

2445 men had complete data available on falls at follow-up and FP at baseline and 2396 men had complete data on primary care visits at follow-up and FP at baseline. Of these 404 (16.5%) reported one fall and 262 (10.7%) reported two or more falls in the previous 12 months. 381 (15.9%) reported almost never visiting their GP, 878 (36.6%) rarely visiting, 759 (31.7%) about 4 times per year and 378 (15.8%) visiting about once a month or more. An increasing trend in both number of falls and number of GP visits was seen with an increase in frailty status (FP) (see Table 5.3). Thus, for example, a greater proportion of frail men (35%) reported two or more falls compared to robust men (9%). Also, the frequency of GP visits tended to increase with increased levels of frailty. Using ordinal regression, the odds for having more falls compared with the reference group (no falls), was higher in frail and pre-frail men compared to robust men. This association remained significant after adjusting for age, centre, BMI, smoking, alcohol and comorbidities (Figure 5.3). Similarly, those who were frail and pre-frail were more likely to attend their primary care physician; with the strength of this association attenuated, though remaining significant after adjusting for age and centre, (see Figure 5.3).

	Participants (n=2736)	Non-responders ∫ (n=106)	Died (n=193)	Lost to follow-up (n=334)
	Mean ± SD			
Age (Years)	59.2 ± 10.7	70.6 ± 8.5[a]	69.4 ± 8.2[b]	57.9 ± 11.6[c]
Body Mass Index (BMI) (kg/m^2)	27.7 ± 4.0	27.7 ± 3.9	27.6 ± 4.9	27.9 ± 4.5
Physical activity (PASE Score)	200.1 ± 88.9	126.5 ± 75.3[a]	140.0 ± 89.6[b]	212.9 ± 101.3[c]
Depression (BDI-II total)	6.6 ± 6.2	9.5 ± 6.7[a]	10.6 ± 8.2[b]	7.1 ± 6.9
SF-36 physical score	50.5 ± 7.9	45.8 ± 10.4[a]	44.3 ± 9.3[b]	50.1 ± 7.4
SF-36 mental score	52.0 ± 9.0	47.4 ± 11.0[a]	47.6 ± 11.0[b]	51.0 ± 10.1
Frailty Index(FI)	0.12 ± 0.10	0.23 ± 0.14[a]	0.25 ± 0.14[b]	0.13 ± 0.11[c]
Frailty (FP)	Count (%)			
Robust	1832 (73.6)	38 (39.2) [a]	63 (37.7)[b]	215 (72.9)
Pre-frail	618 (24.8)	47 (48.5) [a]	83 (49.7) [b]	73 (24.8)
Frail	38 (1.5)	12 (12.4) [a]	21 (12.6) [b]	7 (2.4)
Frailty (FS)				
Robust	2114 (80.0)	60 (57.1) [a]	82 (46.9) [b]	237 (77.7)
Pre-frail	479 (18.1)	34 (32.4) [a]	72 (41.1) [b]	64 (21.0)
Frail	50 (1.9)	11 (10.5) [a]	21 (12.0) [b]	4 (1.3)
Frailty(FI)				
Robust	2244 (82.0)	47 (44.3) [a]	80 (41.5) [b]	252 (75.5)[c]
Pre-frail	428 (15.6)	45 (42.5) [a]	82 (42.5) [b]	77 (23.1) [c]
Frail	64 (2.3)	14 (13.2) [a]	31 (16.1) [b]	5 (1.5) [c]
Current smoker	537 (20.0)	20 (19.1)	51 (27.4)[b]	97 (29.6)[c]
Alcohol consumption≥5 days per week	634 (23.3)	23 (22.1)	34 (18.0)	71 (21.5)
Comorbidities >=1	1340 (49.6)	80 (75.5) [a]	157 (84.0)[b]	151 (46.8)

Table 5.1 Baseline characteristics of follow-up participants and non-participants

∫ Non responders reported they were unable to take part due to poor health or living in an institution,

[a] p <0.05 t-test, Wilcoxon rank-sum test or chi-square test between follow-up participants vs. non responders

[b] p <0.05 t-test, Wilcoxon rank-sum test or chi-square test between follow-up participants vs. died

[c] p <0.05 t-test, Wilcoxon rank-sum test or chi-square test between follow-up participants vs. lost to follow-up

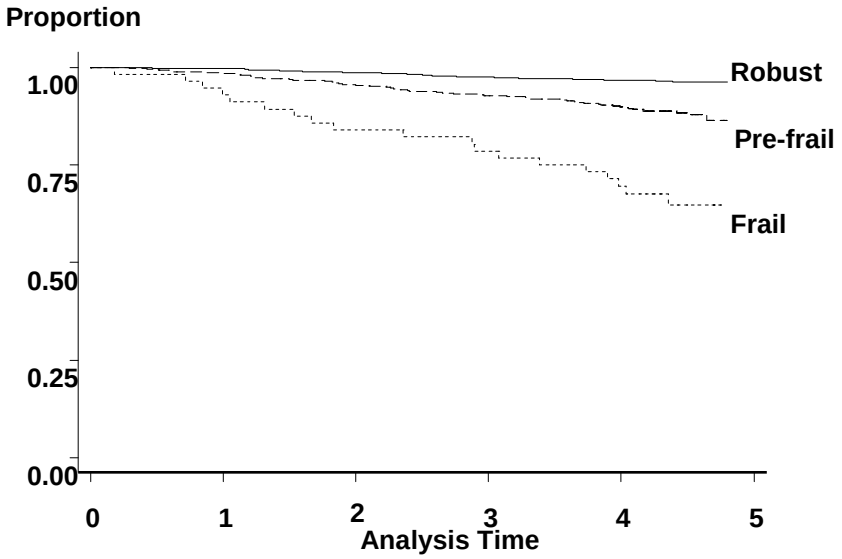


Figure 5.1 Survival curves by Frailty status (FP). Log rank p <0.001

	Hazard Ratios(95% Confidence Interval)		
	Unadjusted	**Model 1**	**Model 2**
Robust	1.0	1.0	1.0
Pre-frail	3.6 (2.6 to 5.0)***	2.0 (1.4 to 2.8)***	1.9 (1.3 to 2.7)**
Frail	12.9 (7.8 to 21.1)***	5.4 (3.2 to 9.0)***	4.4 (2.6 to 7.7)***

Table 5.2 Risk of mortality by frailty status (FP): Cox Proportional Hazard model

Model 1: adjusted for age and centre, Model 2: adjusted for age, centre, BMI, smoking, alcohol consumption and comorbidities, ***p <0.001, **p <0.01

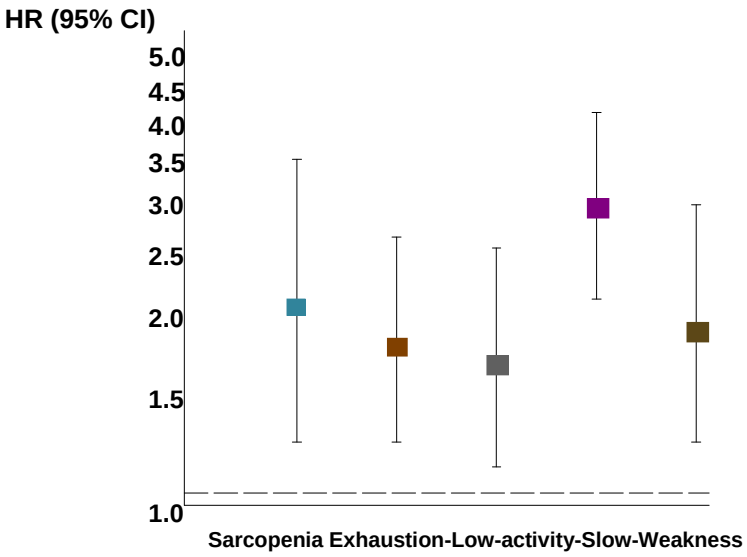


Figure 5.2 Mortality risk by components of frailty (FP)

Note:Adjusted for age,centre,BMI,smoking, alcohol consumption and comorbidities
HR=Hazard Ratios, CI=Confidence Intervals

	Count (%)			
Number of falls at Phase 2	**Total**	**Robust**	**Pre-frail**	**Frail**
0	1779 (72.8)	1365 (75.5)	401 (66.9)	13 (35.1)
1	404 (16.5)	282 (15.6)	111 (18.5)	11 (29.7)
2 or more	262 (10.7)	162 (9.0)	87 (14.5)	13 (35.1)
Number of GP visits				
Almost never	381 (15.9)	315 (17.9)	65 (10.9)	1 (2.9)
Rarely	878 (36.6)	693 (39.3)	180 (30.1)	5 (14.3)
About 4 times a year	759 (31.7)	526 (29.9)	215 (35.9)	18 (51.4)
About once a month or more	378 (15.8)	228 (12.9)	139 (23.2)	11 (31.4)

Table 5.3 Frailty status (FP), by number of falls and number of GP visits reported at follow-up

Chi-squared test p <0.005 for falls and no of GP visits and association with frailty status

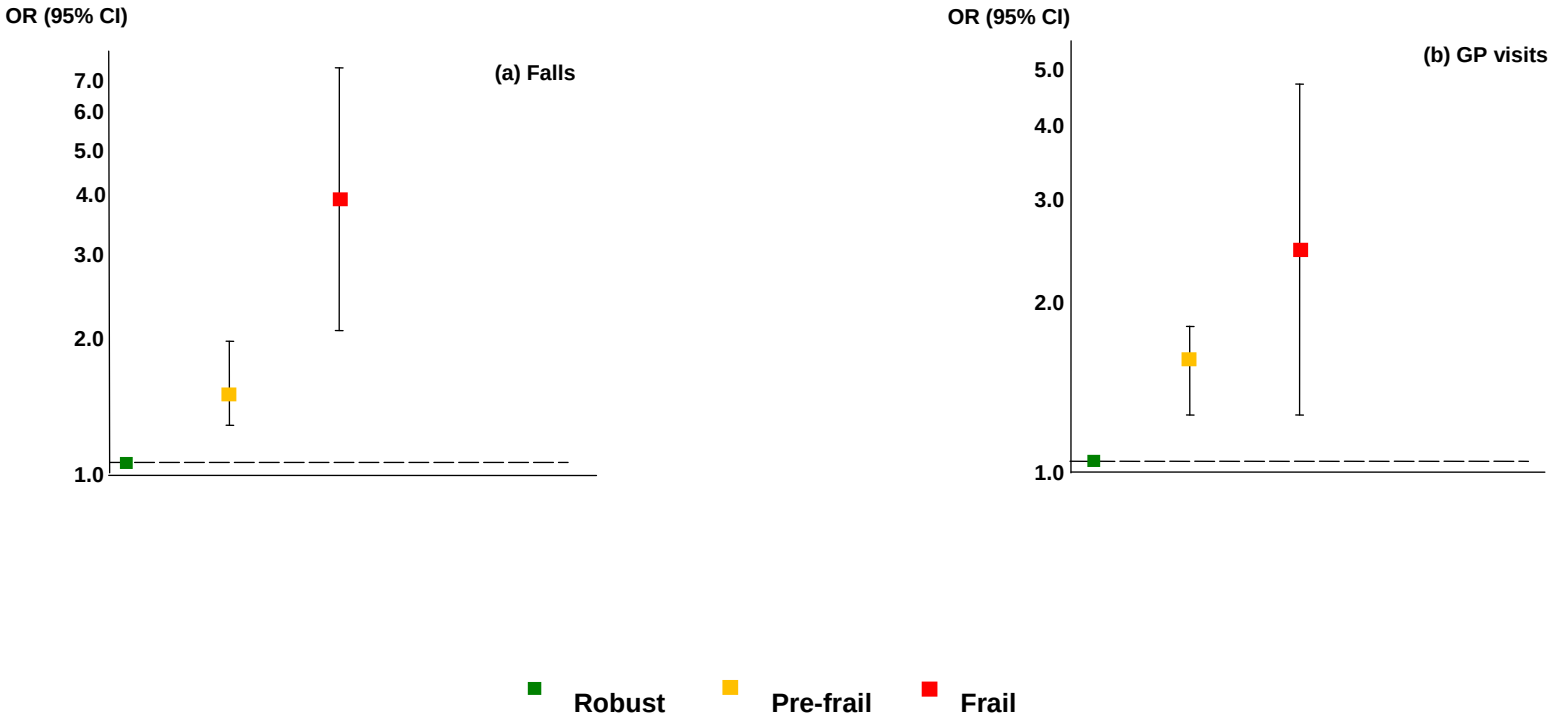


Figure 5.3 Ordinal logistic regression models for the relationship between FP frailty status and (a) falls (b) frequency of GP visits reported at follow-up

Note(a)Adjusted for age,centre,BMI,smoking, alcohol consumption and comorbidities; (b) adjusted for age and centre

5.5.4 Frailty (FS) and its association with mortality

Compared to those who took part at follow-up, those who died were more likely to be frail (FS) at baseline (1.9% vs. 12% respectively), (see Table 5.1). The survival curves of those who were frail, pre-frail and robust at baseline are shown in Figure 5.4, with a significant difference in survival between the groups (log rank of $p<0.001$). Using Cox proportional hazard models, those who were frail at baseline had a 9 fold increased risk of death and those who were pre-frail a 3.7 fold increased risk of death compared to those who were robust (see Table 5.4). This relationship remained significant after adjustment for age, centre, BMI, smoking and alcohol consumption, i.e. those men who were frail had a 4 fold increased risk of death (HR=4.5; 95% CI 2.6 to 7.5) and those who were pre-frail had a 2 fold increased risk of death (HR=2.2; 95% CI 1.5 to 3.0) compared to robust men (see Table 5.4). Further adjustment for depression in the model did not markedly change the nature of this association (data not shown). Each of the five FS frailty criteria also predicted mortality as shown in Figure 5.5. Of the FS criteria, ambulation (self-reported ability to walk 100m) was the strongest predictor of mortality (HR=2.8; 95% CI 1.9 to 4.1). There was no evidence of any interaction effects between FS frailty and centre, age or BMI (all $p>0.05$, data not shown).

5.5.5 Frailty (FS) and its association with falls and GP visits at follow-up.

2599 men had complete data available on falls at follow-up and FS at baseline and 2544 men had complete data on primary care visits at follow-up and FS at baseline. Of these, 419 (16%) reported one or more falls and 285 (11%) reported two or more falls in the previous 12 months. Similar to frailty assessed by the FP, a clear trend of an increase in the number of falls and an increase in the number of primary care visits was seen with an increase in frailty status, (see Table 5.5). For example, a greater proportion of frail men, 16 (33%), reported two or more falls compared to robust men, 181 (8.7 %). Similar trends were seen with primary care visits and an increased frailty status (FS). Using ordinal regression, the odds for having more falls (reference group = no falls) were higher in frail and pre-frail men compared to robust men, this remained significant after adjusting for age, centre, BMI, smoking and alcohol consumption, (see Figure 5.6). Similarly those men who were frail and pre-frail were more likely to attend their primary care physician than those who were robust (see Figure 5.6).

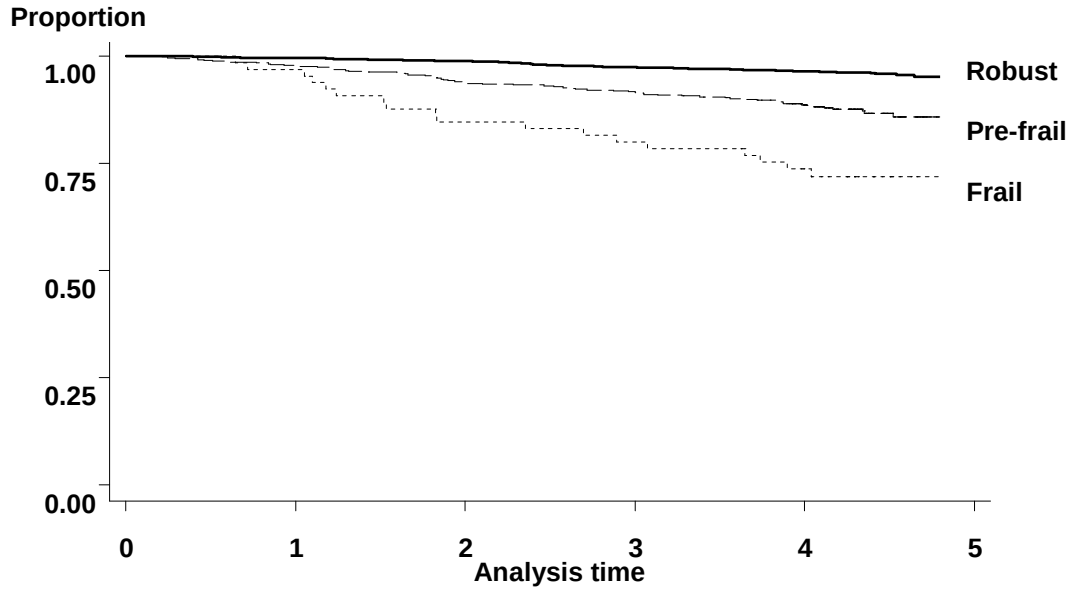


Figure 5.4 Survival curves by Frailty status (FS). Log rank p <0.001

	Hazard Ratios(95% Confidence Interval)		
	Unadjusted	**Model 1**	**Model2**
Robust	1.0	1.0	1.0
Pre-frail	3.7 (2.7 to 5.0)***	2.1 (1.5 to 2.9)***	2.2 (1.5 to 3.0)***
Frail	9.3 (5.7 to 15.0)***	4.2 (2.6 to 7.0)***	4.5 (2.6 to 7.5)***

Table 5.4 Risk of mortality by frailty status (FS): Cox Proportional Hazard model

Model 1 -adjusted for age and centre, Model 2- adjusted for age, centre, BMI, smoking and alcohol consumption ***p <0.001

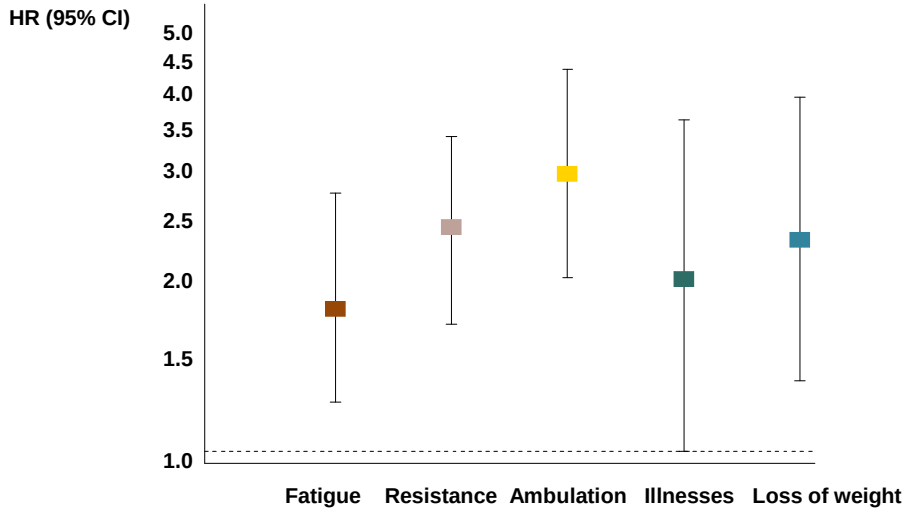


Figure 5.5 Mortality risk by components of frailty (FS)

Note:Adjusted for age,centre,BMI,smoking and alcohol consumption; HR=Hazard Ratio, CI=Confidence Intervals

Number of falls at Phase 2	Total	Robust	Pre-frail	Frail
0	1895 (72.9)	1581 (76.0)	292 (62.1)	22 (44.9)
1	419 (16.1)	318 (15.3)	90 (19.2)	11 (22.5)
2 or more	285 (11.0)	181 (8.7)	88 (18.7)	16 (32.7)
Number of GP visits				
Almost never	417 (16.4)	369 (18.1)	46(10.0)	2 (4.2)
Rarely	917 (36.1)	807 (39.7)	105(22.7)	5 (10.4)
About 4 times a year	798 (31.4)	599 (29.5)	182(39.4)	17 (35.4)
About once a month or	412 (16.2)	259 (12.7)	129(27.9)	24 (50.0)

Table 5.5 Frailty status (FS), by number of falls and number of GP visits reported at follow-up

Chi-squared test p <0.005 for falls and number of GP visits and its association with frailty status

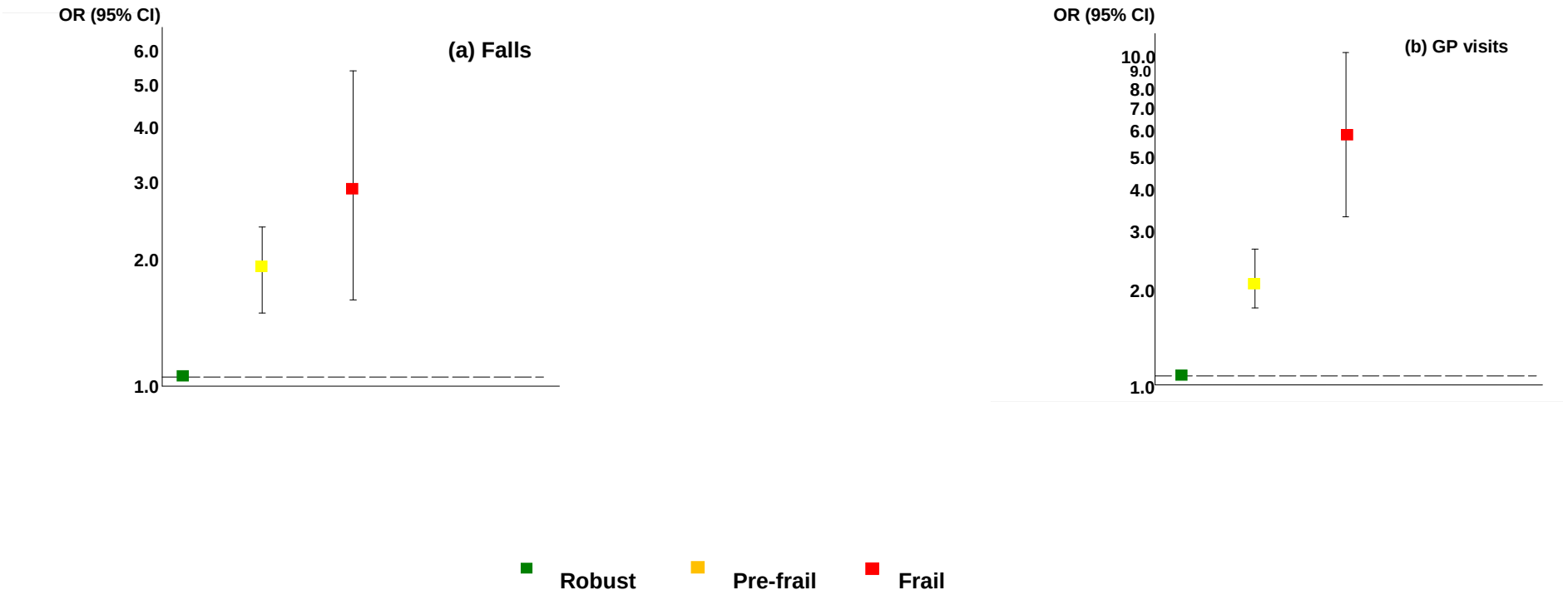


Figure 5.6 Ordinal logistic regression models for the relationship between FS frailty status and (a)falls (b) frequency of GP visitsreported at follow-up

Note(a)Adjusted for age,centre,BMI,smoking and alcohol consumption; (b) adjusted for age and centre

5.5.6 Frailty (FI) and its association with mortality

Compared to those who took part in the follow-up phase, those who died had a higher mean FI at baseline (0.12 vs. 0.25 respectively). This was also true when the FI was categorised into robust, pre-frail and frail with a higher proportion of men who were frail at baseline dying compared to those who were robust at baseline (16.1% vs. 2.3%, respectively), (see Table 5.1). The survival curves for those who were frail, pre-frail and robust at baseline are shown in Figure 5.7, with a significant difference in survival between groups (log rank of $p<0.001$). The probability of death increased significantly with each unit increase in FI (OR=2.04; 95% CI=1.85 to 2.27) and the probability of death also increased significantly with age (OR=1.10; 95% CI=1.08 to 1.12) (Figure 5.8).

Using Cox proportional hazards, those who were frail at baseline had a 12 fold increased risk of death and those who were pre-frail at baseline a 5 fold increased risk of death, compared to those who were robust (see Table 5.6). This association remained significant after adjustment for age, centre, BMI, smoking and alcohol consumption, i.e., those who were frail had a 4 fold increased risk of death (HR=4.4; 95% CI 2.8 to 7.1), and those who were pre-frail had a 2 fold increased risk of death (HR=2.1; 95%CI 1.5 to 3.0), compared to those who were robust (see Table 5.6). Further adjustment for depression in the model did not markedly change the nature of this association (data not shown). When the FI was examined as a continuous variable each unit increase in FI was significantly associated with an increased risk of death (HR=1.9; 95% CI 1.8 to 2.1). Further adjustment for age, BMI, smoking and alcohol consumption attenuated this relationship although it remained significant (HR=1.6; 95% CI 1.4 to 1.7). The majority of the deficits that were used to make the FI individually predicted mortality significantly, although there were a few exceptions such as problems with urination and certain comorbidities (Table 5.7). There was no evidence of an interaction between FI and centre, age or BMI (all $p>0.05$, data not shown).

5.5.7 Frailty (FI) and its association with falls and GP visits at follow-up.

Similar to the FP and FS models, the trend of an increase in number of falls and number of GP visits was seen with an increase in FI frailty status (Table 5.8). A greater proportion of frail men 29 (44.6%) reported two or more falls compared to robust men 179 (8%). Men who had two or more falls had a higher mean FI (0.19 (SD=0.14)) compared to men who had no falls (0.10 (SD=0.09)). The men who had more falls also had an increased number of deficits indicated by the FI count. Similar trends were seen with primary care visits and an increase in FI frailty status. Using ordinal regression, the odds for having more falls compared (reference group = no falls) was higher in frail and pre-frail men compared to robust men, and this remained significant after adjusting for age, centre, BMI, smoking and alcohol consumption, (see Figure 5.9). Similarly, those who were frail and pre-frail at baseline were more likely to use the services of their primary care physician than those who were robust (see Figure 5.9).

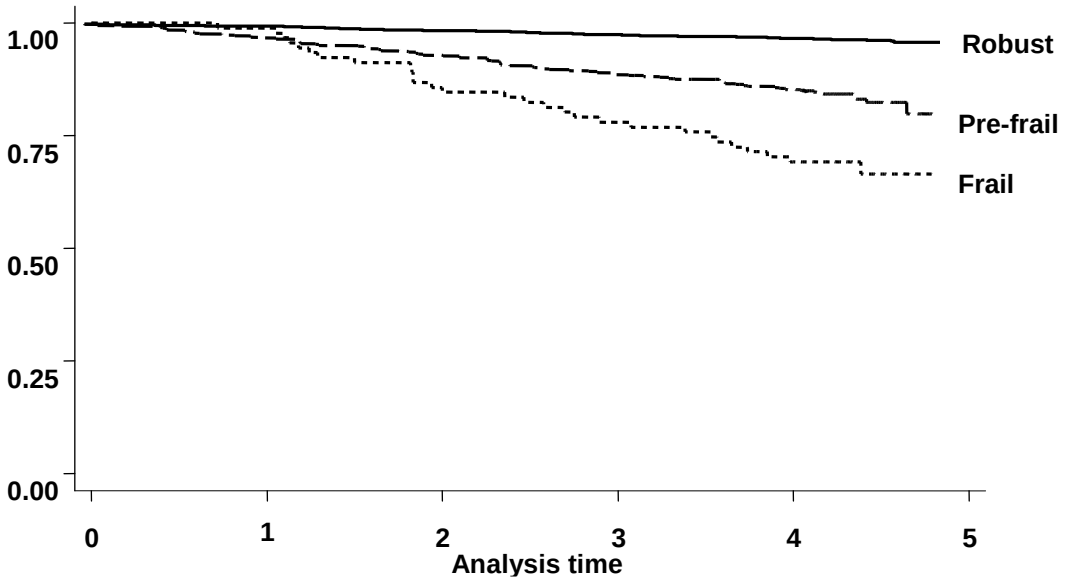


Figure 5.7 Survival curves by Frailty status (FI categorised). Log rank p <0.001

Robust: [FI <=0.2], Pre-frail: [FI 0.2-0.4], Frail: [FI >=0.4]

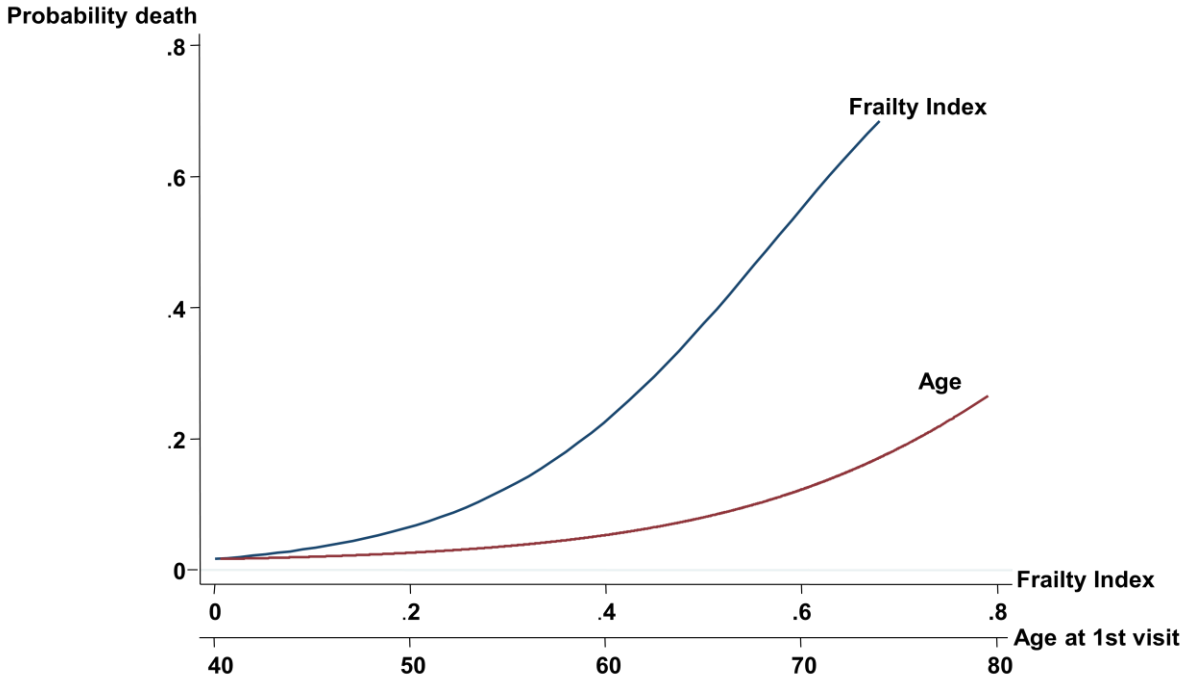


Figure 5.8 Probability curves of death by FI ( ) and by Age ( ) at baseline.

	Hazard Ratios(95% Confidence Interval)		
	Unadjusted	**Model 1**	**Model2**
Robust	1.0	1.0	1.0
Pre-frail	4.9 (3.6 to 6.7)***	2.2 (1.6 to 3.1)***	2.1 (1.5 to 3.0)***
Frail	11.6 (7.7 to 17.6)***	4.4 (2.8 to 7.0)***	4.4 (2.8 to 7.1)***
FI	1.9 (1.8 to 2.1)***	1.6 (1.4 to 1.7)***	1.6 (1.4 to 1.7)***

Table 5.6 Risk of mortality by frailty status (FI): Cox proportional Hazard Model

Model 1: adjusted for age and centre, Model 2: adjusted for age, centre, BMI, smoking and alcohol consumption ***p <0.001

		Hazard Ratio (95% CI)[a]	
		Unadjusted	**Model 1**
Deficit 1	Good/fair/poor self-rated general health†	3.1 (2.0 to 4.8)***	2.0 (1.2 to 3.3)*
Deficit 2	Need help feeding yourself	2.1 (1.3 to 3.3)**	1.8 (1.1 to 3.0)*
Deficit 3	Problems walking in your home	2.6 (1.6 to 4.2)***	1.3 (0.7 to 2.2)
Deficit 4	Need help bathing/dressing yourself	3.3 (2.2 to 4.8)***	2.1 (1.4 to 3.1)**
Deficit 5	Problems walking 1 km†	5.1 (3.8 to 6.9)***	2.6 (1.9 to 3.6)***
Deficit 6	Problems walking more than 1 km†	4.5 (3.4 to 6.0)***	2.4 (1.7 to 3.3)***
Deficit 7	Problems climbing one flight of stairs†	4.5 (3.3 to 6.1)***	2.4 (1.7 to 3.3)***
Deficit 8	Problems climbing several flights of stairs†	5.4 (4.0 to 7.3)***	2.7 (1.9 to 3.9)***
Deficit 9	Limited ability to do moderate activities†	4.4 (3.3 to 5.8)***	2.4 (1.7 to 3.2)***
Deficit 10	Limited ability to do vigorous activities†	4.3 (2.7 to 6.9)***	2.0 (1.2 to 3.2)**
Deficit 11	Accomplished less due to your physical health†	3.2 (2.4 to 4.2)***	1.8 (1.3 to 2.5)**
Deficit 12	Cut down on activities due to emotional problems†	3.3 (2.4 to 4.5)***	1.9 (1.3 to 2.7)***
Deficit 13	Did not feel full of life†	2.3 (1.7 to 3.1)***	1.8 (1.3 to 2.4)***
Deficit 14	Felt down in the dumps†	3.2 (2.3 to 4.4)***	1.7 (1.2 to 2.5)**
Deficit 15	Felt downhearted and low†	2.4 (1.8 to 3.3)***	1.5 (1.1 to 2.1)*
Deficit 16	Felt tired†	2.0 (1.5 to 2.8)***	1.5 (1.1 to 2.2)*
Deficit 17	Experienced serious illness or injury	2.7 (1.9 to 3.8)***	2.0 (1.3 to 2.9)***
Deficit 18	Experienced declines in sleep quality	1.8 (1.2 to 2.5)**	1.3 (0.9 to 1.9)
Deficit 19	Had difficulty in concentrating†	1.6 (1.2 to 2.2)**	1.0 (0.7 to 1.3)
Deficit 20	Had difficulty postponing urination†	1.4 (1.0 to 2.0)	1.1 (0.7 to 1.5)
Deficit 21	Has to get up in the night to urinate	1.7 (1.3 to 2.2)***	0.9 (0.7 to 1.3)

		Hazard Ratio (95% CI)[a]	
		Unadjusted	**Model 1**
Deficit 22	Had a weak urinary stream†	1.5 (1.1 to 2.1)*	0.8 (0.6 to 1.1)
Deficit 23	Poor visual-constructional ability	3.1 (2.2 to 4.4)***	1.6 (1.1 to 2.4)*
Deficit 24	Poor visuo-spatial recall	3.6 (2.5 to 5.1)***	2.1 (1.4 to 3.1)***
Deficit 25	Poor topographical recall	3.5 (2.5 to 5.0)***	1.5 (1.0 to 2.2)*
Deficit 26	Poor psychomotor processing speed	4.9 (3.6 to 6.7)***	1.9 (1.3 to 2.7)**
Deficit 27	Slow walk speed	5.9 (4.4 to 7.9)***	2.7 (1.9 to 3.7)***
Deficit 28	Poor postural/balance outcome	5.0 (3.5 to 7.2)***	2.7 (1.8 to 4.1)***
Deficit 29	Heart condition	3.1 (2.3 to 4.1)***	1.5 (1.1 to 2.1)*
Deficit 31	Bronchitis	4.0 (2.7 to 6.0)***	1.9 (1.2 to 2.9)**
Deficit 32	Asthma	1.9 (1.0 to 3.5)*	1.3 (0.7 to 2.5)
Deficit 33	Diabetes	2.7 (1.8 to 3.9)***	1.6 (1.1 to 2.5)*
Deficit 34	Liver condition	4.6 (2.7 to 7.9)***	2.8 (1.5 to 5.1)**
Deficit 35	Kidney condition	2.3 (1.3 to 4.3)**	1.3 (0.7 to 2.4)
Deficit 36	Prostate disease	2.0 (1.4 to 2.9)***	0.8 (0.5 to 1.2)
Deficit 37	Thyroid disease	2.0 (0.9 to 4.2)	1.0 (0.4 to 2.2)
Deficit 38	Cancer (ever)	3.1 (2.1 to 4.6)***	1.8 (1.2 to 2.7)**
Deficit 39	Stroke (ever)	5.0 (3.3 to 7.5)***	2.9 (1.8 to 4.4)***

Table 5.7 Mortality risk by FI deficits

[a] Cox proportional hazard models adjusted for baseline age, centre, BMI, smoking and alcohol consumption.

†These deficits are divided into three categories for inclusion in the EMAS FI, to calculate the Hazard ratios the defict if present to a certain degree coded as 0.5 was collapsed into those with deficit present as 1(so two categories instead of 3)

*p <0.05, **p <0.01, ***p <0.001

	FI count	FI	Robust	Pre-frail	Frail
	Mean ± SD			Count (%)	
Number. of Falls					
0	4.0 ± 3.5	0.10 ± 0.09	1698 (76.8)	236 (56.6)	26 (40.0)
1	5.3 ± 4.1	0.14 ± 0.11	334 (15.1)	92 (22.1)	10 (15.4)
2	7.2 ± 5.4	0.19 ± 0.14	179 (8.1)	89 (21.3)	29 (44.6)
Number of GP visits					
Almost never	2.5 ± 2.7	0.06 ± 0.07	409 (19.0)	18 (4.4)	3 (4.8)
Rarely	3.5 ± 2.9	0.09 ± 0.08	869 (40.3)	80 (19.3)	7 (11.1)
About 4 times a year	5.6 ± 4.1	0.14 ± 0.11	633 (29.4)	164 (39.6)	24 (38.1)
About once a month or more	7.7 ± 4.6	0.20 ± 0.12	245 (11.4)	152 (36.7)	29 (46.0)

Table 5.8 Frailty status (FI), by number of falls and number of GP visits reported at follow-up

Chi-squared test $p < 0.05$

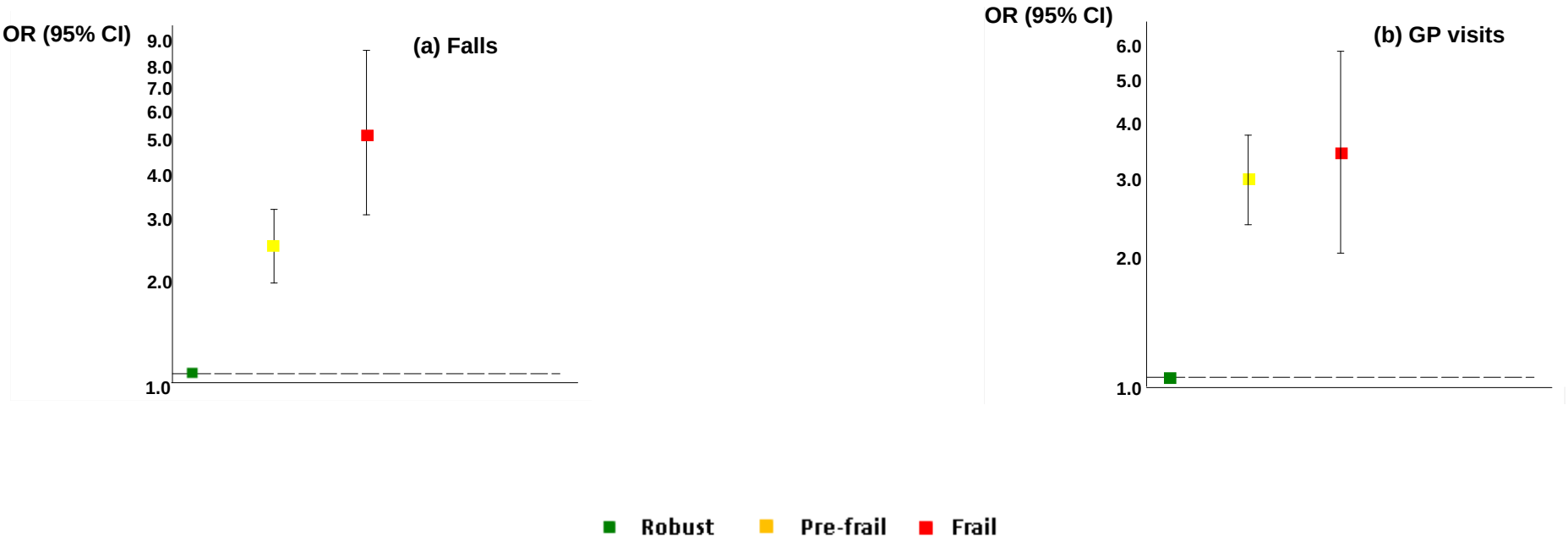


Figure 5.9 Ordinal logistic regression models for the relationship between frailty status (FI) and (a) falls, (b) frequency of GP visits reported at follow-up

Note(a)Adjusted for age,centre,BMI,smoking and alcohol consumption; (b) adjusted for age and centre

5.6 Discussion

In the analysis presented in this chapter, frailty defined using the FP, FS and FI were all associated with an increased risk of mortality and an increased risk of both falls and health care utilisation. Depending on the frailty model used there was approximately a 4-5 fold increased risk of death among those who were frail at baseline compared to those who were robust. The strength of these associations were attenuated, although remained significant after adjustment for age, centre, body mass index, smoking, alcohol intake and also comorbidities. The risk of death appeared greater in older (>65 years) than younger men. Although derived using different variables the magnitude of effect appeared broadly similar for the different frailty definitions. Similar positive associations were observed between all frailty models and the occurrence of falls and also health care utilisation as assessed by the number of visits to a primary care physician.

The major strengths of the study are its sample size and the standard methods used in recruitment and conduct of the study as discussed previously. The overall retention rate was also high (86%). There are, however, a number of limitations that need to be considered when interpreting these data. The overall loss to follow-up was 13%. Compared with participants, however, it has been shown that those lost to follow-up were likely to be current smokers (19.8% vs.29.2%, respectively), and as a consequence may have been at an increased risk of mortality, falls and GP attendance [295]. Findings concerning adverse outcomes amongst the participants may, therefore, have underestimated the true experience of the baseline cohort. However, the most important comparison was whether health status differed in a systematic fashion between subjects who participated and those lost to follow-up in relation to frailty status. No systematic differences were observed, and therefore losses to follow-up are unlikely to have influenced the main findings. Data on deaths was determined by a variety of measures. Efforts were made to determine vital status in all subjects. It was however not possible to determine the vital status of subjects lost to follow-up some of whom may have died. The effect of this would be to underestimate the mortality in the cohort. There are also possible differences in the quality of data available obtained on mortality, across centres which may have caused some variations in mortality. In the case of mortality data Manchester and Malmo was able to verify deaths by

the National Statistics records of Health and Welfare Statistical database and therefore more likely to be accurate though it does not exclude incomplete data. Efforts were made to characterise deaths in other centres using a variety of approaches though because of the potential for underreporting particularly caution is needed in interpretation of the data. EMAS cohort at baseline was a young cohort with an age range of 40-79 which is relatively a young age to study the frailty syndrome although studies have shown that factors influencing frailty begin in middle age [264, 296]. As some of the components used to measure frailty in the frailty models and are based on self-report it is possible that this is subject to recall bias. This may also be the case in reporting certain outcomes measured such as falls and visits to the doctor. Lastly EMAS was a relatively healthy community-based sample of European men and the models of frailty used here may perform differently with regard to predicting adverse outcomes in other settings.

As described above all measures of frailty were linked with an increased risk of mortality. There was however some differences in the risk of mortality for individual frailty components. In the FP definition, 'slowness' assessed by the time taken to walk 50 feet, was the strongest predictor of mortality with a HR of 2.8 (95% CI 2.0 to 3.9). In the FS, 'slowness' assessed by the self-reported ability to walk 100m was also the strongest criteria also in predicting mortality with a HR of 2.8 (95% CI 1.9 to 4.1). These data are in accord with previous findings showing that gait speed has strong and consistent associations with adverse outcomes and is often considered the 'best' marker of frailty in clinical and research settings [40, 297, 298] [6]. It has been shown also that older frail individuals are unable or having difficulty completing physical tests [299] making self-reported measures ideal to identify frail individuals.

The results are similar to previous studies which have shown that adverse outcomes were more common in frail individuals however frailty was measured [3, 5, 60, 285, 300-303]. In the original CHS study, in which the phenotypic frailty model was developed, frailty status was not as strongly linked with mortality as in EMAS with an adjusted HR for death of 2.2 (95% CI 1.5 to 3.3) at 3 years follow-up and an adjusted HR for death of 1.6 (95% CI 1.3 to 2.1) at 7 years of follow-up [5]. It is possible that differences in cohort composition (men and women) may have explained these discrepant findings. The results also support previous studies which

have shown that at any given age a higher FI is associated with increased mortality and the FI predicts death better than chronological age [33, 61, 304]. There are relatively few data on frailty from Europe particularly among men. Overall, the data presented in this chapter support findings from most, though not all, of the studies suggesting an increased risk of mortality linked with frailty in this population-based setting. Thus in the Survey of Health, Ageing and Retirement in Europe (SHARE), frailty status was associated with an increased risk of death in both women; Odds Ratio (OR=4.8 (95% CI 3.1 to 7.4)) and in men aged ≥50 years (OR=6.9 (95% CI 4.7 to10.2) [33]. Frailty, identified as the presence of low energy intake and weight loss in the Zutphen Elderly study on 450 men aged 69-89 years, was linked with a 4 fold increased odds of mortality after 3 years of follow-up [75]. In another cohort of men in Finland (Helsinki Businessmen Study) frailty and pre-frailty significantly predicted mortality after 8 years of follow-up with an adjusted HR of 4.1 (95% CI 2.6 to 6.4) for frail men and an adjusted HR of 2.3 (95% CI 1.6 to 3.3) for pre-frail men, compared to those who were robust [305]. In contrast to these observations, a study of French community dwelling elderly men and women aged ≥65 years found no association between frailty and mortality after adjustment for confounders [28], while a study of 687 community dwelling elderly people aged 70 & over in the Netherlands found frailty status as assessed using a 3-item self-reported screening instruments was a poor predictor of mortality (and also disability and hospital admissions) [306]. In EMAS the risk of falling was significantly increased among those who were frail as compared to those who were robust. These findings are consistent with a number of earlier studies [3, 5, 31, 293, 301], although in a recent study [307] community dwelling older adults aged >=65 years, frailty was linked with two or more falls only in those aged over 75 years old. However, in this study frailty was assessed using a different method [78] which included somatic, psychological and cognitive markers and it is possible, therefore that this could explain the discrepancies with the findings reported in this thesis. Another study [37], the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE), among men and women aged 65 and over has shown that those individuals of pre-frail had an increased risk of future falls compared to those who were frail, suggesting that pre-frail individuals may be more prone to falling perhaps as a result of being more mobile and/or having less social support. Data presented in this chapter fails to show such

a relationship, this may be due in part to cultural and socio-economic differences between the samples [308].

In the analyses presented above there was a trend of increased visits to the primary care physician associated with frailty status. As expected once adjusted for illnesses in the FP model the relationship was no longer significant in the FP model. Studies on the use of health services and its association with frailty status are limited. Physical frailty measured by the Tilburg frailty indicator (a measure of frailty which contains self-reported questions excluding any questions related to disability covering physical, psychological and social domains) has been shown to be associated with an increased use of health care services [309]. In a study of older adults in Canada, frailty status was not, however, linked with emergency department (ED) visits [310]. Hastings *et al* also showed that frailty status did not predict repeat visits to the ED [311]. However, a study on a Italian community dwelling cohort showed that frailty status was associated with an increased risk of ED admission (OR=1.8 95%CI 1.01 to 3.35,p=0.05) [301]. Taken together with the data presented in the chapter the impression is that there is an increased tendency for frail older people to visit non-emergency services for care. This in turn is almost certainly related to their increased risk of developing new illnesses [311] and also for the treatment of pre-existing conditions.

5.7 Conclusion

In summary, frailty status predicted an increased risk of mortality, an increased likelihood of falling and an increased frequency of primary care visits. The prediction of an increased mortality risk by increasing levels of frailty among middle-aged and older European men was approximately the same irrespective of the frailty measure used.

Chapter 6 Frailty and Measures of Adiposity

6.1 Summary

In this chapter the results of analyses looking at the association between frailty and measures of adiposity assessed at the baseline phase of EMAS are presented. Measures of adiposity included body mass index (BMI), waist circumference (WC), waist hip ratio (WHR) and % body fat (assessed using skin fold thickness). Frailty was assessed using the Fried Phenotype (FP) model, FRAIL scale (FS) and the Frailty Index (FI). All adiposity measures were assessed continuously (z scores) and categorically (either based on existing World Health organisation cut-points or tertiles/quartiles). The association between frailty (FP & FS) and these adiposity measures was examined using multinomial logistic regression, and the association between FI and the adiposity measures was examined by multiple linear regressions. The association between individual FP and FS criteria and adiposity measures was assessed using binary logistic regression. The prevalence of frailty assessed using the FP and the FS was higher in the lower and upper quartiles of certain adiposity measures, whereas frailty assessed by the FI tends to increase with increase in adiposity measure. Of the adiposity measures WC was the only measure which showed a consistent association with frailty assessed by all 3 frailty models. Using multinomial logistic regression, a 1 SD increase in WC was associated with frailty assessed both by the FS and the FP; however, the association with frailty defined by FP was attenuated and became non-significant after adjusting for age and centre. A 1 SD increase in WC was also associated with a 15.2% increase in the FI score and the Relative Risk Ratios (RRR) for frailty assessed by the FS was 1.4. Of the FP criteria, slowness, exhaustion and low activity, were associated with adiposity measures and of the FS criteria, fatigue, ambulation, resistance and, illness>=5 were associated with increase in adiposity measures. Sarcopenia was not associated with any of the adiposity measures; however, the odds of sarcopenia were higher in the lower quartile of adiposity measures. In this cross-sectional analysis obesity, and in particular central obesity as determined using WC, appears to be associated with frailty status.

6.2 Introduction

Body composition changes with age include a decrease in skeletal muscle mass and lean mass and an increase in fat mass [243, 312]. The distribution of fat mass also changes with age, with an increase in abdominal fat. These changes in body composition in the elderly are not entirely due to the imbalance between energy intake and energy expenditure. Other age-related conditions, such as changes in sex, metabolic and growth hormones, and also changes related to nutrient intake, absorption and metabolism and the burden of chronic illness [313], play a role in altering body composition measures. A number of studies suggest obesity is linked with frailty [150, 259]. However, there is not much data linking measures of increased adiposity and frailty in European populations, and also using different approaches to defining frailty. The hypothesis underlying the work presented here is that frailty is associated with adiposity.

6.3 Aims

The broad aim of the work described in this chapter was to determine the relationship between adiposity measures and frailty. The specific objectives were i) to determine whether there is an association between adiposity measures including waist circumference, BMI, Waist hip ratio and percentage body fat, and frailty using established criteria, and ii) to determine whether the strength of any observed association varies by both the adiposity measure and also frailty criteria used.

6.4 Methods

Detailed methods for the EMAS study, including recruitment and also exposures assessed at baseline, have been summarised in the Chapter 3. In this chapter, further details about the assessment of measures of adiposity are presented, including body mass index, (BMI), waist circumference (WC), waist hip ratio (WHR) and % body fat, and also the statistical analysis undertaken.

6.4.1 Anthropometric assessment

Body weight was measured using electronic scales (SECA, model no.8801321009) to the nearest 0.1kg and height was determined by using a stadiometer to the nearest 1mm. Measurements were repeated twice and the highest reading recorded. Body mass index was

recorded as weight in kg divided by height in m^2. A flexible measurement tape was used to record waist, hip, mid-calf and mid-upper arm circumference. Three measurements were repeated at each site and the median of all the readings was recorded. All measurements were taken on the left side of the body. Waist circumference was measured between the tips of the lowest ribs and the tips of the hipbones. Hip circumference was measured as the widest part of the hips. Mid-calf circumference was measured as the area between the top of the knees and the malleolus. The mid upper arm was initially identified as midway between the top of the arm and the tip of the elbow, and the anthropometric tape placed horizontally to measure the mid upper arm circumference.

Measurements of skinfold were made at the biceps, triceps, sub scapular and supra iliac regions using calipers (HSK-BI, Harpenden, Baty International, Burgess Hill, UK). The median of the 3 readings was recorded. Body fat was calculated by the Siri formula, which combines the median circumferences of the triceps, supra ililac, sub scapular and biceps [314]. Further details of the measurements are provided in Appendix 2.

6.4.2 Assessment of adiposity measures

BMI, WC, WHR and % body fat were standardized into z scores, which is a unit-free measure (per standard deviation change), and also categorised into quartiles and, where available with World Health Organisation (WHO) cut-points [315, 316] or tertiles in the case of WHR and % body fat. Individuals are defined as obese by the WHO if they have a BMI of ≥30 kg/m^2, overweight having a BMI in the range of (25-30) kg/m^2 and normal as ≤25 kg/m^2. Those having a BMI ≤18 kg/m^2 are categorised as underweight and those who have a BMI of ≥40 kg/m^2 are categorised as morbidly obese. Due to the small number of men in underweight and morbidly obese groups (n=9 were underweight & n=31 were morbidly obese) the underweight were pooled into the normal group and the morbidly obese to the obese category. Men having a WC of 94-102 cm are considered at high risk for metabolic disorders and those with a WC of ≥102 cm at even greater risk, according to the guidelines proposed by the WHO [315]. The WHO cut-point for WHR is >1.00 in men, similar to the upper tertile of WHR in the EMAS data set, and so this variable was categorised as tertiles. There are no categories provided by the WHO for % body fat.

6.4.3 Frailty models

The Frailty models used included the Frailty Index (FI), an operationalized Frailty Phenotype (FP) and the FRAIL scale (FS). The construction and operationalization of the models are described in detail in Chapter 3 (FI & FP) and Chapter 4 (FS).

6.4.4 Statistical Analysis

Descriptive statistics were used to describe the distribution of measures of adiposity by frailty status. Smoking in the analysis was categorised as current/never/ex-smoker. Alcohol consumption was categorised as drinking 5 days or more/less than 5 days. Comorbidities were categorised as none or any (1 or more). The association between frailty status and the measures of adiposity was assessed, visually by plotting the prevalence of frailty/pre-frailty by quartiles of the adiposity measures. In the case of the FI, the mean and median FI was plotted by quartiles of the adiposity measures. Differences in the measures of adiposity by frailty status were tested using analysis of variance (ANOVA) or Kruskal-Wallis for continuous variables, and Chi-square tests for categorical variables. Spearman correlations were used to examine the associations between Frailty Index (FI) and the various continuous adiposity measures. The relationship between FI and adiposity was explored also graphically (adjusting for age) using the Locally Weighted Scatter plot Smoothing technique (LOWESS) plot [317]. This is an exploratory analysis where linear regression is repeated to small sections of the linear relationship between the independent variable and the outcome variable.

Multinomial logistic regression was used to explore the association between the various adiposity measures and frailty status assessed by FP and FS with frailty as the outcome and the results expressed as relative risk ratios (RRR) with 95% Confidence Intervals (CI). Multiple linear regressions were used to assess the relationship between the various adiposity measures and frailty measured by the FI. As the distribution of the FI was positively skewed, it was transformed using the natural logarithm prior to the regression analysis. Post-analysis of the regression where FI was log transformed confirmed that the residuals approximated a normal distribution (data not shown). In order to interpret the results as an average percentage change in FI for a unit/category change in adiposity, the regression coefficients were expressed as 100 X(exp(ß coefficient)- 1). In all these models adjustments were made initially for age and centre

and subsequently for smoking and alcohol. In the case of frailty assessed by the FP it was further adjusted for comorbidities, this adjustment was not done when frailty was assessed by the FS and FI as comorbidities contributed to the development of the frailty models. Finally, the association between adiposity measures and the individual items of the models FS and the FP was further explored using binary logistic regression models with the results were expressed as Odds Ratio(OR) and 95% confidence intervals (CI).

6.5 Results

6.5.1 Participant Characteristics

The mean age of the EMAS men at baseline was 60.0 years (SD=11.0), mean BMI was 27.7 kg/m^2 (SD=4.1), WC 98.5 cm (SD=11.1), WHR 0.98(SD=0.06) and % body fat 28 (SD=5), (Table 6.1). Fifty six men had missing data for weight or height which precluded assessment of BMI, 50 men had missing data for WC, 53 for WHR and 57 for percentage (%) body fat.

6.5.2 Frailty assessed using FP and measures of adiposity

As outlined in Chapter 4 the prevalence of frailty in EMAS men, using the Frailty Phenotype was 2.6%, pre-frailty 26.9% and robust 70.5%. Both WC and WHR were significantly greater in those who were frail than either pre-frail or robust, though there was no statistically significant difference in BMI or % body fat. However, when BMI was categorised into normal, overweight and obese, there was a significant association with frailty status. WC categories and WHR tertiles also showed a significant association with frailty status (Table 6.1). When categorised into quartiles there was an increase in the prevalence of frailty and pre-frailty with increasing quartile of WHR (Figure 6.1). There was less of a clear linear relationship for the other adiposity measures. Using frailty (FP) as the dependent variable with the robust category as referent, increased levels of WC (per 1 SD increase) were associated with being pre frail (RRR=1.2; 95% CI; 1.1 to1.3) and frail (RRR=1.3; 95% CI; 1.0 to1.6), (Table 6.2). The associations, however, became non-significant after adjustment for age and centre. Increased WHR (per 1 SD increase) was associated also with being pre-frail (RRR=1.2; 95%CI; 1.1 to 1.3), though after further adjustment for smoking, alcohol intake and comorbidities, the association became non-significant. An increase in 1 SD of BMI or % body fat was not linked with frailty status.

Because of the non-linear relationship between BMI and waist circumference with pre-frailty (Figure 6.1), with a nadir at the second quartile, this quartile was used as the referent category in subsequent analysis. Compared to those in the second quartile, those with a BMI in the lowest quartile and those in the upper quartile were more likely to be pre-frail than robust, (Table 6.2). After adjustment for age, centre and life style factors, the RRR of being pre frail compared to being in the robust category for those with a BMI in the lowest quartile compared with those in the second quartile of BMI was 1.7. The RRR for men with a BMI in the upper quartile compared with the reference category (second quartile) was 1.3 (both significant). Similar increased RRR's were seen for the comparison between frail and robust; however, these associations were not significant, (Table 6.2).

Compared to those in the second quartile, those with a WC in the upper and also lower quartile were more likely to be frail and pre-frail than robust. After adjustment for age, centre, smoking, alcohol consumption and comorbidities, the RRR for being pre-frail over robust for men in the lowest (vs second) quartile of WC was 1.7, and for those in the highest (vs second) quartile it was 1.7. After adjustment for age, centre, smoking, alcohol consumption and comorbidities the RRR for being frail over robust for men in the lowest (vs second) quartile of WC was 2.6, and for those in the highest (vs second) quartile it was 2.1 (all values significant), (Table 6.2).

Obesity categorised using WHO cut-points as well as WHR and % body fat in the upper tertile (compared to those who were normal or in the lowest tertile) was not linked with an increased risk of frailty or pre-frailty (data not shown).

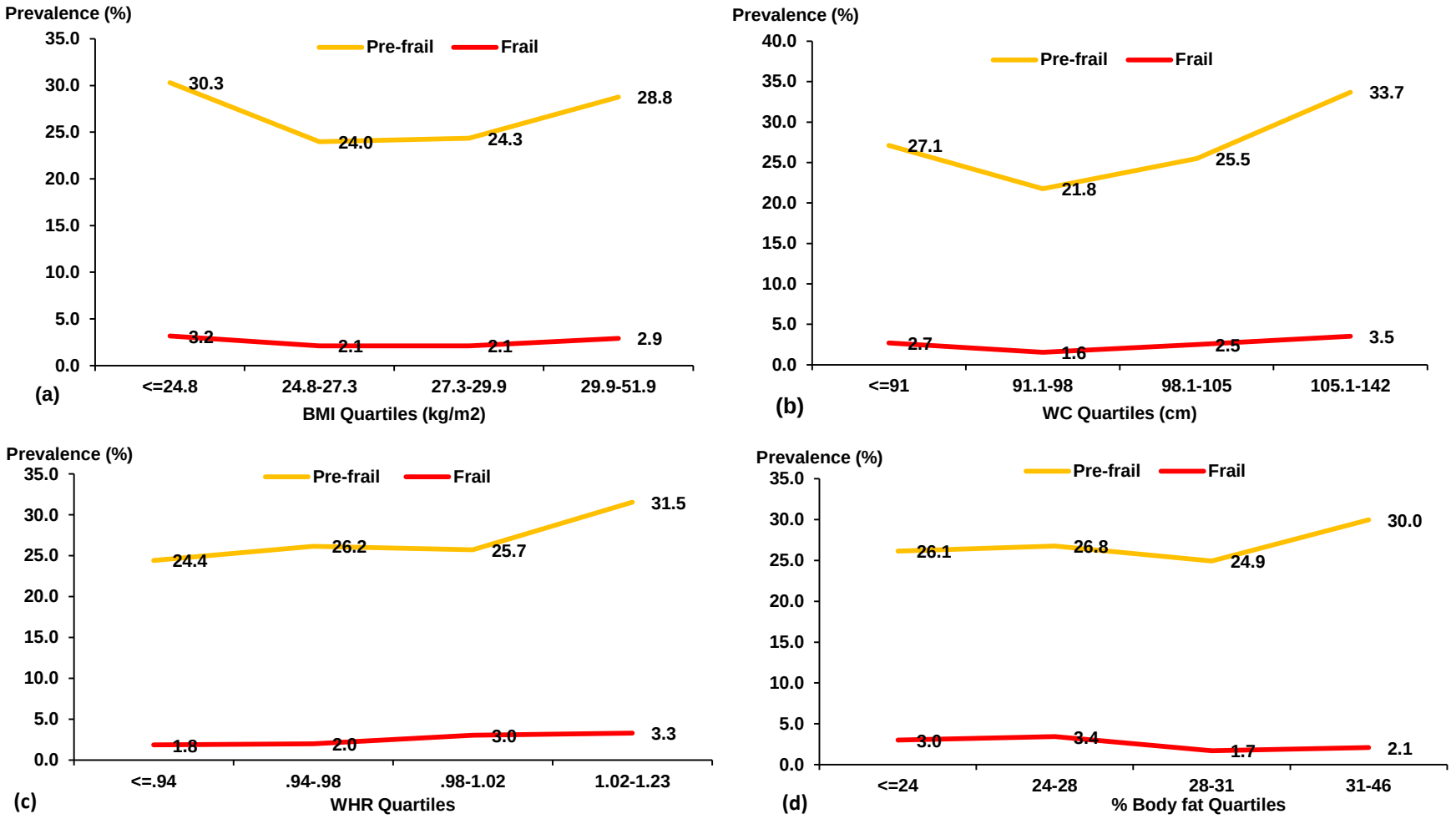
Variable	Total 3047 (100%)	Robust 2148 (70.6%)	Pre-frail 821 (26.9%)	Frail 78 (2.6%)	p value
	Mean ± SD				
BMI (kg/m^2)	27.7 ± 4.1	27.7 ± 3.8	27.7 ± 4.7	28.1 ± 5.7	0.6˜
WC (cm)	98.4 ± 11.1	97.9 ± 10.3	99.6 ± 12.6	100.6 ± 15.0	<0.001˜
WHR	0.98 ± 0.06	0.98 ± 0.06	0.99 ± 0.06	0.99 ± 0.07	<0.001˜
% Body Fat	28.0 ± 5	28.0 ± 5	28.0 ± 6	27.0 ± 7	0.1˜
	Count (%)				
BMI Categories (kg/m^2)					
Normal (≤25)	798 (26.3)	531 (24.8)	241 (29.6)	26 (33.3)	0.001*
Overweight (25-30)	1496 (49.3)	1108 (51.7)	358 (43.9)	30 (38.5)	
Obese (≥30)	742 (24.4)	504 (23.5)	216 (26.5)	22 (28.2)	
WC Categories (cm)					
<94	1063 (34.9)	764 (35.6)	270 (32.9)	29 (37.2)	<0.001*
94-102	918 (30.1)	684 (31.8)	222 (27.0)	12 (15.4)	
>=102	1066 (35.0)	700 (32.6)	329 (40.1)	37 (47.4)	
WHR Tertiles					
≤.95	1016 (33.4)	740 (34.5)	257 (31.3)	19 (24.7)	<0.01*
.96-1.01	1015 (33.3)	737 (34.3)	251 (30.6)	27 (35.1)	
1.01-1.23	1015 (33.3)	671 (31.2)	313 (38.1)	31 (40.3)	
% Body Fat Tertiles					
≤26	1019 (33.5)	716 (33.4)	275 (33.5)	28 (35.9)	0.7*
26-30	1014 (33.3)	730 (34.0)	259 (31.6)	25 (32.1)	
30-46	1011 (33.2)	700 (32.6)	286 (34.9)	25 (32.1)	

Table 6.1 Adiposity measures (baseline phase) by frailty status (FP).

˜ ANOVA,* Chi-square tests

BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

Figure 6.1 Prevalence of pre-frailty and frailty (FP) by quartiles of adiposity measures (a) BMI (b) WC (c) WHR (d) % Body fat



	Relative Risk Ratios (95% Confidence Intervals)					
	Unadjusted		Model 1		Model 2	
Adiposity measure	**Pre-frail**	**Frail**	**Pre-frail**	**Frail**	**Pre-frail**	**Frail**
BMI (per 1SD increase)	1.0 (0.9 to 1.1)	1.1 (0.9 to 1.4)	1.0 (0.9 to 1.1)	1.0 (0.8 to 1.3)	1.0 (0.9 to 1.0)	1.0 (0.8 to 1.3)
WC (per 1SD increase)	1.2 (1.1 to 1.3)***	1.3 (1.0 to 1.6)*	1.1 (1.0 to 1.2)	1.0 (0.8 to 1.3)	1.1 (1.0 to 1.2)	1.0 (0.8 to 1.3)
WHR (per 1SD increase)	1.2 (1.1 to 1.3)***	1.2 (1.0 to 1.5)	1.1 (1.0 to 1.2)*	1.0 (0.8 to 1.3)	1.0 (0.9 to 1.0)	1.0 (0.8 to 1.3)
% Body fat (per 1SD increase)	1.0 (1.0 to 1.1)	0.8 (0.7 to 1.0)	1.0 (0.9 to 1.1)	0.8 (0.6 to 1.1)	1.0 (0.9 to 1.0)	0.8 (0.6 to 1.1)
BMI Quartiles (kg/m^2)						
≤ 24.8	1.4 (1.1 to 1.8)**	1.7 (0.9 to 3.2)	1.7 (1.3 to 2.2)***	2.2 (1.1 to 4.3)*	1.7 (1.3 to 2.2)***	1.9 (0.9 to 3.7)
24.8 - 27.2	Reference		Reference		Reference	
27.2 - 29.9	1.0 (0.8 to 1.3)	1.0 (0.5 to 2.0)	0.9 (0.7 to 1.2)	0.8 (0.4 to 1.6)	0.9 (0.7 to 1.2)	0.8 (0.4 to 1.6)
29.9 - 45.7	1.3 (1.1 to 1.7)*	1.5 (0.8 to 2.9)	1.4 (1.1 to 1.8)*	1.4 (0.7 to 2.7)	1.3 (1.0 to 1.7)*	1.2 (0.6 to 2.4)
WC Quartiles (cm)						
>=91	1.4 (1.1 to 1.7)*	1.9 (0.9 to 3.9)	1.7 (1.3 to 2.2)***	2.7 (1.3 to 5.6)**	1.7 (1.3 to 2.2)***	2.6 (1.2 to 5.8)*
91.1-98	Reference		Reference		Reference	
98.1-105	1.2 (1.0 to 1.6)	1.7 (0.8 to 3.6)	1.2 (0.9 to 1.5)	1.5 (0.7 to 3.2)	1.1 (0.9 to 1.5)	1.4 (0.7 to 3.1)
105.1-155	1.9 (1.5 to 2.4)***	2.8 (1.4 to 5.5)**	1.8 (1.4 to 2.3)***	2.3 (1.1 to 4.7)*	1.7 (1.3 to 2.2)***	2.1 (1.01 to 4.5)*
WHR Quartiles						
<=.94	0.9 (0.7 to 1.2)	0.8 (0.4 to 1.5)	1.1 (0.8 to 1.4)	1.0 (0.5 to 2.1)	1.1 (0.9 to 1.4)	1.0 (0.4 to 2.0)
.94-.98	Reference		Reference		Reference	
.98-1.02	1.0 (0.8 to 1.3)	1.1 (0.6 to 2.2)	1.0 (0.8 to 1.2)	1.0 (0.5 to 2.0)	1.0 (0.8 to 1.2)	0.9 (0.5 to 1.8)
1.02-1.19	1.3 (1.1 to 1.7)*	1.6 (0.8 to 2.9)	1.2 (1.0 to 1.6)	1.3 (0.7 to 2.4)	1.2 (0.9 to 1.5)	1.1 (0.6 to 2.0)

	Relative Risk Ratios (95% Confidence Intervals)					
	Unadjusted		**Model 1**		**Model 2**	
	Pre-frail	**Frail**	**Pre-frail**	**Frail**	**Pre-frail**	**Frail**
% Body Fat Quartiles						
≤24	1.0 (0.8 to 1.2)	0.9 (0.5 to 1.5)	1.1 (0.8 to 1.4)	0.9 (0.5 to 1.7)	1.0 (0.8 to 1.3)	0.8 (0.4 to 1.5)
24-28	Reference		Reference		Reference	
28-31	0.9 (0.7 to 1.1)	0.5 (0.2 to 1.0)*	0.9 (0.7 to 1.1)	0.5 (0.3 to 1.0)	0.8 (0.7 to 1.1)	0.5 (0.2 to 1.0)
31-45	1.1 (0.9 to 1.4)	0.6 (0.3 to 1.2)	1.2 (0.9 to 1.5)	0.7 (0.4 to 1.4)	1.1 (0.8 to 1.4)	0.6 (0.31 to 1.2)

Table 6.2 Multinomial logistic regression: association of frailty status (FP) with adiposity measures

Multinomial logistic regression models: Model 1 adjusted for age and centre. Model 2 adjusted for age,centre,smoking,alcohol consumption and comorbidities: Comorbidities included heart condition, high blood pressure, stroke, cancer, bronchitis, asthma, peptic ulcer, epilepsy,diabetes, and liver, kidney and prostate diseases.
Relative Risk Ratios(RRR) corresponds for a 1SD increase in adiposity measure (continuous) or in comparison to the referent category in adiposity categories.SD, standard deviation; BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio, *p <0.05,**p <0.01,***p <0.001,

6.5.3 Association of adiposity measures with frailty status (FS)

The prevalence of frailty in EMAS men using the FS was 2.7%, pre-frailty was 20.1% and robust was 77.2%. Similar to the FP, both WC and WHR were significantly greater in those who were frail than those who were pre-frail or robust, though there was no significant difference in BMI or % body fat. However, when BMI was categorised into normal, overweight and obese, there was a significant association with frailty status. WC categories and WHR tertiles also showed a significant association with frailty status, but % body fat tertiles did not show any significant association with frailty status, (Table 6.3). When categorised into quartiles there was an increase in the prevalence of frailty and pre-frailty with increasing quartile of WHR, (Figure 6.2). The relationships with the other adiposity measures were less clearly linear. Using frailty (FS) as the dependent variable, with the robust category as referent, increased levels of WC (per 1SD increase) were associated with being pre-frail (RRR=1.1; 95% CI; 1.0 to 1.2) and frail (RRR=1.4; 95% CI; 1.2 to 1.7) and increased levels of WHR (per 1SD increase) were also associated with being pre-frail (RRR=1.2; 95% CI; 1.1 to 1.3) and frail (RRR=1.3; 95% CI; 1.0 to 1.6). However, the associations between pre-frailty and increased WC (1SD increase), and frailty and increased WHR (per 1SD increase), became non-significant after adjustment for age and centre. Increased WC (per 1 SD increase) remained significantly associated with frailty, and increased WHR (per 1SD increase) with pre-frailty, even after further adjustment for smoking and alcohol intake. An increase in 1 SD of BMI or % body fat was not linked with frailty status.

Using the second quartile as referent category, those with a BMI in the lowest quartile and those in the upper quartile were more likely to be pre-frail than robust. After adjustment for age, centre and life-style factors, the RRR of being pre frail compared to being in the robust category for those with a BMI in the lowest quartile compared with those in the second quartile of BMI was 1.8. The RRR for men with a BMI in the upper quartile compared with the reference category (second quartile) was 1.7 (both significant). Similar increased RRR's were seen for the comparison between frail and robust; however, neither of these associations was significant after adjustment for confounders.

Compared to those in the second quartile, those with a WC in the upper and also lower quartile were more likely to be frail and pre-frail than robust. After adjustment for age, centre,

smoking and alcohol consumption, the RRR for being pre-frail over robust for men in the lowest (vs. second) quartile of WC was 1.8, and for those in the highest (vs. second) quartile it was 2.0. After adjustment for confounders, the RRR for being frail over robust for men in the lowest (vs. second) quartile of WC was 3.2 and for those in the highest (vs. second) quartile it was 4.3. The associations were all significant. Compared to those in the second quartile those with a WHR in the upper and also lower quartile were more likely to be pre-frail than robust, after adjustment for confounders. Pre-frailty was also significantly associated with increased body fat in the upper quartile (vs. second) quartile compared to robust men, see Table 6.4.

Similar to FP, obesity categorised using WHO cut-points as well as WHR and % body fat in the upper tertile (compared to those who were normal or in the lowest tertile) was not linked with an increased risk of frailty or pre-frailty (data not shown).

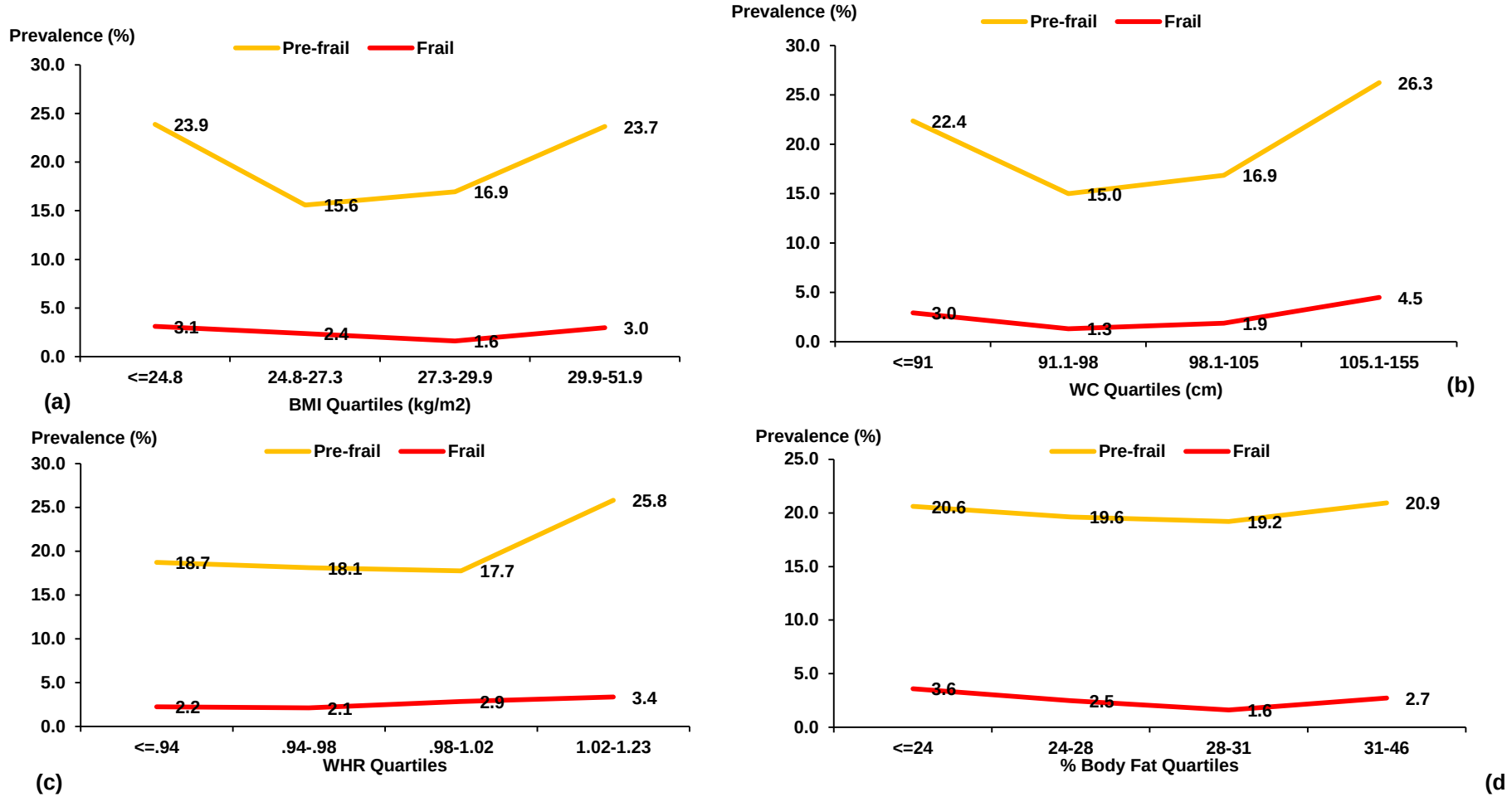
	Total	Robust	Pre-frail	Frail	
	3228 (100%)	2493 (77.2%)	649 (20.1%)	86 (2.7%)	
		Mean ± SD			p value
BMI(kg/m^2)	27.7 ± 4.1	27.7 ± 3.8	27.8 ± 5.0	28.3 ± 6.5	0.3˜
WC (cm)	98.5 ± 11.1	98.1 ± 10.2	99.5 ± 13.0	102.2 ± 17.2	<0.001˜
WHR	0.99 ± 0.06	0.98 ± 0.06	0.99 ± 0.07	1.00 ± 0.07	<0.001˜
% Body Fat	28.0 ± 5	28.0 ± 5	28.0 ± 6	27.0 ± 7	0.5˜
		Count (%)			
BMI Categories (kg/m^2)					
Normal (≤25)	843 (26.2)	617 (24.8)	200 (31.1)	26 (32.1)	<0.001*
Overweight (25-30)	1576 (49.1)	1291 (51.9)	254 (39.5)	31 (38.3)	
Obese (≥30)	794 (24.7)	581 (23.3)	189 (29.4)	24 (29.6)	
WC Categories (cm)					
<94	1110 (34.4)	853 (34.2)	230 (35.4)	27 (31.4)	<0.001*
94-102	978 (30.3)	818 (32.8)	143 (22.0)	17 (19.8)	
≥102	1140 (35.3)	822 (33.0)	276 (42.5)	42 (48.8)	
WHR Tertiles					
≤.95	1075 (33.3)	850 (34.1)	198 (30.6)	27 (31.8)	<0.001*
.96-1.01	1075 (33.3)	868 (34.8)	185 (28.6)	22 (25.9)	
1.01-1.23	1075 (33.3)	774 (31.1)	265 (40.9)	36 (42.4)	
% Body Fat Tertiles					
≤26	1075 (33.4)	817 (32.8)	224 (34.6)	34 (40.5)	0.4*
26-30	1077 (33.4)	847 (34.0)	208 (32.2)	22 (26.2)	
30-46	1075 (33.3)	774 (31.1)	265 (40.9)	36 (42.4)	

Table 6.3 Adiposity measures (baseline phase) by frailty status (FS)

˜ANOVA,*Chi-square tests

BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

Figure 6.2 Prevalence of pre-frailty and frailty (FS) by quartiles of adiposity measures (a) BMI (b) WC (c) WHR (d) %Body fat



	Relative Risk Ratios (95% Confidence Intervals)					
	Unadjusted		Model 1		Model 2	
	Pre-frail	Frail	Pre-frail	Frail	Pre-frail	Frail
BMI (per 1SD increase)	1.0 (0.9 to 1.1)	1.2 (0.9 to 1.4)	1.0 (0.9 to 1.1)	1.1 (0.9 to 1.4)	1.0 (0.9 to 1.1)	1.2 (1.0 to 1.5)
WC (per 1SD increase)	1.1 (1.0 to 1.2)**	1.4 (1.2 to 1.7)**	1.0 (0.9 to 1.1)	1.3 (1.0 to 1.6)*	1.1 (1.0 to 1.2)	1.4 (1.1 to 1.7)**
WHR (per 1SD increase)	1.2 (1.1 to 1.3)***	1.3 (1.0 to 1.6)*	1.1 (1.0 to 1.2)*	1.1 (0.9 to 1.4)	1.1 (1.0 to 1.2)*	1.1 (0.9 to 1.4)
% Body Fat (per 1SD increase)	1.0 (0.9 to 1.1)	0.9 (0.7 to 1.1)	1.0 (0.9 to 1.1)	1.0 (0.8 to 1.3)	1.1 (1.0 to 1.2)	1.2 (0.9 to 1.5)
BMI Quartiles (Kg/m^2)						
≤24.8	1.7 (1.3 to 2.2)***	1.5 (0.8 to 2.7)	2.0 (1.5 to 2.6)***	1.8 (1.0 to 3.4)	1.8 (1.4 to 2.3)***	1.8 (0.9 to 3.5)
24.8 - 27.2	Reference		Reference		Reference	
27.2 - 29.9	1.1 (0.8 to 1.4)	0.7 (0.3 to 1.4)	1.0 (0.8 to 1.3)	0.6 (0.3 to 1.3)	1.0 (0.8 to 1.3)	0.6 (0.3 to 1.4)
29.9 - 45.7	1.7 (1.3 to 2.2)***	1.4 (0.8 to 2.6)	1.6 (1.3 to 2.1)***	1.4 (0.7 to 2.6)	1.7 (1.3 to 2.2)***	1.6 (0.8 to 3.1)
WC Quartiles (cm)						
≤91	1.7 (1.3 to 2.2)***	2.5 (1.2 to 5.1)*	1.9 (1.5 to 2.5)***	2.9 (1.4 to 6.1)**	1.8 (1.4 to 2.4)***	3.2 (1.4 to 7.0)**
91.1-98	Reference		Reference		Reference	
98.1-105	1.2 (0.9 to 1.5)	1.4 (0.7 to 3.2)	1.0 (0.8 to 1.4)	1.2 (0.6 to 2.7)	1.1 (0.8 to 1.4)	1.4 (0.6 to 3.4)
105.1-155	2.1 (1.6 to 2.7)***	4.1 (2.0 to 8.0)***	1.9 (1.4 to 2.4)***	3.4 (1.7 to 6.9)**	2.0 (1.5 to 2.6)***	4.3 (2.0 to 9.1)***
WHR Quartiles						
≤.94	1.0 (0.8 to 1.3)	1.1 (0.5 to 2.1)	1.3 (1.0 to 1.7)	1.4 (0.7 to 2.8)	1.3 (1.0 to 1.7)*	1.4 (0.7 to 2.9)
.94-.98	Reference		Reference		Reference	
.98-1.02	1.0 (0.8 to 1.3)	1.4 (0.7 to 2.6)	0.9 (0.7 to 1.2)	1.3 (0.7 to 2.5)	1.0 (0.7 to 1.3)	1.4 (0.7 to 2.7)
1.02-1.19	1.6 (1.3 to 2.0)***	1.8 (1.0 to 3.3)	1.4 (1.1 to 1.8)**	1.5 (0.8 to 2.9)	1.5 (1.1 to 1.9)**	1.5 (0.8 to 2.9)

	Relative Risk Ratios (95% Confidence Intervals)					
	Unadjusted		Model 1		Model 2	
	Pre-frail	Frail	Pre-frail	Frail	Pre-frail	Frail
% Body Fat Quartiles						
≤24	1.1 (0.8 to 1.4)	1.5 (0.8 to 2.7)	1.1 (0.9 to 1.4)	1.5 (0.8 to 2.8)	1.0 (0.8 to 1.3)	1.3 (0.7 to 2.4)
24-28	Reference		Reference		Reference	
28-31	1.0 (0.8 to 1.2)	0.6 (0.3 to 1.3)	1.0 (0.8 to 1.3)	0.8 (0.4 to 1.7)	1.1 (0.8 to 1.4)	0.9 (0.4 to 1.8)
31-45	1.1 (0.9 to 1.4)	1.1 (0.6 to 2.1)	1.2 (1.0 to 1.6)	1.8 (0.9 to 3.5)	1.3 (1.0 to 1.7)*	1.9 (1.0 to 3.7)

Table 6.4 Multinomial logistic regression: association of frailty status (FS) with adiposity measures

Multinomial logistic regression models: Model 1 adjusted for age and centre. Model 2 adjusted for age,centre,smoking and alcohol consumption:
Relative Risk Ratios(RRR) corresponds for a 1SD increase in adiposity measure (continous) or in comparison to the referent category in adiposity categories. SD, standard deviation; BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio,*p <0.05,**p <0.01,***p <0.001

6.5.4 Association of adiposity measures with frailty status (FI)

At baseline the mean (SD) of the Frailty Index was 0.13 (0.11); the median [inter-quartile range] values were 0.10 [0.05 – 0.18]. The FI correlated significantly with all adiposity measures (BMI, WC, WHR and % body fat) and showed the strongest correlation with WHR (0.26). The mean and median FI increased significantly with increase in BMI, WC and WHR, (Table 6.5 and Figure 6.3). The results from the LOWESS analyses exploring the association between BMI, WC, WHR and % body fat and FI (adjusted for age) are shown in Figure 6.4. The LOWESS plots indicate the same 'directionality of relationship' with an increase in FI with an increase in adiposity measures.

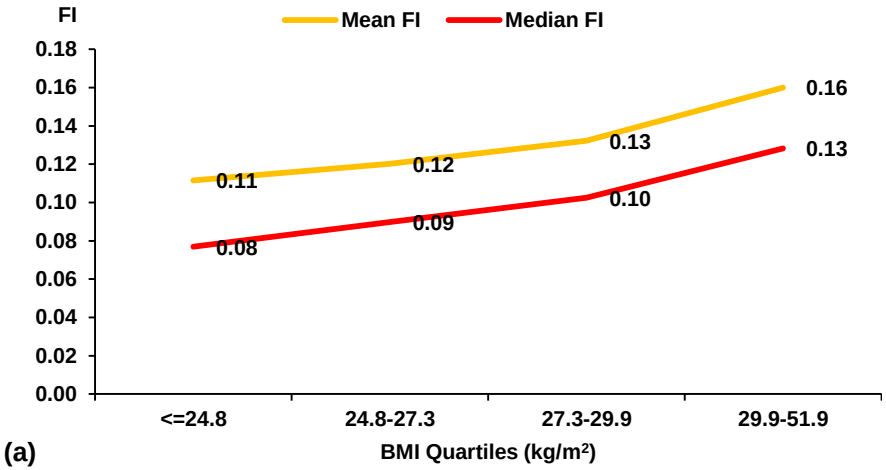
The results from the linear regression models exploring the association of the adiposity measures with frailty (FI) are summarised in Table 6.6. After adjustment for age, centre, smoking and alcohol consumption, an increase in BMI, WC, WHR and % body fat (per 1SD increase) were all significantly associated with a higher FI score, indicating increased frailty status (e.g. a 1 SD increase in WHR was associated with an average increase of 15.2% in the FI), (Table 6.6). Again, after adjustment for age, centre, smoking and alcohol consumption, and using the second quartile as the referent category, those with WC and WHR in the third and fourth quartile had a significantly increased FI score. Those in the lower quartile (vs. second quartile) failed to show an association with increased FI. Using the second quartile as referent, those with % body fat and BMI in the upper quartile also had a significantly increased FI.

Variable		r	p value
BMI (kg/m^2)	0.17		<0.001
WC (cm)	0.24		<0.001
WHR	0.26		<0.001
Body Fat	0.05		<0.01
	FI (Mean ± SD)	**FI (Median [25-75 IQR])**	
BMI Categories (Kg/m^2)			
Normal (≤25)	0.11 ± 0.10	0.08 [0.04-0.15]	<0.001
Overweight (25-30)	0.13 ± 0.11	0.10 [0.05-0.18]	
Obese (≥30)	0.16 ± 0.12	0.13 [0.06-0.23]	
WC categories (cm)			
<94	0.11 ± 0.10	0.08 [0.04-0.14]	<0.001
94-102	0.12 ± 0.10	0.10 [0.05-0.18]	
≥102	0.16 ± 0.12	0.13 [0.06-0.23]	
WHR Tertiles			
≤.95	0.11 ± 0.10	0.08 [0.04-0.14]	<0.001
.96-1.01	0.12 ± 0.11	0.09 [0.05-0.17]	
1.01-1.23	0.16 ± 0.12	0.14 [0.08-0.23]	
% Body Fat Tertiles			
≤26	0.13 ± 0.11	0.09 [0.05-0.18]	0.08
26-30	0.13 ± 0.11	0.10 [0.05-0.18]	
30-46	0.14 ± 0.11	0.10 [0.05-0.19]	

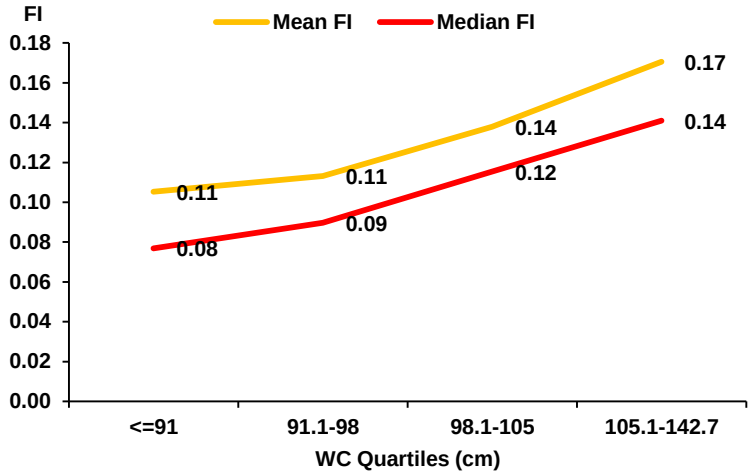
Table 6.5 Adiposity measures and Frailty Index.

At top of table "r" is Spearman's rank correlation coefficients and p values for the association between adiposity measure and Frailty Index. Bottom half of table the p values are based on Kruskal Wallis test.
BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

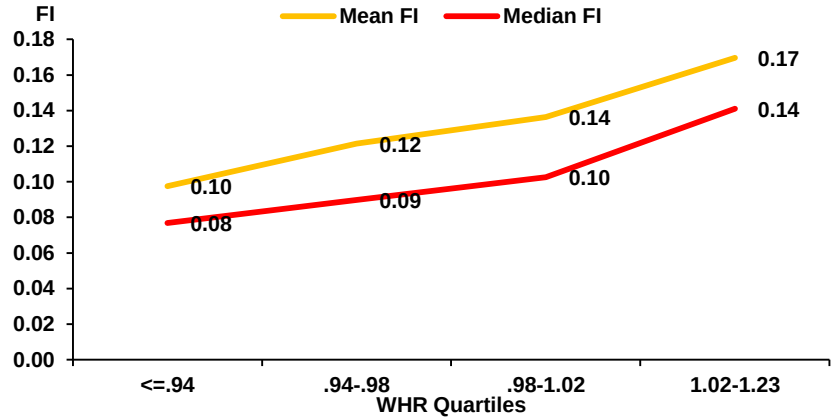
Figure 6.3 Mean and Median FI across the adiposity quartiles (a) BMI (b) WC(c) WHR (d) % Body Fat



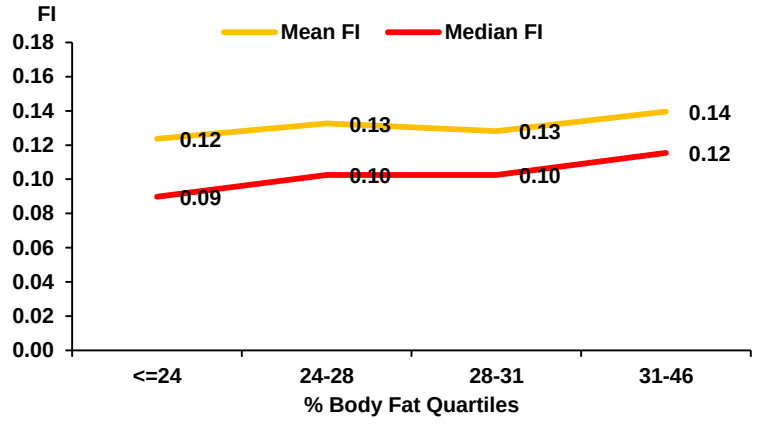
(a)



(b)

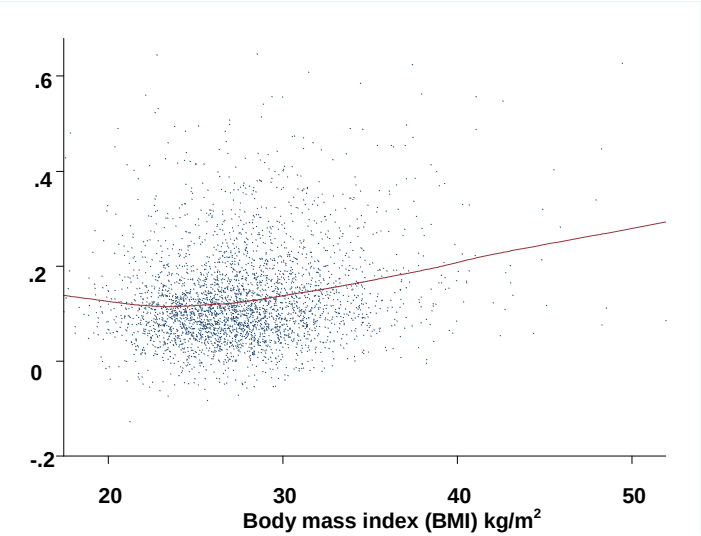


(c)

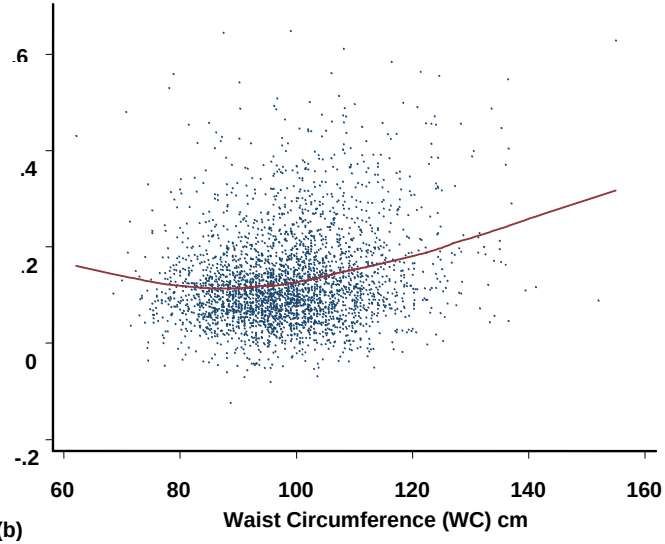


(d)

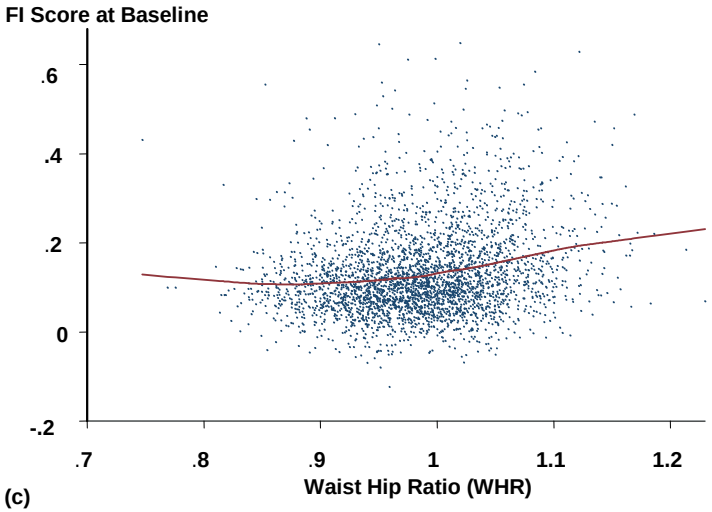
Figure 6.4 Lowess plots of FI & adiposity measures adjusted for age (a) BMI (b) WC(c) WHR (d) % Body Fat



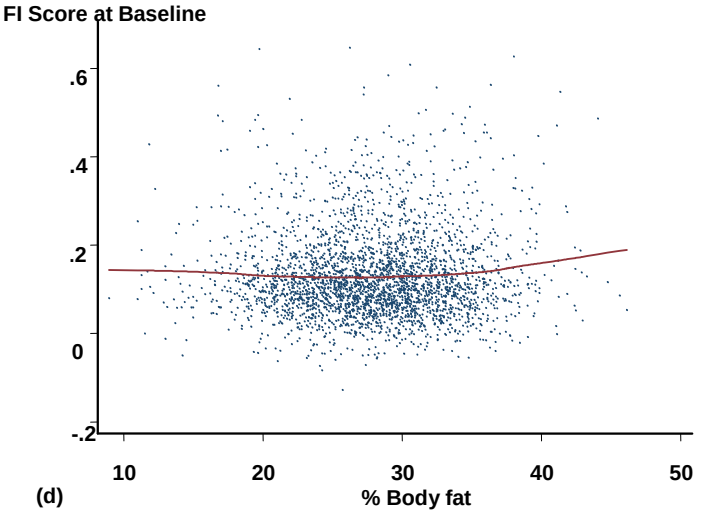
(a)



(b)


FI Score at Baseline
.6
.4
.2
0
-.2
.7
.8
.9
1
1.1
1.2
Waist Hip Ratio (WHR)

(c)


FI Score at Baseline
.6
.4
.2
0
-.2
10
20
30
40
50
% Body fat

(d)

	Percentage change (95% CI) in FI score per unit/category change in adiposity measure [a]		
	Unadjusted	**Model 1**	**Model 2**
BMI (per 1SD increase)	14.4 (10.9 to 17.9)***	11.4 (8.5 to 14.3)***	12.4 (9.5 to 15.3)***
WC (per 1SD increase)	20.8 (17.2 to 24.5)***	14.4 (11.4 to 17.4)***	15.0 (12.0 to 18.0)***
WHR (per 1SD increase)	22.8 (19.2 to 26.6)***	15.4 (12.3 to 18.6)***	15.2 (12.1 to 18.4)***
% Body Fat (per 1SD increase)	4.3 (1.1 to 7.6)**	7.9 (5.0 to 10.8)***	8.8 (5.9 to 11.8)***
BMI Quartiles (Kg/m2)			
≤ 24.8	-7.1 (-14.8 to 1.4)	0.6 (-6.5 to 8.3)	-1.1 (-8.2 to 6.5)
24.8 - 27.2	Reference	Reference	Reference
27.2 - 29.9	9.1 (0.0 to 18.9)*	5.7 (-1.8 to 13.7)	5.7 (-1.8 to 13.7)
29.9 - 45.7	31.7 (20.9 to 43.6)***	29.4 (20.3 to 39.3)***	29.5 (20.3 to 39.4)***
WC Quartiles (cm)			
<=91	-6.1 (-13.8 to 2.3)	0.6 (-6.6 to 8.2)	-0.5 (-7.5 to 7.1)
91.1-98	Reference	Reference	Reference
98.1-105	21.3 (11.3 to 32.1)***	16.5 (8.3 to 25.3)***	16.0 (7.8 to 24.7)***
105.1-155	50.8 (38.5 to 64.1)***	37.1 (27.4 to 47.5)***	37.3 (27.6 to 47.7)***
WHR Quartiles			
<=.94	-15.1 (-22.1 to -7.4)***	-6.3 (-13.0 to 1.0)	-6.2 (-12.9 to 1.1)
.94-.98	Reference	Reference	Reference
.98-1.02	13.3 (4.1 to 23.3)**	9.4 (1.7 to 17.6)*	9.7 (2.1 to 18.0)*
1.02-1.19	46.3 (34.4 to 59.2)***	34.1 (24.6 to 44.4)***	33.7 (24.2 to 43.9)***

	Percentage change (95% CI) in FI score per unit/category change in adiposity measure [a]		
	Unadjusted	**Model 1**	**Model 2**
% Body Fat Quartiles			
≤24	-7.4 (-15.2 to 1.0)	-6.2 (-12.8 to 1.0)	-8.1 (-14.6 to -1.0)*
24-28	Reference	Reference	Reference
28-31	-1.5 (-9.8 to 7.5)	3.6 (-3.8 to 11.6)	3.4 (-4.0 to 11.4)
31-45	4.3 (-4.4 to 13.7)	14.5 (6.3 to 23.5)***	14.6 (6.4 to 23.6)***

Table 6.6 Percentage change in Frailty Index associated with adiposity measures

[a] To derive average percentage change in FI score from log FI (dependent variable in linear regression models)= 100 x [exp (β coefficient)-1].
Model 1: adjusted for age and centre; Model 2: Adjusted for age, centre, smoking and alcohol consumption.
BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio, *p <0.05, **p <0.01, ***p <0.001

6.5.5 Association of adiposity measures with frailty components (FP and FS)

The associations between individual FP and FS criteria and the adiposity measures are shown in Tables 6.7 and 6.8. The results for the FP criteria are adjusted for age, centre, smoking, alcohol consumption and comorbidities, while the results for the FS criteria are adjusted for age, centre, smoking and alcohol consumption. For the FP component criteria, a 1 SD increase in adiposity measures was significantly associated with slowness, exhaustion and low activity. Weakness was only significantly associated with a 1SD increase in WC. The odds of sarcopenia, however, ***reduced*** with a 1SD increase in adiposity measures, (Table 6.7). Compared to those with a BMI in the second quartile, those with a BMI in the first quartile (≤24.8 kg/m^2) were 6.4 times more likely to have sarcopenia. Similar results were observed for the other adiposity measures when analysed as categorical variables, (Table 6.7).

For the FS component criteria, a 1 SD increase in adiposity measure as well as increased adiposity categories and quartiles were significantly positively associated with most FS criteria (ambulation, fatigue, resistance, illnesses) other than the sarcopenia criteria which, as with the FP criteria, declined with increasing measures of adiposity. When the sarcopenia criteria from the FP and the FS models was removed and frailty re-defined as having >=3 of the 4 criteria and (for pre-frailty1-2 criteria) the prevalence of frailty and pre-frailty increased with increasing measures of adiposity (though FP failed to show a significant association with a 1SD increase in body fat) – and the U shaped relationship seen with BMI and WC disappeared (data not shown).

	Odds Ratio (95% Confidence Intervals)				
	Sarcopenia	**Slowness**	**Exhaustion**	**Low Activity**	**Weakness**
BMI (per 1SD increase)	0.1 (0.1 to 0.1)***	1.2 (1.1 to 1.4)**	1.3 (1.1 to 1.4)***	1.2 (1.1 to 1.4)**	1.1 (0.9 to 1.2)
WC (per 1SD increase)	0.2 (0.1 to 0.2)***	1.3 (1.2 to 1.5)***	1.3 (1.1 to 1.5)***	1.3 (1.2 to 1.5)***	1.2 (1.0 to 1.4)*
WHR (per 1SD increase)	0.4 (0.3 to 0.4)***	1.2 (1.0 to 1.3)*	1.2 (1.1 to 1.4)**	1.3 (1.1 to 1.5)***	1.1 (1.0 to 1.3)
% Body Fat (per 1SD increase)	0.4 (0.4 to 0.5)***	1.2 (1.0 to 1.3)*	1.2 (1.0 to 1.3)*	1.1 (1.0 to 1.3)*	1.0 (0.9 to 1.2)
BMI Quartiles (Kg/m^2)					
≤24.8	6.4 (4.2 to 9.8)***	1.0 (0.7 to 1.4)	0.9 (0.6 to 1.4)	1.4 (1.0 to 2.0)	1.3 (0.9 to 2.0)
24.8 - 27.2	Reference	Reference	Reference	Reference	Reference
27.2 - 29.9	0.2 (0.1 to 0.5)***	1.0 (0.7 to 1.5)	1.0 (0.7 to 1.4)	1.2 (0.8 to 1.7)	1.0 (0.7 to 1.6)
29.9 - 45.7	0.09 (0.03 to 0.3)***	1.3 (0.9 to 1.9)	1.3 (0.9 to 1.9)	1.7 (1.2 to 2.5)**	1.3 (0.8 to 2.0)
WC quartiles (cm)					
≤91	5.6 (3.7 to 8.3)***	1.1 (0.7 to 1.6)	1.5 (1.0 to 2.3)	1.2 (0.8 to 1.7)	1.2 (0.7 to 1.8)
91.1-98	Reference	Reference	Reference	Reference	Reference
98.1-105	0.3 (0.2 to 0.6)***	1.2 (0.8 to 1.7)	1.5 (1.0 to 2.2)*	1.4 (1.0 to 2.0)*	1.5 (1.0 to 2.3)
105.1-155	0.2 (0.1 to 0.4)***	1.7 (1.2 to 2.4)**	2.4 (1.6 to 3.4)***	1.9 (1.4 to 2.8)***	1.6 (1.1 to 2.4)*
WHR quartiles					
≤.94	2.3 (1.6 to 3.4)***	0.9 (0.6 to 1.3)	0.8 (0.5 to 1.2)	1.2 (0.8 to 1.7)	1.1 (0.7 to 1.7)
.94-.98	Reference	Reference	Reference	Reference	Reference
.98-1.02	0.3 (0.2 to 0.6)***	1.3 (0.9 to 1.8)	0.9 (0.6 to 1.3)	1.4 (1.0 to 2.0)*	1.5 (1.0 to 2.2)
1.02-1.19	0.3 (0.2 to 0.5)***	1.2 (0.9 to 1.7)	1.5 (1.0 to 2.1)*	1.9 (1.4 to 2.8)***	1.3 (0.9 to 2.0)

	Odds Ratio (95% Confidence Intervals)				
% Body fat quartiles	**Sarcopenia**	**Slowness**	**Exhaustion**	**Low Activity**	**Weakness**
≤24	3.4 (2.2 to 5.2)***	0.6 (0.5 to 0.9)*	0.9 (0.6 to 1.4)	0.7 (0.5 to 1.1)	0.9 (0.6 to 1.4)
24-28	Reference	Reference	Reference	Reference	Reference
28-31	1.0 (0.6 to 1.6)	0.7 (0.5 to 0.9)*	1.1 (0.7 to 1.5)	0.6 (0.4 to 0.8)**	1.1 (0.7 to 1.6)
31-45	0.6 (0.3 to 1.0)*	1.0 (0.7 to 1.4)	1.4 (1.0 to 2.0)	0.9 (0.7 to 1.3)	1.0 (0.7 to 1.5)

Table 6.7 Association between adiposity measures and individual frailty criteria (FP)

Logistic regression model adjusted for age,centre,smoking,alcohol consumption and co-morbidities:
Odds Ratios(OR) corresponds for a 1SD increase in adiposity measure (continous) or in comparison to the referent category in adiposity categories. SD, standard deviation; CI,confidence Interval, BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio, *p <0.05,**p <0.01,***p <0.001

	Odds Ratio (95% Confidence Intervals)				
	Sarcopenia	**Fatigue**	**Ambulation**	**Resistance**	**Illness ≥5**
BMI (per 1SD increase)	0.1 (0.1 to 0.1)***	1.3 (1.2 to 1.5)***	1.3 (1.1 to 1.5)***	1.4 (1.3 to 1.6)***	1.4 (1.1 to 1.8)**
WC (per 1SD increase)	0.2 (0.1 to 0.2)***	1.4 (1.2 to 1.5)***	1.4 (1.2 to 1.6)***	1.5 (1.3 to 1.7)***	1.5 (1.2 to 1.9)**
WHR (per 1SD increase)	0.4 (0.3 to 0.4)***	1.3 (1.1 to 1.5)***	1.2 (1.1 to 1.4)**	1.5 (1.3 to 1.7)***	1.4 (1.0 to 1.8)*
% Body Fat (per 1SD increase)	0.4 (0.4 to 0.5)***	1.2 (1.1 to 1.4)**	1.2 (1.0 to 1.4)*	1.3 (1.1 to 1.4)***	1.6 (1.2 to 2.1)**
BMI Quartiles (Kg/m^2)					
≤24.8	6.5 (4.2 to 9.9)***	0.9 (0.6 to 1.4)	1.0 (0.6 to 1.5)	0.9 (0.6 to 1.3)	0.8 (0.3 to 2.0)
24.8 - 27.2	Reference	Reference	Reference	Reference	Reference
27.2 - 29.9	0.2 (0.1 to 0.5)***	1.0 (0.7 to 1.5)	1.1 (0.7 to 1.8)	1.0 (0.7 to 1.5)	1.1 (0.5 to 2.3)
29.9 - 45.7	0.1 (0.03 to 0.3)***	1.5 (1.1 to 2.1)*	1.7 (1.1 to 2.6)*	1.9 (1.4 to 2.6)***	1.7 (0.8 to 3.4)
WC quartiles (cm)					
≤91	5.6 (3.7 to 8.4)***	1.5 (1.0 to 2.2)	1.0 (0.6 to 1.6)	1.1 (0.8 to 1.6)	0.4 (0.1 to 1.0)
91.1-98	Reference	Reference	Reference	Reference	Reference
98.1-105	0.3 (0.2 to 0.6)**	1.6 (1.1 to 2.4)*	1.2 (0.7 to 1.9)	1.2 (0.8 to 1.7)	0.7 (0.3 to 1.5)
105.1-155	0.2 (0.1 to 0.4)***	2.7 (1.8 to 3.9)***	2.1 (1.4 to 3.2)***	2.7 (2.0 to 3.8)***	1.3 (0.7 to 2.6)
WHR quartiles					
≤.94	2.3 (1.6 to 3.4)***	0.8 (0.5 to 1.2)	1.1 (0.7 to 1.8)	1.0 (0.7 to 1.4)	1.6 (0.6 to 4.3)
.94-.98	Reference	Reference	Reference	Reference	Reference
.98-1.02	0.3 (0.2 to 0.6)***	0.9 (0.6 to 1.4)	1.7 (1.1 to 2.7)*	1.4 (1.0 to 1.9)	2.6 (1.1 to 5.9)*
1.02-1.19	0.3 (0.2 to 0.5)***	1.6 (1.2 to 2.3)**	1.6 (1.1 to 2.5)*	1.9 (1.4 to 2.6)***	2.1 (0.9 to 5.0)

	Odds Ratio (95% Confidence Intervals)				
	Sarcopenia	**Fatigue**	**Ambulation**	**Resistance**	**Illness ≥5**
% Body fat quartiles					
≤24	3.4 (2.2 to 5.2)***	0.9 (0.6 to 1.3)	0.7 (0.4 to 1.0)*	0.8 (0.6 to 1.1)	0.8 (0.3 to 1.7)
24-28	Reference	Reference	Reference	Reference	Reference
28-31	1.0 (0.6 to 1.6)	1.1 (0.7 to 1.5)	0.7 (0.5 to 1.1)	0.9 (0.6 to 1.3)	1.2 (0.6 to 2.7)
31-45	0.6 (0.3 to 1.0)*	1.5 (1.1 to 2.2)*	1.2 (0.8 to 1.8)	1.6 (1.1 to 2.1)**	2.2 (1.1 to 4.7)*

Table 6.8 Association between adiposity measures and individual frailty criteria (FS)

Logistic regression model adjusted for age,centre,smoking and alcohol consumption.
Odds Ratios(OR) corresponds for a 1SD increase in adiposity measure (continous) or in comparison to the referent category in adiposity categories. SD, standard deviation; CI,confidence Interval , BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio. *p <0.05,**p <0.01,***p <0.001

6.6 Discussion

The main finding of the analyses presented in this chapter is that frailty is positively associated with an increase in adiposity though the strength of the association, varied by adiposity measure, being stronger for waist circumference than the other measures of adiposity. The strength of the association appeared broadly similar for both FS and FP criteria. A small increase in the prevalence of frailty defined using the FP and FS criteria in those in the lowest quartiles of BMI and WC (and thus a U shaped distribution) could in part be explained by the presence of the "sarcopenia" criteria.

The strengths of the study, as noted in previous chapters, include the standardised assessment of both exposures (measures of adiposity) and also outcome (frailty). There are a number of limitations to consider in interpreting the results. The response rate in EMAS was 41%, as discussed in Chapter 4. It is possible that those who took part may differ from those who were invited but did not take part, and thus the absolute prevalence of frailty (and also measures of adiposity) may be an under or overestimate; this should not, though, affect the results of the main analyses relating to adiposity and frailty as these were based on an internal comparison of responders. Given the cross sectional design, it is not possible to determine the temporal nature of the observed associations. It is possible, for example, that a decline in physical activity due to frailty results in obesity or alternatively that obesity results in a decline in physical activity and perhaps an increase in comorbidities leading to further decline in physical activity and development of frailty. Finally, the analysis was restricted to samples of European men and should be extrapolated beyond this setting with caution.

This is the first study to compare 3 models of frailty and its association with adiposity measures (both visceral (WC and WHR) and peripheral (% body fat)). The data are consistent with previous studies, suggesting that frail individuals are more likely to have higher BMI and WC [114, 150, 251, 259, 261]. In the analysis presented in this chapter, however, it appeared to be primarily visceral fat, determined by an increased waist circumference, which was most strongly and consistently associated with frailty. The findings are similar to Hubbard *et al* [259], who showed that even those who were underweight but had higher waist circumference were at increased risk of frailty. Blaum *et al* looked at the association between obesity and frailty in

women aged 70 to 79 (WHAS I and II) though they excluded underweight women from their analysis as they had defined unintentional weight loss to be all those being <18.5 Kg/m^2 or those who had lost >=10% of weight at 60 years from the date the study commenced. Baseline weight was self-reported. They showed, broadly in keeping with the results in this chapter, that increasing BMI was linked with increased risks of frailty and pre-frailty. They did not however, look at WC or WHR [150].

Data from the literature suggests that BMI is not an ideal measure of adiposity in the elderly due to its inability to differentiate lean mass from fat mass and due to age-related changes in body composition such as loss of lean mass, bone, height and rise in fat mass [265]. It has been suggested that BMI may not represent the actual body fat of an individual [318]. WC and WHR have been suggested to be better at predicting risks of comorbidity and mortality [319-321] compared to BMI. In a recent editorial, Zamboni *et al* suggested that WC alone or together with BMI could be used as an indicator of obesity in older adults [322]. In the results presented here, percentage body fat appeared less strongly linked with frailty than other adiposity measures. It is possible that imprecision in assessment which was based on a combination of 4 anthropometric measures, may have resulted in some misclassification and reduced the ability to detect a true biological association. Another possible explanation, though, is related to the fact that because % body fat is a measure of subcutaneous fat: this type of fat may not be as harmful as visceral fat in the pathway leading to frailty.

It has been suggested that with ageing there is a simultaneous increase in fat and loss of muscle [116, 323]. Studies have suggested that a decrease in lean mass and an increase in fat mass is associated with low physical activity [189]. The loss of muscle mass with age, thus leading to loss in body weight, has been hypothesised as the cause of loss in muscle strength in older adults. However, evidence has increasingly suggested that muscle quality plays an important role in muscle weakness, and the effect of fat infiltration or “marbling” into muscle may reduce muscle quality, hence reducing physical function [180]. It has been suggested that the increase in fat mass and the loss of muscle mass may act together to cause disability and morbidity associated with obesity and frailty [189]. In the CHS, using the FP to assess frailty it was shown that weight loss (assessed as unintentional loss of weight) was the least common

criteria of the frailty syndrome suggesting that weight loss may be present at the end stage of the disease linked with adverse outcome such as death [115].

A number of mechanisms may be suggested for the role of fat/adiposity in the development of frailty. One of the suggested mechanisms is through immune and endocrine changes, which are also associated with frailty [148, 324, 325]. Inflammatory markers (including IL-6) have been shown to increase with age and frailty [116] Obesity has been shown to be associated with increases in inflammatory markers including Il-6 and CRP even after adjustment for sarcopenia [323]. It may also be hypothesised that being frail may reduce physical activity and lead to metabolic imbalance hence leading to obesity. Another suggested mechanism may be that the increased accumulation of deficits resulting from excess body fat could lead to the development of frailty. The possible mechanisms linking frailty and obesity are discussed in further detail in Chapter 9 of this thesis.

6.7 Conclusion

In summary, frailty was associated with increased measures of adiposity, though the strength of the relationship was greatest for waist circumference, suggesting that central obesity is the important determinant of frailty. Prospective data are needed to understand the temporal nature of the relationship; these data are presented in Chapter 8.

Chapter 7 Incidence of Frailty in European Men

7.1 Summary

This chapter presents the results of an analysis looking at the incidence of frailty and the influence of lifestyle factors and comorbidity on the new occurrence of frailty. Frailty status was defined at follow-up using three approaches; the Frailty Phenotype (FP), the FRAIL Scale (FS) and the Frailty Index (FI). For each approach frailty status was determined at both baseline and follow-up as either non-frail (i.e. for FP and FS either robust or pre-frail and for FI an index <0.4) or frail (≥3 criteria or ≥0.4 FI score). Incident frailty was defined as those who were non-frail at baseline and who were frail at follow-up. During a mean of 4.3 years follow-up, using the FP approach 76 (3.5%) men who were non-frail at baseline were frail at follow-up. Using the FS approach, 39 (2%) of those who were non-frail at baseline were frail at follow-up. For the FI the corresponding figure was 73 (2.7%). For all definitions the incidence of frailty increased with age and varied by centre. Compared to those who did not develop frailty, those who developed frailty were more likely to be smokers and have a greater number of comorbidities.

7.2 Introduction

Previous studies have reported on the incidence of frailty in different regions and populations though there are limited data concerning the incidence of frailty (or its determinants) in European men [27, 172, 266]. Defining the incidence or new occurrence of frailty is important both in characterising the clinical and public health burden and also in understanding the causes or determinants of frailty. Knowledge of the determinants of frailty is an important first step in the development of population wide or targeted prevention measures.

7.3 Aims and Objectives

The broad aim of this chapter is to characterise the new occurrence and lifestyle determinants of frailty in middle-aged and older European men. The specific objectives were to, i) determine the incidence of frailty based on the operationalised models; FP, FS and FI, ii) determine the influence of age and centre on the new occurrence of frailty, and iii) determine the influence of smoking, alcohol consumption, physical activity and comorbidities on the new occurrence of frailty.

7.4 Methods

The detailed methods for EMAS have been presented in Chapter 3. The methods used to define frailty at baseline have been presented in Chapters 3 and 4.

7.4.1 Measurement of frailty at Phase 2:-

Similar variables to those used at baseline were used to define FP, FS and the FI using data from the follow-up survey (see Chapter 4 and 5). In the case of constructing the FI at baseline, only deficits in which there were less than 5% missing data were considered. Similar deficits were used to define the frailty index at follow-up though for some the proportion of missing data exceeded 5%. The FI was categorised, as outlined previously, as frail if the FI score was greater or equal to 0.4.

7.4.2 Definition of incident frailty

Participants were characterised as being either frail or non-frail (using all three definitions of frailty) at both the baseline and follow-up surveys. Individuals who were characterised as non-frail were those who were robust and pre-frail. Incident frailty was defined as those who were not frail at baseline but who were frail at follow-up.

7.4.3 Analysis

Descriptive statistics were used to characterise the occurrence of frailty using the different approaches at baseline and follow-up, the new occurrence of frailty, and how this varied by age and centre. Descriptive statistics were also used also to describe the baseline characteristics of participants including age, smoking status, alcohol consumption and occurrence of comorbidities. Differences in these characteristics in men who did and did not develop frailty at follow-up were determined using t-tests for continuous variables and Chi-

square tests for categorical variables. Logistic regression was used to determine the strength of the associations between these variables and incident frailty, both unadjusted and adjusted for age and centre. In these analyses incident frailty was the outcome and the results expressed as Odds Ratios (OR) and 95% Confidence Intervals (CI).

7.5 Results

7.5.1 Frailty (FP)

Of the 3047 men in whom it was possible to characterise frailty status using the FP approach at baseline, 167 (5.5%) subsequently died and 295 (9.7%) were lost to follow-up.

7.5.2 Frailty (FP) at follow-up

2355 men had complete frailty data available at follow-up. Of these, 1504 (63.8%) were classified as robust, 758 (32.2%) as pre-frail and 93 (4.0%) as frail. The prevalence of individual FP criteria at follow-up was; slowness 361 (13.9%); exhaustion 230 (8.7%); weakness 231 (8.9%); low activity 361 (14.6%) and sarcopenia weight loss 236 (8.9%). The prevalence of frailty at follow-up increased with age from 4 (1.3%) in the youngest age group (40-49 years) to 20 (16.3%) in those who were 80 years and over.

7.5.3 Frailty Incidence (FP)

As outlined in the analysis section, FP frailty status was dichotomised into non-frail and frail groups at baseline and follow-up. Transitions in status between baseline and follow-up in those where data were available are presented in Table 7.1. Those who remained frail (n=10) at both phases, and those who changed state from frail to non-frail (n=15), were excluded from the analysis of incident frailty. Of the 2149 men included in the final analysis 76 (3.5%) developed frailty (incident frailty). The incidence of frailty increased with age from 0.7% at age 40-49 years to 10.7% at age 70 years and over (Figure 7.1). The incidence also varied by centre, with frailty incidence highest in Szeged (5.6%) and lowest in Tartu (1.2%), (Figure 7.2).

7.5.4 Lifestyle, comorbidity and frailty

Compared to those who did not develop frailty, those who developed frailty at follow-up were more likely at baseline to have smoked (34.7% vs 19.5%; $p < 0.05$) and to have had more than one comorbidity (76.3% vs 46.8%; $p < 0.05$). There was no difference in the frequency of alcohol consumption between the groups (Table 7.2). Using logistic regression compared to those who did not develop frailty, those who developed frailty were more likely to smoke (OR=2.2; 95%CI 1.3, 3.6), and have more than one comorbidity (OR=3.7; 95% CI 2.1, 6.3). After adjustment for age and centre, the strength of the association with comorbidities was attenuated and became non-significant (p=0.06), (Table 7.3).

	Frailty at Follow-up			
Baseline	**Robust**	**Pre-frail**	**Frail**	**Total**
	n (%)	n (%)	n (%)	n (%)
Robust	1196 (85.6)	402 (58.2)	25 (29.1)	1623 (74.7)
Pre-frail	199 (14.2)	276 (39.9)	51 (59.3)	526 (24.2)
Frail	2 (0.14)	13 (1.9)	10 (11.6)	25 (1.2)

Table 7.1 FP frailty status at baseline and follow-up

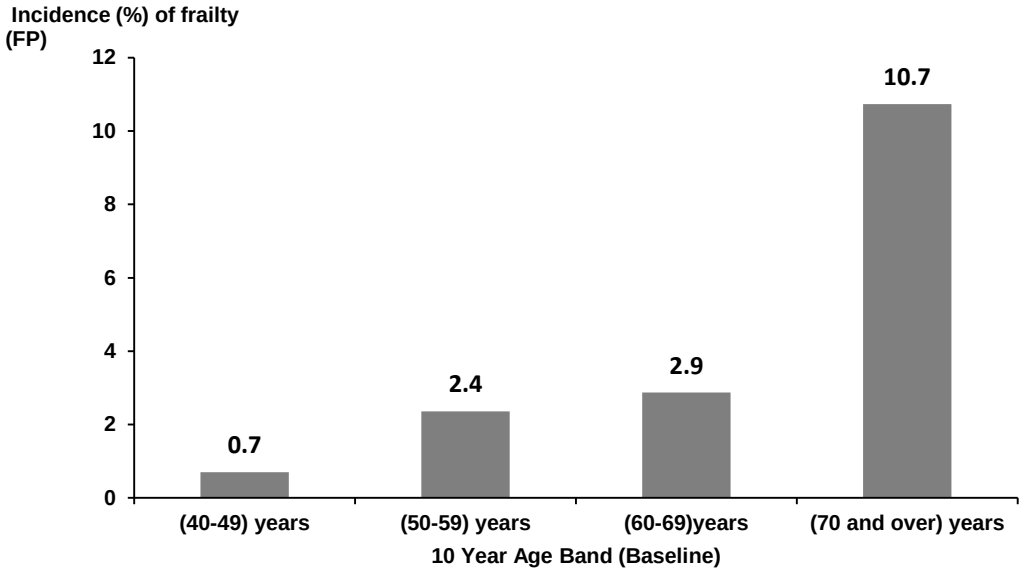


Figure 7.1 Incidence of frailty (FP) by 10 year age bands

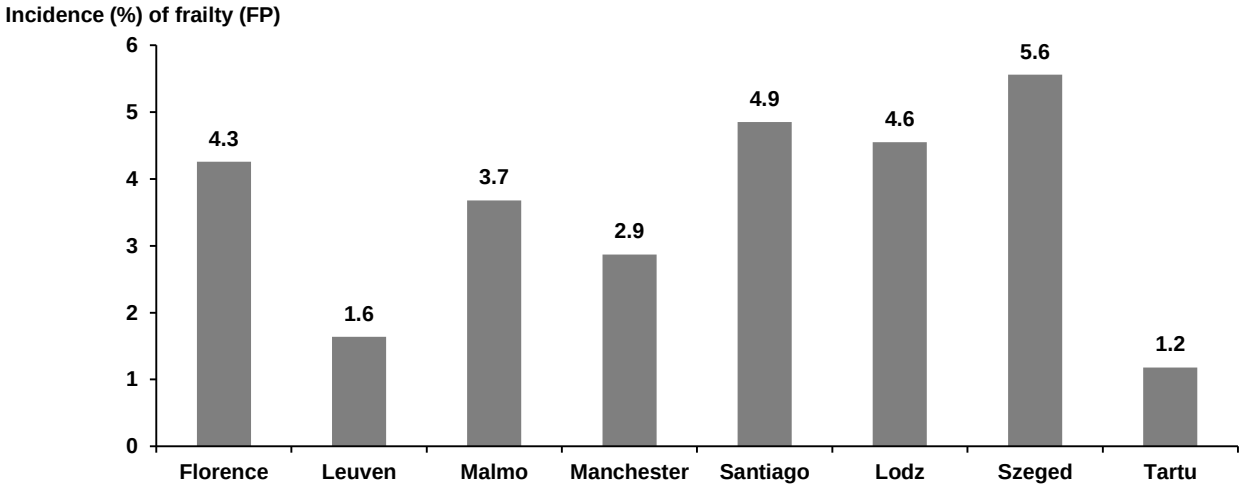


Figure 7.2 Incidence of frailty (FP) by centre

	Total (n=2149)	Non-frail (n=2073)	Incident Frail (n=76)	p value
		Mean ± SD		
Age (years)	58.3 ± 10.4	58.0 ± 10.3	67.5 ± 10.3	<0.001˜
		Count (%)		
Smoking status (current)	423 (20.1)	397 (19.5)	26 (34.7)	<0.001*
Alcohol Intake (≥5 days/week)	506 (23.6)	489 (23.7)	17 (22.4)	0.8*
Comorbidities (more than 1)	1017 (47.9)	959 (46.8)	58 (76.3)	<0.001*

Table 7.2 Baseline characteristics of men who did and did not develop frailty (FP)

* Chi-square test; ˜t test

	Odds Ratio (95% Confidence Intervals)	
	Unadjusted	**Model 1**
Age	1.1 (1.1 to 1.1)***	1.1 (1.1 to 1.1)***
Smoking status (current)	2.2 (1.3 to 3.6)**	3.9 (2.3 to 6.7)***
Alcohol Intake (≥5 days/week)	0.9 (0.5 to 1.6)	0.8 (0.5 to 1.5)
Comorbidities (more than 1)	3.7 (2.1 to 6.3)***	1.8 (1.0 to 3.2)∫

Table 7.3 Risk of incident frailty (FP)

Model 1 adjusted for baseline age and centre (in the association between age and frailty incidence adjustment was only made for centre). ***p <0.001, **p <0.01, *p <0.05, ∫p=0.06

7.5.5 Frailty (FS)

Of the 3228 men who had frailty data as assessed by the FS approach at baseline, 175 (5.4%) died and 305 (9.5%) were lost to follow-up.

7.5.6 Frailty (FS) at follow-up

1962 men had complete frailty data available at follow-up. Of these, 1472 (75%) were classified as robust, 443 (22.6%) as pre-frail and 47 (2.4%) as frail. The prevalence of individual FS criteria at follow-up was; fatigue 230 (8.7%), resistance 382 (14.6%), ambulation 237 (9.1%), illness 24 (1.2%) and sarcopenia/weight loss 236 (8.9%). The prevalence of frailty at follow-up increased with age, ranging from 0% in the youngest age groups (40-49 years) to 8% in those aged 80 years and over.

7.5.7 Frailty Incidence

As described in the analysis section, FS frailty status was dichotomised into non-frail and frail groups. Transitions in frailty status between baseline and follow-up in those where data were available are presented in Table 7.4. The transition of frailty state was more likely to occur in a deteriorating direction, i.e., to a worsening of frailty status rather than an improvement, similar to the FP model. Twenty-five men who were frail at baseline were excluded from this analysis, of which 8 were frail at both phases and 17 who were frail at baseline and changed categories at follow-up (n=2 robust, n=15 pre-frail). Of the 1882 men considered in the analysis, 39 (2.1%) of men who were non-frail at baseline became frail at follow-up. Incident frailty cases increased with age from 0.6% in those aged 40 to 49 years to 5.3% in those aged over 70 years, see Figure 7.3. Frailty incidence also varied by centre and was highest in Lodz (4.2%) and lowest in Florence (0%).

7.5.8 Lifestyle and frailty

Compared to those who did not develop frailty, those who developed frailty at follow-up were more likely to be older and have lower levels of physical activity as assessed by the PASE score at baseline ($p < 0.05$). There were no significant differences in the frequency of alcohol consumption and smoking status between the groups, (see Table 7.5). Using logistic regression, and after adjusting for centre, compared to those who did not develop frailty, those who

developed frailty were more likely to be older (OR=1.1; 95%CI 1.0, 1.1) and have lower physical activity scores, (see Table 7.6).

	Frailty at Follow-up			
Baseline	**Robust**	**Pre-frail**	**Frail**	**Total**
	n (%)	n (%)	n (%)	n (%)
Robust	1312 (91.7)	242 (56.4)	11 (23.4)	1565 (82.1)
Pre-frail	117 (8.2)	172 (40.1)	28 (59.6)	317 (16.6)
Frail	2 (0.1)	15 (3.5)	8 (17.0)	25 (1.3)

Table 7.4 Frailty status (FRAIL Scale) at baseline and follow-up

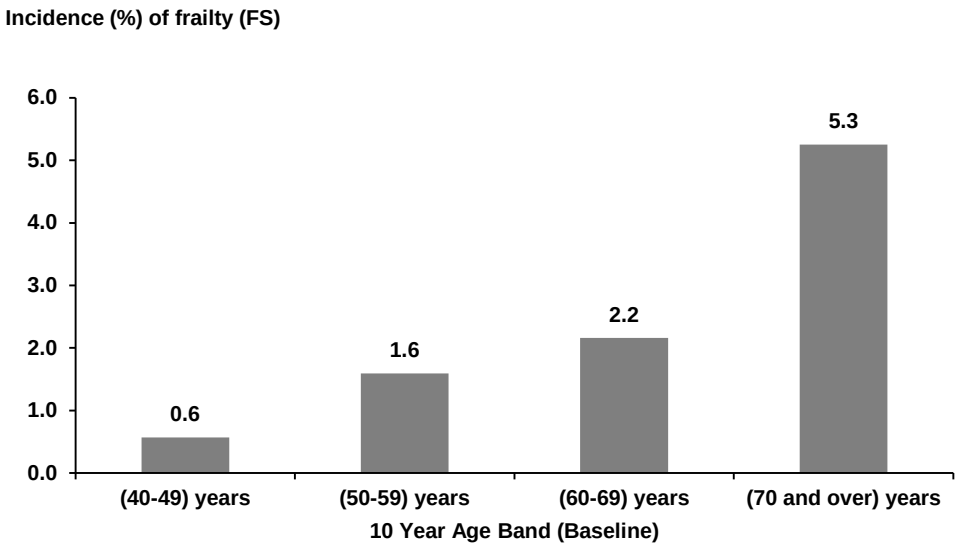


Figure 7.3 Incidence of frailty (FS) by 10 year age bands

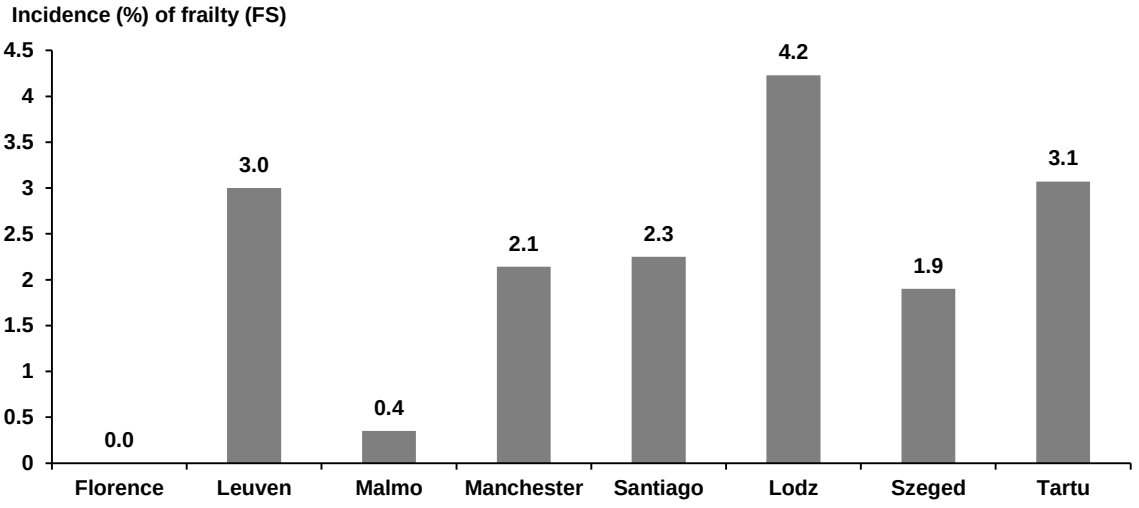


Figure 7.4 Incidence of frailty (FS) by centre

	Total (n=1843)	Non-frail (n=2071)	Incident Frail (n=39)	p value
		Mean ± SD		
Age (years)	57.9 ± 10.5	57.7 ± 10.4	65.7 ± 10.1	< 0.001˜
Physical Activity (PASE[a] score)	205.4 ± 85.3	206.8 ± 85.1	138.3 ± 64.4	< 0.001˜
		Count (%)		
Smoking status (current)	310 (16.8)	302 (16.7)	8 (21.1)	0.5*
Alcohol Intake (≥5 days/week)	448 (23.9)	441(24.0)	7 (18.0)	0.4*

Table 7.5 Baseline characteristics of men who did and did not develop frailty (FS)

* Chi-square test; ˜t test

[a] PASE: Physical Activity Scale for the Elderly

	Odds Ratio (95% Confidence Interval)	
	Unadjusted	**Model 1**
Age	1.1 (1.0 to 1.1)***	1.1 (1.0 to 1.1)***
Physical Activity (PASE[a] score)	0.99 (0.99 to 0.99)***	0.99 (0.99 to 1.00)***
Smoking Status (current)	1.4 (0.6 to 3.0)	2.2 (0.9 to 5.1)
Alcohol Intake (≥5 days/week)	0.8 (0.3 to 1.7)	0.7 (0.3 to 1.7)

Table 7.6 Risk of incident frailty (FS)

Model 1 adjusted for baseline age and centre (in the association between age and frailty incidence adjustment was only made for centre). ***p <0.001

7.5.9 Frailty (FI)

Of the 3369 men who had a FI score at baseline, 193(5.7%) subsequently died and 334(9.9%) were reported as lost to follow-up. Those who had died at follow-up had the highest FI at baseline [mean=0.25 (SD=0.14)]. The baseline FI score of those who were lost to follow-up was similar to those who returned at phase 2 [mean (SD) 0.13 (0.11) vs.0.12 (0.10].

7.5.10 Frailty (FI) at follow-up

Of the 2736 men at follow-up with a FI score, 109 (4.0%) were categorised as frail (FI score ≥0.4). The mean (SD) of the FI at follow-up was 0.13 (0.12) with a median of 0.09. The distribution of the FI was positively skewed at both phases (Figure 7.5A). The mean FI at follow-up increased with age from 0.07 to 0.25. The mean change in FI between baseline and follow-up was in the range from -.4 to .4) and was normally distributed (Figure 7.5B). The mean change increased with age and there was an increase in FI in most centres except for Santiago, (Figure7.6).

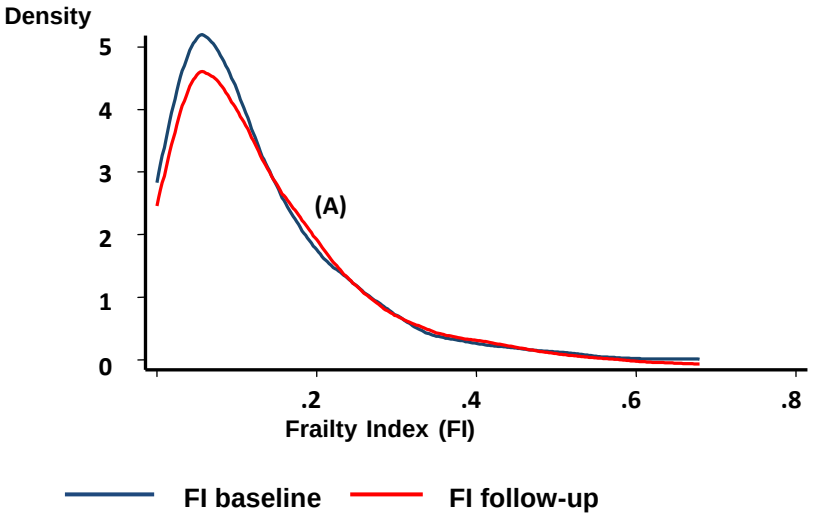
7.5.11 Frailty incidence (after categorisation into frail/pre-frail/robust)

As outlined in the analysis section, individuals with a FI score ≥0.4 were categorized as frail at baseline and follow-up. Those who were non-frail at baseline and became frail at follow-up were considered incident frail. Transitions in frailty status between baseline and follow-up in men, where, data available are presented in Table 7.7. Men who remained frail at both phases (n=36) and those who changed state from frail to non-frail (n=28), were excluded from this analysis. Of the 2672 men included in the analysis, 73 (2.7%) who were non frail at baseline became frail at follow-up (FI Frailty Incidence). Frailty incidence increased with age from 1.7% at age 50-59 years to 7.5% at age 70 years and over, (see Figure 7.7). Frailty incidence was highest in Lodz (4.8%) and lowest in Florence (0.9%), (Figure 7.8).

7.5.12 Determinants of frailty (FI)

Compared to those who did not develop frailty, those who developed frailty at follow-up were more likely to be older ($p < 0.05$) and consumed less alcohol at baseline ($p < 0.05$). There were no significant differences in smoking status between the groups, (see Table 7.8). After adjusting for centre, increasing age was associated with a significant increased risk of

developing frailty (OR=1.1). After adjusting for age and centre, current smoking though not alcohol intake was associated with a significant increased risk of developing frailty (Table 7.9).



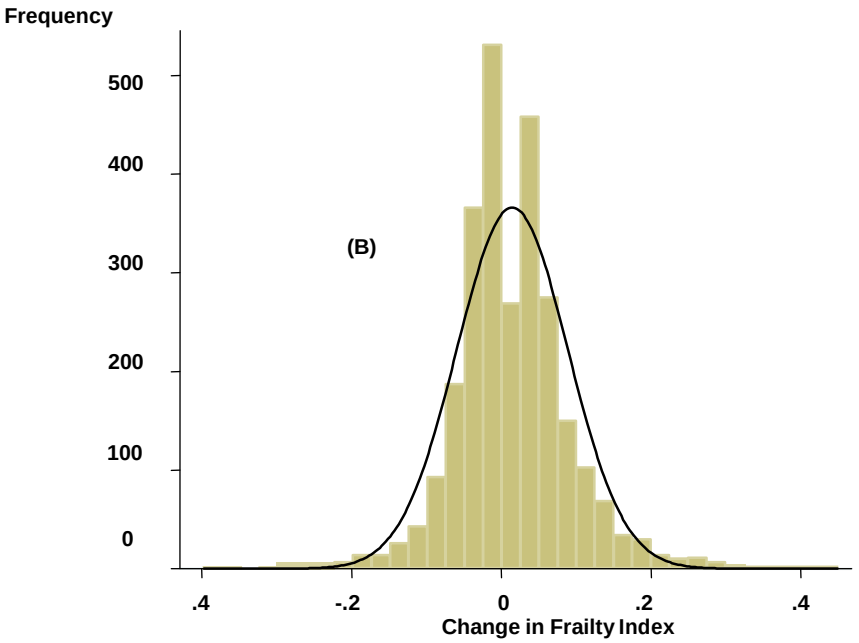


Figure 7.5 (A) Distribution of Frailty Index (FI) at baseline and Follow-up (n=2786).

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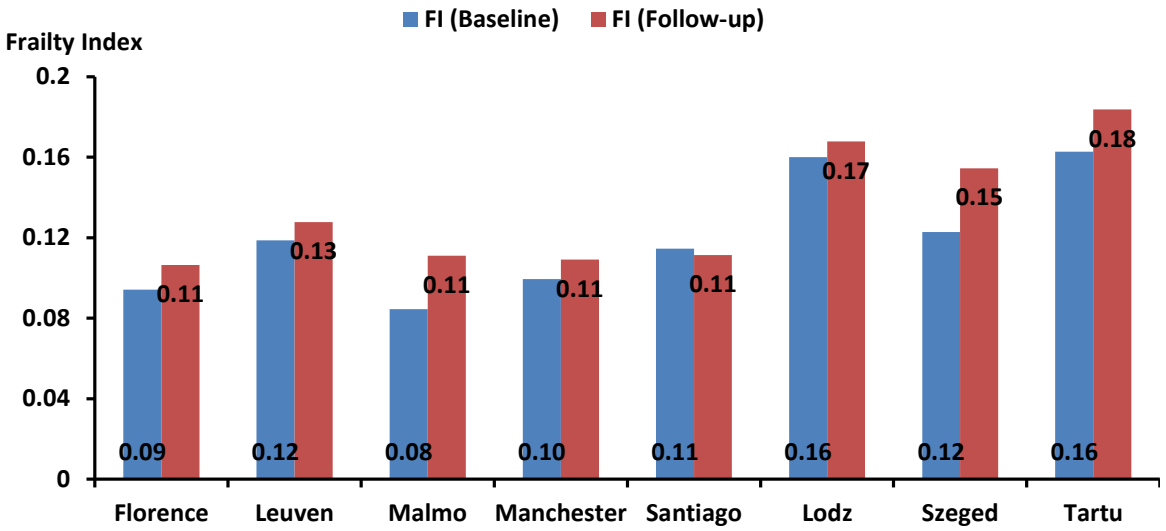


Figure 7.6 Mean FI at baseline and follow-up by centre (n=2786)

	Follow-up n (%)	
Baseline	**Non-frail**	**Frail**
Non-frail	2599(97.3)	73(2.7)
Frail	28(43.8)	36(56.3)

Table 7.7 Frailty status (FI) at baseline and follow-up

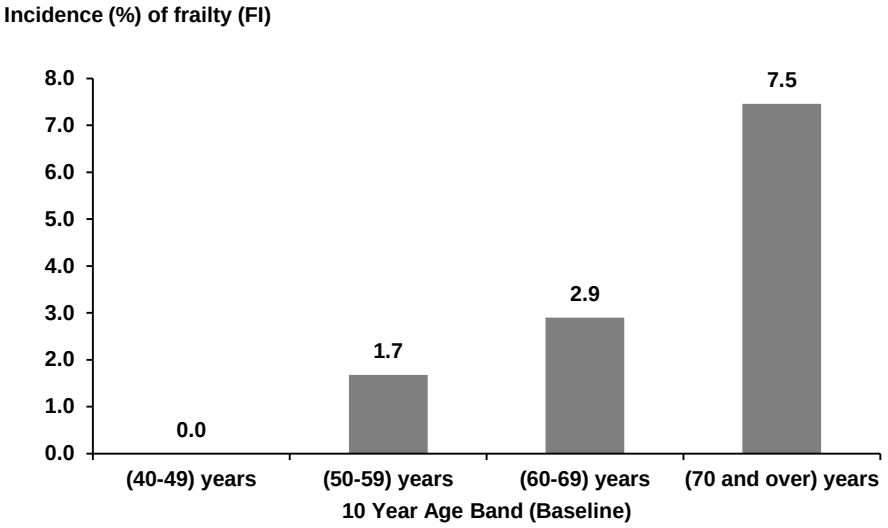


Figure 7.7 Incidence of frailty (FI) by 10 year age bands

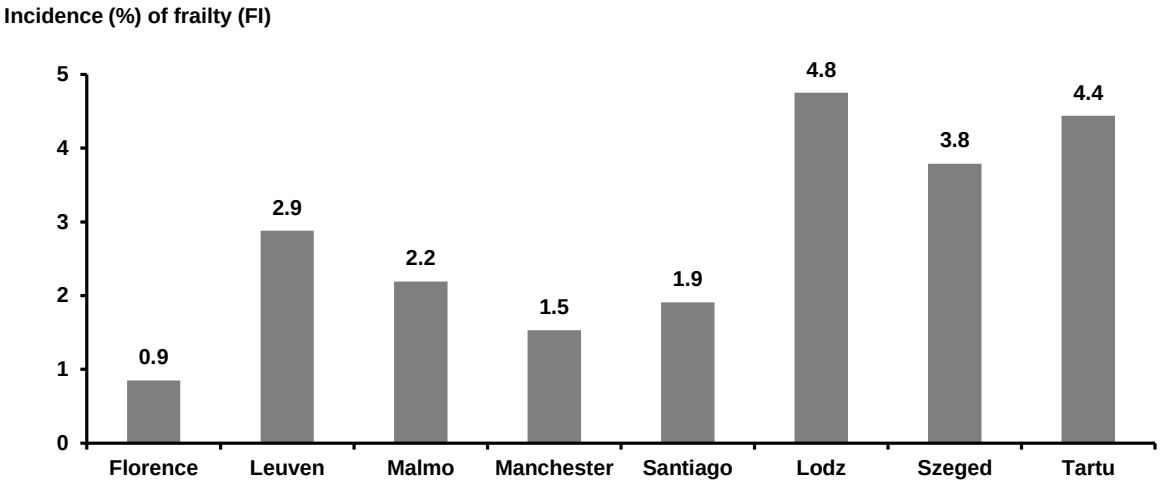


Figure 7.8 Incidence of frailty (FI) by centre

	Total (n=2672)	Non-frail (n=2599)	Frail Incidence (n=73)	p value
	Mean ± SD			
Age (years)	59.0 ± 10.6	58.7 ± 10.5	68.7 ± 8.2	˜<0.001
	Count (%)			
Smoking status (current)	437 (17.1)	422 (17.0)	15 (21.7)	*0.3
Alcohol Intake (≥5 days/week)	628 (23.6)	619 (23.9)	9 (12.3)	*0.02

Table 7.8 Baseline characteristics of men who did and did not develop frailty (FI)

* Chi-square test; ˜t test

	Odds Ratio (95% Confidence Interval)	
	Unadjusted	Model 1
Age (years)	1.1 (1.1 to 1.1)***	1.1 (1.1 to 1.1)***
Smoking status (current)	1.4 (0.8 to 2.4)	2.6 (1.4 to 4.9)**
Alcohol Intake (≥5 days/week)	0.4 (0.2 to 0.9)*	0.5 (0.3 to 1.1)

Table 7.9 Risk of incident frailty (FI)

Model 1 adjusted for baseline age and centre (in the association between age and frailty incidence, adjustment was only made for centre). ***p <0.001, **p <0.01,*p <0.05

7.6 Discussion

Frailty incidence, defined as those who were non-frail at baseline (i.e., either robust or pre-frail) and became frail at follow-up, was 3.5% using the FP approach, 2.1% using the FS approach and 2.7% using the FI approach. The incidence of frailty increased with age and varied by centre. Smoking was linked with an increased risk of developing frailty, though the strength of the association varied according to the frailty model used. The number of comorbidities at baseline also predicted frailty incidence (FP), although this association could be largely explained by age. Lower physical activity was also linked with frailty incidence (FS). Lower physical activity, and its association with frailty, was explored only in the FS model as a low physical activity measure contributed to the development of the FP model and the FI score.

The major strengths of the study are its large population, prospective nature, multi-centre design and the broad range of data collected. Follow-up rates were high (86%) and comparable with other similar longitudinal studies [280]. There are, however, a number of limitations to be considered in interpreting the data. Those who were lost to follow-up may have been more likely to be frail and so the results in relation to incidence may be an underestimate of the true occurrence of frailty. While attempts were made to standardise the study methods in different centres it is possible that differences in either the study instruments used or their application/interpretation in different centres may have contributed to some variability in the assessment of either exposures or outcome resulting in some imprecision. The effect of this would be, if anything, to reduce the chance of observing significant associations. In relation to the FI at baseline, only those deficits, with <5% missing data were considered (except for the SF-36). This is the cut-point provided in the literature for constructing the FI [49]. However, at follow-up variables with missing data greater than 5% were included because they had been used at baseline. The number, however were small (eight variables out of the thirty nine considered) and unlikely to have had a significant impact on the FI. As previously outlined the FS and FP models were operationalised for use in EMAS and hence some variables were not the exact measurements used in the original definitions. This approach of using

modified or adapted frailty models [26, 285] is similar to the approach used in other studies. The age of subjects included in EMAS was relatively younger than other frailty studies and so the prevalence of frailty correspondingly lower; furthermore, the follow-up time was relatively short (4.8years) and the numbers with incident frailty relatively small. It is possible that with a larger sample of incident frail subjects that there would have been greater statistical power to detect true biological associations. Finally, as discussed in previous chapters, the data relate to middle-aged and older European men and may not relate to other populations.

FI constructed at both phases satisfied the characteristics of a FI with its positively skewed distribution and association with age. These characteristics were similar to other populations where FI was assessed [43, 52, 60, 304, 326-328]. At baseline the mean FI was lower than at follow-up suggesting individuals became frailer during the follow-up period. These results support the robustness of the FI as a measure of frailty as applied in a European setting. The Cardiovascular Health Study (CHS) reported the 4 year incidence of frailty to be 7.2% among subjects who were non-frail at baseline. This slightly higher incidence (compared to the EMAS data) may be due to the older (aged 65-101 years) population and the inclusion of both men and women [5] as studies have suggested that the prevalence of frailty is higher in females compared to males. In the Hispanic Established populations for Epidemiological Studies of the Elderly (H-EPESE) a study on Mexican Americans aged 65 years and older the reported frailty incidence was slightly higher than observed in EMAS men; 3.6% at 2 years, 6.6% at 5 years and 7.9% at 7 years [329]. Frailty incidence (adapted FP model) in the WHAS was 14.8% after an average of 5.9 years of follow-up [266]. The results from the MacArthur Study of Successful Aging (MSSA), where participants were aged 70-79 years at baseline, showed that after 3 years of follow-up 6% of participants became frail (frailty assessed using an adapted FP model) [172]. Similar to our findings, the results from the Yale Precipitating Events Project showed that the FI (using 36 deficits) increased from 0.17 to 0.22 after 54 months of follow-up. Age and mobility were associated with transitions in frailty state. The results also suggested that for example a 77 year old man with 6 deficits and who took 10 seconds to walk 20 feet at baseline would have

13 deficits after 3 years, of which 1 deficit gained would be associated with age, 1 would be associated with mobility and the other 5 related to deficits associated with baseline FI [330]. Compared to most studies mentioned above, frailty incidence in EMAS was lower, ranging from 2.1% to 3.5%, which may possibly be due to the relatively young and healthy Caucasian population studied and the all-male cohort in EMAS.

Similar to our findings, Fugate Woods *et al* showed in the WHAS study that frailty incidence was associated with age, comorbidities and those who smoked were at a 2.9 times increased risk of becoming frail [266]. In addition, the WHAS data have also shown that hyperglycaemia predicted frailty incidence [152]. The results from the MSSA also suggested that those who consumed moderate amount of alcohol were at a lower risk of developing frailty than non-drinkers [172]. Age, comorbidity, limitations in physical activity and baseline pre-frailty was associated with frailty after 3 years [172]. The results published by the Canadian Study of Health and Ageing [211] also showed that smoking to be associated with frailty incidence. Results from the San Antonio Longitudinal Study of Aging (SALSA) data showed that age & diabetes mellitus were significant predictors of worsening frailty status after an average of 6.4 years, where frailty was assessed using an adapted FP model [202].

The incidence of frailty differed across centres according to the frailty model. In the case of the FI, frailty incidence was highest in the transitional countries (4.8%-Lodz, 3.8%-Szeged and 4.4%-Tartu) and lowest in Florence (0.9%). FS incidence across centres was high in Lodz (4.2%), Tartu (3.1%) and Szeged (1.9%) and none in Florence. FP incidence was high across centres ranging from 5.6% in Szeged to 1.2% in Tartu. The discrepancy of a lower frailty incidence when frailty was assessed using the FP model in Tartu, compared to when frailty was assessed using the FS and FI was explored further. The results showed that for physical tests such as walk time (used to assess slowness) and sit-to stand test (used to assess weakness) participants from Tartu showed an improvement in their scores from baseline although their self-reported scores on ambulation and resistance showed a worsening state at follow-up. There could be a number of reasons which could be suggested for this observation; it may be possible that the participants assumed their health status to be worse off when in-fact

they are not as unhealthy as they assumed. Despite the measures taken to train the local research teams including centralized workshops at baseline, and follow-up it is possible though that systematic differences in assessments at baseline and follow-up by the local research team in Tartu may have resulted in the finding.

Our results also support previous findings that frailty is a dynamic state with all possible transitions [78, 199]. They provide further evidence though to support the idea that as individuals age they are increasingly likely to accumulate more deficits and die, despite some people improving, with the general trend going from “bad to worse” [5]. Improvement in frailty status between baseline and phase 2 in EMAS was relatively rare and it was more common for men to transition from robust to pre-frail and pre-frail to frail by both the FP and FS model. These results were similar to a previous study in the osteoporotic fractures in men (MrOS) [27] where transitions from a frail to a non-frail state were rare.

7.7 Conclusion

In summary, the incidence of frailty varied from 2.1% to 3.5% depending on the frailty definition used. Transition in frailty state was more common towards a worsening frailty state. The incidence of frailty increased with age and varied across centres. Increased age and current smoking were associated with an increased risk of developing frailty at follow-up. Influence of adiposity measures on the development of frailty in European men.

Chapter 8 Influence of adiposity measures on frailty in European men

8.1 Summary

This chapter presents the results of the analyses looking at the association between baseline adiposity measures including BMI, waist circumference (WC), waist-hip ratio (WHR) and percentage (%) body fat and the development of frailty. Frailty was defined using an adapted Frailty Phenotype (FP) model, FRAIL Scale (FS) and Frailty Index (FI), both at baseline and at follow-up. Incident frailty was defined as being non-frail at baseline and frail at follow-up. Change in FI was defined as the difference in FI between baseline and follow-up with a positive value indicating worsening frailty. Adiposity measures were explored as both continuous variables and after categorisation as previously described. Excluding those who were frail at baseline, compared to those who were non-frail at follow-up, an increase in WC and WHR (at baseline) was associated with an increased risk of frailty at follow-up. This was true for frailty defined using the FP, FS and FI models. There was, however, no association with BMI or % body fat. An increase in adiposity assessed by WHR, WC, BMI or % body fat was associated with a change in FI score indicating worsening frailty. The data suggest that adiposity measures particularly WC and WHR are linked with the new development of frailty.

8.2 Introduction

As reported in Chapter 6 there was evidence in EMAS of an association between measures of adiposity and frailty. Given the cross sectional analysis, however, it was not possible to determine the temporal nature of the association for which prospective data are needed. There are few published prospective data and those that have been published have focused primarily on BMI as a measure of obesity. There are no data available looking at the impact of other measures of adiposity including WC and WHR and the new occurrence of frailty.

8.3 Aims

The broad aim of the work described in this chapter is to determine the influence of baseline adiposity measures on the development of frailty. The specific objectives are i) to determine whether baseline adiposity measures predict the new occurrence of frailty at follow-up using established frailty criteria, and ii) to determine whether there are differences in the strength of any observed associations with different adiposity measures, specifically BMI, WHR, WC and % body fat.

8.4 Methods

The detailed methods have been described in Chapter 3. Assessment of prevalent frailty including the FP, FS and FI are described in Chapters 3 and 4, and assessment of incident frailty in Chapter 7. The different categories used for the different adiposity measures are described in Chapter 6.

8.4.1 Statistical Analysis

Descriptive statistics were used to summarise the adiposity measures and frailty at baseline and follow-up. T-tests and Chi-square tests were used to test differences in adiposity measures (at baseline) by frailty status at follow-up (incident frail and incident non-frail). Logistic regression was used to explore the relationship between frailty incidence (outcome) and the various adiposity measures (assessed at baseline), with the results expressed as Odds Ratio (OR) and 95% Confidence Intervals (95% CI). In these analyses the adiposity measures were summarised as continuous measures and also after categorisation into quartiles, and if appropriate WHO categories. Adjustments were initially made for baseline age and centre, with additional adjustments for smoking, alcohol and comorbidities. In the case of the FI and FS, adjustments were only made for baseline age, centre, smoking and alcohol consumption; comorbidities were not used as they contributed to the development of the FI score and the FS model. Spearman's correlations were used to examine the association between change in FI and baseline adiposity measures. Linear regression was used to explore the relationship between baseline adiposity measures and the change in FI with adjustments for age, centre and lifestyle factors and also for the baseline FI.

8.5 Results

8.5.1 Frailty Phenotype; Baseline adiposity measures and new occurrence of Frailty

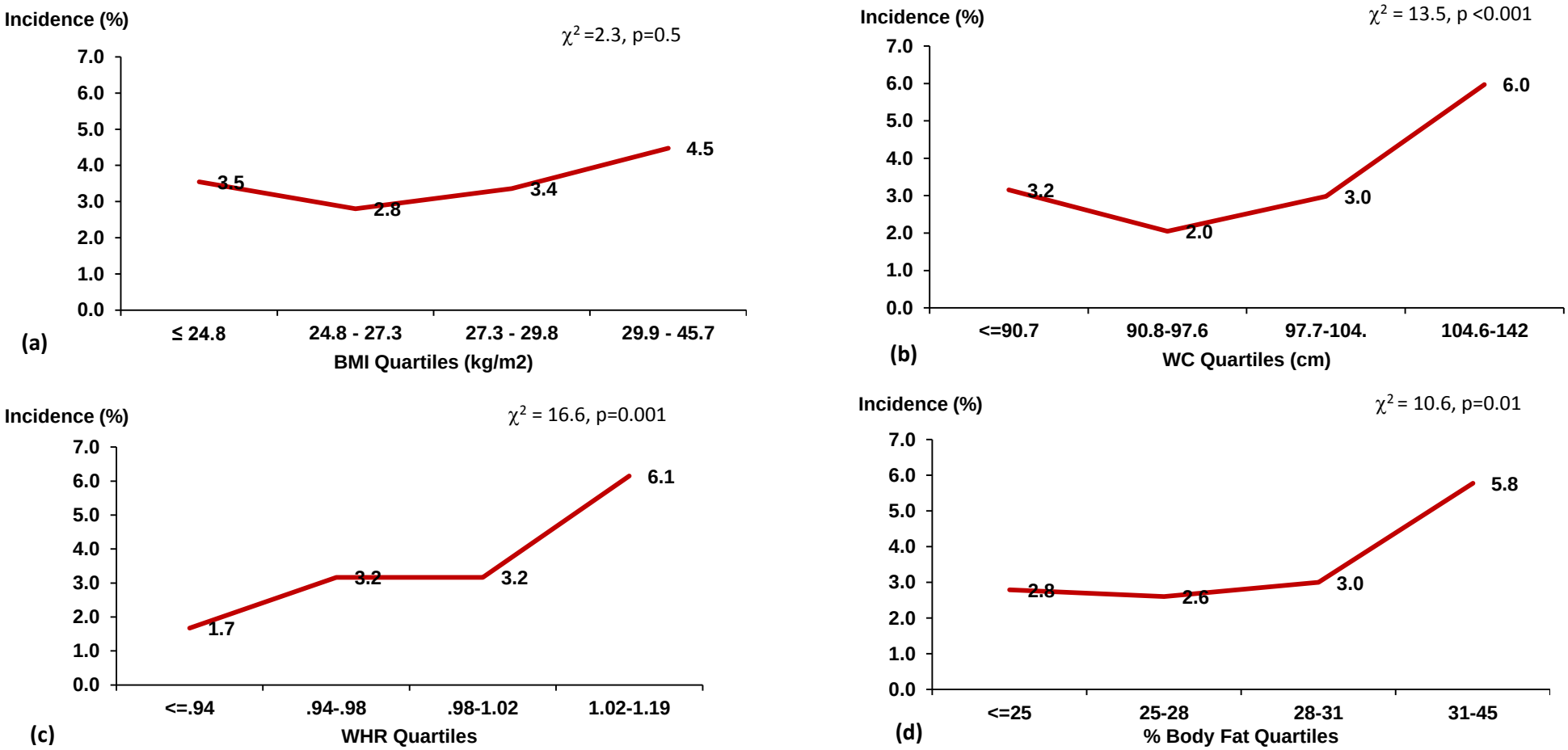
Ten men who were frail at both phases and fifteen who changed status from frail at baseline to non-frail at follow-up were excluded from this analysis. As outlined in Chapter 7, a total of 76 (3.6%) men who were not frail at baseline became frail at follow-up. Those men who developed frailty had significantly higher WC, WHR and % body fat than those who remained non-frail. This was true when the measure of adiposity was analysed either as a continuous or categorical variable (see Table 8.1). When the adiposity measures were categorised as quartiles, for all measures of adiposity there was an increase in the new occurrence of frailty from the second to fourth quartile (Figure 8.1). Apart from WHR, the frequency declined from the first to the second quartile for the other adiposity measures. Using logistic regression, with the new occurrence of frailty as outcome and adjusting for age, centre, lifestyle factors and comorbidities, participants with a 1SD higher value of either baseline WC or WHR were significantly more likely to have new occurrence of frailty (WC:OR=1.4; 95%CI 1.1,1.8 and WHR=1.5; 95%CI:1.1,1.9). BMI and %body fat were not associated with frailty incidence, (Table 8.2). When WHR was categorised into tertiles, those men in the highest tertile were 2.3 times more likely to develop frailty compared to those in the lowest tertile, after adjustment for age and centre. These associations remained significant after further adjustment for lifestyle factors and comorbidities. Compared to those in the lowest tertile of either WC or % body fat, men in the highest tertile were more likely to develop frailty, (OR=2.1 and 1.9) respectively. However, the results became non-significant after adjustment for age and centre. There was no significant association between frailty incidence and obesity defined by BMI categories.

	Non-frail (n=2073)	Frail Incidence (n=76)	p value
	Mean ± SD		
BMI (kg/m^2)	27.6 ± 4.0	27.9 ± 4.9	0.5˜
WC (cm)	98.0 ± 10.7	102.7 ± 13.4	<0.001˜
WHR	0.98 ± 0.06	1.01 ± 0.06	<0.001˜
% Body Fat	28.0 ±5	29.0 ± 6	<0.001˜
	Count (%)		
BMI Categories (kg/m^2)			
Normal (≤25)	536 (25.9)	20 (26.3)	0.2*
Overweight (25-30)	1039 (50.2)	32 (42.1)	
Obese (≥30)	493 (23.8)	24 (31.6)	
WC Categories (cm)			
<94	742 (35.8)	21 (27.6)	<0.001*
94-102	636 (30.7)	13 (17.1)	
>=102	695 (33.5)	42 (55.3)	
WHR Tertiles			
<=.95	704 (34.0)	13 (17.1)	<0.001*
.96-1.01	691 (33.3)	25 (32.9)	
1.01-1.19	678 (32.7)	38 (50.0)	
% Body Fat Tertiles			
≤26	699 (33.7)	20 (26.3)	<0.05*
26-30	693 (33.5)	20 (26.3)	
30-45	680 (32.8)	36 (47.4)	

Table 8.1 Baseline adiposity measures of men in the European Male Ageing Study in those who did and did not develop frailty (FP) at follow-up.

* Chi-square test; ˜t test, BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

Figure 8.1 Frailty incidence by adiposity variables (quartiles) (a) BMI (b) WC (c) WHR (d) % Body fat



	Odds Ratio (95% Confidence Intervals)		
	Unadjusted	**Model 1**	**Model 2**
BMI(per 1SD increase)	1.1 (0.9 to 1.4)	1.1 (0.8 to 1.4)	1.1 (0.9 to 1.4)
WC(per 1SD increase)	1.5 (1.2 to 1.8)***	1.4 (1.1 to 1.8)**	1.4 (1.1 to 1.8)**
WHR(per 1SD increase)	1.7 (1.4 to 2.1)***	1.6 (1.2 to 2.0)**	1.5 (1.1 to 1.9)**
% Body Fat (per 1SD increase)	1.3 (1.1 to 1.7)*	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.7)
BMI Categories (kg/m^2)			
Normal (≤25)	1.0	1.0	1.0
Overweight (25-30)	0.8 (0.5 to 1.5)	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.3)
Obese (≥30)	1.3 (0.7 to 2.4)	1.2 (0.6 to 2.2)	1.3 (0.7 to 2.6)
WC Categories (cm)			
<94	1.0	1.0	1.0
94-102	0.7 (0.4 to 1.5)	0.5 (0.3 to 1.1)	0.5 (0.3 to 1.1)
≥102	2.1 (1.3 to 3.6)**	1.6 (0.9 to 2.8)	1.6 (0.9 to 2.9)
WHR Tertiles			
≤.95	1.0	1.0	1.0
.96-1.01	2.0 (1.0 to 3.9)	1.7 (0.9 to 3.5)	1.6 (0.8 to 3.2)
1.01-1.19	3.0 (1.6 to 5.7)**	2.3 (1.2 to 4.5)*	2.0 (1.0 to 4.0)*
% Body Fat Tertiles			
≤26	1.0	1.0	1.0
26-30	1.0 (0.5 to 1.9)	1.0 (0.5 to 1.9)	1.0 (0.5 to 2.0)
30-45	1.9 (1.1 to 3.2)*	1.7 (0.9 to 3.1)	1.8 (1.0 to 3.3)

Table 8.2 Baseline adiposity measures and frailty incidence [FP]

Logistic regression models: Model 1 adjusted and centre, Model 2 adjusted for age, centre, smoking, alcohol and comorbidities: SD, standard deviation;

Odds Ratios(OR) corresponds to the risk/odds of becoming frail at follow-up for participants with a 1SD higher adiposity measure (continuous variable) or, for an individual category of each adiposity variable compared to the referent category.

*p <0.05,**p <0.01,***p <0.001

8.5.2 FRAIL Scale: Baseline adiposity measures and new occurrence of frailty

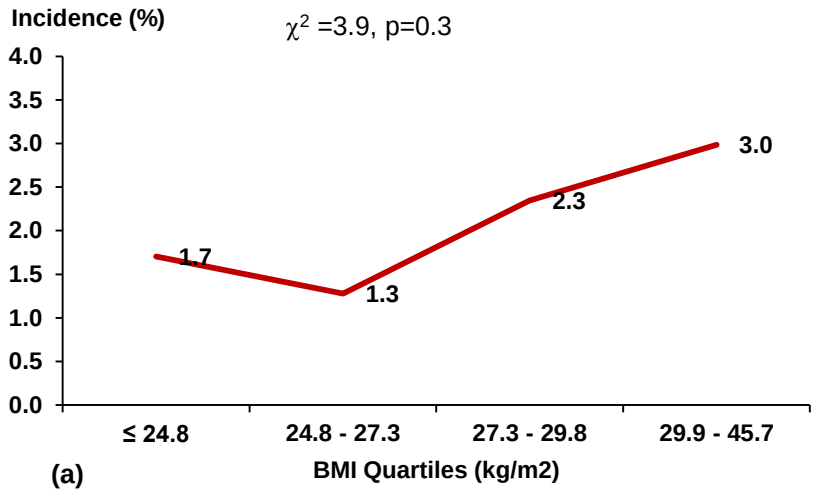
Twenty five men were excluded from this analysis, of which eight were frail at both phases and 17 who were frail at baseline and changed status to non-frail at follow-up. Using the FS to define frailty status, a total of 39 (2.1%) men who were not frail at baseline became frail at follow-up. These men had significantly higher WC and WHR at baseline, though not BMI or % body fat, compared to those who remained non-frail at both phases. This was true when the measure of adiposity was analysed either as a continuous or categorical variable (see Table 8.3). When the adiposity variables were categorised into quartiles, there was an increase in frequency of frailty (new occurrence) from the second to fourth quartiles for BMI, WC and WHR, though not % body fat (Figure 8.2). Using logistic regression, with the new occurrence of frailty as the outcome and adjusting for age, centre and lifestyle factors, participants with a 1SD higher baseline WC and WHR were significantly more likely to have new occurrence of frailty, (WC:OR=1.5; 95%CI 1.1,2.0 and WHR=1.8; 95%CI:1.3,2.5). No significant associations were observed between either BMI or % body fat and the new occurrence of frailty (see Table 8.4). When WHR was categorised into tertiles, men in the highest tertile were three times more likely to develop frailty compared to those in the lowest tertile. Those men in the upper tertile of WC also had a 2.7 times increased odds of becoming frail at follow-up compared to those in the lowest tertile. These results remained significant after further adjustment for age, centre, and lifestyle factors. No significant associations were observed between the new occurrence of frailty and either BMI (WHO cut-points) and % body fat (tertiles).

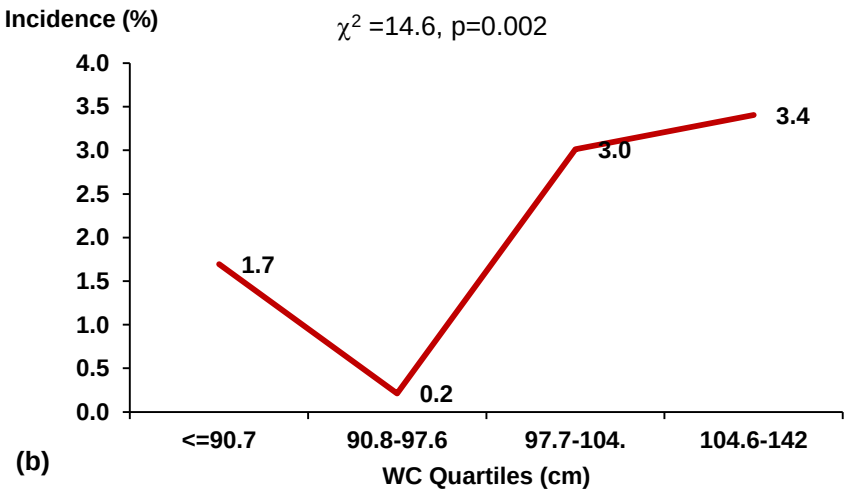
	Non-frail (n=1843)	Frail Incidence (n=39)	p value
	Mean ± SD		
BMI (kg/m^2)	27.4 ± 3.9	28.4 ± 4.6	0.1˜
WC (cm)	97.5 ± 10.5	102.1 ± 12.9	<0.01˜
WHR	0.98 ± 0.06	1.01 ± 0.07	<0.001˜
% Body Fat	28.0 ± 5	28.0 ± 5	0.9˜
	Count (%)		
BMI Categories (kg/m^2)			
Normal (≤25)	507 (27.6)	9 (23.1)	0.4*
Overweight (25-30)	935 (50.9)	18 (46.2)	
Obese (≥30)	396 (21.6)	12 (30.8)	
WC Categories (cm)			
<94	683 (37.1)	9 (23.1)	0.01*
94-102	572 (31.0)	9 (23.1)	
>=102	588 (31.9)	21 (53.9)	
WHR Tertiles			
<=.95	620 (33.6)	8 (20.5)	< 0.01*
.96-1.01	619 (33.6)	8 (20.5)	
1.01-1.19	604 (32.8)	23 (59.0)	
% Body Fat Tertiles			
≤26	614 (33.4)	13 (33.3)	0.9*
26-30	614 (33.4)	12 (30.8)	
30-45	612 (33.3)	14 (35.9)	

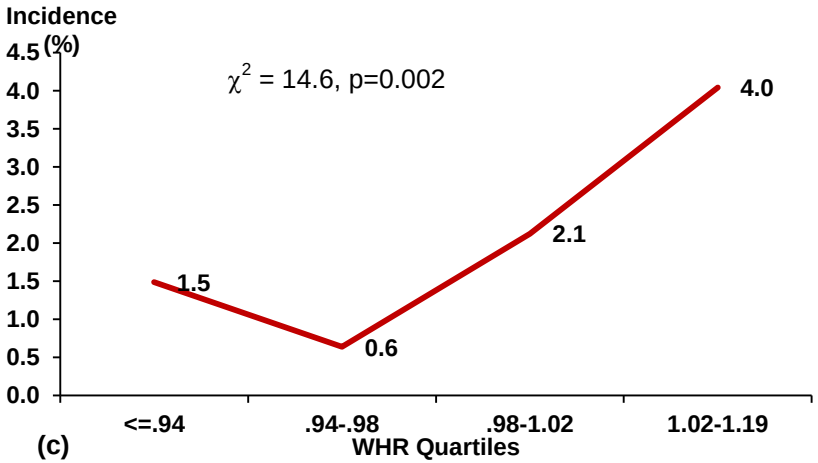
Table 8.3 Baseline adiposity measures of men in the European Male Ageing Study in those who did and did not develop frailty (FS) at follow-up.

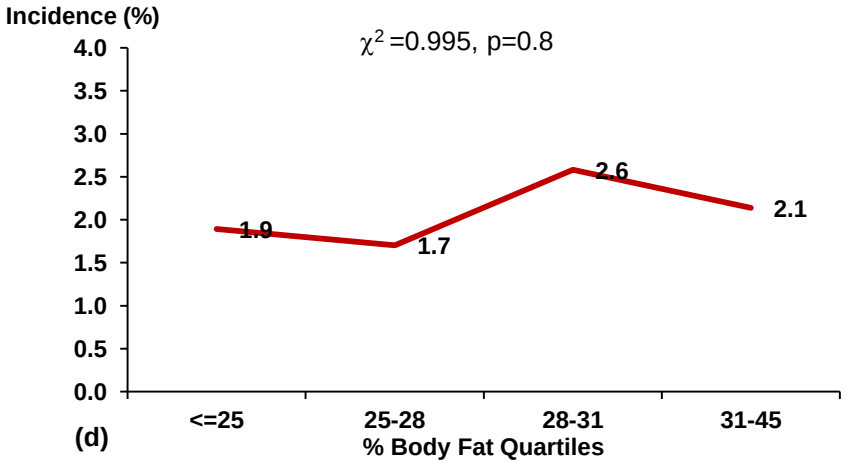
* Chi-square test; ˜t test
BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

Figure 8.2 Frailty incidence (FS) by adiposity variables (quartiles) (a) BMI (b) WC (c) WHR (d) % Body fat









	Odds Ratio (95% Confidence Intervals)		
	Unadjusted	**Model 1**	**Model 2**
BMI (per 1SD increase)	1.3 (0.9 to 1.7)	1.2 (0.9 to 1.6)	1.3 (0.9 to 1.8)
WC (per 1SD increase)	1.5 (1.1 to 2.0)**	1.4 (1.0 to 1.9)*	1.5 (1.1 to 2.0)*
WHR (per 1SD increase)	1.8 (1.3 to 2.4)***	1.7 (1.2 to 2.4)**	1.8 (1.3 to 2.5)**
% Body Fat (per 1SD increase)	1.0 (0.8 to 1.4)	1.2 (0.8 to 1.7)	1.3 (0.9 to 1.9)
BMI Categories (kg/m^2)			
Normal (≤25)	1.0	1.0	1.0
Overweight (25-30)	1.1 (0.5 to 2.4)	0.9 (0.4 to 2.0)	1.1 (0.4 to 2.5)
Obese (≥30)	1.7 (0.7 to 4.1)	1.4 (0.6 to 3.5)	1.7 (0.7 to 4.4)
WC Categories (cm)			
< 94	1.0	1.0	1.0
94-102	1.2 (0.5 to 3.0)	1.1 (0.4 to 2.7)	1.3 (0.5 to 3.4)
>= 102	2.7 (1.2 to 6.0)*	2.2 (1.0 to 5.0)*	2.6 (1.1 to 6.1)*
WHR Tertiles			
≤.95	1.0	1.0	1.0
.96-1.01	1.0 (0.4 to 2.7)	0.9 (0.3 to 2.6)	1.1 (0.4 to 3.0)
1.01-1.19	3.0 (1.3 to 6.6)**	2.7 (1.1 to 6.5)*	3.1 (1.2 to 7.6)*
% Body Fat Tertiles			
≤ 26	1.0	1.0	1.0
26-30	0.9 (0.4 to 2.0)	1.0 (0.5 to 2.3)	1.2 (0.5 to 2.7)
30-45	1.1 (0.5 to 2.3)	1.5 (0.7 to 3.4)	1.8 (0.8 to 4.2)

Table 8.4 Baseline adiposity measures and frailty incidence [FS]

Logistic regression models: Model 1 adjusted and centre. Model 2 adjusted for age, centre, smoking and alcohol; SD, standard deviation

Odds Ratios(OR) corresponds to the risk/odds of becoming frail at follow-up per 1SD higher adiposity measure (continuous variable) or, for an individual category of each adiposity variable compared to the referent category.

*p <0.05,**p <0.01,***p <0.001

BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

8.5.3 Frailty Index; Baseline adiposity measures and Frailty Incidence

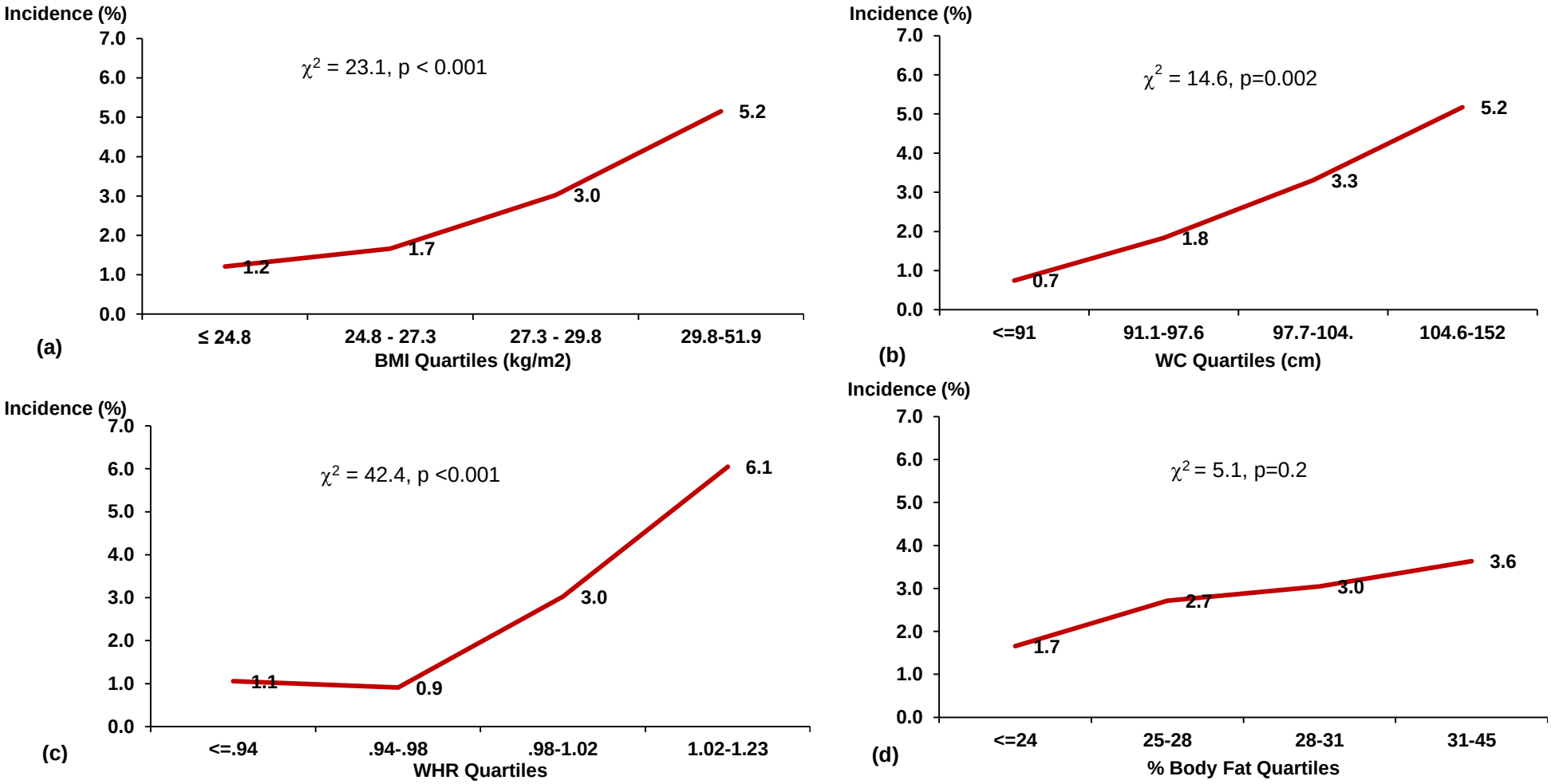
Those who were frail at both phases and who changed status from frail to non-frail (total, n=64) were excluded from the analysis. Using the FI to define frailty status, a total of 73 (2.7%) men who were not frail at baseline became frail at follow-up. All baseline adiposity measures were significantly higher in those who were not frail at baseline but developed frailty at follow-up compared to those who remained non-frail at both time points. This was true also when BMI and WC were categorised by WHO cut-points and WHR tertiles, although not % body fat, (see Table 8.5). When the variables were categorised as quartiles, for all measures of adiposity other than WHR there was an increase in the frequency (new occurrence) of frailty with increasing adiposity measure, (see Figure 8.3). WHR was the only measure where the new occurrence of frailty declined slightly from the first to the second quartile. Using logistic regression and after adjustment for age, centre and lifestyle factors, an increase in all of the adiposity measures (assessed at baseline) were associated with the new occurrence of frailty, (see Table 8.6). This association was also seen when all adiposity measures were categorised into tertiles, with those in the highest tertile of WHR, for example, having a 6.4 times increased odds of becoming frail at follow-up compared to those in the lowest tertile. These associations persisted and remained significant after adjustment for age, centre and lifestyle factors.

	Non-frail (n=2599)	Frail incidence (n=73)	p value
	Mean ± SD		
BMI (kg/m^2)	27.6 ± 3.9	29.6 ± 3.9	<0.001˜
WC (cm)	98.0 ± 10.6	104.9 ± 10.6	<0.001˜
WHR	0.98 ± 0.06	1.02 ± 0.05	<0.001˜
% Body Fat	28.0 ± 5	29.0 ± 5	0.02˜
	Count (%)		
BMI Categories (kg/m^2)			
Normal (≤25)	677 (26.3)	8 (11.0)	<0.001*
Overweight (25-30)	1297 (50.5)	35 (48.0)	
Obese (≥30)	596 (23.2)	30 (41.1)	
WC Categories (cm)			
<94	915 (35.6)	9 (12.3)	<0.001*
94-102	799 (31.1)	18 (24.7)	
>=102	858 (33.4)	46 (63.0)	
WHR Tertiles			
<=.95	874 (34.0)	8 (11.0)	<0.001*
.96-1.01	865 (33.6)	16 (21.9)	
1.01-1.19	832 (32.4)	49 (67.1)	
% Body Fat Tertiles			
≤26	862 (33.6)	19 (26.0)	0.4*
26-30	855 (33.3)	26 (35.6)	
30-45	852 (33.2)	28 (38.4)	

Table 8.5 Baseline adiposity measures of men in the European Male Ageing Study in those who did and did not develop frailty at follow-up (FI).

* Chi-square test; ˜t test,
BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

Figure 8.3 Frailty incidence (FI) by adiposity variables (quartiles) (a) BMI (b) WC (c) WHR (d) % Body fat



	Odds Ratio (95% Confidence Intervals)		
	Unadjusted	**Model 1**	**Model 2**
BMI(per 1SD increase)	1.5 (1.3 to 1.9)***	1.5 (1.2 to 1.9)***	1.6 (1.3 to 2.0)***
WC(per 1SD increase)	1.8 (1.4 to 2.2)***	1.6 (1.3 to 2.0)***	1.7 (1.3 to 2.1)***
WHR(per 1SD increase)	2.0 (1.6 to 2.5)***	1.8 (1.4 to 2.4)***	1.9 (1.4 to 2.4)***
% Body Fat(per 1SD increase)	1.3 (1.0 to 1.7)*	1.5 (1.2 to 2.0)**	1.6 (1.3 to 2.1)***
BMI Categories (kg/m^2)			
Normal (≤25)	1.0	1.0	1.0
Overweight (25-30)	2.3 (1.1 to 5.0)*	1.9 (0.9 to 4.2)	2.4 (1.0 to 5.6)*
Obese (≥30)	4.3 (1.9 to 9.4)***	3.6 (1.6 to 8.0)**	4.8 (2.0 to 11.2)***
WC Categories (cm)			
<94	1.0	1.0	1.0
94-102	2.3 (1.0 to 5.1)*	1.9 (0.9 to 4.4)	2.4 (1.0 to 5.8)*
>=102	5.5 (2.7 to 11.2)***	4.0 (1.9 to 8.4)***	5.0 (2.3 to 10.8)***
WHR Tertiles			
<=.95	1.0	1.0	1.0
.96-1.01	2.0 (0.9 to 4.7)	1.8 (0.7 to 4.2)	2.1 (0.8 to 5.3)
1.01-1.19	6.4 (3.0 to 13.7)***	5.1 (2.4 to 11.2)***	6.0 (2.6 to 13.7)***
% Body Fat Tertiles			
≤26	1.0	1.0	1.0
26-30	1.4 (0.8 to 2.5)	1.7 (0.9 to 3.2)	2.0 (1.0 to 3.8)*
30-45	1.5 (0.8 to 2.7)	2.1 (1.1 to 4.0)*	2.5 (1.3 to 4.9)**

Table 8.6 Baseline adiposity measures and frailty incidence [FI]

Logistic regression models:Model 1 adjusted and centre. Model 2 adjusted for age, centre, smoking and alcohol:

Odds Ratios(OR) corresponds to the risk/odds of becoming frail at follow-up per 1SD higher baseline adiposity measure (continuous variable) or, for an individual category of adiposity variable compared to the referent category.

*p <0.05,**p <0.01,***p <0.001

SD, standard deviation;BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

8.5.4 Baseline adiposity measures and change in Frailty Index from baseline to follow-up

Of those men who contributed data at both baseline and follow-up, the mean (SD) of FI at baseline was 0.12(0.1) and follow-up 0.13(0.12). The mean FI change from baseline to follow-up was 0.02(0.08). The FI change was positively correlated with baseline BMI, WC and WHR, though the magnitude of the correlation coefficients was small, (Table 8.7). The correlation was strongest for WHR. There was no significant correlation between % body fat and change in FI. Using linear regression and with change in FI as the outcome, an increase in BMI, WC or WHR was significantly associated with an increase in frailty, (Table 8.8). The magnitude of the association appeared strongest for WHR and FI change. For participants with a 1SD higher baseline WHR the FI change increased by 0.007 (95%CI 0.04, 0.01). The association remained significant after adjustment for age, centre and lifestyle factors and remained significant after further adjustment for baseline FI. Although change in FI was not associated with % body fat in the unadjusted linear model, after adjustment for baseline FI this association too became significant. When categorised into tertiles of the adiposity measures, broadly similar findings were observed, with an increase in measures of adiposity at baseline linked with greater change in frailty index (indicating worsening frailty).

Baseline Adiposity measure	r	p value
BMI(Kg/m^2)	0.05	0.01
WC (cm)	0.07	<0.001
WHR	0.1	<0.001
% Body Fat	0.005	0.8

Table 8.7 Correlations between baseline adiposity measures and FI change

r= Spearman's rank correlation coefficient

BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio

	Coefficient(95% Confidence Intervals)			
	Unadjusted	**Model 1**	**Model 2**	**Model 3**
BMI(per 1SD increase)	0.004 (0.001 to 0.006)*	0.003 (0.000 to 0.006)*	0.004 (0.001 to 0.007)*	0.008 (0.005 to 0.010)***
WC(per 1SD increase)	0.005 (0.003 to 0.008)***	0.004 (0.001 to 0.006)*	0.004 (0.001 to 0.007)**	0.009 (0.006 to 0.012)***
WHR(per 1SD increase)	0.007 (0.004 to 0.010)***	0.004 (0.001 to 0.007)**	0.004 (0.001 to 0.007)**	0.009 (0.006 to 0.012)***
% Body Fat(per 1SD increase)	0.0003 (-0.002 to 0.003)	0.0004 (-0.002 to 0.003)	0.001 (-0.002 to 0.004)	0.004 (0.001 to 0.007)*
BMI Categories (kg/m^2)				
Normal (≤25)	Reference	Reference	Reference	Reference
Overweight (25-30)	0.003 (-0.004 to 0.010)	0.003 (-0.004 to 0.009)	0.004 (-0.003 to 0.011)	0.006 (-0.0002 to 0.013)
Obese (≥30)	0.009 (0.001 to 0.016)*	0.006 (-0.002 to 0.014)	0.009 (0.001 to 0.017)*	0.018 (0.010 to 0.026)***
WC Categories (cm)				
<94	Reference	Reference	Reference	Reference
94-102	0.007 (0.0000 to 0.014)	0.005 (-0.002 to 0.012)	0.006 (-0.001 to 0.013)	0.008 (0.002 to 0.01)*
>=102	0.012 (0.006 to 0.019)***	0.008 (0.001 to 0.015)*	0.01 (0.003 to 0.017)**	0.02 (0.01 to 0.03)***
WHR Tertiles				
<=95	Reference	Reference	Reference	Reference
.96-1.01	0.006 (-0.001 to 0.013)	0.003 (-0.004 to 0.010)	0.004 (-0.003 to 0.011)	0.006 (-0.001 to 0.012)
1.01-1.19	0.018 (0.01 to 0.02)***	0.011 (0.004 to 0.02)**	0.012 (0.005 to 0.02)**	0.02 (0.01 to 0.03)***
% Body Fat Tertiles				
<=26	Reference	Reference	Reference	Reference
26-30	0.0005 (-0.006 to 0.007)	0.002 (-0.005 to 0.008)	0.002 (-0.005 to 0.009)	0.004 (-0.003 to 0.011)
30-45	0.0009 (-0.006 to 0.008)	0.002 (-0.005 to 0.009)	0.003 (-0.005 to 0.010)	0.008 (0.001 to 0.015)*

Table 8.8 Baseline adiposity measures and change in Frailty Index (Frailty Index at follow-up – Frailty Index at baseline)

Linear regressions: BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist Hip Ratio, Data are expressed as β coefficient (95% Confidence Interval [CI]): Model 1: adjusted for age and centre: Model 2: adjusted for age, centre, smoking and alcohol: Model 3: adjusted for age, centre, smoking, and alcohol consumption and baseline frailty status: *p <0.05,**p <0.01,***p <0.001

8.6 Discussion

The main finding in this chapter is that higher baseline adiposity measures and particularly WC and WHR predicted the new occurrence of frailty at follow-up. The association of frailty incidence with increased adiposity measures/obesity was consistent when frailty status was assessed using the FP model, FS model or FI and also when considering change in FI as continuous variable. An increase in all measures of adiposity at baseline was linked with an increased risk of developing frailty defined using the FI and also a change in the FI. Further analysis was also carried out to explore whether change in measures of adiposity (WC, BMI, %body fat, WHR) were associated with change in frailty (using FI as a continuous measure); however, no association was observed.

The major strengths of the study as explained previously are the large sample and standardised methods used in assessment in the different centres for both the outcome and exposure variables. There are, however, a number of limitations which need to be considered in interpreting the data. As discussed in Chapter 3 the response rate at baseline was 40% and at follow-up was 86% (after adjustment for mortality). It is possible that those who took part may have differed from those who declined and so estimates of the occurrence of frailty may be an over or underestimate of the true prevalence, however, this is unlikely to have affected the results relating to the relationship between adiposity measures and frailty as this was based on an internal comparison within the cohort. Adiposity measures were assessed from anthropometric measurements. These were standardised at the start of the study and also prior to the follow-up by formal training sessions at which all the study nurses attended. Errors of measurement, however, may have occurred and contributed to imprecision resulting in reduced statistical power to detect significant associations. It is possible that this may have explained the weaker association observed between frailty status and % body fat which relied on assessment of skin-fold thickness at a number of sites, and may perhaps therefore have been more prone to measurement error. As discussed in previous chapters, the FP and the FS were modified and adapted for our data set. Most studies use this approach as the original criteria are not always available [28, 325, 331]. Finally, as discussed in previous chapters, the data are based on

middle aged and elderly, predominantly Caucasian men and therefore caution is required in extrapolating the findings beyond this setting.

There are few prospective data looking at measures of adiposity and frailty. Woods et al [266] showed in the Women's Health Initiative Observational Study that underweight women (BMI <18.5 kg/m^2), as well as overweight and obese women were at increased risk of frailty and pre-frailty after 3 years of follow-up, compared to those of normal weight, suggesting a U shaped association. The study used the FP model to assess frailty status. A recent prospective study on the Helsinki business men (HBM) cohort showed that, compared to men with a normal BMI (<25 kg/m^2), overweight (BMI [25-29] kg/m^2) and obese men (BMI >30 kg/m^2) were at increased risk of subsequently developing frailty and pre-frailty, after adjustment for potential confounders. Similar results were also shown by a recent study using data from the Mini-Finland Health Examination Survey in 1119 men and women aged 30 years and older. This study found that baseline obesity measured by BMI defined by WHO cut-points predicted pre-frailty and frailty assessed using an adapted FP model after 22 years of follow-up [264]. The data presented here in contrast did not show and association between BMI and incident frailty defined using the FP. Differences in the duration of follow-up (26 years for the HBM study vs. 4.6 years for EMAS) and the different adaptations of the frailty models in studies may possibly explain the discrepancy in findings.

The consistent association of central obesity defined by WC and WHR predicting frailty incidence provides support that central obesity may be important risk factor in the development of frailty. The results from this chapter suggest WHR is the strongest predictor of the new occurrence of frailty. A possible explanation for this finding is that WHR is related to increased visceral fat (captured also by a higher waist circumference), and also a lower hip circumference which tends to be related to lower leg muscle mass and perhaps indicative of peripheral muscle loss [332, 333]. In men narrow hips are more indicative of relatively low leg muscle mass than in women, as they have less gluteal- subcutaneous fat compared to women [334, 335]. As loss of muscle mass is a key feature of the frailty syndrome, WHR, particularly in men, captures the adverse effects associated with increased visceral fat and muscle atrophy. Further possible

mechanisms whereby obesity especially central obesity is linked to the development of frailty are discussed in detail in Chapter 9.

8.7 Conclusion

Higher baseline central obesity, as assessed by WHR and WC, was consistently associated with an increased risk of developing frailty at follow-up and worsening frailty as evidenced by a higher FI change score. Obesity defined using WHR was the strongest predictor of incident frailty among older European men.

Chapter 9 Discussion

9.1 Summary

This chapter summarises the main findings of the thesis, and some of the strengths and limitations of the data. Three frailty definitions were used in this thesis; advantages and disadvantages of each are discussed. The potential mechanisms through which adiposity and frailty are linked are discussed and suggestions for future work considered.

9.2 Main Findings

A FRAIL Scale (FS) was developed using the EMAS data set. The prevalence of frailty as determined by the FS was 2.6%; prevalence increased with age from 0.3 % at age 40-49 years, rising to 5.9% in those aged 70 years and over. Frailty, defined using the FS, was associated with an increased risk of falls and mortality. Two other definitions of frailty had already been developed in EMAS, the Frailty Phenotype (FP) and Frailty Index (FI). The prevalence of frailty varied depending on the method used. At baseline, 4.3% of the EMAS cohort (146 men) was frail according to at least one definition of frailty. Of these, only 23 men were classified as frail using all three definitions, highlighting the disparity between the FS, FP and FI methods. The new occurrence or incidence of frailty over a mean follow-up of 4.8 years also varied by the definition used, with incidence rates of 2.0%, 3.7% and 2.7% for the FS, FP and FI, respectively. Incidence also increased with age. For example, the new occurrence of frailty using the FP definition ranged from 0.7% at age 40-49 years to 10.7% at age 70 years and over. There was also evidence of variation in frailty incidence by EMAS study centre. Frailty assessed by all three models was associated with an increased risk of mortality, after adjustment for confounders. Frailty was also associated with a higher risk of falls and an increased number of visits to a primary care physician in the EMAS cohort.

Frailty assessed at baseline was associated with adiposity measures, although the strength of the associations differed according to the frailty definition and the adiposity measure used. Higher waist circumference (WC) was associated with an increased prevalence of frailty according to all three definitions. Baseline adiposity measures, in particular measures of central obesity (WC and waist hip ratio (WHR)), predicted the new occurrence of frailty at follow-up. An

increase in WC, WHR, body mass index (BMI) and % body fat were also associated with an increase in the FI between baseline and follow-up.

9.3 Strengths and limitations

The strengths of the study include the large population-based sample, prospective design and standardisation of assessments. There are, however, a number of limitations which need to be considered. Given the multicentre, multinational design one of the concerns at the start of the study was that the data obtained in different centres should be comparable. The potential effect of any lack of comparability due to variation in the study instruments/assessments could result in differential misclassification of exposure/outcome data between centres and potentially compromise the study validity. At the outset, standardisation of the study instruments and study conduct were considered to be vital in ensuring the quality of data from the study. To reduce variation in data quality due to differences in the study instruments, where possible, instruments were chosen if they had been previously translated and validated in each of the centre's languages. If this was not possible, and to reduce errors due to language differences, questionnaires were initially translated from the original English version to the local language by a professional translator. The translated questionnaires were then sent to each centre where they were back-translated into English and checked for authenticity. Despite the strenuous efforts to ensure standardisation and harmonisation of data, it is possible that subtle differences in questionnaire design or responses (in part related to differences in the meaning of some words or phrases) may have differed between centres contributing to misclassification. It is difficult to determine what the effect of any such misclassification on the observed findings, although in most of the analyses undertaken adjustments for centre had relatively little impact on the results, suggesting that differential misclassification between centres may not have been important.

In relation to the assessments undertaken, including performance tests and anthropometric measurements, standard operating procedures (SOPs) were developed and used in each of the different EMAS centres. Anthropometry training videos were distributed to each centre and all physiological and anthropometric measurements were carried out by trained metrologists, according to the agreed SOPs. To ensure high standards, formal training

sessions were carried out at the start of the study, during the study and also prior to the follow-up to which all the study metrologists attended. Identical equipment was used in all centres where possible. Notwithstanding these attempts at standardisation, variation both within and between observers are likely to have contributed to some error in the measurements obtained; the effect of this is likely to have reduced the chance of finding real biological associations towards the null, and would not explain the presence of any significant associations observed. It is possible, however, that between centre variations in data quality may have contributed to some of the observed centre differences in the prevalence and/or incidence of frailty. Another limitation of EMAS was that it did not have a detailed measure of socioeconomic status (SES) and therefore it was not possible to adequately control for this. The effect of this is uncertain; if acting as a confounder (being linked with obesity and also frailty) then we cannot exclude that our observed association between measures of obesity and frailty could be due in part to an effect of social class. Adjusting for educational level though which could be considered to be a marker for socioeconomic class did not affect our main findings providing some support for a direct effect though some caution is needed in interpretation.

Information on falls was obtained by retrospective self-report over the preceding 12 months. It is possible that falls which occurred may have been forgotten over the time and resulting in misclassification of fall status. There is some evidence for this in the literature: in a study of 252 volunteers from the National Seniors association found that over a third of the population did not accurately recall a fall in the past 12 months [336]. In EMAS the effect of misclassification of falls would though if anything be to tend to reduce the chance of finding significant associations between falls and frailty.

As outlined earlier the response rate for the baseline phase of EMAS was 41%. It is possible that those who took part may have differed from those who were invited but did not take part. Therefore, the absolute prevalence of frailty and other exposure/outcome variables may be an under or overestimate compared to the true population prevalence. This should not, however, affect the results of the main risk factor analyses which were based on an internal comparison of responders. Losses to follow-up were relatively small with an overall follow-up rate of 81%. The non-responders (those who reported as institutionalised or unable to attend

due to poor health) were more likely to have been frail at baseline compared to those who were retained in the study. However, this is unlikely to have affected the results of any analysis looking at the impact of baseline variables including lifestyle factors and adiposity measures on the new occurrence of frailty, which again was based on an internal comparison of responders. Finally, it is important again to highlight that the results presented were obtained from European, predominately Caucasian men, and extrapolating any findings to other populations should be done with caution.

9.4 Which frailty model?

There is no current consensus on a definition for the frailty syndrome [4]. There are many tools proposed in the literature to identify frail individuals, of which the three most widely accepted models were used in this thesis. The FP was put forward by Linda Fried as a measure of physical frailty, distinct from comorbidity and disability and comprising five criteria; unintentional weight loss of 10 or more pounds in the previous year, self-reported exhaustion, weakness assessed by grip strength, slowness assessed by walk speed, and a reduction in physical activity. Individuals with three or more criteria are considered as frail and those with 1-2 criteria are considered pre-frail. A recent systematic review on the prevalence of frailty suggested that the FP model was the most commonly used model in assessing frailty [177]. Limitations of the definition are that it focuses on primarily physical aspects, rather than mental health, and does not include comorbidity as a component. It also relies on measurement of physical performance and relies on a comparison with reference data from the same population, and as a consequence it is time consuming and relatively expensive. Further, the physical measures may put off the elderly who may not be in good health and may refuse to take part in these tests [111]. The FS on the other hand is simpler and quicker to complete as it is based on self-reported questions and does not require population based reference values. It consists also of five criteria; fatigue, resistance (ability to climb 1 block of stairs), ambulation (ability to walk 100m), illnesses (5 or more) and loss of weight, with individuals classified as being frail if they have three or more criteria. It has been less well studied than the FP and having mostly self-reported data it is likely to face certain disadvantages such as participants overestimating or

underestimating their health conditions. Finally, the other frailty model considered in this thesis is the Frailty Index (FI). This relies on assessment of a relatively large number of deficits and is more time consuming to construct; it does not, however, require population based reference values. While primarily a continuous measure, the FI can be categorised using thresholds into robust, pre-frail and frail categories [61]. Compared to the FP and FS, the FI seems to be perform better at predicting adverse outcomes due to its continuous nature as well as due to the inclusion of deficits which have a causal relationship with adverse outcomes [337].

As outlined earlier the occurrence of frailty was similar for all three methods (including the FI when categorised into frail/pre-frail and robust), though they identify different individuals, and show no important differences in the link with mortality and other adverse health outcomes. For associations with measures of adiposity, there were no major differences between the FP and FS. Consistent associations were observed, however, with FI when used as a continuous measure. In summary, there does not appear to be much to differentiate between the two phenotypic models (FP and FS), in terms of occurrence or their ability to predict adverse outcomes. The FS is the easiest to assess requiring less time and without need for population reference data, making its use in a busy clinical environment the most feasible. Although it takes time to construct because of its continuous nature, the FI is, however, a more powerful method of detecting exposure-outcome associations.

9.5 What is the mechanism linking obesity and frailty?

There a number of possible mechanisms linking markers of obesity, including WC and WHR, with frailty. Obesity is associated with lower physical activity and decreased muscle strength which may in turn contribute to loss of physical function, disability and predispose to frailty [338]. In the obese elderly, studies have indicated that the main reason for functional disability is loss of strength to a degree where the individual is incapable of supporting the higher body weight for physical function [339]. Sternfeld *et al* were able to show that an increased fat mass was associated with lower physical activity and decreased muscle strength [338]. Changes in muscle quality or strength may also occur due to fat infiltration into muscle (also termed as “marbling”) in older adults, which may contribute to reductions in physical

function [189]. In this thesis it was not possible to look at the potential role of physical activity and strength as possible mediators of the relationship between obesity and frailty because of the limited number of time points.

Obesity in older adults makes them more vulnerable to chronic illnesses such as diabetes, metabolic syndrome, high blood pressure, cancer, cardiovascular disease, respiratory problems and osteoarthritis, which may result in a decline in function and a poorer quality of life [243, 254, 322, 340]. It is possible that these comorbidities may increasingly predispose an individual to the development of the frailty. An increase in visceral fat mass, together with a reduction in lean mass, leads to insulin resistance in the elderly. Type 2 diabetes has been linked with the frailty syndrome [153]. This is thought to occur as a result of increases in intramuscular fat and intra-hepatic fat, which in turn reduces insulin sensitivity through release of adipokines and free fatty acids. An increase in fat in the pancreas, together with reduced ß cell function, may also lead to the development of type 2 diabetes [341]. Again, it was not possible to explore the contribution of comorbid factors in explaining the occurrence of frailty in this thesis because of the limited number of available time points.

Other downstream factors are also linked with both obesity and frailty and suggest that the mechanism is more complex, with effects of these factors both on muscle and end organ damage [112, 113]. Inflammatory markers, such as TNF-α, CRP and IL-6 are associated with frailty and sarcopenia [111, 112, 116, 342]. These inflammatory markers are linked with comorbidities, including type 2 diabetes and metabolic syndrome, which in turn are linked to obesity [339, 343]. Leptin and pro-inflammatory cytokines are secreted from adipocytes which activate stress pathways including those involved in oxidative stress, which in turn fuel muscle catabolism, and this in turn may potentially lead to a downward cycle of increased sarcopenia and increased fat gain leading to physical disability and, possibly, a pathway leading to frailty [339, 344]. In a recent study, using the data from the Beijing Longitudinal of Ageing, frailty assessed by the FI increased as the number of cardio-metabolic disorders increased and this was also associated with an increased risk of death [345]. The results suggested that the concurrent occurrence of illnesses related to inflammation may play a role in the development of

the frailty syndrome. Since inflammation is associated with lifestyle factors, such as obesity, smoking and low physical activity, subsequent comorbidities could be one link to explain the aetiology and pathophysiology of the frailty syndrome [346].

Endocrine factors may also contribute to the link between obesity and frailty. Hormone dysregulations in a variety of endocrine axes, such as the hypothalamic-pituitary-adrenal (HPA) axis and sex steroids, are associated with changes in body composition including fat and lean mass, though the temporal nature of these associations remains unclear [225, 347-350]. Previous studies have shown an association between frailty and hormone dysregulations [111, 114, 116, 123, 142, 351, 352]; it is possible, therefore, that such dysregulations may contribute to frailty at least in part through an effect on body composition. Figure 9.1 summarises the complex ways in which obesity and frailty may be linked.

The data in this thesis highlight that central obesity, rather than other markers of obesity, were stronger determinants of frailty, suggesting that visceral rather than total fat was more important in the predisposition to frailty and points to a role of metabolic factors (which are linked with central obesity), rather than simple mechanical factors which may contribute to reduction in activity.

Studies have shown that the prevalence of obesity in the elderly as assessed by waist circumference was higher than that assessed by BMI [225, 254]. It has been suggested that while BMI is an appropriate measure to assess underweight in the elderly, measures of central obesity are more appropriate to assess excess adiposity [353]. The findings from this thesis pointing to WHR as the best indicator for future frailty are probably due to the mechanisms discussed in Chapter 8, where an increased WHR encompasses both an increase in visceral fat and also muscle atrophy due to loss of gluteal muscles resulting in peripheral muscle wastage. A high WHR has been associated with reduced leg muscle area and increased visceral fat in alcoholic men [354]. An increased waist circumference and a high WHR have also been linked to lifestyle factors such as smoking, higher intake of alcohol and low physical activity [335, 355, 356]. Due to this complexity, understanding the different potential interactions between the

frailty syndrome and obesity in the elderly will require advanced analytical techniques, perhaps similar to the approaches commonly used in systems biology [357].

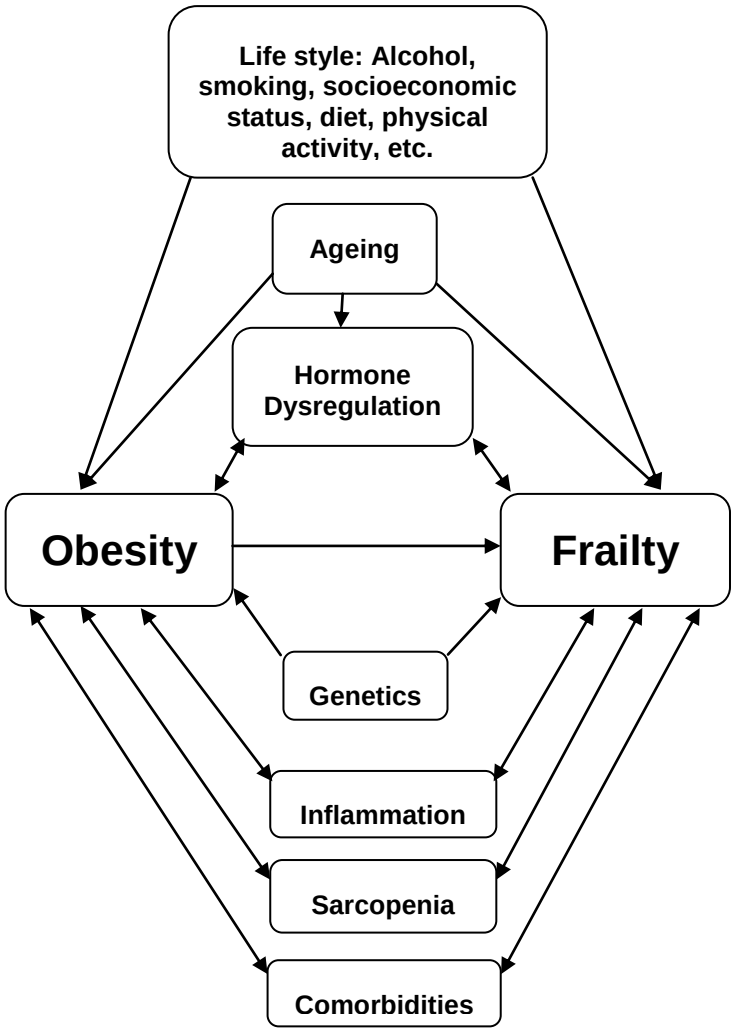


Figure 9.1 Possible mechanisms by which obesity plays a role in the development of frailty.

9.6 What are the implications of the findings?

There are an increasing number of people surviving into older age and consequently the numbers of frail elderly are set to increase, posing an important challenge for future health care provision. Those who are frail are at an increased risk of adverse outcomes such as falls, disability, long term care and mortality [5, 285]. Our data suggesting that obesity, particularly central obesity, may be an important risk factor for developing frailty highlighting a possible target for intervention. Obesity is a risk factor for other adverse outcomes including cardiovascular disease, diabetes mellitus, and osteoarthritis and interventions to reduce obesity are likely to have beneficial effects on reducing the risk of developing these disorders too.

Exercises based on resistance, strength, co-ordination, balance training and multi-component exercises including Tai-Chi, have been shown to improve function in older adults [358]. Gill *et al* [76], showed that a home based RCT "prehabilitation" program prevented a decrease in physical function after seven months in those who were moderately frail, although such an improvement was not seen in the severely frail. These authors also showed a different prehabilitation program could prevent, or at least reduce, high level functional decline in those who were physically frail [359]. Toulotte *et al* [360], showed that physical training exercises could improve the balance of demented, frail older adults with a history of falls. Faber *et al* [361], showed in a RCT among institutionalised elderly people that moderate exercise reduced falls in a group of pre-frail individuals after 11 weeks of training; however, the risk of falling increased in the frail group after exercise intervention. These studies suggest that it is important to note the severity of frailty before implementing any training program and more specific exercises needs to be developed to enhance the safety of frail elders. It would be more valuable to identify the pre-frail individuals before they face the consequences of frailty, such as institutionalisation or disability, so as to prevent further deterioration in their quality of life. Recent guidance was published by the British Geriatrics Society to help health and social care professionals on identifying, treating and putting forward a care plan for frail individuals, which might be a first step in dealing with this issue [362]. It may also be beneficial in routine health checks for the elderly to record anthropometric measurements of waist and hip to highlight any potential

obesity. Other studies [363, 364] have also shown that progressive resistance training in older adults can be used to reduce, or reverse, the onset of sarcopenia by increasing lean mass and muscle strength. A recent systematic review, which examined 20 studies on the effects of exercise training, recommended that a multi-component exercise program should include endurance, resistance and balance training to offer optimal improvements in function and falls reduction in the elderly [358].

Introducing physical activity to the care of the elderly is an important step in reducing the negative effect of frailty and reducing levels of obesity, and these steps need to be taken across all population settings. Elderly people in care homes are more likely to be physically inactive due to fear of falling and also restricted by staff due to legal issues and lack of time [360]. To reduce the effects of frailty on the obese elderly weight loss programmes, which concentrate on exercise and diet, could prove to be a beneficial intervention. Loss of weight in the elderly is a controversial issue, as it is believed it may increase the effects of sarcopenia and frailty due to muscle loss, together with loss of bone mineral density and nutritional deficiencies [190, 365]. However, the benefits of weight loss, specifically intentional weight loss, in the elderly seem to outweigh any potential hazards [225, 353, 366]. Weight loss in the elderly is associated with a better control of, or improvement in, comorbidities such as diabetes, cardio-vascular disease, hypertension, respiratory function, obstructive sleep apnoea, depression and an overall improvement in quality of life. The possible risks include increased mortality due to unintentional weight loss, loss of lean mass if weight loss is not combined with resistance exercise, loss of bone mineral density, osteoporosis, increased risk of fractures and nutritional deficiencies.

A recent scoping review by Porter Starr *et al* on the intervention trials on the effect of obesity and physical frailty in older adults showed that lean body mass was not maintained in weight loss interventions which did not include exercise, hence aggravating sarcopenia and resulting in frailty [367]. It appears important, therefore, among obese older adults with symptoms of frailty that any steps taken to reduce weight should also include maintenance of muscle [368]. Villareal *et al* [369] showed in a one year RCT among obese older adults with mild

or moderate frailty that weight loss, which included diet and exercise, was the most effective in improving physical function, strength, gait and balance. Those groups which included only exercise or only diet interventions also showed improvement, but there were some drawbacks as the diet alone group also lost lean mass and bone mineral density at the hip. The findings from Villareal's study suggest it is important to include high doses of vitamin D and calcium when recommending diet interventions in the elderly. Exercise was also associated with musculoskeletal injuries and it was suggested that necessary screening and safeguards be put in place during such programs to avoid or minimise any adverse events. A limitation of the above study [369] was that it was not able to determine the differences in the outcomes between genders due to the low number of participants. Some studies have shown non-routine exercise programs, such as whole body vibration exercises [370], Yoga breathing exercises [371], and Tai-Chi exercises to be effective in improving function in the frail elderly, although these techniques have not been applied to obese frail elderly people.

Bariatric surgery for those who are morbidly obese, i.e., a BMI (>40 or >35) kg/m^2 with comorbidity, is increasingly recommended [238], although this procedure may be deemed unsafe among the obese elderly. Laproscopic gastric banding is considered a safer alternative for elderly people [238, 372]. Drugs for the management of obesity, such as Orlistat, have not been used among obese elderly people as clinical trial data remain lacking [372]. As a wide range of comorbidities are associated with frailty, the efficient management of comorbidities among the frail elderly may prove beneficial in avoiding progression to, or worsening of, the frailty syndrome.

Intentional and controlled weight loss among older obese adults remains a difficult problem and medications used in younger adults may not always be applicable for use in the elderly due to possible adverse effects such as sarcopenia and osteoporosis. Published data on weight loss treatments in the elderly remain limited. A systematic review by Witham *et al,* on weight loss in obese older adults from nine studies found that although there was a significant weight loss observed, the actual usefulness of this weight loss in the elderly was not clear [373]. Diet and lifestyle changes (less sedentary behaviour, exercise and behavioural modification)

can be suggested as interventions which may improve quality of life and ameliorate frailty in the obese frail elderly. Diet should include sufficient protein to avoid further loss of fat-free muscle mass and include sufficient vitamin-D, calcium and multivitamin supplements as appropriate. A possible route to maximise protein intake is through an increased intake of leucine rich foods such as soy beans, fish and beef [238].

Another new potential target for the treatment of obesity in the elderly is the recently discovered hormone irisin [374]. Irisin has been shown to stimulate the development of brown adipose tissue, which has been widely suggested to partly explain variation between individuals with regard to basal energy expenditure (EE). Exercise has shown to increase levels of irisin and Swick *et al* [375] showed in a study on 17 postmenopausal women that irisin levels were significantly correlated with EE for subjects whose EE was greater than predicted. Accordingly, increasing irisin responsiveness may be a plausible mechanism for preventing and treating obesity in the elderly, although further studies and trials need to be carried out in different populations, particularly the frail elderly, to confirm the safety and any clinical application for this potential treatment. Therefore, it is important that future research not only concentrates on identifying obese older people who are frail, but also focusses on treatments designed to target this particular group as part of a broader, and arguably urgent, public health need.

Due to the multi-factorial nature of the frailty syndrome, any future interventions and treatments are likely to be complex. Exercise, together with hormone replacement therapies may prove beneficial, although studies will have to rigorously test the appropriate hormone doses required to maximise treatment effects while minimising side effects. Interventions to specifically reduce abdominal obesity would be an important intervention in the treatment of the obese frail elderly.

9.7 Future studies

Further studies are needed to validate the findings presented in this thesis in relation to the impact of adiposity measures on the occurrence of frailty. The data from EMAS are derived from predominately Caucasian men and future studies will need to examine the associations between adiposity and frailty in women and within different racial and ethnic groups. Additional

studies are also needed to better define the potential roles of central and peripheral obesity in predicting frailty, and explore underlying mechanisms, particularly the role of sex hormones and inflammation. In addition, clinical trials need to be designed and implemented to safely reduce weight in the obese frail elderly without aggravating the symptoms of frailty.

9.8 Summary

In summary, frailty in men is linked with adverse health factors including mortality and impaired quality of life. Excess adiposity is linked with the occurrence and new development of frailty the reasons for which remains uncertain and for which further studies are needed.

Appendix 1

Measurements in the European Male Ageing Study (EMAS)[268]

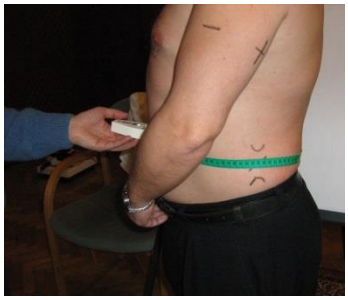
Postal questionnaire	Assisted questionnaire	Clinic assessments	Biological measures
• Demographic and lifestyle characteristics (current smoker, frequency of alcohol consumption) • Medical history (self-reported morbidities) • Employment, occupation details • Self-reported health • Pain (number of sites and chronicity) ❖ Details of heart conditions (angina, MI, heart failure, other) ❖ Diabetes (insulin dependent, insulin independent) ❖ Enlarged prostate (benign or cancerous) ❖ Chest pain (exercise induced) ❖ Cancer (date, type/site and clinic attended) ❖ Stroke (hospitalised) ❖ Fractures (date, bone broken, clinic attended) ❖ Ageing Male Symptoms (AMS) scale ❖ Smoking (*pack years*)	• Quality of life (Short Form-36 version 2) • Depression (Beck's Depression Inventory-II) • Adverse life events • Physical activity (Physical Activity Scale for the Elderly) • Lower urinary tract symptoms (International Prostate Symptom Score) • Sexual function questionnaire • Current prescription and non-prescription medications • Surgery/operations ❖ Utilisation of healthcare/medical services ❖ Sleep problem scale ❖ Hearing problems (Hearing Handicap Inventory for the Elderly-Screening) ❖ Alcohol consumption (frequency, type and quantity)	• Anthropometry (height, weight, waist/arm/hip circumference, skinfolds) • Bone health (calcaneal ultrasound) • Neuromuscular function (Reuben's Physical Performance Test) • Balance (Tinetti Assessment Tool) • Cognitive function (visual memory, processing speed) • Blood pressure and pulse • Visual acuity (Bailey-Lovie LogMAR charts) • 4-day food diary ❖ Resting/post-exercise ankle-brachial index ❖ Grip strength ❖ Mini-Mental State Examination *(≥65 years only*) ❖ Food frequency questionnaire	• Routine assessments (full blood count, total cholesterol, high density lipoprotein, glucose, triglycerides, albumin, creatinine, prostate specific antigen, Ca^{2+}, Na^{+}, K^{+}) • Sex hormones and associated proteins (testosterone, oestradiol, dihydrotestosterone, dehydroepiandrosterone sulphate, luteinising hormone, follicle stimulating hormone, sex hormone-binding globulin) • Metabolic hormones/factors (insulin, IGF-1, IGF binding protein-1 IGF binding protein-3, growth hormone, 25-hydroxyvitamin D, parathyroid hormone, free thyroxine [T4], leptin, prolactin, TSH, C-reactive protein) ❖ Cortisol (saliva samples) ❖ 1,25-dihydroxyvitamin D

• Baseline study
❖ Follow-up study

Appendix 2

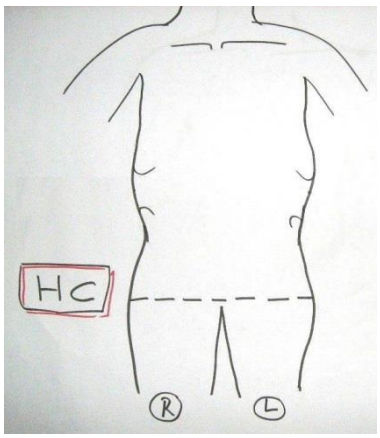
WAIST CIRCUMFERENCE

- Find the tips of lowest ribs and the tips of the hip bones
- Place the tape **horizontally** midway between these points to measure
- If you can't find the top of hip bones in very big men, then 2 cm below the tips of the lowest ribs is OK
- Subjects should be asked not to hold in their stomach.



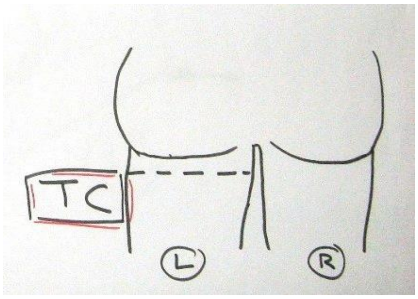
HIP CIRCUMFERENCE (HC)

- Find the widest part of the hips where the bones stick out
- Make sure the subject stand with feet 20 cm apart
- Place the tape **horizontally** over hip to measure



THIGH CIRCUMFERENCE (TC)

- Measure the LEFT thigh 1 cm below the natural fold of left buttock
- Make sure the left leg is relaxed by bending the left knee slightly

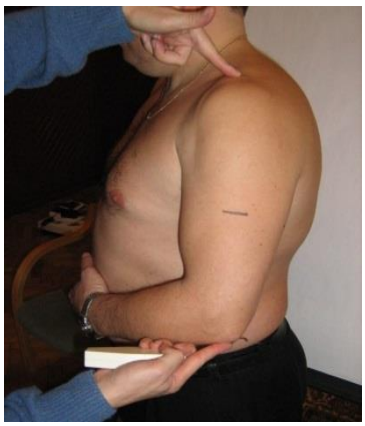


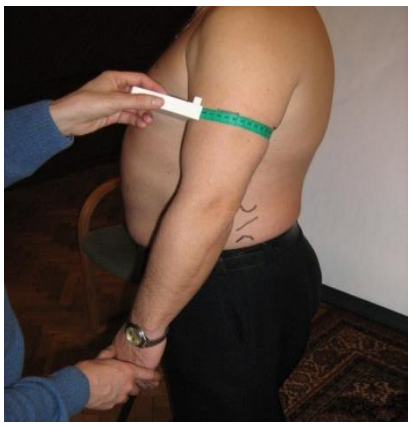
MID-CALF (not shown)

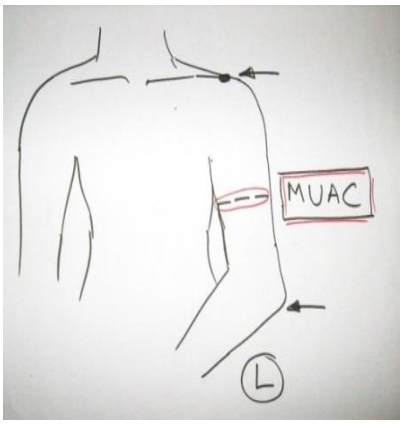
- Measure the LEFT calf midway between the top of the knee and the maleolus
- Make sure the subject sit in a chair of similar height to knee height.

Mid-upper arm circumference (MUAC)

- Bend the LEFT elbow to 90 degrees.
- Measure the length between the top of the arm where a round tip of the collar bone is and the tip of the elbow
- Mark midway between these sites then ask the subject to straighten his LEFT before placing the tape horizontally around the ink mark to measure.

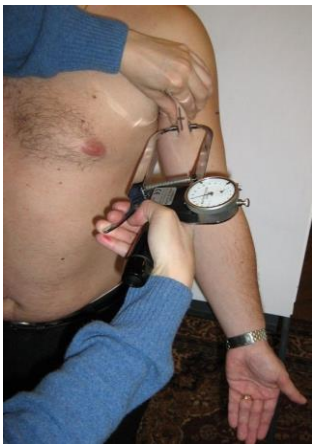


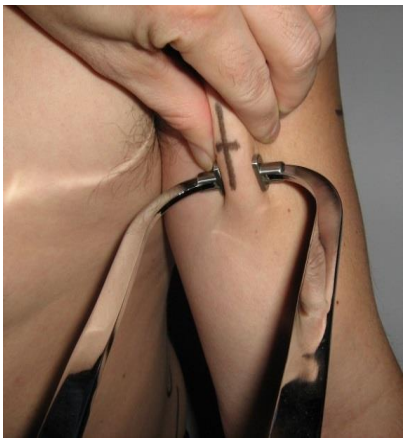


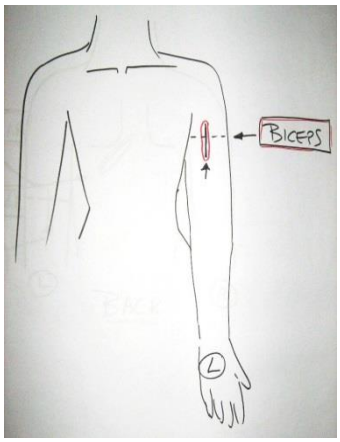


BICEPS

- Ask the subject to rotate his LEFT hand out and the arm is relaxed and straight.
- Grab the skin and fat with thumb and **all** of your four fingers
- Lift the skin and fat fold gently and apply the callipers half a centimetre away from your fingers to measure

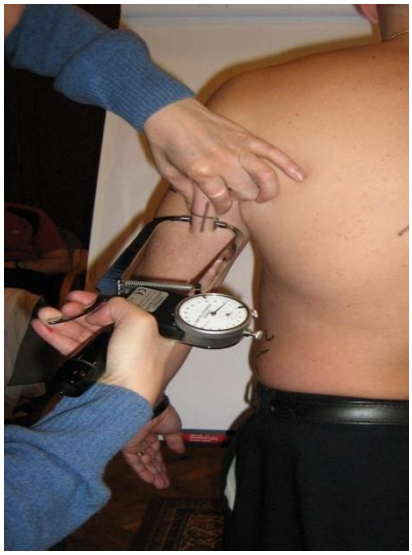


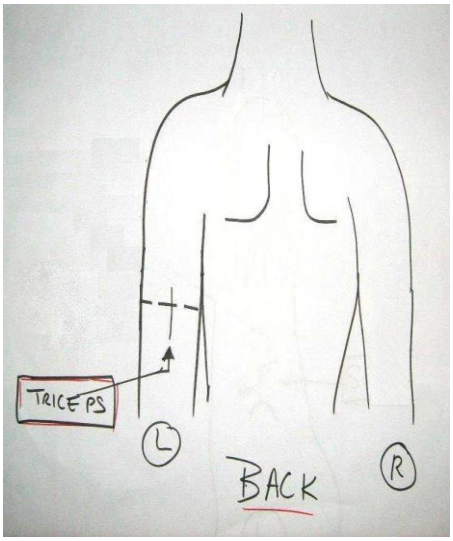




TRICEPS

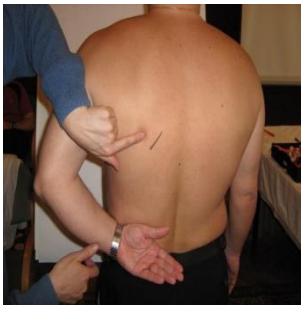
- Ask the subject to keep his LEFT arm straight
- Grab the skin and fat fold
- Lift the skin and fat fold gently and apply the callipers to measure

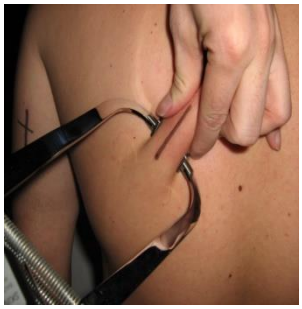


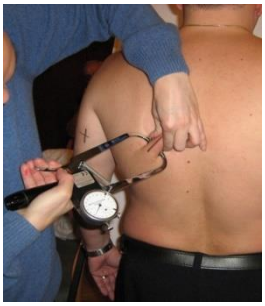


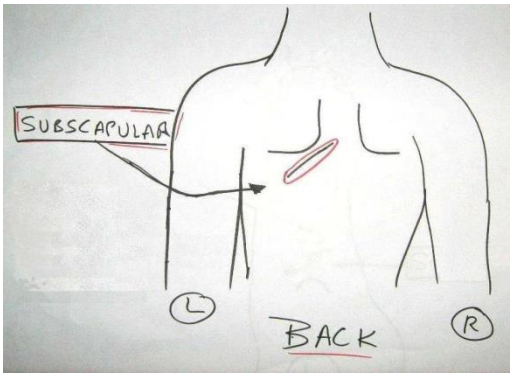
SUBSCAPULAR

- Bend the arm to the back to find the shoulder blade
- Make an oblique mark 1 cm below the shoulder blade
- Grab the skin and fat fold and apply the callipers to measure



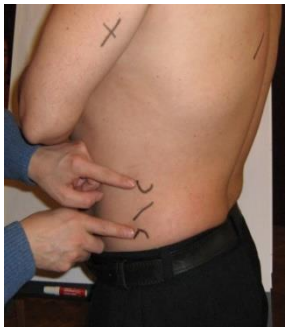


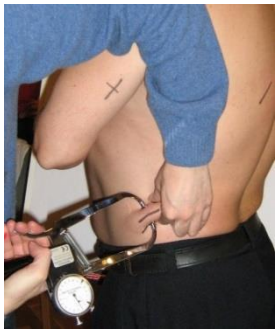


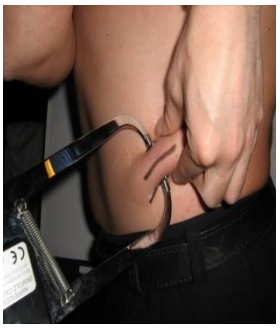


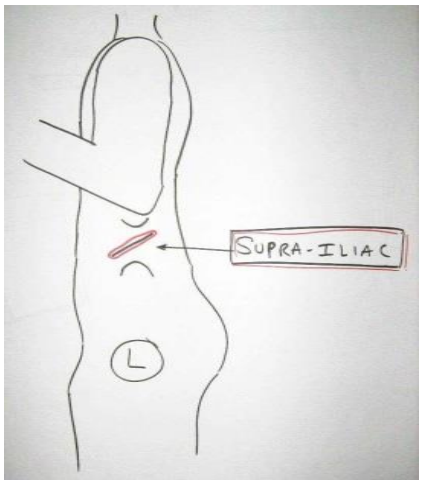
SUPRA-ILIAC

- Make an oblique mark between the lowest rib and the hip on the LEFT side of the body.
- Grab the skin and fat fold with your thumb and all four fingers
- Lift the skin and fat fold gently and measure









References

1. Rose Maria Li, C.Ladarola A, C.Maisano C. Why population aging matters, A global perspective: Summit on Global Aging, hosted by the U.S. State Department in collaboration with the National Institute on Aging. 2007 [updated March 15 2007]; Available from: http://www.nia.nih.gov/sites/default/files/WPAM.pdf.

2. Zaidi A, Sidorenko A, Association WD, Gallen US. Features and Challenges of Population Ageing Using the European Perspective: World Demographic Association; 2008.

3. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, et al. Comparison of 2 Frailty Indexes for Prediction of Falls, Disability, Fractures, and Death in Older Women. Arch Intern Med. 2008;168:382-9.

4. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of frailty in population-based studies: an overview. BMC Geriatr. 2013;13.

5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56:M146-57.

6. Van Kan G, Rolland Y, Bergman H, Morley J, Kritchevsky S, Vellas B, et al. The I.A.N.A. task force on frailty assessment of older people in clinical practice. The Journal of Nutrition, Health and Aging. 2008;12:29-37.

7. Brocklehurst JC. The day hospital. In Textbook of Geriatric Medicine and Gerontology. 1985;3rd edition. London: Churchill, .

8. Woodhouse KW, Wynne Hilary, Baillie Shelagh, James O.F.W, M.D R. Who are the Frail Elderly? Quarterly Journal of Medicine, . 1988;New Series 68:505-6.

9. Brown I, Renwick R, Raphael D. Frailty - Constructing a common meaning, definition and conceptual framework. Int J Rehabil Res. [Article]. 1995;18:93-102.

10. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. Nursing Outlook. 2010;58:76-86.

11. Morley JE, Vellas B, Abellan van Kan G, Anker SD, Bauer JM, Bernabei R, et al. Frailty Consensus: A Call to Action. Journal of the American Medical Directors Association. 2013;14:392-7.

12. Kirkwood TBL. Understanding the Odd Science of Aging. Cell. 2005;120:437-47.

13. Hayflick L. How and why we age. Experimental Gerontology.33:639-53.

14. Medvedev ZA. An attempt at a rational classification of theories of ageing.G. Biological Reviews. 1990;65:375-98.

15. Ekerdt DJ, Ed. The Macmillan Encyclopedia of Aging. [Macmillan]. 2002.

16. Gavrilov* LA, Gavrilova NS. Evolutionary Theories of Aging and Longevity. The Scientific World Journal (2002), [Review Article]. 2002;2: 339-56

17. Ungewitter E, Scrable H. Antagonistic pleiotropy and p53. Mechanisms of Ageing and Development.130:10-7.

18. Gavrilov LA, Gavrilova NS. The reliability theory of aging and longevity. J Theor Biol. 2001;213:527 - 45.

19. Rockwood K, Hogan DB, MacKnight C. Conceptualisation and measurement of frailty in elderly people. Drugs Aging. [Review]. 2000;17:295-302.

20. Powell C. Frailty : Help or Hindrance. Journal of the Royal society of Medicine. 1997;90:23-6.

21. Morley JE, Perry HM, Miller DK. Editorial: Something About Frailty. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2002;57:M698-M704.

22. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JPJ. Old or Frail: What Tells Us More? The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004;59:M962-M5.

23. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people; an evolving concept. CMAJ. 1994;150:489 - 95.

24. Graham JE, Mitnitski AB, Mogilner AJ, Rockwood K. The dynamics of cognitive aging: distinguishing functional age and disease from chronological age in a population. Am J Epidumiol. 1999;150:1045 - 54.

25. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: Design and rationale. Annals of Epidemiology. 1991;1:263-76.

26. Bandeen-Roche K, Xue Q-L, Ferrucci L, Walston J, Guralnik JM, Chaves P, et al. Phenotype of Frailty: Characterization in the Women's Health and Aging Studies. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61:262-6.

27. Cawthon PM, Marshall LM, Michael Y, Dam T-T, Ensrud KE, Barrett-Connor E, et al. Frailty in Older Men: Prevalence, Progression, and Relationship with Mortality. Journal of the American Geriatrics Society. 2007;55:1216-23.

28. Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Goff ML, Ritchie K, et al. Frailty Among Community-Dwelling Elderly People in France: The Three-City Study. The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63:1089-96.

29. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of Frailty in Middle-Aged and Older Community-Dwelling Europeans Living in 10 Countries. The journals of gerontology Series A, Biological sciences and medical sciences. 2009:glp012.

30. Solfrizzi V, Scafato E, Frisardi V, Sancarlo D, Seripa D, Logroscino G, et al. Frailty syndrome and all-cause mortality in demented patients: the Italian Longitudinal Study on Aging. AGE. 2012;34:507-17.

31. Tom SE, Adachi JD, Anderson FA, Boonen S, Chapurlat RD, Compston JE, et al. Frailty and Fracture, Disability, and Falls: A Multiple Country Study From the Global Longitudinal Study of Osteoporosis in Women. Journal of the American Geriatrics Society. 2013;61:327-34.

32. Xue QL. The Frailty Syndrome: Definition and Natural History. Clinics in Geriatric Medicine. 2011;27:1-15.

33. Romero-Ortuno R, Walsh C, Lawlor B, Kenny R. A Frailty Instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC Geriatrics. 2010;10:57.

34. Macklai NS, Spagnoli J, Junod J, Santos-Eggimann B. Prospective association of the SHARE-operationalized frailty phenotype with adverse health outcomes: evidence from 60+ community-dwelling Europeans living in 11 countries. BMC Geriatr. 2013;13:1471-2318.

35. Chang YW, Chen WL, Lin FG, Fang WH, Yen MY, Hsieh CC, et al. Frailty and its impact on health-related quality of life: a cross-sectional study on elder community-dwelling preventive health service users. PLoS One. 2012;7:25.

36. Ottenbacher KJ, Ostir GV, Peek MK, Snih SA, Raji MA, Markides KS. Frailty in Older Mexican Americans. Journal of the American Geriatrics Society. 2005;53:1524-31.

37. Samper-Ternent R, Karmarkar A, Graham J, Reistetter T, Ottenbacher K. Frailty as a Predictor of Falls in Older Mexican Americans. Journal of Aging and Health. 2011.

38. Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA, et al. A Comparison of Frailty Indexes for the Prediction of Falls, Disability, Fractures, and Mortality in Older Men. Journal of the American Geriatrics Society. 2009;57:492-8.

39. Kiely DK, Cupples LA, Lipsitz LA. Validation and Comparison of Two Frailty Indexes: The MOBILIZE Boston Study. Journal of the American Geriatrics Society. 2009;9999.

40. Rothman MD, Leo-Summers L, Gill TM. Prognostic Significance of Potential Frailty Criteria. Journal of the American Geriatrics Society. 2008;56:2211-6.

41. Rockwood K, Stadnyk K, MacKnight C. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999;353:205 - 6.

42. Hogan DB, Fox RA. A Prospective Controlled Trial of a Geriatric Consultation Team in an Acute-care Hospital. Age Ageing. 1990;19:107-13.

43. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62:722-7.

44. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mechanisms of Ageing and Development. 2006;127:494-6.

45. Rockwood K, Mitnitski; A. How might deficit accumulation give rise to frailty? [Invited presentation to the IAGG/WHO/SFGG Workshop on Frailty scheduled for Athens, Greece on January 20 & 21, 2012]. 2012.

46. Mitnitski A, Graham J, Mogilner A, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatrics. 2002;2:1.

47. Gavrilov LA, Gavrilova NS. Reliability Theory of Aging and Longevity. Handbook of the biology of ageing. 2006;sixth edition.

48. Jones D, Xiaowei Song, Arnold Mitnitski, Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. Aging Clin Exp Res. 2005.

49. Searle S, Mitnitski A, Gahbauer E, Gill T, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatrics. 2008;8:24.

50. Gu D, Dupre ME, Sautter J, Zhu H, Liu Y, Yi Z. Frailty and Mortality Among Chinese at Advanced Ages. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2009;64B:279-89.

51. Woo J, Goggins W, Sham A, Ho SC. Public health significance of the frailty index. Disability & Rehabilitation. 2006;28:515-21.

52. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative Fitness and Frailty of Elderly Men and Women in Developed Countries and Their Relationship with Mortality. Journal of the American Geriatrics Society. 2005;53:2184-9.

53. Song X, Mitnitski A, Rockwood K. Prevalence and 10-Year Outcomes of Frailty in Older Adults in Relation to Deficit Accumulation. Journal of the American Geriatrics Society. 2010;58:681-7.

54. Kulminski A, Ukraintseva SV, Akushevich I, Arbeev KG, Land K, Yashin AI. Accelerated accumulation of health deficits as a characteristic of aging. Experimental Gerontology. 2007;42:963-70.

55. Yang Y, Lee LC. Dynamics and Heterogeneity in the Process of Human Frailty and Aging: Evidence From the U.S. Older Adult Population. J Gerontol B Psychol Sci Soc Sci. 2009:gbp102.

56. Hubbard RE, Rockwood K. Frailty in older women. Maturitas. 2011;69:203-7.

57. Puts MTE, Lips P, Deeg DJH. Sex Differences in the Risk of Frailty for Mortality Independent of Disability and Chronic Diseases. Journal of the American Geriatrics Society. 2005;53:40-7.

58. Romero-Ortuno R, Kenny RA. The frailty index in Europeans: association with age and mortality. Age and Ageing. 2012;41:684-9.

59. Kulminski AM, Ukraintseva SV, Kulminskaya IV, Arbeev KG, Land K, Yashin AI. Cumulative Deficits Better Characterize Susceptibility to Death in Elderly People than Phenotypic Frailty: Lessons from the Cardiovascular Health Study. Journal of the American Geriatrics Society. 2008;56:898-903.

60. Rockwood K, Andrew M, Mitnitski A. A Comparison of Two Approaches to Measuring Frailty in Elderly People. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62:738-43.

61. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. Canadian Medical Association Journal. 2011;183:E487-E94.

62. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SAP, et al. Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study. The Journal of clinical endocrinology and metabolism. 2010:jc.2009-754.

63. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging. 2012;16:601-8.

64. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173:489-95.

65. Rockwood K, Wolfson C, McDowell I. The Canadian Study of Health and Aging: organizational lessons from a national, multicenter, epidemiologic study. Int Psychogeriatr 2001;13:233-7.

66. Canadian study of health and aging: study methods and prevalence of dementia. Canadian Medical Association Journal. 1994;150:899-913.

67. Hubbard RE, Andrew MK, Fallah N, Rockwood K. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. Diabetic Medicine. 2010;27:603-6.

68. Woo J, Leung J, Morley JE. Comparison of Frailty Indicators Based on Clinical Phenotype and the Multiple Deficit Approach in Predicting Mortality and Physical Limitation. Journal of the American Geriatrics Society. 2012;60:1478-86.

69. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing. 2006;35:526-9.

70. Rolfson DB, Majumdar SR, Taher A, RT T. Development and validation of a new instrument for frailty. Clin Invest Med. 2000;23:336.

71. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, et al. Frailty: An Emerging Research and Clinical Paradigm Issues and Controversies. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62:731-7.

72. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. J Gerontol B Psychol Sci Soc Sci. 1998;53:S9-16.

73. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Patterson C. Development of an easy prognostic score for frailty outcomes in the aged. Age Ageing. 2008:afm195.

74. Forti P, Rietti E, Pisacane N, Olivelli V, Maltoni B, Ravaglia G. A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. Archives of Gerontology and Geriatrics. 2012;54:16-20.

75. Paw MJMCA, De Groot LCPGM, Van Gend SV, Schoterman MHC, Schouten EG, Schroll M, et al. Inactivity and Weight Loss, Effective Criteria to Identify Frailty. JNHA,Journal of nutrition, health and ageing. 2003.

76. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A Program to Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home. N Engl J Med. 2002;347:1068-74.

77. Sayer AA, Syddall HE, Martin HJ, Dennison EM, Roberts HC, Cooper C. Is grip strength associated with health-related quality of life? Findings from the Hertfordshire Cohort Study. Age Ageing. 2006;35:409-15.

78. Puts MTE, Lips P, Deeg DJH. Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning. Journal of Clinical Epidemiology. 2005;58:1188-98.

79. Cesari M, Kritchevsky SB, Penninx BWHJ, Nicklas BJ, Simonsick EM, Newman AB, et al. Prognostic Value of Usual Gait Speed in Well-Functioning Older People—Results from the Health, Aging and Body Composition Study. Journal of the American Geriatrics Society. 2005;53:1675-80.

80. Wou F, Gladman JRF, Bradshaw L, Franklin M, Edmans J, Conroy SP. The predictive properties of frailty-rating scales in the acute medical unit. Age and Ageing. 2013.

81. Hoogendijk EO, van der Horst HE, Deeg DJH, Frijters DHM, Prins BAH, Jansen APD, et al. The identification of frail older adults in primary care: comparing the accuracy of five simple instruments. Age and Ageing. 2013;42:262-5.

82. Mitnitski A, Fallah N, Rockwood MR, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. J Nutr Health Aging 2011;15:863-7.

83. Gurina NA, Frolova EV, Degryse JM. A Roadmap of Aging in Russia: The Prevalence of Frailty in Community-Dwelling Older Adults in the St. Petersburg District—The “Crystal” Study. Journal of the American Geriatrics Society. 2011;59:980-8.

84. Lucicesare A, Hubbard R, Fallah N, Forti P, Searle S, Mitnitski A, et al. Comparison of two frailty measures in the Conselice Study of Brain Ageing. The Journal of Nutrition, Health & Aging. 2010;14:278-81.

85. Pilotto A, Rengo F, Marchionni N, Sancarlo D, Fontana A, Panza F, et al. Comparing the Prognostic Accuracy for All-Cause Mortality of Frailty Instruments: A Multicentre 1-Year Follow-Up in Hospitalized Older Patients. PLoS ONE. [doi:10.1371/journal.pone.0029090]. 2012;7:e29090.

86. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing Models of Frailty: The Health and Retirement Study. Journal of the American Geriatrics Society. 2009;57:830-9.

87. Van Iersel M, B, Marcel GMOR. Frailty Criteria Give Heterogenous Results When Applied In Clinical Practice. Journal of the American Geriatrics Society. 2006;54:728-9.

88. Lipsitz LA. Dynamics of Stability: The Physiologic Basis of Functional Health and Frailty. The journals of gerontology Series A, Biological sciences and medical sciences. 2002;57:B115-25.

89. Lipsitz LA. Physiological Complexity, Aging, and the Path to Frailty. Sci Aging Knowl Environ. 2004;2004:.

90. Chaves PHM, Varadhan R, Lipsitz LA, Stein PK, Windham BG, Tian J, et al. Physiological Complexity Underlying Heart Rate Dynamics and Frailty Status in Community-Dwelling Older Women. Journal of the American Geriatrics Society. 2008;56:1698-703.

91. Bortz WM, II. A Conceptual Framework of Frailty: A Review. The journals of gerontology Series A, Biological sciences and medical sciences. 2002;57:M283-8.

92. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. Age Ageing. 1997;26:315-8.

93. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. The journals of gerontology Series A, Biological sciences and medical sciences. 2004;59:M255-63.

94. Lupien SJ, N.Wan. Successful ageing: from cell to self. The Royal Society. 2004;359:1413–26.

95. Drey M, Wehr H, Wehr G, Uter W, Lang F, Rupprecht R, et al. The frailty syndrome in general practitioner care. Zeitschrift für Gerontologie und Geriatrie.1-6.

96. Foundation of Healthy Aging. Immunity. 2006;24:489.

97. Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. Current Cardiovascular Risk Reports. 2011;5:467-72.

98. Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest. 2013;123:966-72.

99. Weiss CO. Frailty and Chronic Diseases in Older Adults. Clinics in Geriatric Medicine. 2011;27:39-52.

100. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381:752-62.

101. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research Agenda for Frailty in Older Adults: Toward a Better Understanding of Physiology and Etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. Journal of the American Geriatrics Society. 2006;54:991-1001.

102. Morley JE, Kim MJ, Haren MT. Frailty and Hormones. Reviews in Endocrine & Metabolic Disorders. 2005;6:101-8.

103. Woo J, Tang NLS, Suen E, Leung JCS, Leung PC. Telomeres and frailty. Mechanisms of Ageing and Development. [doi: DOI: 10.1016/j.mad.2008.08.003]. 2008;129:642-8.

104. Collerton J, Ashok D, Martin-Ruiz C, Pyle A, Hudson G, Yadegarfar M, et al. Frailty and mortality are not influenced by mitochondrial DNA haplotypes in the very old. Neurobiology of Aging. 2013.

105. Ho Y-Y, Matteini AM, Beamer B, Fried L, Xue Q-l, Arking DE, et al. Exploring Biologically Relevant Pathways in Frailty. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2011;66A:975-9.

106. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. The Lancet. 2003;361:393-5.

107. Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat Rev Genet. 2012;13:878-90.

108. Walston J, Fedarko N, Yang H, Leng S, Beamer B, Espinoza S, et al. The Physical and Biological Characterization of a Frail Mouse Model. The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63:391-8.

109. Parks RJ, Fares E, MacDonald JK, Ernst MC, Sinal CJ, Rockwood K, et al. A Procedure for Creating a Frailty Index Based on Deficit Accumulation in Aging Mice. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2012;67A:217-27.

110. Feridooni HA, Sun MH, Rockwood K, Howlett SE. Reliability of a Frailty Index Based on the Clinical Assessment of Health Deficits in Male C57BL/6J Mice. The journals of gerontology Series A, Biological sciences and medical sciences. 2014.

111. Collerton J, Martin-Ruiz C, Davies K, Hilkens CM, Isaacs J, Kolenda C, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: Cross-sectional findings from the Newcastle 85+ Study. Mechanisms of Ageing and Development. 2012;133:456-66.

112. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. Journal of Cellular and Molecular Medicine. 2009;9999.

113. Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW. Nutrition, Inflammation, and Leptin Levels in Aging and Frailty. Journal of the American Geriatrics Society. 2008;56:279-84.

114. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, et al. Frailty and Activation of the Inflammation and Coagulation Systems With and Without Clinical Comorbidities: Results From the Cardiovascular Health Study. Arch Intern Med. 2002;162:2333-41.

115. Barzilay JI, Blaum C, Moore T, Li Xue Q, Hirsch CH, Walston JD, et al. Insulin Resistance and Inflammation as Precursors of Frailty: The Cardiovascular Health Study. Arch Intern Med. 2007;167:635-41.

116. Leng S, Chaves P, Koenig K, Walston J. Serum Interleukin-6 and Hemoglobin as Physiological Correlates in the Geriatric Syndrome of Frailty: A Pilot Study. Journal of the American Geriatrics Society. 2002;50:1268-71.

117. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and Frailty in Older Women. Journal of the American Geriatrics Society. 2007;55:864-71.

118. Leng SX, Hung W, Cappola AR, Yu Q, Xue Q-L, Fried LP. White Blood Cell Counts, Insulinlike Growth Factor-1 Levels, and Frailty in Community-Dwelling Older Women. The journals of gerontology Series A, Biological sciences and medical sciences. 2009:gln047.

119. Puts MTE, Visser M, Twisk JWR, Deeg DJH, Lips P. Endocrine and inflammatory markers as predictors of frailty. Clinical Endocrinology. 2005;63:403-11.

120. Schmaltz HN, Fried LP, Xue Q-L, Walston J, Leng SX, Semba RD. Chronic Cytomegalovirus Infection and Inflammation Are Associated with Prevalent Frailty in Community-Dwelling Older Women. Journal of the American Geriatrics Society. 2005;53:747-54.

121. Wang GC, Kao WHL, Murakami P, Xue Q-L, Chiou RB, Detrick B, et al. Cytomegalovirus Infection and the Risk of Mortality and Frailty in Older Women: A Prospective Observational Cohort Study. Am J Epidemiol.171:1144-52.

122. Chang SS, Weiss CO, Xue Q-L, Fried LP. Patterns of Comorbid Inflammatory Diseases in Frail Older Women: The Women's Health and Aging Studies I and II. The journals of gerontology Series A, Biological sciences and medical sciences. 2009:glp181.

123. Alemán H, Esparza J, Ramirez FA, Astiazaran H, Payette H. Longitudinal evidence on the association between interleukin-6 and C-reactive protein with the loss of total appendicular skeletal muscle in free-living older men and women. Age and Ageing. 2011;40:469-75.

124. Baylis D, Bartlett DB, Syddall HE, Ntani G, Gale CR, Cooper C, et al. Immune-endocrine biomarkers as predictors of frailty and mortality: a 10-year longitudinal study in community-dwelling older people. AGE. 2013;35:963-71.

125. Carcaillon L, Blanco C, Alonso-Bouzon C, Alfaro-Acha A, Garcia-Garcia FJ, Rodriguez-Manas L. Sex differences in the association between serum levels of testosterone and frailty in an elderly population: the Toledo Study for Healthy Aging. PLoS One. 2012;7.

126. Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. Testosterone, Sex Hormone-Binding Globulin, and Frailty in Older Men. Journal of the American Geriatrics Society. 2007;55:548-55.

127. Cawthon PM, Ensrud KE, Laughlin GA, Cauley JA, Dam T-TL, Barrett-Connor E, et al. Sex Hormones and Frailty in Older Men: the Osteoporotic Fractures in Men (MrOS) Study. The Journal of clinical endocrinology and metabolism. 2009:jc.2009-0417.

128. Tajar A, Lee DM, Pye SR, O'Connell MDL, Ravindrarajah R, Gielen E, et al. The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men. Age and Ageing. 2013;42:352-9.

129. Travison TG, Nguyen A-H, Naganathan V, Stanaway FF, Blyth FM, Cumming RG, et al. Changes in Reproductive Hormone Concentrations Predict the Prevalence and Progression of the Frailty Syndrome in Older Men: The Concord Health and Ageing in Men Project. Journal of Clinical Endocrinology & Metabolism. 2011.

130. Krasnoff JB, Basaria S, Pencina MJ, Jasuja GK, Vasan RS, Ulloor J, et al. Free Testosterone Levels Are Associated with Mobility Limitation and Physical Performance in Community-Dwelling Men: The Framingham Offspring Study. The Journal of clinical endocrinology and metabolism.jc.2009.

131. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. Current Opinion in Clinical Nutrition & Metabolic Care. 2004;7:271-7.

132. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of Graded Doses of Testosterone on Erythropoiesis in Healthy Young and Older Men. The Journal of clinical endocrinology and metabolism. 2008;93:914-9.

133. Kenny AM, Gallagher JC, Prestwood KM, Gruman CA, Raisz LG. Bone Density, Bone Turnover, and Hormone Levels in Men Over Age 75. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 1998;53A:M419-M25.

134. Stanley HL, Schmitt BP, Poses RM, WP. D. Does hypogonadism contribute to the occurrence of a minimal trauma hip fracture in elderly men? J Am Geriatr Soc. 1991 Aug;39:766-71.

135. Perry HM, Miller DK, Patrick P, Morley JE. Testosterone and leptin in older African-American men: Relationship to age, strength, function, and season. Metabolism. 2000;49:1085-91.

136. Morley JE. Editorial: Andropause. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2001;56:M263-M5.

137. Srinivas-Shankar U, Roberts SA, Connolly MJ, O' Connell MDL, Adams JE, Oldham JA, et al. Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men: A Randomized, Double-Blind, Placebo-Controlled Study. The Journal of clinical endocrinology and metabolism. 2010:jc.2009-1251.

138. Carcaillon L, Garcia-Garcia FJ, Tresguerres JA, Gutierrez Avila G, Kireev R, Rodriguez-Manas L. Higher levels of endogenous estradiol are associated with frailty in postmenopausal women from the toledo study for healthy aging. The Journal of clinical endocrinology and metabolism. 2012;97:2898-906.

139. Eichholzer M, Barbir A, Basaria S, Dobs AS, Feinleib M, Guallar E, et al. Serum sex steroid hormones and frailty in older American men of the Third National Health and Nutrition Examination Survey (NHANES III). Aging Male. 2012;15:208-15.

140. Nieschlag E, H.M.Behre. Andrology. [Book].Third Edition.

141. Sanders JL, Cappola AR, Arnold AM, Boudreau RM, Chaves PH, Robbins J, et al. Concurrent Change in Dehydroepiandrosterone Sulfate and Functional Performance in the Oldest Old: Results From the Cardiovascular Health Study All Stars Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.

142. Voznesensky M, Walsh S, Dauser D, Brindisi J, Kenny AM. The association between dehydroepiandosterone and frailty in older men and women. Age Ageing. 2009:afp015.

143. Muller M, van den Beld AW, van der Schouw YT, Grobbee DE, Lamberts SWJ. Effects of Dehydroepiandrosterone and Atamestane Supplementation on Frailty in Elderly Men. The Journal of clinical endocrinology and metabolism. 2006;91:3988-91.

144. Nair KS, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, et al. DHEA in Elderly Women and DHEA or Testosterone in Elderly Men. N Engl J Med. 2006;355:1647-59.

145. Forti P, Maltoni B, Olivelli V, Pirazzoli GL, Ravaglia G, Zoli M. Serum dehydroepiandrosterone sulfate and adverse health outcomes in older men and women. Rejuvenation Res 2012;15:349-58.

146. Cappola AR, Xue Q-L, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-Like Growth Factor I and Interleukin-6 Contribute Synergistically to Disability and Mortality in Older Women. J Clin Endocrinol Metab. 2003;88:2019-25.

147. Cappola AR, Bandeen-Roche K, Wand GS, Volpato S, Fried LP. Association of IGF-I Levels with Muscle Strength and Mobility in Older Women. The Journal of clinical endocrinology and metabolism. 2001;86:4139-46.

148. Cappola AR, Xue Q-L, Fried LP. Multiple Hormonal Deficiencies in Anabolic Hormones Are Found in Frail Older Women: The Women's Health and Aging Studies. The journals of gerontology Series A, Biological sciences and medical sciences. 2009;64A:243-8.

149. Harman SM, Blackman MR. Hormones and Supplements: Do They Work? The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004;59:B652-B8.

150. 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. Journal of the American Geriatrics Society. 2005;53:927-34.

151. Blaum CS, Xue QL, Tian J, Semba RD, Fried LP, Walston J. Is Hyperglycemia Associated with Frailty Status in Older Women? Journal of the American Geriatrics Society. 2009;57:840-7.

152. Kalyani RR, Tian J, Xue QL, Walston J, Cappola AR, Fried LP, et al. Hyperglycemia and Incidence of Frailty and Lower Extremity Mobility Limitations in Older Women. Journal of the American Geriatrics Society. 2012;60:1701-7.

153. Goulet EDB, Hassaine A, Dionne IJ, Gaudreau P, Khalil A, Fulop Tamas, et al. Frailty in the elderly is associated with insulin resistance of glucose metabolism in the postabsorptive state only in the presence of increased abdominal fat. Experimental Gerontology. 2009;44:740-4.

154. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. 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;15:857-62.

155. Hirani V, Naganathan V, Cumming RG, Blyth F, Le Couteur DG, Handelsman DJ, et al. Associations Between Frailty and Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Concentrations in Older Australian Men: The Concord Health and Ageing in Men Project. J Gerontol A Biol Sci Med Sci 2013.

156. Reichel H, Koeffler HP, AW N. The role of the vitamin D endocrine system in health and disease. New Englan Journal of Medicine. 1989;320:981-91.

157. Semba RD, Garrett E, Johnson BA, Guralnik JM, Fried LP. Vitamin D deficiency among older women with and without disability. Am J Clin Nutr. 2000;72:1529-34.

158. Zamboni M, Zoico E, Tosoni P, Zivelonghi A, Bortolani A, Maggi S, et al. Relation Between Vitamin D, Physical Performance, and Disability in Elderly Persons. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2002;57:M7-M11.

159. Visser M, Deeg DJH, Lips P. Low Vitamin D and High Parathyroid Hormone Levels as Determinants of Loss of Muscle Strength and Muscle Mass (Sarcopenia): The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88:5766-72.

160. Kim MK, Baek KH, Song K-H, Il Kang M, Park CY, Lee WY, et al. Vitamin D Deficiency Is Associated with Sarcopenia in Older Koreans, Regardless of Obesity: The Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) 2009. Journal of Clinical Endocrinology & Metabolism. 2011;96:3250-6.

161. Visser M, Deeg DJH, Puts MTE, Seidell JC, Lips P. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. Am J Clin Nutr. 2006;84:616-22.

162. Janssen HCJP, Samson MM, Verhaar HJJ. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr. 2002;75:611-5.

163. Chang C-I, Chan D-C, Kuo K-N, Hsiung CA, Chen C-Y. Vitamin D insufficiency and frailty syndrome in older adults living in a Northern Taiwan community. Archives of Gerontology and Geriatrics. 2010;50, Supplement 1:S17-S21.

164. Smit E, Crespo CJ, Michael Y, Ramirez-Marrero FA, Brodowicz GR, Bartlett S, et al. The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. Eur J Clin Nutr. 2012;66:1024-8.

165. Wilhelm-Leen ER, Hall YN, DeBoer IH, Chertow GM. Vitamin D deficiency and frailty in older Americans. Journal of Internal Medicine. 2010;268:171-80.

166. Ensrud KE, Blackwell TL, Cauley JA, Cummings SR, Barrett-Connor E, Dam T-TL, et al. Circulating 25-Hydroxyvitamin D Levels and Frailty in Older Men: The Osteoporotic Fractures in Men Study. Journal of the American Geriatrics Society. 2011;59:101-6.

167. Ensrud KE, Ewing SK, Fredman L, Hochberg MC, Cauley JA, Hillier TA, et al. Circulating 25-Hydroxyvitamin D Levels and Frailty Status in Older Women. Journal of Clinical Endocrinology & Metabolism. 2010;95:5266-73.

168. Wong YYE, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health In Men Study. Journal of Clinical Endocrinology & Metabolism. 2013.

169. Shardell M, D'Adamo C, Alley DE, Miller RR, Hicks GE, Milaneschi Y, et al. Serum 25-Hydroxyvitamin D, Transitions Between Frailty States, and Mortality in Older Adults: The Invecchiare in Chianti Study. Journal of the American Geriatrics Society. 2012.

170. Zaslavsky O, Cochrane BB, Thompson HJ, Woods NF, Herting JR, Lacroix A. Frailty: A Review of the First Decade of Research. Biol Res Nurs 2012.

171. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A 2001;98:4770-5.

172. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic Load and Frailty in Older Adults. Journal of the American Geriatrics Society. 2009;9999.

173. Szanton SL, Allen JK, Seplaki CL, Bandeen-Roche K, Fried LP. Allostatic load and frailty in the women's health and aging studies. Biol Res Nurs. 2009;10:248-56.

174. Cappola AR, Maggio M, Ferrucci L. Is Research on Hormones and Aging Finished? No! Just Started! The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2008;63:696-8.

175. Fried LP, Xue Q-L, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear Multisystem Physiological Dysregulation Associated With Frailty in Older Women: Implications for Etiology and Treatment. The journals of gerontology Series A, Biological sciences and medical sciences. 2009:glp076.

176. Michelon E, Blaum C, Semba RD, Xue Q-L, Ricks MO, Fried LP. Vitamin and Carotenoid Status in Older Women: Associations With the Frailty Syndrome. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61:600-7.

177. Semba RD, Bartali B, Zhou J, Blaum C, Ko C-W, Fried LP. Low Serum Micronutrient Concentrations Predict Frailty Among Older Women Living in the Community. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61:594-9.

178. Rosenberg IH. Summary comments. The American Journal of Clinical Nutrition. 1989;50:1231-3.

179. Clark BC, Manini TM. Sarcopenia != Dynapenia. The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63:829-34.

180. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age and Ageing. 2010;39:412-23.

181. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12:249-56.

182. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. Clinical Nutrition. 2010;29:154-9.

183. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age and Ageing. 2014;43:748-59.

184. Morley JE. Sarcopenia in the elderly. Family practice. 2012;29 Suppl 1:i44-i8.

185. Landi F, Liperoti R, Fusco D, Mastropaolo S, Quattrociocchi D, Proia A, et al. Prevalence and Risk Factors of Sarcopenia Among Nursing Home Older Residents. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2012;67A:48-55.

186. Kim JH, Lim S, Choi SH, Kim KM, Yoon JW, Kim KW, et al. Sarcopenia: an independent predictor of mortality in community-dwelling older Korean men. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69:1244-52.

187. Tanimoto Y, Watanabe M, Sun W, Sugiura Y, Hayashida I, Kusabiraki T, et al. Sarcopenia and falls in community-dwelling elderly subjects in Japan: Defining sarcopenia according to criteria of the European Working Group on Sarcopenia in Older People. Arch Gerontol Geriatr. 2014;59:295-9.

188. Rolland Y, Lauwers-Cances V, Cristini C, van Kan GA, Janssen I, Morley JE, et al. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. The American Journal of Clinical Nutrition. 2009;89:1895-900.

189. Roubenoff R. Sarcopenic Obesity: Does Muscle Loss Cause Fat Gain?: Lessons from Rheumatoid Arthritis and Osteoarthritisa. Annals of the New York Academy of Sciences. 2000;904:553-7.

190. Roubenoff R. Sarcopenic Obesity: The confluence of two epidemics. Obesity Research. 2004;12:887.

191. Bouchard DR, Dionne IJ, Brochu M. Sarcopenic/Obesity and Physical Capacity in Older Men and Women: Data From the Nutrition as a Determinant of Successful Aging (NuAge)[mdash]the Quebec Longitudinal Study. Obesity. 2009;17:2082-8.

192. Waters DL, Baumgartner RN. Sarcopenia and obesity. Clin Geriatr Med. 2011;27:401-21.

193. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutrition, Metabolism and Cardiovascular Diseases. 2008;18:388-95.

194. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology—update 2014. Journal of Cachexia, Sarcopenia and Muscle. 2014;5:253-9.

195. Bauer JM, Sieber CC. Sarcopenia and frailty: A clinician's controversial point of view. Experimental Gerontology. 2008;43:674-8.

196. 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;60:1487-92.

197. Shamliyan T, Talley K, Ramakrishnan R, Kane RL. Association of frailty with survival: A systematic literature review. Ageing Research Reviews. [doi: 10.1016/j.arr.2012.03.001]. 2012.

198. Rockwood K, Howlett SE, MacKnight C, Beattie BL, Bergman H, Hébert R, et al. Prevalence, Attributes, and Outcomes of Fitness and Frailty in Community-Dwelling Older Adults: Report From the Canadian Study of Health and Aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004;59:1310-7.

199. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions Between Frailty States Among Community-Living Older Persons. Arch Intern Med. 2006;166:418-23.

200. Ruiz M, Cefalu C, Reske T. Frailty syndrome in geriatric medicine. Am J Med Sci. 2012;344:395-8.

201. Hirsch C, Anderson ML, Newman A, Kop W, Jackson S, Gottdiener J, et al. The Association of Race With Frailty: The Cardiovascular Health Study. Annals of Epidemiology. [doi: 10.1016/j.annepidem.2005.10.003]. 2006;16:545-53.

202. Espinoza SE, Jung I, Hazuda H. Frailty Transitions in the San Antonio Longitudinal Study of Aging. Journal of the American Geriatrics Society. 2012:n/a-n/a.

203. Espinoza SE, Hazuda HP. Frailty in Older Mexican-American and European-American Adults: Is There an Ethnic Disparity? Journal of the American Geriatrics Society. 2008;56:1744-9.

204. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of Frailty in Middle-Aged and Older Community-Dwelling Europeans Living in 10 Countries. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2009;64A:675-81.

205. Szanton SL, Seplaki CL, Thorpe RJ, Allen JK, Fried LP. Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. Journal of Epidemiology and Community Health.64:63-7.

206. Lang IA, Hubbard RE, Andrew MK, Llewellyn DJ, Melzer D, Rockwood K. Neighborhood Deprivation, Individual Socioeconomic Status, and Frailty in Older Adults. Journal of the American Geriatrics Society. 2009;57:1776-80.

207. Theou O, Brothers TD, Rockwood MR, Haardt D, Mitnitski A, Rockwood K. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. Age and Ageing. 2013.

208. Gale CR, Syddall HE, Bergman H, Brunner EJ, Cooper C, Sayer AA. Close Relationships and Risk of Frailty: The Hertfordshire Cohort Study. Journal of the American Geriatrics Society. 2012;60:390-2.

209. Garre-Olmo J, Calvo-Perxas L, Lopez-Pousa S, de Gracia Blanco M, Vilalta-Franch J. Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort. Age Ageing. 2013;42:46-51.

210. Sternberg SA, Schwartz AW, Karunananthan S, Bergman H, Mark Clarfield A. The Identification of Frailty: A Systematic Literature Review. Journal of the American Geriatrics Society. 2011;59:2129-38.

211. Hubbard R, Searle S, Mitnitski A, Rockwood K. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: A secondary analysis from the Canadian study of health and aging. The Journal of Nutrition, Health & Aging. 2009;13:468-72.

212. Wang C, Song X, Mitnitski A, Yu P, Fang X, Tang Z, et al. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. The journals of gerontology Series A, Biological sciences and medical sciences. 2013;68:338-46.

213. Walters MJ, Paul-Clark MJ, McMaster SK, Ito K, Adcock IM, Mitchell JA. Cigarette Smoke Activates Human Monocytes by an Oxidant-AP-1 Signaling Pathway: Implications for Steroid Resistance. Molecular Pharmacology. 2005;68:1343-53.

214. Rapuri PB, Gallagher JC, Smith LM. Smoking Is a Risk Factor for Decreased Physical Performance in Elderly Women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2007;62:93-9.

215. Roland KP, K MDC, Theou O, Jakobi JM, Jones GR. Physical Activity across Frailty Phenotypes in Females with Parkinson's Disease. J Aging Res. 2012;468156:7.

216. Moreira VG, Lourenco RA. Prevalence and factors associated with frailty in an older population from the city of Rio de Janeiro, Brazil: the FIBRA-RJ Study. Clinics (Sao Paulo) 2013;68:979-85.

217. Savela SL, Koistinen P, Stenholm S, Tilvis RS, Strandberg AY, Pitkala KH, et al. Leisure-time physical activity in midlife is related to old age frailty. The journals of gerontology Series A, Biological sciences and medical sciences. 2013;68:1433-8.

218. OL C. Physical activity and aging: a life-long story. Discov Med 2011;12:177-85.

219. Andreyeva T, Michaud PC, van Soest A. Obesity and health in Europeans aged 50 years and older. Public Health. 2007;121:497-509.

220. Visser M. Obesity, sarcopenia and their functional consequences in old age. Proceedings of the Nutrition Society. 2011;70:114-8.

221. Salihu HM, Bonnema SM, Alio AP. Obesity: What is an elderly population growing into? Maturitas. 2009;63:7-12.

222. WHO. Global Strategy on diet, physical activity and health,2003.

223. Waters DL, RN. B. Sarcopenia and obesity. Clin Geriatr Med 2011;2011 Aug;27.401-21.

224. Lakdawalla DN, Goldman DP, Shang B. The Health And Cost Consequences Of Obesity Among The Future Elderly. Health Aff. 2005.

225. Mathus-Vliegen EMH, Basdevant A, Finer N, Hainer V, Hauner H, Micic D, et al. Prevalence, Pathophysiology, Health Consequences and Treatment Options of Obesity in the Elderly: A Guideline. Obesity Facts. 2012;5:460-83.

226. Nguyen DM, El-Serag HB. The Epidemiology of Obesity. Gastroenterology clinics of North America. 2010;39:1-7.

227. Public Health England. Adult Obesity and socioeconomic status data factsheet. [http://www.noo.org.uk/securefiles/150318_0807/AdultSocioeconomic_Aug2014_v2.pdf] 2014.

228. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. Psychological bulletin. 1989;105:260-75.

229. McLaren L. Socioeconomic Status and Obesity. Epidemiologic Reviews. 2007;29:29-48.

230. Kang HT, Lee HR, Lee YJ, Linton JA, Shim JY. Relationship between employment status and obesity in a Korean elderly population, based on the 2007-2009 Korean National Health and Nutrition Examination Survey (KNHANES). Arch Gerontol Geriatr. 2013;57:54-9.

231. Gallagher D, DeLegge M. Body composition (sarcopenia) in obese patients: implications for care in the intensive care unit. JPEN Journal of parenteral and enteral nutrition. 2011;35:21S-8S.

232. Arterburn DE, Crane PK, Sullivan SD. The coming epidemic of obesity in elderly Americans. J Am Geriatr Soc. 2004;52:1907-12.

233. Han TS, Tajar A, O'Neill TW, Jiang M, Bartfai G, Boonen S, et al. Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. European Journal of Endocrinology. 2011;164:1003-11.

234. Bales CW, GT. B. Body Mass Trajectory, Energy Balance, and Weight Loss as Determinants of Health and Mortality in Older Adults. Obesity Facts,The European Journal of Obesity. 2009:171-8.

235. M.Chapman I. Obesity Paradox during Aging. Karger. 2010;37:20-36.

236. Auyeung TW, Lee JSW, Leung J, Kwok T, Leung PC, Woo J. Survival in Older Men May Benefit From Being Slightly Overweight and Centrally Obeseâ€"A 5-Year Follow-up Study in 4,000 Older Adults Using DXA. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2010;65A:99-104.

237. Gallagher D, Visser M, SepÃºlveda D, Pierson RN, Harris T, Heymsfield SB. How Useful Is Body Mass Index for Comparison of Body Fatness across Age, Sex, and Ethnic Groups? American Journal of Epidemiology. 1996;143:228-39.

238. Mathus-Vliegen L, Toouli J, Fried M, Khan AG, Garisch J, Hunt R, et al. World Gastroenterology Organisation global guidelines on obesity. J Clin Gastroenterol. 2012;46:555-61.

239. Chau D, Cho LM, Jani P, St Jeor ST. Individualizing recommendations for weight management in the elderly. Curr Opin Clin Nutr Metab Care. 2008;11:27-31.

240. Bradway C, DiResta J, Fleshner I, Polomano RC. Obesity in nursing homes: a critical review. J Am Geriatr Soc 2008;56:1528-35.

241. Roberts SB, Dallal GE. Energy requirements and aging. Public Health Nutr 2005 Oct;8(7A):1028-36. 2005.

242. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. Int J Obes Relat Metab Disord. 2005;29:1011-29.

243. Villareal DT, Apovian CM, Kushner RF, Klein S. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr. 2005;82:923-34.

244. Haslam DW, James WPT. Obesity. The Lancet. 2005;366:1197-209.

245. Bowen ME. The Relationship Between Body Weight, Frailty, and the Disablement Process. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2012;67:618-26.

246. Alley DE, Ferrucci L, Barbagallo M, Studenski SA, Harris TB. A Research Agenda: The Changing Relationship Between Body Weight and Health in Aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2008;63:1257-9.

247. Lang IA, Llewellyn DJ, Alexander K, Melzer D. Obesity, Physical Function, and Mortality in Older Adults. Journal of the American Geriatrics Society. 2008;56:1474-8.

248. Castaneda-Sceppa C, Price LL, Noel SE, Bassett Midle J, Falcon LM, Tucker KL. Physical Function and Health Status in Aging Puerto Rican Adults: The Boston Puerto Rican Health Study. Journal of Aging and Health. 2010;22:653-72.

249. Buvat J, Maggi M, Guay A, Torres LO. Testosterone Deficiency in Men: Systematic Review and Standard Operating Procedures for Diagnosis and Treatment. The Journal of Sexual Medicine. 2013;10:245-84.

250. Sakuma K, Yamaguchi A. Sarcopenic Obesity and Endocrinal Adaptation with Age. International Journal of Endocrinology. 2013;2013:12.

251. Cesari Matteo, Leeuwenburgh Christiaan, Lauretani Fulvio, Onder Graziano, Bandinelli Stefania, Maraldi Cinzia, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr. 2006;83:1142-8.

252. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. 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. 2006;61:1059-64.

253. Visser M, Harris TB, Langlois J, Hannan MT, Roubenoff R, Felson DT, et al. 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. 1998;53A:M214-M21.

254. Han TS, Tajar A, Lean MEJ. Obesity and weight management in the elderly. British Medical Bulletin. 2011;97:169-96.

255. McCarthy LH, Bigal ME, Katz M, Derby C, Lipton RB. Chronic Pain and Obesity in Elderly People: Results from the Einstein Aging Study. Journal of the American Geriatrics Society. 2009;57:115-9.

256. Blyth FM, Rochat S, Cumming RG, Creasey H, Handelsman DJ, Couteur DGL, et al. Pain, frailty and comorbidity on older men: The CHAMP study. Pain. [doi: DOI: 10.1016/j.pain.2008.08.011]. 2008;140:224-30.

257. O'Connell MD, Tajar; A, O'Neill; TW, Roberts; SA, Lee; DM, Pye; SR, et al. Frailty is associated with impaired quality of life and falls in middle-aged European Men. J Frailty Aging 2013;2:77-83.

258. Wu IC, Shiesh S-C, Kuo P-H, Lin X-Z. High Oxidative Stress Is Correlated with Frailty in Elderly Chinese. Journal of the American Geriatrics Society. 2009;9999.

259. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, Body Mass Index, and Abdominal Obesity in Older People. The journals of gerontology Series A, Biological sciences and medical sciences. 2009:glp186.

260. Shah K, Hilton TN, Myers L, Pinto JF, Luque AE, Hall WJ. A new frailty syndrome: central obesity and frailty in older adults with the human immunodeficiency virus. J Am Geriatr Soc. 2012;60:545-9.

261. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical Frailty and Body Composition in Obese Elderly Men and Women[ast][ast]. Obesity. 2004;12:913-20.

262. Bylow K, Hemmerich J, Mohile SG, Stadler WM, Sajid S, Dale W. Obese frailty, physical performance deficits, and falls in older men with biochemical recurrence of prostate cancer on androgen deprivation therapy: a case-control study. Urology. 2011;77:934-40.

263. Strandberg TE, Sirola J, Pitkala KH, Tilvis RS, Strandberg AY, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. Int J Obes. 2012.

264. Stenholm S, Strandberg TE, Pitkala K, Sainio P, Heliovaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69:73-8.

265. Sezginsoy B, Ross K, Wright JE, Bernard MA. Obesity in the elderly: survival of the fit or fat. The Journal of the Oklahoma State Medical Association. 2004;97:437-9;

266. Fugate Woods N, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: Emergence and Consequences in Women Aged 65 and Older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society. 2005;53:1321-30.

267. Lee D, M, O'Neill TW, Pye SR, Silman AJ, Finn JD, Pendleton N, et al. The European Male Ageing Study (EMAS): design, methods and recruitment. International Journal of Andrology. 2008;32:11-24.

268. Lee DM, Pye SR, Tajar A, O'Neill TW, Finn JD, Boonen S, et al. Cohort Profile: The European Male Ageing Study. International Journal of Epidemiology. 2012.

269. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. British Medical Journal. 1992;305:160-4.

270. Beck A, Steer R, Brown GK. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX. 1996.

271. Brugha T, Bebbington P, Tennant C, J. H. The list of threatening experiences: a subset of 12 life event categories with considerable long-term contextual threat. . Psychol Med. 1985;15:189–94.

272. Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): Development and evaluation. Journal of Clinical Epidemiology. 1993;46:153-62.

273. Bosch JL, Hop WC, Kirkels WJ, Schroder FH. The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. Br J Urol 1995 May;75(5):622-30.

274. O'Connor DB, Corona G, Forti G, Tajar A, Lee DM, Finn JD, et al. Assessment of Sexual Health in Aging Men in Europe: Development and Validation of the European Male Ageing Study Sexual Function Questionnaire. The Journal of Sexual Medicine. 2008;5:1374-85.

275. Reuben D, Siu A. An objective measure of physical function of elderly outpatients. The Physical Performance Test. Journal of the American Geriatrics Society. 1990;38:1105-12.

276. Tinetti ME, Franklin Williams T, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. The American Journal of Medicine. 1986;80:429-34.

277. Osterrieth P. Le test de copie d'une figure complexe. Arch Psychologie. 1944;30:206-356.

278. Warrington E, The Camden Memory Tests. Psychology Press. 1996.

279. Wechsler d. Adult Intelligence Scale – Revised. New York: Psychological Corporation

1981.

280. Huisman M, Poppelaars J, van der Horst M, Beekman AT, Brug J, van Tilburg TG, et al. Cohort Profile: The Longitudinal Aging Study Amsterdam. International Journal of Epidemiology. 2011;40:868-76.

281. Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman* AJ, Reeve* J, et al. Incidence of Limb Fracture across Europe: Results from the European Prospective Osteoporosis Study (EPOS). Osteoporosis International. 2002;13:565-71.

282. O'Connell M. Frailty and anabolic hormones [PhD Thesis]: University of Manchester; 2011.

283. Tajar A, Matthew DL O'Connell, Arnold B. Mitnitski, Terence W. O'Neill, Samuel D. Searle, Ilpo T. Huhtaniemi, et al. Frailty in relation to variations in hormone levels of the hypothalamic-pituitary-testicular axis in older men: Results from the European Male Aging Study. Journal of the American Geriatrics Society.2011;59:814-821.

284. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mechanisms of Ageing and Development. 1999;107:123-36.

285. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, et al. 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. 2007;62:744-51.

286. Lee DM, Tajar A, Ravindrarajah R, Pye SR, O'Connor DB, Corona G, et al. Frailty and Sexual Health in Older European Men. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2013;68:837-44.

287. van Kan GA, Rolland YM, Morley JE, Vellas B. Frailty: Toward a Clinical Definition. Journal of the American Medical Directors Association. 2008;9:71-2.

288. Anthony J. Viera M, Joanne M. Garrett P. Understanding Interobserver Agreement:The Kappa Statistic. Family Medicine. 2005;37:360-3.

289. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SAP, et al. Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study. The Journal of clinical endocrinology and metabolism.jc.2009-754.

290. Masel M, Graham J, Reistetter T, Markides K, Ottenbacher K. Frailty and health related quality of life in older Mexican Americans. Health and Quality of Life Outcomes. 2009;7:70.

291. Langlois F, Vu TTM, Kergoat M-J, Chassé K, Dupuis G, Bherer L. The multiple dimensions of frailty: physical capacity, cognition, and quality of life. International Psychogeriatrics. 2012;24:1429-36.

292. Landi F, Russo A, Liperoti R, Pahor M, Tosato M, Capoluongo E, et al. Midarm muscle circumference, physical performance and mortality: Results from the aging and longevity study in the Sirente geographic area (ilSIRENTE study). Clinical Nutrition.29:441-7.

293. Nowak A, Hubbard RE. Falls and frailty: lessons from complex systems. J R Soc Med. 2009;102:98-102.

294. Kenneth R, Arnold M, Xiaowei S, Bertil S, Ingmar S. Long-Term Risks of Death and Institutionalization of Elderly People in Relation to Deficit Accumulation at Age 70. Journal of the American Geriatrics Society. 2006;54:975-9.

295. Lee DM, Pye SR, Tajar A, O'Neill TW, Finn JD, Boonen S, et al. Cohort Profile: The European Male Ageing Study. Int J Epidemiol. 2012.

296. Mitnitski A, Song X, Rockwood K. Improvement and decline in health status from late middle age: Modeling age-related changes in deficit accumulation. Experimental Gerontology. 2007;42:1109-15.

297. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. N Engl J Med. 1995;332:556-62.

298. Hardy SE, Perera S, Roumani YF, Chandler JM, Studenski SA. Improvement in Usual Gait Speed Predicts Better Survival in Older Adults. Journal of the American Geriatrics Society. 2007;55:1727-34.

299. Hubbard RE, O'Mahony MS, Woodhouse KW. Characterising frailty in the clinical setting—a comparison of different approaches. Age and Ageing. 2009;38:115-9.

300. Barbieri M, Ferrucci L, Ragno E, Corsi A, Bandinelli S, Bonafe M, et al. Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. Am J Physiol Endocrinol Metab. 2003;284:E481-7.

301. Bilotta C, Nicolini P, Casè A, Pina G, Rossi S, Vergani C. Frailty syndrome diagnosed according to the Study of Osteoporotic Fractures (SOF) criteria and adverse health outcomes among community-dwelling older outpatients in Italy. A one-year prospective cohort study. Archives of Gerontology and Geriatrics. [doi: 10.1016/j.archger.2011.06.037]. 2012;54:e23-e8.

302. Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA, et al. A Comparison of Frailty Indexes for the Prediction of Falls, Disability, Fractures, and Mortality in Older Men. Journal of the American Geriatrics Society. 2009;57:492-8.

303. Buchman AS, Wilson RS, Bienias JL, Bennett DA. Change in Frailty and Risk of Death in Older Persons. Experimental Aging Research. [doi: 10.1080/03610730802545051]. 2009;35:61-82.

304. Kulminski A, Yashin A, Arbeev K, Akushevich I, Ukraintseva S, Land K, et al. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: Results from analyses of the National Long Term Care Survey. Mechanisms of Ageing and Development. 2007;128:250-8.

305. Sirola J, Pitkala K, Tilvis R, Miettinen T, Strandberg T. Definition of frailty in older men according to questionnaire data (RAND-36/SF-36): The Helsinki Businessmen study. The Journal of Nutrition, Health & Aging. 2011;15:783-7.

306. Daniels R, van Rossum E, Beurskens A, van den Heuvel W, de Witte L. The predictive validity of three self-report screening instruments for identifying frail older people in the community. BMC public health. 2012;12:69.

307. Vries OJ, Peeters GMEE, Lips P, Deeg DJH. Does frailty predict increased risk of falls and fractures? A prospective population-based study. Osteoporosis International. 2013:1-7.

308. Seeman TE, Berkman LF, Charpentier PA, Blazer DG, Albert MS, Tinetti ME. Behavioural and psychosocial predictors of physical performance: MacArthur studies of successful aging. The journals of gerontology Series A, Biological sciences and medical sciences. 1995;50:M177 - M83.

309. Gobbens RJJ, van Assen MALM, Luijkx KG, Schols JMGA. The Predictive Validity of the Tilburg Frailty Indicator: Disability, Health Care Utilization, and Quality of Life in a Population at Risk. The Gerontologist. 2012.

310. Au A, Puts MTE, Fletcher JD, Sourial N, Bergman H. Frailty Markers Predicting Emergency Department Visits in a Community-Dwelling Sample of Vulnerable Seniors in Montreal. Canadian Journal on Aging/Revue canadienne du vieillissement. 2011;30:647-55.

311. Hastings SN, Purser JL, Johnson KS, Sloane RJ, Whitson HE. Frailty Predicts Some but Not All Adverse Outcomes in Older Adults Discharged from the Emergency Department. Journal of the American Geriatrics Society. 2008;56:1651-7.

312. Roubenoff R, Rall LC. Humoral Mediation of Changing Body Composition During Aging and Chronic Inflammation. Nutrition Reviews. 1993;51:1-11.

313. Baumgartner RN. Body Composition in Healthy Aging. Annals of the New York Academy of Sciences. 2000;904:437-48.

314. Siri WE. Body composition from fluid space and density. National Academy of science. 1961:223-44.

315. Organization WH. Waist Circumference and Waist-Hip-Ratio. Report of a WHO Expert Consultation, Geneva,. 2008:39.

316. WHO. The WHO Global Database on Body Mass Index 2004.

317. Cleveland WS. Robust Locally Wighted Regression and smoothing Scatterplots. Journal of the American Statistical Association. 1979;74:829-36.

318. Woo J, Leung J, Kwok T. BMI, Body Composition, and Physical Functioning in Older Adults[ast]. Obesity. 2007;15:1886-94.

319. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. The American Journal of Clinical Nutrition. 2004;79:379-84.

320. Yusuf S, Hawken S, Ôunpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27[punctuation space]000 participants from 52 countries: a case-control study. The Lancet. [doi: DOI: 10.1016/S0140-6736(05)67663-5]. 2005;366:1640-9.

321. Kragelund C, Omland T. A farewell to body-mass index? The Lancet. [doi: 10.1016/S0140-6736(05)67642-8]. 2005;366:1589-91.

322. Zamboni M, Mazzali G. Obesity in the elderly: an emerging health issue. Int J Obes.36:1151-2.

323. Jensen GL, Hsiao PY. Obesity in older adults: relationship to functional limitation. Curr Opin Clin Nutr Metab Care. 2010;13:46-51.

324. Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The Association Between Vitamin D and Inflammation with the 6-Minute Walk and Frailty in Patients with Heart Failure. Journal of the American Geriatrics Society. 2008;56:454-61.

325. Cawthon PM, Ensrud KE, Laughlin GA, Cauley JA, Dam T-TL, Barrett-Connor E, et al. Sex Hormones and Frailty in Older Men: The Osteoporotic Fractures in Men (MrOS) Study. J Clin Endocrinol Metab. 2009;94:3806-15.

326. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. The Scientific World. 2001;1:323 - 36.

327. Goggins WB, Woo J, Sham A, Ho SC. Frailty Index as a Measure of Biological Age in a Chinese Population. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2005;60:1046-51.

328. Woo J, Goggins W, Sham A, Ho SC. Social Determinants of Frailty. Gerontology. 2005;51:402-8.

329. Ostir GV, Ottenbacher KJ, Markides KS. Onset of Frailty in Older Adults and the Protective Role of Positive Affect. Psychology and Aging. [doi:]. 2004;19:402-8.

330. Fallah N, Mitnitski A, Searle SD, Gahbauer EA, Gill TM, Rockwood K. Transitions in Frailty Status in Older Adults in Relation to Mobility: A Multistate Modeling Approach Employing a Deficit Count. Journal of the American Geriatrics Society. 2011;59:524-9.

331. Travison TG, Shackelton R, Araujo AB, Morley JE, Williams RE, Clark RV, et al. Frailty, Serum Androgens, and the CAG Repeat Polymorphism: Results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2010;95:2746-54.

332. Seidell JC, Han TS, Feskens EJM, Lean MEJ. Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin-dependent diabetes mellitus. Journal of Internal Medicine. 1997;242:401-6.

333. Han; T, Bijnen; F, Lean; M, Seidell J. Seperate associations of waist and hip circumference with lifestyle factors. International Journal of Epidemiology. 1998;27:422-30.

334. Perissinotto E, Pisent C, Sergi G, Grigoletto F, Enzi G, null IWG. Anthropometric measurements in the elderly: age and gender differences. British Journal of Nutrition. 2002;87:177-86.

335. Han T, Bijnen F, Lean M, Seidell J. Seperate associations of waist and hip circumference with lifestyle factors. International Journal of Epidemiology. 1998;27:422-30.

336. Peel N. Validating recall of falls by older people. Accident Analysis & Prevention. 2000;32:371-2.

337. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. Clinical interventions in aging. 2014;9:433-41.

338. Sternfeld B, Ngo L, Satariano WA, Tager IB. Associations of Body Composition with Physical Performance and Self-reported Functional Limitation in Elderly Men and Women. American Journal of Epidemiology. 2002;156:110-21.

339. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. Journal of Applied Physiology. 2007;102:919-25.

340. DeCaria; J, Sharp; C, Petrella R. Scoping review report: obesity in older adults. International Journal of Obesity. 2012;36:1141-50.

341. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506-14.

342. Bruunsgaard H, Andersen-Ranberg K, Hjelmborg JvB, Pedersen BK, Jeune B. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. The American journal of medicine. 2003;115:278-83.

343. Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity (Silver Spring) 2012;20:2101-6.

344. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord. 1998;22:1145-58.

345. Tang Z, Wang C, Song X, Shi J, Mitnitski A, Fang X, et al. Co-occurrence of cardiometabolic diseases and frailty in older Chinese adults in the Beijing Longitudinal Study of Ageing. Age and Ageing. 2013;42:346-51.

346. Krabbe KSr, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Experimental Gerontology. 2004;39:687-99.

347. Michalakis K, Goulis DG, Vazaiou A, Mintziori G, Polymeris A, Abrahamian-Michalakis A. Obesity in the ageing man. Metabolism. 2013.

348. Rigamonti AE, Pincelli AI, Corra B, Viarengo R, Bonomo SM, Galimberti D, et al. Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients. Journal of Endocrinology. 2002;175:R1-R5.

349. Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. Clinical Endocrinology. 2006;65:125-31.

350. Seo JA, Cho H, Eun CR, Yoo HJ, Kim SG, Choi KM, et al. Association Between Visceral Obesity and Sarcopenia and Vitamin D Deficiency in Older Koreans: The Ansan Geriatric Study. Journal of the American Geriatrics Society. 2012;60:700-6.

351. Tajar A, O'Connell MDL, Mitnitski AB, O'Neill TW, Searle SD, Huhtaniemi IT, et al. Frailty in Relation to Variations in Hormone Levels of the Hypothalamic–Pituitary–Testicular Axis in Older Men: Results From the European Male Aging Study. Journal of the American Geriatrics Society. 2011;59:814-21.

352. O'Donnell AB, Travison TG, Harris SS, Tenover JL, McKinlay JB. Testosterone, Dehydroepiandrosterone, and Physical Performance in Older Men: Results from the Massachusetts Male Aging Study. The Journal of clinical endocrinology and metabolism. 2006;91:425-31.

353. Kyrou I, Tsigos C. Obesity in the Elderly Diabetic Patient: Is weight loss beneficial? No. Diabetes Care. 2009;32:S403-S9.

354. Kvist H, Hallgren P, Jönsson L, Pettersson P, Sjöberg C, Sjöström L, et al. Distribution of adipose tissue and muscle mass in alcoholic men. Metabolism. 1993;42:569-73.

355. Seidell JC, Cigolini M, Deslypere J-P, Charzewska J, Ellsinger B-M, Cruz A. Body Fat Distribution in Relation to Physical Activity and Smoking Habits in 38-year-old European Men: The European Fat Distribution Study. American Journal of Epidemiology. 1991;133:257-65.

356. Seidell JC, Perusse L, Despres J-P, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. The American Journal of Clinical Nutrition. 2001;74:315-21.

357. Kirkwood TBL. A systematic look at an old problem. Nature. 2008;451:644-7.

358. Cadore EL, Rodriguez-Manas L, Sinclair A, Izquierdo M. Effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults: a systematic review. Rejuvenation Res. 2013;16:105-14.

359. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Van Ness PH. A prehabilitation program for the prevention of functional decline: effect on higher-level physical function. Archives of Physical Medicine and Rehabilitation. 2004;85:1043-9.

360. Toulotte C, Fabre C, Dangremont B, Lensel G, Thevenon A. Effects of physical training on the physical capacity of frail, demented patients with a history of falling: a randomised controlled trial. Age Ageing. 2003;32:67-73.

361. Faber MJ, Bosscher RJ, Chin A Paw MJ, van Wieringen PC. Effects of Exercise Programs on Falls and Mobility in Frail and Pre-Frail Older Adults: A Multicenter Randomized Controlled Trial. Archives of Physical Medicine and Rehabilitation. 2006;87:885-96.

362. Society ArftBG. Fit For frailty- consensus best practice guidance for the care of older people living in community and outpatient settings. 2014.

363. Binder EF, Yarasheski KE, Steger-May K, Sinacore DR, Brown M, Schechtman KB, et al. Effects of Progressive Resistance Training on Body Composition in Frail Older Adults: Results of a Randomized, Controlled Trial. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2005;60:1425-31.

364. Sundell J. Resistance Training Is an Effective Tool against Metabolic and Frailty Syndromes. Advances in Preventive Medicine. 2011.

365. Darmon P. Intentional weight loss in older adults: useful or wasting disease generating strategy? Curr Opin Clin Nutr Metab Care. 2013;16:284-9.

366. Wannamethee S, Shaper A, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. Archives of Internal Medicine. 2005;165:1035-40.

367. Porter Starr KN, McDonald SR, Bales CW. Obesity and physical frailty in older adults: a scoping review of lifestyle intervention trials. J Am Med Dir Assoc. 2014;15:240-50.

368. Jensen GL. Obesity and functional decline: epidemiology and geriatric consequences. Clin Geriatr Med. 2005;21:677-87, v.

369. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of Weight Loss and Exercise on Frailty in Obese Older Adults. Arch Intern Med. 2006;166:860-6.

370. Zhang L, Weng C, Liu M, Wang Q, Liu L, He Y. Effect of whole-body vibration exercise on mobility, balance ability and general health status in frail elderly patients: a pilot randomized controlled trial. Clin Rehabil. 2014;28:59-68.

371. Cebria IIMD, Arnall DA, Igual Camacho C, Tomas JM. Effects of Inspiratory Muscle Training and Yoga Breathing Exercises on Respiratory Muscle Function in Institutionalized Frail Older Adults: A Randomized Controlled Trial. J Geriatr Phys Ther 2013 Jul 17. 2013.

372. Kennedy RL, Chokkalingham K, Srinivasan R. Obesity in the elderly: who should we be treating, and why, and how? Curr Opin Clin Nutr Metab Care. 2004;7:3-9.

373. Witham MD, Avenell A. Interventions to achieve long-term weight loss in obese older people: A systematic review and meta-analysis. Age and Ageing. 2010;39:176-84.

374. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481:463-8.

375. Swick AG, Orena S, O'Connor A. Irisin levels correlate with energy expenditure in a subgroup of humans with energy expenditure greater than predicted by fat free mass. Metabolism. 2013;62:1070-3.

Publications

Lee DM, Vanderschueren D, Boonen S, O'Neill TW, Pendleton N, Pye SR, **Ravindrarajah R** et al. Association of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone with mortality among middle-aged and older European men. Age & Ageing. 2014 Jul; 43(4):528-35

Ravindrarajah R, Lee DM, Pye SR et al. The ability of three different models of frailty to predict all-cause mortality: results from the European Male Aging Study (EMAS) Archives of Gerontology and Geriatrics. 2013 Nov-Dec;57(3):360-8.

Lee DM, Tajar A, **Ravindrarajah R** et al. Frailty and Sexual Health in Older European Men. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 2013 Jul; 68(7):837-44

Tajar A, Lee DM, Pye SR, O'Connell MD, Ravindrarajah R et al. The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men Age Ageing, 2013 May; 42(3):352-9

Gielen E, Verschueren S, O'Neill TW, Pye SR, O'Connell MD, Lee DM, Ravindrarajah R et al Musculoskeletal frailty: a geriatric syndrome at the core of fracture occurrence in older age. Calcified Tissue International, September 2012, 161-77

O'Connell MDL, **Ravindrarajah R**, Tajar A, Roberts SA, Wu FCW. Low testosterone: A modifiable risk factor for frailty? Trends in Endocrinology and Metabolism, December 2011, 491-8

Conference Presentations

R Ravindrarajah, DM Lee, N Pendleton, S Boonen, FF CasanuevaK Kula, D Vanderschueren, TW O'Neill, FCW Wu and the EMAS group Influence of obesity on frailty incidence in European men. (Poster Presentation). International Congress of Andrology, Sydney-2013

R Ravindrarajah, D M Lee, N Pendleton, FCW Wu, TW O'Neill and EMAS group. Influence of body mass index, waist circumference and waist-hip ratio on frailty incidence in European men. (Platform Presentation). The ERA (Emerging Researchers in Ageing) conference. 'Researching and living later life'.Keele University-2012

R Ravindrarajah, D M Lee, N Pendleton, FCW Wu, TW O'Neill and EMAS group. Influence of body mass index and waist circumference on frailty status in European men. (Poster Presentation). The British Geriatrics Society Spring Meeting, Llandudno- 2012

R Ravindrarajah, D M Lee, N Pendleton, FCW Wu, TW O'Neill and EMAS group. Frailty is linked with an increased mortality in European men. (Platform Presentation). The British Geriatrics Society Spring Meeting, Llandudno- 2012