FRAILTY IN OLDER AGE IN THE WHITEHALL II STUDY:

Measurement, validation, and predictive algorithms

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Declaration of authorship

I, Kim Bouillon, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Publications

Peer-reviewed papers resulting from this thesis

Bouillon K, Sabia S, Jokela M, Gale CR, Singh-Manoux A, Shipley M, Kivimaki M, Batty GD. Validating a widely used measure of frailty: are all sub-components necessary? Evidence from the Whitehall II cohort study. Age (forthcoming). Permission to reproduce excerpts of this article has been granted by Springer.

Bouillon K, Kivimaki M, Hamer M, Fransson EI, Singh-Manoux A, Gale CR, Batty GD. Measures of frailty in population-based studies: an overview. BMC Geriatr (provisionally accepted).

Bouillon K, Batty GD, Hamer M, Sabia S, Shipley M, Britton A, Singh-Manoux A, Kivimaki M. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study. Heart (accepted).

Bouillon K, Kivimaki M, Sabia S, Hamer M, Shipley M, Akbaraly TN, Tabak A, Singh-Manoux A, Batty GD. Diabetes risk factors and risk algorithms in identifying future frailty: the Whitehall II prospective cohort study (in submission).

Conference presentation

Bouillon K, Sabia S, Batty GD, and Kivimaki M. Methods and measurement: Validation of the phenotype of frailty measurement in the Whitehall II study. J Epidemiol Community Health. 2011;65:A27-A28, 2011. (Society for Social Medicine Annual Scientific Meeting, September 2011, Warwick, UK – oral presentation)

Other publication

Bouillon K, Singh-Manoux A, Jokela M, Shipley M, Batty GD, Brunner E, Sabia S, Tabak A, Akbaraly T, Ferrie J, Kivimaki M. Decline in LDL-cholesterol Concentration: Lipid Lowering Drugs, Diet, or Physical Activity? Evidence from a Population-based Cohort Study. Heart. 2011;97:923-30.

Abstract

BACKGROUND: With population ageing, prevention of frailty is increasingly important. However, significant gaps in the evidence base exist. Accordingly, the purpose of this thesis was to: (1) identify the current measures of frailty undertaking an overview; (2) validate the 'phenotype of frailty' using data from the Whitehall II study; and (3) examine the relation of cardiovascular disease (CVD) and diabetes risk factors with future frailty risk.

METHODS AND RESULTS: For objective 1, a literature review identified 27 original articles describing 27 different frailty measurements. Of them, the most tested and frequently used measure was the 'phenotype of frailty' which comprises five components: weight loss, exhaustion, physical activity, walking speed, and grip strength.

For objectives 2 and 3, I used data from the Whitehall II study, an occupationally-based cohort of 10,308 British men and women aged 35-55 years followed-up since 1985. Of the participants aged 55 to 79 years in 2007-2009 (n=5,169), 2.8% were frail and 38.6% pre-frail.

Using survival analyses, in sex- and age-adjusted model, compared with the non-frail group, the frail group was 2.40 (95% confidence interval (CI): 1.83, 3.14) times more likely to be hospitalised for any cause during the mean follow-up of 15.2 months, while for the pre-frail group the risk was 1.20 (95%CI: 1.06, 1.35) greater.

Logistic regression models were used to examine the performance of risk algorithms for CVD and diabetes assessed in 1997-1999 in predicting frailty in 2007-2009. CVD and diabetes risk scores were significantly associated with frailty: odds ratios per 1-standard deviation increment (disadvantage) in CVD scores ranged from 1.17 (95%CI: 1.10, 1.25) to 1.20 (95%CI: 1.13, 1.28) and in diabetes scores ranged from 1.05 (95%CI: 0.98, 1.14) to 1.27 (95%CI: 1.17, 1.37) depending on the risk score used.

CONCLUSIONS: Both frailty and pre-frailty are associated with increased risk of hospitalisation. Better prevention of cardiovascular and diabetes risk factors in midlife is likely to reduce frailty at older ages.

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Contents

Figures

Tables

Appendices

Abbreviations

AUC	Area under the curve
BADL	Basic activity daily living
BMI	Body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CMV	Cytomegalovirus
CVD	Cardiovascular disease
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
HES	Hospital Episode Statistics
HR	Hazard ratio
IADL	Instrumental activity daily living
ICD	International classification of diseases
ICE	Imputation by chained equations
IGF-1	Insulin-like growth factor-1
IQR	Interquartile range
MeSH	Medical Subject Heading (Medline)
MET	Metabolic equivalent
MMSE	Mini mental state examination
NHS	National Health Service
OR	Odds ratio
ROC	Receiver operating curve
SD	Standard deviation
WHO	World Health Organization

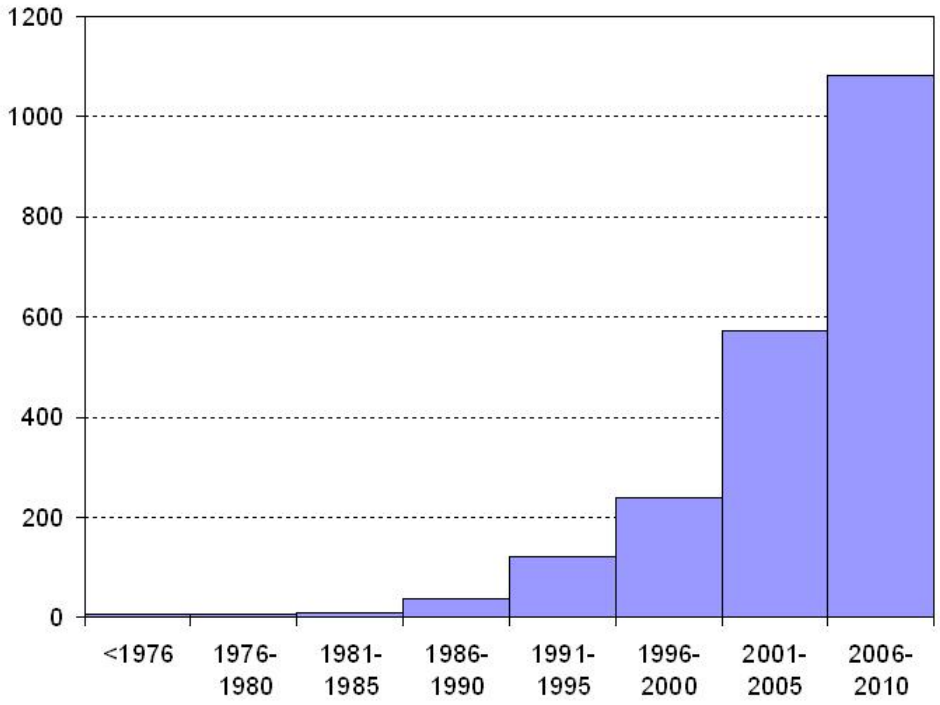
1 Introduction

1.1 Frailty as a public health concern

During the 20th century, life expectancy has increased by 30 years or more in developed countries.[1] It continues to increase at the rate of five or more hours per day.[2] As a result, populations of these countries are ageing.[1,2] Resource-poor countries are also experiencing similar demographic shifts.[3] In the UK, over the last 25 years, the percentage of the population aged 65 or over increased from 15% in 1984 to 16% in 2009 representing 1.7 million people. By 2034, it is predicted that 23% of the population is expected to be aged 65 or over compared to 18% under 16 years.[4] This success in growth of longevity raises obvious challenges related to an increased burden of diseases.

Ageing is strongly related to a range of diseases such as selected cancers, coronary heart disease, and Alzheimer's disease,[2] but also conditions such as frailty which, in principle, is distinct from diagnosed diseases or disability.[2,5] The term 'frailty' has been used for many years in everyday and academic language. It is simple in its meaning, yet it has been used in a variety of ways to describe both individuals and a condition that applies to people. There has been a growing research interest in this condition as evidenced by the increasing number of publications utilising the term (Figure 1.1).

Figure 1.1. Number of publications including the term 'frailty' from 1953 to 2010 (Medline, n=2,071)



1.2 Defining frailty

Efforts to define frailty are relatively new. It appeared as a Medical Subject Heading (MeSH) in Medline, 'frail elderly', appeared in 1991. According to MeSH, frail elderly is defined as 'older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity'.[6] At a clinical level, frailty may refer to a 'state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality'.[7] This definition is similar to the MeSH. There are several other definitions, typically variations of these, listed by Gobbens and colleagues (Table 1.1).[8]

In order to find a consensus on a conceptual definition of frailty, experts in the field of frailty have been consulted.[8] During the course of 2 meetings, 14 respondents were asked

by Gobbens and colleagues which of the 11 definitions given in Table 1.1 placed most emphasis on the integral functioning of older people. The definition given the highest score by the committee was that of Schuurmans and colleagues:[9] 'frailty is a loss of resources in several domains of functioning, which leads to a declining reserve capacity for dealing with stressors'. Putting these semantics aside, the main consequence of such vulnerability is an increased risk of multiple adverse health-related outcomes.[10,11]

From these conceptual definitions, frailty is distinguished from other concepts such as ageing, comorbidity, and disability (see following section). Although these terms overlap, it is now established that these are distinct clinical entities.[7,10-14]

Table 1.1. Conceptual definitions of frailty ranked according to scores[a] assigned by experts[8]

Definition	Investigators	Score
Frailty is a loss of resources in several domains of functioning, which leads to a declining reserve capacity for dealing with stressors.	Schuurmans et al, 2004[9]	142
A syndrome involving grouping of problems and losses of capacities in multiple domains, which make the individual vulnerable to environmental challenge.	Strawbridge et al, 1998[15]	123
A syndrome of multisystem reduction in reserve capacity as a result of which an older person's function may be severely compromised by minor environmental stresses, giving rise to the condition of 'unstable disability'.	Campbell et al, 1997[13]	107
A biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes.	Fried et al, 2001[16]	104
A combination of biological, physiological, social, and environmental changes that occur with advancing age and increase vulnerability to changes in the surroundings and to stress.	Nourhashemi et al, 2001[17]	104
A vulnerability state resulting from a precarious balance between the assets maintaining health and the deficits threatening it.	Rockwood et al, 1994[18]	87
A state of reduced physiological reserve associated with increased susceptibility to disability.	Buchner and Wagner, 1992[19]	74
A combination of aging, disease, and other factors that make some people vulnerable.	Rockwood et al, 1999[20]	67
Complex and cumulative expression of altered homeostatic responses to multiple stresses resulting in metabolic imbalance.	Hamerman, 1999[21]	60
Frailty is diminished ability to carry out important practical and social activities of daily living.	Brown et al, 1995[22]	49
A state of being neither 'too independent' nor 'too impaired' that puts the person at risk for adverse health outcomes.	Winograd et al, 1988[23]	40

[a] Overall, 14 experts were asked to assigned 11 points to the definition that is close to that expected and 1 point to the least suited. The scores ranged between 14 and 154.

Frailty and ageing

Many characteristics of frailty also apply to the ageing process in general. Although frailty is closely related to ageing, the concept of frailty is suggested to help in understanding the heterogeneity of functional decline observed with chronological ageing.[10] Bergman and colleagues found that chronological age alone was only an approximate indicator of a person's vulnerability to adverse outcomes. This implies that although ageing predisposes to frailty, not all elderly are frail, suggesting a heterogeneity in ageing.[10,11] The heterogeneity of functional decline, which is the result of the interaction between genes and environment, is observed through lifetime, at all levels: (1) at molecular level: decrease in the capacity for deoxyribonucleic acid (DNA) repair, telomere (repetitive DNA sequences at the ends of chromosomes) length decreased with age, accumulation of mitochondrial DNA damage, impairment of protein turnover;[24] (2) at cellular level: deterioration in cell function;[24] (3) at organ level: decrease in cognitive,[25] cardiac[26], pulmonary,[27] hepatic,[28] and kidney functions,[29] hormonal alterations (cortisol)[30] or deficiencies (dehydroepiandrosterone, testosterone, sex hormone-binding globulin, insulin growth factor-1);[31,32] (4) at vascular level: coronary atherosclerosis develops at early age and can be symptomatic at middle or older age;[33] (5) at inflammation level: presence of low level of inflammation;[34-38] (6) at immunological level:[39] decrease or abnormality in the immune response responsible for chronic cytomegalovirus (CMV) infection,[40,41] autoimmunity,[42] and decreased response to vaccination;[43] (7) at muscle level: sarcopenia;[44] (8) at bone level: osteoporosis.[45-51] Other characteristics observed among older adults are: low nutrition intake,[52,53] polymedication,[54] pain,[55,56] and sleep disturbances.[57-59]

Thus, the distinction between frailty and ageing is relevant. For example, in clinical decision-making for aggressive treatment of a cancer, frail individuals, irrespective of age, are less likely to tolerate some toxic treatments than their non-frail counterparts.[12,14] Figure 1.2 illustrates that the frailty syndrome is sometimes described as a continuum from normal ageing but with a poorer physical performance. It also shows the possibility of frail persons to reach the performance of non-frail individuals after primary and secondary interventions (Figures 1.2 and 1.3). The term 'primary' and 'secondary' frailty

have been used to refer to frailty in the absence or presence of chronic diseases. This distinction supports the bidirectional association between frailty and diseases. Older adults without a clinical disease can be frail because of undiagnosed conditions due to atypical, silent, or subclinical presentation (primary frailty).[60] In addition, among elderly persons with a chronic condition, the burden generated by these diseases (pain, fatigue, complications of disease or treatment) can lead to frailty (secondary frailty).

Figure 1.2. Comparison of evolution of physical performance among participants with normal ageing and among frail participants[61]

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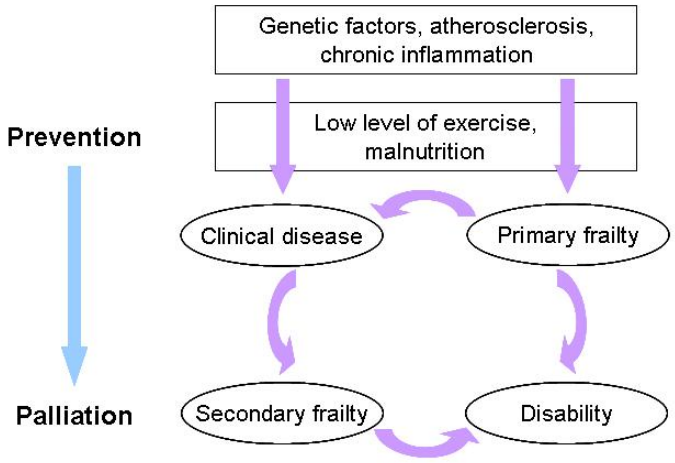
Figure 1.3. Pathways to frailty[62]



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As Figures 1.2 and 1.3 suggest, there is strong evidence from observational[63,64] and randomised controlled trials[65-68] that frailty may be prevented[5,18,63,64,69,70] and perhaps even reversed with appropriate intervention. Existing interventions intend to limit some function declines due to age-related conditions. These interventions are: (1) physical exercise programs: muscles in older adults are adaptable to resistance exercise as it increases muscle protein synthesis rates,[71] Tai Chi-like exercise can decrease risk of fall and physical performance in pre-frail participants;[65] (2) hormonal therapy: dehydroepiandrosterone (DHEA) and testosterone were shown to improve lower extremity strength and performance and to improve body composition by increasing lean mass and decreasing fat mass in frail participants;[66-68] and (3) vitamin D: by increasing bone density and quality and muscle strength, vitamin D supplementation reduces the risk of fall[72] and fractures[48] in persons 65 years of age or older. There are strong assumptions that vitamin D has pleiotropic effects in particular on cardiovascular disease (CVD), immune system, and cancer.[72]

Frailty and comorbidity

Comorbidity is defined as the concurrent presence of two or more medically diagnosed diseases in the same individual, with the diagnosis of each contributing disease based on established, widely recognised criteria.[7]

With ageing, the presence of comorbidity increases as individual chronic diseases rise with age. In the United States, 87.6% of adults aged ≥ 65 years old were reported to have at least one chronic condition and 69.2% of them more than two conditions.[73] In the Newcastle 85+ study conducted among those aged 85 years old or more, all participants had at least one chronic condition.[74] CVD was the highest prevalent disease with 57.5% of hypertension, 31.4% of ischemic heart disease, and 31.4% of cerebrovascular disease. Second prevalent disease was osteoarthritis (51.8%). Diabetes mellitus was also frequent with 13.1%. CVD and diabetes were shown to be highly prevalent in frail individuals.[60,75-77]

The association between frailty and chronic disease has been theorised by Bouchon and named '1 + 2 + 3' (Figure 1.4).[78] According to this theory, for a given organ, a chronic disease (state 2) accelerates its physiological decline (state 1). An acute event (state 3) can further accelerate it. States 2 and 3 can be reversible with an appropriate intervention. However, the reserve function is lost when organ function passes through the failure threshold, leading to loss of homeostatic capability to withstand stressors and resulting vulnerabilities.

Figure 1.4. Combined effect of physiological ageing, chronic disease, and acute event on reserve function ('1+2+3' theory)[78]

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Frailty and disability

Disability is defined as difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently in a home, and desired activities important to one's quality of life.[7] Disability in self-care tasks is measured using the Basic Activities of Daily Living (BADL) instrument,[79] and in tasks of household management using the Instrumental Activities of Daily Living (IADL) instrument.[80]

In research on frailty, disability is usually considered as an adverse health outcome caused by frailty. However, disability can also be a predictor of frailty.

Although overlapping with comorbidity and disability, frailty is distinct from them.[7] Frailty and comorbidity predict disability. Disability can exacerbate frailty and comorbidity. Comorbidity may contribute to the development of frailty. These interrelationships explain why these three entities co-occur (Figure 1.3).

It is important to distinguish these entities as each of them confers specific interventions. In the management of frail individuals, interventions can include the treatment of the underlying conditions, weakness, and undernutrition. These interventions may minimise risk for falls, disability, hospitalisation, and mortality.

1.3 Measurement of frailty

This paragraph reviews how the concept of frailty has been operationalised. Most general reviews or editorials on frailty have implicitly presented the measure called 'phenotype of frailty' developed by Fried and colleagues[16] as reference,[10,47,81-90] and a few others[91] that of Mitnitski and colleagues named 'frailty index'.[92] Description of the operationalisation of these instruments is presented in Chapter 2. However, in recently published reviews on frailty measures[61,93-95] where authors have identified more than 20 alternative measures of frailty, the recommendations on the instrument – 'gold standard' – to use to identify frail elderly are not clear.

Aims of this thesis

My coverage of conceptual and operational definitions, together with the epidemiological evidence, support frailty as an emerging public health issue. In the elderly, there is growing evidence that frailty predicts various adverse health outcomes such as disability,[75,96] institutionalisation,[75] falls,[97] fractures,[97] hospitalisation,[98] and mortality.[75,97,99] However, significant gaps in knowledge exist. First, there is a lack of consensus regarding the measurement of frailty, with existing tools largely having been poorly validated. Second, there is insufficient understanding of frailty predictors, so hindering efforts at prevention. There is some evidence suggesting that individual CVD and diabetes risk factors are also related to frailty but whether established risk engines for

CVD and diabetes, often used in primary care, also have predictive utility for frailty remains unclear.

To address important limitations in frailty research, this thesis has 3 aims:

i. using systematic review, identify current measures of frailty;

ii. using the British Whitehall II cohort study validate the most commonly used measure;

iii. again using the British Whitehall II cohort study, examine the predictive capacity of CVD and diabetes risk factors and the corresponding diseases risk algorithms for frailty.

Findings from the systematic review on frailty measures are provided in Chapter 2 to respond to the objective (i). Description of the Whitehall II study, its design and data used in this thesis is reported in Chapter 3. Validity and reliability of a selected frailty measure are examined in Chapters 4, 5, and 6 (objective (ii)). Utility of existing CVD and diabetes risk algorithms is evaluated in Chapters 7 and 8 (objective (iii)). Finally, Chapter 9 presents the summary of the main findings, implications of this present work, and suggestion of direction for future research.

2 Systematic review of frailty measures

2.1 Introduction

To date, there is no acknowledged gold standard measurement of frailty. Researchers have shown that age-associated declines in physical capability – reflecting age-related sarcopenia[44] – assessed by grip strength, walking speed, chair rising, and standing balance times are associated with adverse health outcomes such as falls, disability, and mortality.[100-103] These markers of frailty used separately do not constitute frailty but presence of multiple markers does.[13,104,105]

A number of reviews have highlighted that there are several ways of measuring frailty.[61,93-95] However, there is a lack of assessment of each instrument and few evidence-based recommendations on which instrument to use in research on frailty. Therefore, the purpose of this literature review was to identify all existing frailty measurements and to assess their performance in terms of reliability, validity, and utility.[106]

2.2 Objectives

The specific objectives addressed in this Chapter are:

i. to provide a comprehensive catalogue of existing frailty measures

ii. to review evidence on the validity and reliability of these measures

iii. to quantify the popularity of each frailty measure by investigators other than the originators

2.3 Methods

Search strategy

Two approaches were used in the search strategy. First, the electronic database MEDLINE (1948 to May 2011) was used through the OvidSP interface for all articles including the keyword ‘frailty’ (using the term ‘frail’ yielded an unmanageably large

literature with little relevance to the present objectives). This strategy allowed identifying articles where this keyword appeared at least once in the title, abstract, or subject heading. Second, the reference sections of the retrieved articles were scrutinised for additional relevant papers. This overview followed the guidelines for the Meta-analysis of Observational Studies in Epidemiology (MOOSE).[107]

Selection criteria

Studies with participants aged 50 years and older at baseline examination which clearly stated that their measure allowed identification of frail individuals were included. Further inclusion criteria were: (1) articles written in English, French, or Spanish; and (2) articles describing the reliability and validity of a frailty instrument.

Assessment of the reliability and validity of frailty measures

The reliability and validity were assessed using suggested guidelines.[104,106] Reliability, which determines if a scale measures an entity (here frailty) in a reproducible way, has several elements: internal consistency (the average of the correlations among all items in the measure), intra-rater reliability (the agreement between observations made by the same rater on two different occasions), inter-rater reliability (the agreement between different raters), and test-retest reliability (the agreement between observations on the participants on two occasions separated by an interval of time). Validity – whether the scale in question measures what it purports to measure – was first assessed by content validity. That is, items aimed at measuring frailty should not measure other entities, such as disability or comorbidity. While it is recognised that although the concept of frailty overlaps with that of comorbidity and disability, they are different entities.[13,16] Another measure, criterion validity refers to how well the instrument predicts an outcome. When frailty and the outcome data are collected simultaneously, the criterion validity is referred to as the concurrent validity. When the outcome data are prospectively collected, it is called predictive validity. Finally, construct validity refers to the extent to which an instrument measures the theoretical concept it is supposed to measure.[106]

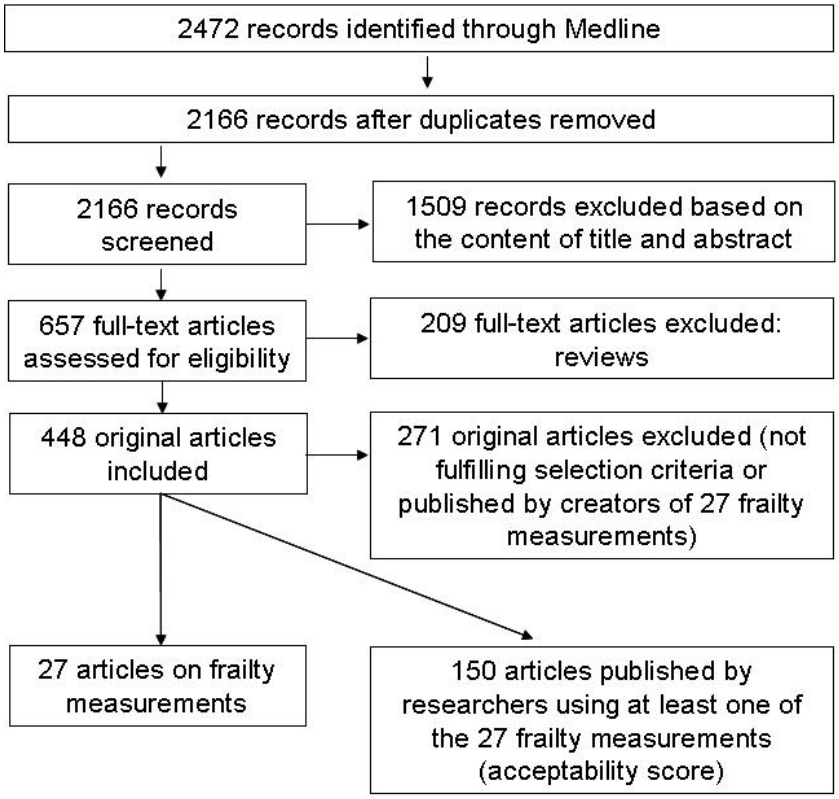
Use of frailty measurements by researchers

To evaluate the level of utilisation of a given frailty instrument by researchers, among the selected articles, the number of publications which had been authored by researchers other than the originators in the periods ≤ 2000, 2001-2005, and ≥ 2006 was counted. In addition to this, the Scopus citation database[108] of peer-reviewed literature was used to analyze the number of citations to original research articles, excluding those cited by the creators of a given frailty instrument, for each frailty scales up to October 2011.

2.4 Results

The initial keyword search using 'frailty' identified 2,166 articles, of which 1,509 were excluded based on the content of the title and the abstract (Figure 2.1). A further 209 papers were excluded because they were reviews rather than empirical papers. Of the remaining 448 articles, 27[15,16,20,92,109-131] described the construction or psychometric properties of measures of frailty, and were included in this review. Among them, five instruments initially created to assess disability,[132] vulnerability,[133] and physical capabilities or performances[134-136] were used subsequently to assess frailty.[110,112,113,119,122] For these 5 and 22 other instruments, reliability, validity, and use were studied as a measure of frailty. A further 150 articles either applying or testing the validity of 27 frailty measurements were also included in this synthesis.

Figure 2.1. Phases of the literature search



Classifications: self-report, objective, and mixed frailty measures

All 27 identified frailty measures were grouped into three categories of administration (Table 2.1): subjective (self-reported items only), objective (inclusion of only directly measured components), or subjective and objective combined. Eleven of the 27 instruments included only subjective components which were either reported by a participant in nine out of 11 cases,[15,20,92,109,113,115,120,122,129] or reported by a clinician or a researcher.[118,126] Of the 27 frailty instruments, only five included directly measured components.[110,112,119,123,124] Finally, the remaining 11 instruments included both self-reported and measured components.[16,111,114,116,117,121,125,127,128,130,131]

Table 2.1. Frailty instruments utilised in individual studies

Frailty instrument	Name	Original paper
Self-reported		
Strawbridge et al, 1998[15]	1994 frailty measure	
Dayhoff et al, 1998[115]		
Rockwood et al, 1999[20]	CSHA rules based definition	
Steverink et al, 2001[129]	Groningen frailty indicator	
Mitnitski et al, 2002[92]	Frailty index	
Gerdhem et al, 2003[118]	Subjective frailty score	
Rockwood et al, 2005[126]	Canadian Study of Health and Aging (CSHA) clinical frailty scale	
Cacciatore et al, 2005[113]	Frailty staging system	Based from Lachs et al, 1990, USA[132]
Amici et al, 2008[109]	Marigliano-Cacciafesta polypathological scale	
Kanauchi et al, 2008[122]	Vulnerable elders survey-13	Based on Morris et al, 1984, USA[137] and Saliba et al, 2001, USA[133]
Gobbens et al, 2010[120]	Tilburg frailty indicator	
Measured		
Brown et al, 2000[112]	Modified physical performance test	Based on Reuben & Siu, 1990, USA[136] and Guralnik et al, 1995, USA[135]
Gill et al, 2002[119]		Based on Gill et al, 1995, USA[134]
Klein et al, 2003[123]	Frailty index	
Bandinelli, 2006[110]	Short physical performance battery	Based on Guralnik et al, 1995, USA[135]
Opasich et al, 2010[124]		
Self-reported and measured		
Speechley & Tinetti, 1991[128]		
Fried et al, 2001[16]	Phenotype of frailty	
Binder et al, 2002[111]	Physical frailty	
Studenski et al, 2004[130]	Clinical global impression of change in physical frailty	
Puts et al, 2005[125]	Static/dynamic frailty index	
Carriere et al, 2005[114]	Score-risk correspondence for dependency	
Rolfson et al, 2006[127]	Edmonton frail scale	
Ensrud et al, 2008[116]	Study of osteoporotic fractures index	
Hyde et al, 2010[121]	FRAIL scale	
Freiheit et al, 2010[117]	Brief frailty index	
Sundermann et al, 2011[131]	Comprehensive assessment of frailty	

General description of frailty measurements

Of the 27 frailty assessments, 19 were developed in population-based samples,[15,16,20,92,110-116,118-121,123,125,126,128] 7 among hospitalised patients,[117,122,124,127,129-131] and 1 without specification.[109] Half of the frailty instruments (n=14) were created by research groups in the USA,[15,16,110-113,115,116,119,122,123,128,130,131] five in Canada,[20,92,117,126,127] three in the Netherlands,[120,125,129] two in Italy,[109,124] and one each in Australia,[121] France,[114] and Sweden;[118] none from the UK. Five of the 27 frailty instruments were adapted from those developed initially to assess functional status,[132] vulnerability,[133] or physical performances.[134-136] These were used to measure frailty for the first time by Cacciatore and colleagues,[113] Kanauchi and colleagues,[122] Brown and colleagues,[112] Gill and colleagues,[119] and Bandinelli and colleagues,[110] respectively. Furthermore, some recently tested tools assessing frailty, such as static/dynamic frailty index,[125] study of osteoporotic fractures index,[116] FRAIL scale,[121] and comprehensive assessment of frailty[131], were based on the Fried's frailty scale[16] and/or the Mitnitski's frailty index.[92]

All identified frailty measures were composed of at least two items, except that of Gerdhem and colleagues[118] where a general assessment of health is made within a 15-second observation by the investigator. Of the subjective and mixed frailty measures, most contained disability and/or comorbidity components. Instruments without disability or comorbidity information were: the 1994 frailty measure,[15] subjective frailty score,[118] Tilburg frailty indicator,[120] all objective measures (modified physical performance test,[112] physical frailty score,[119] Klein's frailty index,[123] short physical performance battery,[110] and Opasich's frailty scale),[124] Speechley & Tinetti's frailty scale,[128] Fried's frailty scale,[16] score-risk correspondence for dependency,[114] study of osteoporotic fractures index,[116] and brief frailty index.[117] Further descriptions of characteristics of population and type of components included in each instrument are also provided in Appendix 1.

Assessment of the reliability and validity of frailty measures

Appendix 2 presents reliability and validity data taken from the original articles and other related articles on the frailty measures. Three approaches were used for reliability assessment: internal consistency, inter-rater, and test-retest reliability. Concurrent and

predictive validity were mainly assessed using outcomes such as mortality, institutionalisation, activities of daily living (ADL) disability, hospitalisation, and quality of life. Only 7 out of 27 instruments (26%) were found to have had both reliability and validity ascertained.[118,120,123,126,127,129,130]

Although the Canadian Study of Health and Aging (CSHA) clinical frailty scale[126] and the Edmonton frail scale[127] had good reliability (Kappa coefficient ≥ 0.7, Appendix 2), they also included items on disability and/or comorbidity. Nineteen instruments had either their reliability or validity assessed. Among them, 4 instruments were tested for validity once only in the original sample/cohort of participants,[20,113,121,131] and the phenotype of frailty by Fried and colleagues[16] and the frailty index by Mitnitski and colleagues[92] had their concurrent or predictive validity assessed in more than 3 samples/cohorts (17 and 13 samples/cohorts, respectively). As the frailty index[92] includes items on disability or comorbidity, it does not only measure frailty, reducing the specificity of this measure. One instrument out of 27, the short physical performance battery, previously used to assess physical functioning,[135] had neither reliability nor validity information in measuring frailty.[110]

Use of frailty instruments

Table 2.2 presents the number of publications in which a frailty measure had been used by investigators other than those who created it. In 69% of publications, a frailty scale developed by Fried and colleagues[16] was utilised, 12% used the frailty index developed by Mitnitski and colleagues,[92] 4% the Edmonton frail scale,[127] and ≤ 2% used the remaining instruments. This analysis also shows that half the frailty instruments (n=14) have not been employed at all by other researchers. [109-111,113-115,117,118,121,123-125,130,131]

Figure 2.2 displays the number of original research articles based on the Scopus citation database, which referenced one of the 27 frailty instruments: the 3 most cited papers were that of Fried and colleagues[16] (n=676), Speechley and colleagues[128] (n=167), and Gill and colleagues[119] (n=150). The citation rank for Mitnitski and colleagues' paper[92] was ninth (n=52).

Table 2.2. Use of subjective, objective and mixed frailty instruments by type and publication year

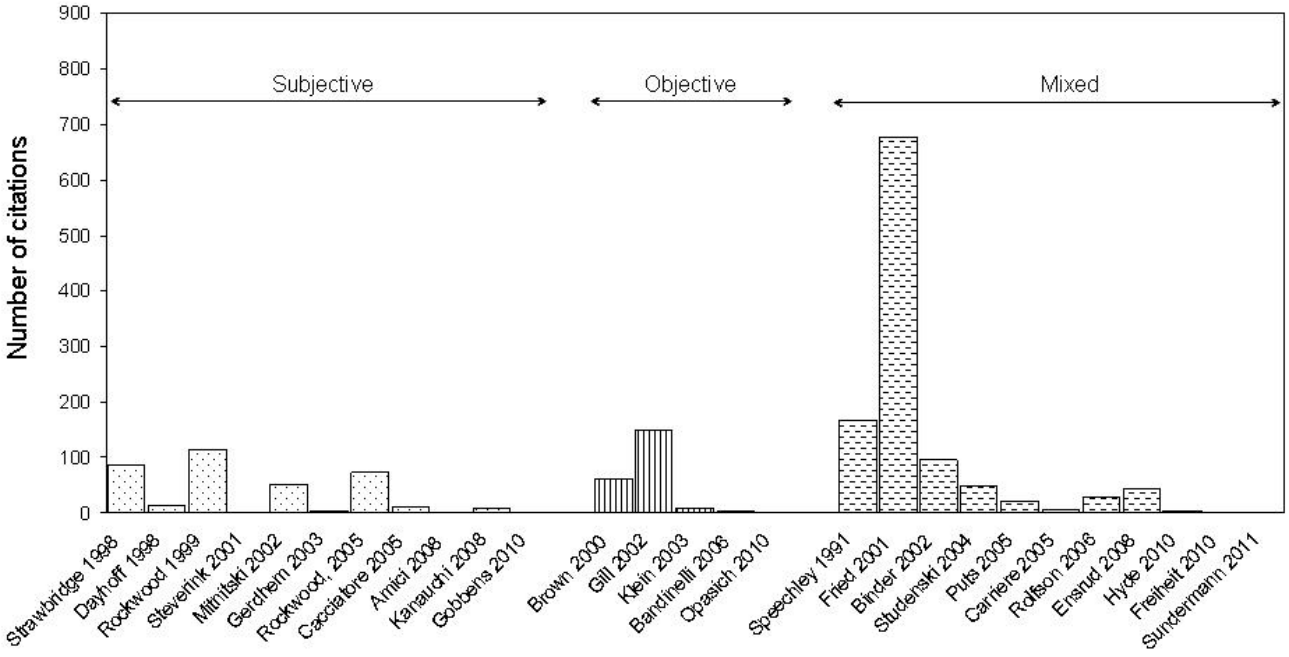
Frailty instrument	Number of publications (%)[a] by year			All N=150
	Before 2000 N=0	2001-2005 N=8	2006 or later N=142	
Subjective				
Strawbridge et al, 1998: 1994 Frailty Measure	0	1 (12.5)	1 (0.7)	2 (1.3)
Dayhoff et al, 1998	0	0	0	0
Rockwood et al, 1999: CSHA rules based definition	0	0	0	0
Steverink et al, 2001: Groningen Frailty Indicator	NA	0	3 (2.1)	3 (2.0)
Mitnitski et al, 2002: Frailty index	NA	2 (25.0)	16 (11.2)	18 (12.0)
Gerdhem et al, 2003: Subjective Frailty Score	NA	0	0	0
Rockwood et al, 2005: CSHA Clinical Frailty Scale	NA	0	3 (2.1)	3 (2.0)
Cacciatore et al, 2005: Frailty Staging System	NA	0	0	0
Amici et al, 2008: MCPS	NA	NA	0	0
Kanauchi et al, 2008: Vulnerable Elderly Survey-13	NA	NA	3 (2.1)	3 (2.0)
Gobbens et al, 2010: Tilburg Frailty Indicator	NA	NA	1 (0.7)	1 (0.7)
Objective				
Brown et al, 2000: Modified Physical Performance Test	NA	1 (12.5)	1 (0.7)	2 (1.3)
Gill et al, 2002: Physical Frailty Score	NA	0	2 (1.4)	2 (1.3)
Klein et al, 2003: Frailty index	NA	0	0	0
Bandinelli, 2006: Short Physical Performance Battery	NA	NA	0	0
Opasich et al, 2010	NA	NA	0	0
Mixed				
Speechley & Tinetti, 1991	0	3 (37.5)	0	3 (2.0)

Fried et al, 2001: Phenotype of frailty	NA	1 (12.5)	103 (72.5)	104 (69.3)
Binder et al, 2002: Physical frailty	NA	0	0	0
Studenski et al, 2004: CGIC-PF	NA	0	0	0
Puts et al, 2005: Static/Dynamic frailty index	NA	0	0	0
Carriere et al, 2005: Score-Risk Correspondence for dependency	NA	0	0	0
Rolfson et al, 2006: Edmonton Frail Scale	NA	NA	6 (4.2)	6 (4.0)
Ensrud et al, 2008: Study of Osteoporotic Fractures index	NA	NA	3 (2.1)	3 (2.0)
Hyde et al, 2010 : FRAIL scale	NA	NA	0	0
Freiheit et al, 2010: Brief Frailty Index	NA	NA	0	0
Sundermann et al, 2011: Comprehensive Assessment of Frailty	NA	NA	0	0

CSHA: Canadian Study of Health and Aging; MCPS: Marigliano-Cacciafesta Polypathological Scale; CGIC-PF: Clinical Global Impression of Change in Physical Frailty

[a] Number of publications / total number of publications during the period x 100

Figure 2.2. Number of original research articles citing individual frailty instruments according to the Scopus Citation Database, October 2011



Phenotype of frailty

Of 150 articles in which authors have used at least one of the 27 frailty instruments described (Figure 2.1), 69 % used the phenotype of frailty. Thus, 104 articles are evaluated in order to study the trend in the use of the phenotype of frailty and the domains of research where it has been employed.

Among articles where the phenotype of frailty was used, I arbitrary selected 7 studies[58,96,138-142] to provide some examples of its adaptation in other studies than the Cardiovascular Health Study (CHS) where the phenotype of frailty has been originally created.[16] Characteristics of these studies are given in Table 2.3.

Table 2.3. Characteristics of studies using the phenotype of frailty

Author	Study	Sex	Nb participants (age in years)
Alvarado et al, 2008[138]	Salud Bienestar y Envejecimiento (SABE) project (multicentric cross-sectional study)	Both sexes	10,661 (≥ 60)
Avila-Funes et al, 2008[96]	Three-City Study (cohort)	Both sexes	6,078 (≥ 65)
Boyd et al, 2005[139]	Women's Health Aging Study-I (cohort)	Women only	749 (≥ 65)
Ensrud et al, 2009[58]	Osteoporotic Fractures in Men Study (MrOS) (cohort)	Men only	3,133 (≥ 65)
Hubbard et al, 2010[140]	English Longitudinal Study of Ageing (cohort)	Both sexes	3,055 (≥ 65)
LaCroix et al, 2008[141]	Women's Health Initiative Observational Study (cohort)	Women only	25,378 (≥ 65)
Masel et al, 2010[142]	Hispanic Established Populations for Epidemiologic Study of the Elderly (cohort)	Both sexes	1,013 (≥ 74)

Concept of frailty according to Fried and colleagues

A total of five criteria (weight loss, grip strength, exhaustion, walking speed, and physical activity) are grouped to constitute the phenotype of frailty following a conceptual model representing frailty associated with declining energetics and reserve of multiple systems resulting in negative energy balance, sarcopenia, and decrease of strength and of tolerance for exertion (Figure 2.3). According to this model, frailty is characterised by following core clinical presentations: shrinking, weakness, poor endurance, slowness, and low activity (Figure 2.3 and Table 2.4, Section A).

Figure 2.3. Cycle of frailty[16]

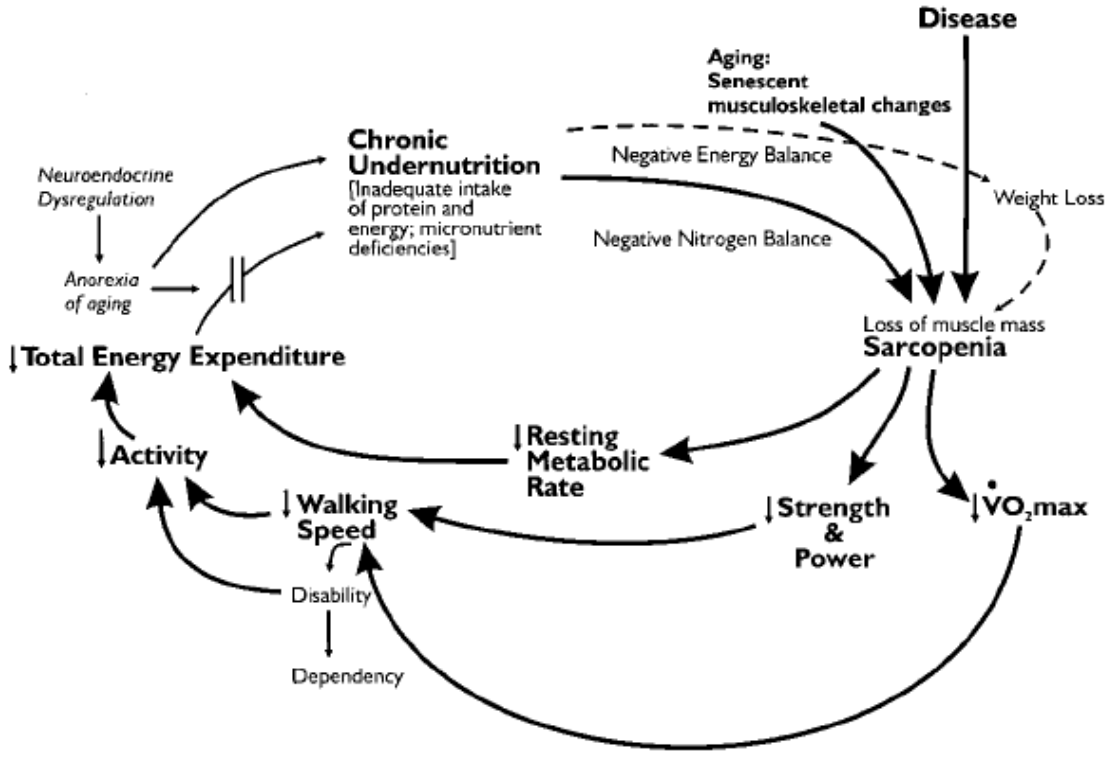


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Table 2.4. Definition of the phenotype of frailty[16]

A. Characteristics of frailty	B. CHS measure (n=5,317) original validation cohort	%
Poor endurance, exhaustion	Self-report of either of: 1) felt that everything I did was an effort in the last week, or 2) could not get going in the last week	21.3
Low physical activity (PA)	Short version of the Minnesota Leisure Time Activity questionnaire (lowest 20% Kcals of PA/week): Men: Those with Kcal of PA/week<383 Women: Those with Kcal of PA/week<270	24.1
Slowness	Usual walking time/15 feet (4.57 m): slowest 20% (by sex, height) Men: Height ≤ 173 cm: ≥ 7sec or height > 173 cm: ≥ 6 sec Women: Height ≤ 159 cm: ≥ 7sec or height > 159 cm: ≥ 6 sec	38.0
Weakness	Grip strength (kg): lowest 20% (by sex and BMI) Men: BMI ≤ 24: ≤ 29 or BMI ≤ 24.1-26: ≤ 30 or BMI ≤ 26.1-28: ≤ 30 or BMI > 28: ≤ 32 Women: BMI ≤ 23: ≤ 17 or BMI ≤ 23.1-26: ≤ 17.3 or BMI ≤ 26.1-29: ≤ 18 or BMI > 29: ≤ 21	26.2
Shrinking: weight loss (unintentional), sarcopenia (loss of muscle mass)	Either of: 1) Lost >10 pounds unintentionally in the last year (self-report) 2) Lost ≥5% of previous year's body weight	7.3
	C. Definition of phenotype of frailty	
	Not frail/robust if 0 criteria	46.4
	Pre-frail if 1 or 2 criteria present	46.7
	Frail if ≥ 3 criteria present	6.9

Original operationalisation of the phenotype of frailty

Table 2.4 describes frailty characteristics – poor endurance/exhaustion, low activity, slowness, weakness, and shrinking – and shows how they were assessed in CHS (Section B). These 5 components are described as follows:

Exhaustion or poor endurance has been defined from two items drawn from the Center for Epidemiologic Studies Depression (CES-D) scale:[143] 'I felt that everything I did was an effort in the last week' and 'I could not get going in the last week'. If participants answered 'occasionally or moderate amount of the time (3-4 days)' or 'most or all of the time (5-7 days)' to either of these items, they were categorised as being exhausted.

Low physical activity: the level of physical activity was assessed in kilocalories expended per week based on each participant's report collected using the short version of the Minnesota Leisure Time Physical Activity Questionnaire.[144] The lowest quintile was used to identify participants with low physical activity.

Slow walking speed was based on usual walking speed over a distance of a 15 feet (4.6 meters) walking test that incorporate physical stature as a proxy for stride length stratified by sex. The lowest quintile was used to identify participants with slowed walking speed.

Low grip strength: Grip strength was measured in kg using the Smedley hand grip dynamometer with the dominant hand. Thresholds are stratified by gender and BMI. The lowest quintile was used to identify participants with low grip strength.

Weight loss: the shrinking phenomenon, which is considered as a result of unintentional weight loss and sarcopenia by Fried and colleagues, is present if a participant reports to have lost more than 10 pounds in weight in the prior year or if he/she has lost $\geq 5\%$ of previous year's weight.

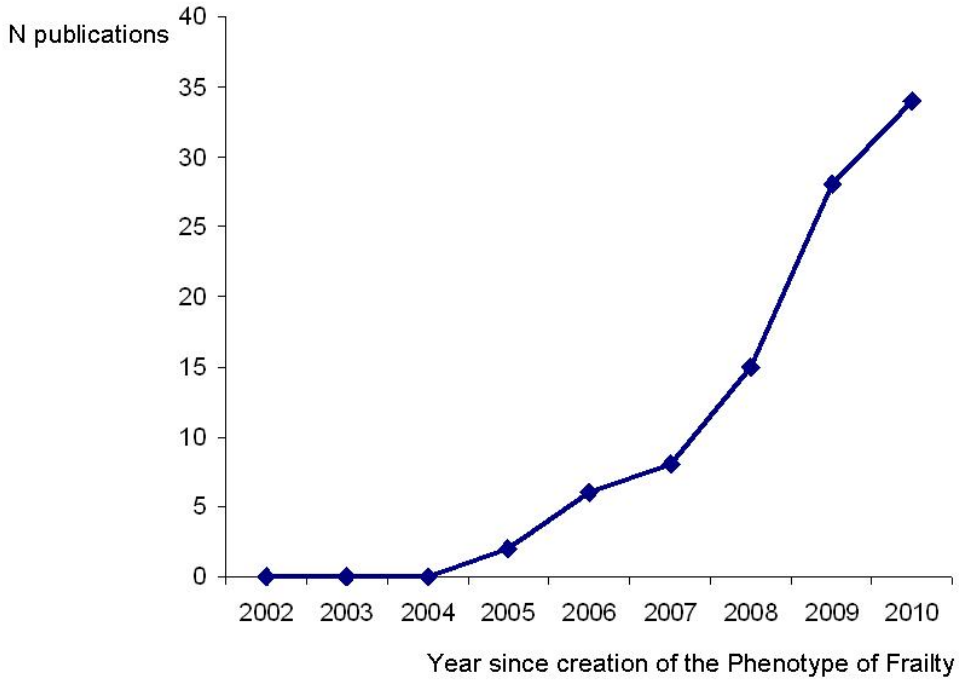
Classification of frailty: a total frailty score was calculated by allocating a value of 1 to each of the above criteria if present, resulting in a range of 0 to 5. Participants with at least three characteristics out of five are classified as 'frail', those with one or two

characteristics as ‘pre-frail’, and those with none of these characteristics as ‘non-frail’ (Section C in Table 2.4).

Trend in the use of the phenotype of frailty

Figure 2.4 shows the number per year of articles authored by researchers other than the originators of the phenotype of frailty since its creation in 2001. The increase was exponential reflecting high level of its utilisation among researchers.

Figure 2.4. Number of publications using the phenotype of frailty



Different versions of the phenotype of frailty

This section presents how the components included in the phenotype of frailty have been defined in studies other than the CHS.

Exhaustion: examples of definition of exhaustion criterion in the literature are listed in Table 2.5. Different questionnaires are used to define this criterion: Geriatric Depression Scale, CES-D, visual analog scale of energy, and Rand-36 Vitality Scale.

Table 2.5. Examples of definitions of frailty for exhaustion

Author	Indication of exhaustion
Alvarado et al, 2008	2 questions on the Geriatric Depression Scale:[145] 'Do you have lots of energy?' (yes/no) and 'have you dropped many of your activities or interests?' (yes/no) A negative response to the first question and/or a positive response to the second were considered indications of exhaustion
Avila-Funes et al, 2008	As in the CHS
Boyd et al, 2005	Any of a score of 3 or less on a visual analog scale of energy from 0 (no energy) to 10 (most energy you have ever had): 'Felt unusually tired in last month most or all of the time' 'Felt unusually weak in the past month most or all of the time'
Ensrud et al, 2009	Negative response to the question from the Geriatric Depression Scale:[145] 'Do you feel full of energy?'
Hubbard et al, 2010	Self-report of 'could not get going' on the CES-D scale
LaCroix et al, 2008	4 items of the Rand-36 Vitality Scale (range 0–100): 'Did you feel…worn out?; tired?; full of pep?; have a lot of energy?'
Masel et al, 2010	As in the CHS

Low physical activity: examples of definitions of low physical activity criterion in the literature are listed in Table 2.6. This criterion is based on individual questions or structured questionnaires such as the Physical Activity Scale for the Elderly and those peculiar to studies such as the English Longitudinal Study of Ageing and the Women's Health Initiative Observational Study.

Table 2.6. Examples of definitions of frailty for low physical activity

Author	Indication of low physical activity
Alvarado et al, 2008	When participants answering 'no' to the question: 'In the last twelve months, have you exercised regularly or participated in vigorous physical activity such as playing a sport, dancing or doing heavy housework 3 or more times a week?'
Avila-Funes et al, 2008	Individuals who reported not doing daily leisure activities such as walking or gardening and/or not doing some sport activity per week
Boyd et al, 2005	≤ 90 kilocalories/week on activity scale of six items, including: Walking for exercise, moderately strenuous household chores, moderately strenuous outdoor chores, dancing, bowling, participating in a regular exercise
Ensrud et al, 2009	Lowest quintile of Physical Activity Scale for the Elderly score
Hubbard et al, 2010	Lowest quintile of physical activity defined using the English Longitudinal Study of Ageing questionnaire
LaCroix et al, 2008	Lowest quintile of physical activity defined using the Women's Health Initiative Observational Study
Masel et al, 2010	Lowest quintile of Physical Activity Scale for the Elderly score

Slow walking time: examples of definitions of slow walking time criterion in the literature are listed in Table 2.7. This criterion is mostly based on measured walking time for a given distance. The cut-off point is usually stratified by sex and height.

Table 2.7. Examples of definitions of frailty for slow walking time

Author	Indication of slow walking time
Alvarado et al, 2008	Participants were considered to have lower body functional limitations if they experienced difficulty walking 100 yards and/or climbing one flight of stairs
Avila-Funes et al, 2008	Slowest quintile of on a timed 6-meter walking test, adjusting for gender and height
Boyd et al, 2005	Slow when the timed walk over 4 m: ≤0.65 m/sec for height ≤159 cm ≤0.76 m/sec for height >159 cm
Ensrud et al, 2009	Slowest quintile of walking time stratified according to median height on a 6-m course
Hubbard et al, 2010	Slowest quintile of walking time on a 8-feet course
LaCroix et al, 2008	Lowest quartile of the Rand-36 physical function scale
Masel et al, 2010	Slowest quintile of walking time adjusted for sex and height

Low grip strength: examples of definitions of low grip strength criterion in the literature are listed in Table 2.8. This criterion is mainly assessed using a hand dynamometer. The cut-off point was usually stratified by sex and BMI.

Table 2.8. Examples of definitions of frailty for low grip strength

Author	Indication of low grip strength
Alvarado et al, 2008	As in the CHS
Avila-Funes et al, 2008	Participants answering 'yes' to the question: 'Do you have difficulty rising from a chair?'
Boyd et al, 2005	As in the CHS
Ensrud et al, 2009	Lowest quintile in grip strength stratified by BMI quartile
Hubbard et al, 2010	Lowest quintile in grip strength
LaCroix et al, 2008	Lowest quartile of the Rand-36 physical function scale
Masel et al, 2010	Lowest quartile in grip strength adjusted for sex and BMI

Weight loss: examples of definitions of weight loss criterion in the literature are listed in Table 2.9. This component is heterogeneously defined.

Table 2.9. Examples of definitions of frailty for weight loss

Author	Indication of weight loss
Alvarado et al, 2008	Self-reported unintentional weight loss of 3 kg (10 pounds) during the previous 3 months
Avila-Funes et al, 2008	Self-reported recent and unintentional weight loss of ≥3 kg or BMI ≤ 21 kg/m^2
Boyd et al, 2005	(Self-report of weight at age 60 years – weight at baseline exam)/ weight at age 60 years ≥10%
Ensrud et al, 2009	(Weight at baseline – weight at sleep exam)/ weight at baseline ≥5% in combination with a self-reported intentional loss. Mean years between baseline and sleep exam of 3.4 years
Hubbard et al, 2010	(Weight at enrolment (1998, 1999, 2002) – weight in 2004)/ weight at enrolment ≥5%
LaCroix et al, 2008	(Weight at baseline – weight at 3-year clinic visits)/ weight at baseline >5% in combination with a self-reported intentional loss.
Masel et al, 2010	Having 10 pounds or more of unintended weight loss in the prior year

Application of the phenotype of frailty in research

The Fried and colleagues' instrument has been used in different disciplines focused on ageing, highlighting an increasing interest of this measure among research community.

Epidemiology: the phenotype of frailty has been shown to predict adverse health outcomes such as disability, hospitalisation, and mortality. Makary and colleagues found that among surgery patients, it also predicted postoperative complications, length of stay, and discharge position.[146] Another longitudinal study showed that frail older individuals had a higher risk for venous thromboembolism.[147] Cross-sectional and longitudinal studies showed that the phenotype of frailty is closely associated with cognitive decline.[148-150] Other studies found that it was associated with socio-demographic

indicators such as being female,[151] having a low income,[138,152] and being a non-European American.[153] Some researchers have observed a cross-sectional U-shaped relationship between BMI and the phenotype of frailty definition, corresponding to the U-shaped association between BMI and mortality.[140,154] Sleep disturbances have been reported to be cross-sectionally associated with frailty.[57-59]

Pharmaco-epidemiology: the associations between use of statins and angiotensin-converting enzyme inhibitors and incidence of frailty have been studied in the Women's Health Initiative Observational Study (WHI-OS).[141,155] The three-year incidence of frailty was similar in current drug users at baseline and nonusers.

Nutrition research: low daily energy, protein, vitamins D and E, and omega-3 fatty acids intakes[52,156] and low serum level of vitamins A, B, D, and E were shown to be associated with the phenotype of frailty.[46,51,157-163] All these associations have been studied with cross-sectional design except that of Semba and colleagues (longitudinal).[162]

Genetics: some mitochondrial single-nucleotide polymorphism (SNP) variations were shown to be related to the phenotype of frailty.[164] On the contrary, apolipoprotein E- and ciliary neurotrophic factor polymorphisms were not shown to be related to the frailty status.[165,166]

Physiology or physical functioning research: the phenotype of frailty was cross-sectionally associated with: high oxidative stress or imbalance,[167,168] low muscle mass,[169] reduced postural control systems,[170] impaired cardiac autonomic control,[171,172] and decreased pulmonary function.[173-175]

Studies of specific diseases: high prevalence of frailty has shown to be associated with Parkinson's disease,[176] chronic renal insufficiency,[177,178] chronic human immunodeficiency virus (HIV)[179] and cytomegalovirus (CMV) infections.[40] It has been suggested that the associations between these infections and frailty may be mediated by the immune and inflammation system status. The prevalence of frailty has been reported lower among HIV-positive patients with intact immune system compared with those with impaired immune system.[180,181] Among CMV-positive patients, those with high level of

interleukine 6 (IL-6) had a high prevalence of frailty than those with low level of IL-6.[40] A longitudinal association has been observed between the level of baseline CMV antibody concentration and the three-year incidence of frailty.[41]

Immunology: a specific T cell subset has been shown to be cross-sectionally associated with frailty status.[182] Another cross-sectional study showed that independent of thyroid function status, older women seropositive for thyroglobulin and thyroid peroxidase antibodies were less likely to be frail than seronegative women.[42]

Inflammation studies: Cross-sectional associations showed that the level of C-reactive protein (CRP), IL-6, tumour necrosis factor-alpha (TNF-α), and white blood cell counts were higher among frail participants than among non-frail participants.[34-38]

Endocrinology: the phenotype of frailty was reported to be cross-sectionally associated with high level and blunted diurnal variation of cortisol.[183] A cross-sectional study found that low level of DHEA was observed among frail male and female participants.[184] Low level of bioavailable testosterone and high level of sex hormone-binding globulin were found to be associated with frailty in two cross-sectional studies.[31,32]

In addition, the phenotype of frailty is now widely used in randomised controlled trials as inclusion criteria[66-68,185-189] to select pre-frail and frail participants aiming at testing effects of intervention (physical exercise versus none, multidisciplinary intervention versus usual care, testosterone versus none, DHEA versus none) on physical functional performance, muscle mass, quality of life, incidence of frailty, mobility, hospitalisation, institutionalisation, and on cardiovascular risk factors.[65,68,185,187-190]

2.5 Discussion

Synopsis of main findings

This overview aimed to provide a comprehensive catalogue of frailty measures, reviewing evidence on their validity and reliability, and quantifying the use of each measure by investigators other than the originators. Of all, 27 frailty scales were identified and used in 150 studies to date. A series of observations can be made.

First, although frailty, disability, and comorbidity are closely inter-related, some researchers suggest that they have distinct characteristics.[7,10] Integrating disability or comorbidity items into a frailty scale may therefore be debatable. However, half the frailty instruments (n=14) include either disability or comorbidity components.[20,92,109,111,113,115,121,122,125-127,129-131]

Second, at least five measures[110,112,113,119,122] of frailty were originally created to measure vulnerability, functional status, and physical performances, suggesting a lack of terminological rigour.

Third, four recent scales[116,121,125,131] are based on existing measures, in particular the Fried scale.

Finally, confusion between frailty scales can be generated because sometimes a specific instrument is named differently in different studies (the Fried scale[16] being labelled as Fried frailty index[159] on occasion). Elsewhere, several instruments are identically named but have different item content: for instance, the term 'frailty index' was used by different researchers.[92,117,123] This was also the case with 'frail scale'.[61,127]

Assessment of the reliability and validity of frailty measures

The Standards for Educational and Psychological Testing,[191] a guideline which describes the best practice in the development of complex measures such as frailty, recommends the reporting of the basic principles of test construction such as reliability and validity. However, this information was available only for a few instruments. Two measures, CSHA clinical frailty scale[20] and Edmonton frail scale,[127] had acceptable reliability and good concurrent and predictive validity, although content validity was weak due to the inclusion of items capturing disability and/or comorbidity. Two instruments were widely tested for their validity but not reliability: the frailty index[92] and the phenotype of frailty.[16] Reliability and validity are the most important indicators when selecting one measure over another. However, even among 7 frailty measurements with such information,[118,120,123,126,127,129,130] none of them appear to be recognised as a 'gold standard'.

Comparison between measures

In several studies, investigators have examined the inter-relationships between different measures of frailty. Thus, the phenotype of frailty has been compared with the frailty index[192-194] and the study of osteoporotic fracture index[98,116] using different methods: correlation analyses,[194] comparison of strength of cross-sectional[192] and prospective associations,[98,193] and use of the c-index statistic.[116] The phenotype of frailty is moderately well correlated with the frailty index,[194] and shows a stronger association with age, sex, and ethnicity[192] but a weaker association with mortality.[193] The phenotype of frailty and the study of osteoporotic fracture index have a similar strength of association with falls, disability, hospitalisation[98] and death.[116] As Streiner and Norman[106] highlighted, it was sometimes difficult to disentangle whether an assessment belongs to concurrent validity or construct validity. Therefore, certain classifications in either category might be arguable.

Use of the frailty instruments

In this Chapter, I have assessed the use of a frailty instrument by counting the number of publications that had adopted the instrument other than the original creators. The frailty scale developed by Fried and colleagues[16] has been most extensively tested for its validity and is the most widely used instrument in frailty research (Table 2.2). Randomised controlled trials have also used the scale to screen elderly participants,[66-68,185-189] or as an outcome of interventions.[65,188,190] The Fried's scale is widely used, allowing comparisons to be made between studies.

In addition to this manual counting procedure to estimate the use of the frailty instruments, I computed the number of citations to the original research articles (excluding those cited by the creators of a given frailty instrument) for the 27 papers describing the frailty instruments. Even though the rank of citations was different for some of the frailty instruments than that of the manual counting, the paper on the Fried's scale was still the most highly cited. Although the number of citations can be easily accessed, this electronic database search cannot replace the manual counting method as the papers citing the original articles do not necessarily use the tool in question.

Phenotype of frailty

Although not recognised as a 'gold standard' in the identification of frail elderly, the phenotype of frailty is, by far, the mostly used measure. Additionally, recent randomised controlled trials have used it to select elderly participants. Wide use of the phenotype of frailty by other researchers allows new results can be compared with the existing ones.

The popularity of use of the phenotype of frailty might, in part, be due to the fact that its criteria are more clearly defined relative to other instruments and it does not include items on comorbidity and disability

Strengths and limitations

Among previously published reviews[61,93-95,195] on frailty measures, only one[93] assessed them in terms of reliability and validity. Compared with the De Vries and colleagues' paper,[93] this review has some strengths. First, to evaluate reliability and validity of a given instrument, data from other studies have been extracted, reflecting the level of external validation of this instrument. Second, to date, no article has been published on the extent to which frailty measures have been used by other researchers. The quantification of their use might reflect the level of preference of researchers for a given frailty measurement in the absence of a consensually recognised tool. Moreover, I identified 18 other frailty instruments,[20,109-113,115,117-121,123,124,126-128,131] five of them created in 2010 or after.

A limitation of this review may lie in the use of a unique keyword 'frailty' to identify relevant publications on frailty measurements. One may find such a strategy restrictive, leading to miss some screening tools helping to identify, for instance, 'frail' elderly. However, most frailty instruments included in the reviews on frailty measures[93,95] were also identified in my review, highlighting that the probability of missing an instrument may have been possible but very low.

Another limitation related to the assessment of use of the 27 identified instruments is that it penalises the more recently published frailty instruments. However, the Fried scale is not the oldest measure in the field and several more recent frailty instruments are either

derived or similar to that measure, suggesting that qualities other than duration of availability explain the popularity of this instrument.

Regarding the phenotype of frailty, the main criticisms are that (1) it only takes into account physical aspects;[91] (2) it does not capture the dynamic nature of frailty because it is not a continuous scoring system or an ordinal scoring system; and (3) it does not include social dimension.[93] These drawbacks may be softened as an ordinal scoring system is possible to construct from the criteria of the phenotype of frailty as Buchman and colleagues did using a scale from 0 to 5.[196] Furthermore, there are a few studies which studied the association between the phenotype of frailty with socio-economic factors.[138,152]

Research on the phenotype of frailty can be criticised for heterogeneity in defining the components included in the measure. This variation in terms of the component definitions and cut-offs is partly because most studies on frailty are based on secondary analyses of already existing data collected for other purposes. The most consistent measurement has been the grip strength and the least consistent the weight loss component. This may limit the comparability of results between studies.

Conclusions

This review provides a comprehensive overview of existing frailty measurements. Twenty-seven measures of frailty were identified but none of them was recognised as a gold standard. Difficulty in accepting one measure as a reference relates to the fact that the existence of frailty as a clinical entity is quite new and the definition of frailty is still debatable. Therefore, it is difficult to create a composite measure that would meet all criteria. Furthermore, none of the measures were supported by high-quality evidence on validity and reliability.

Components to include in the frailty instruments need to be further discussed to reach a consensus, in particular on whether to include disability and/or diseases data. Several existing frailty measurements, such as the frailty scale developed by Fried and colleagues need to be further tested to reach consensus regarding the gold standard.

Researchers have shown that single frailty markers such as grip strength, walking speed, chair rising, and standing balance times are associated with adverse health outcomes such as falls, disability, and mortality.[100-103] Therefore, it was suggested that a single measurement may be sufficient instead of using a multi-component measure to identify a frail elderly.[10] However, evidence to substantiate this argument is scarce. In Chapter 6 of this thesis, I examined whether risk association with frailty measure is greater with combination of components than that of any single component with data from the Whitehall II study.

3 Description of the Whitehall II cohort study

3.1 Introduction

This Chapter provides the description of the Whitehall II study – its design and data – and the operationalisation of the phenotype of frailty based on existing data.

Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committee on the ethics of human research (London, UK).

3.2 Objectives

The specific objectives addressed in this Chapter are:

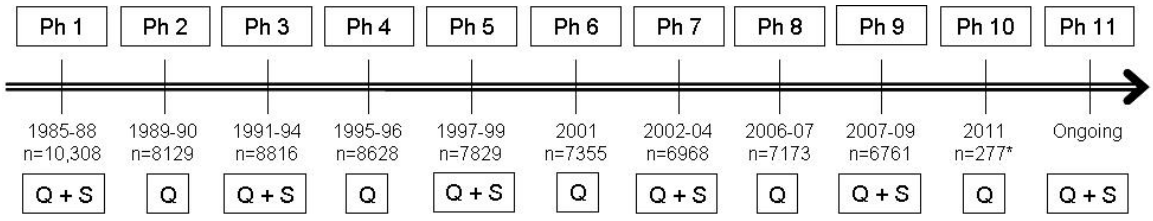
i. to describe the Whitehall II study design, participants, and data

ii. to describe the construction of the phenotype of frailty

3.3 Study design and participants

The Whitehall II study is an ongoing longitudinal study of 10,308 (67% men) London-based British civil servants aged 35-55 years in 1985.[197] While the initial goal of Whitehall II was to investigate the causes of social inequalities in disease, the study has evolved into one of the determinants and health consequences of ageing. The baseline examination (phase 1) took place during 1985-1988 and involved a clinical examination and self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone [phases 2 (1988-1990), 4 (1995-1996), 6 (2001), 8 (2006), and 10 (2011)], and postal questionnaire accompanied by a clinical examination [phases 3 (1991-1993), 5 (1997-1999), 7 (2002-2004), and 9 (2007-2009)] (Figure 3.1).

Figure 3.1. Eleven phases of Whitehall II data collection



Ph: phase
Q: Questionnaire only
Q + S: Questionnaire and clinical examination
* Pilot phase

3.4 Data specific to this thesis

To achieve the objectives of this thesis, analyses were performed using data from phases 5 to 9 and registries (Figure 3.2).

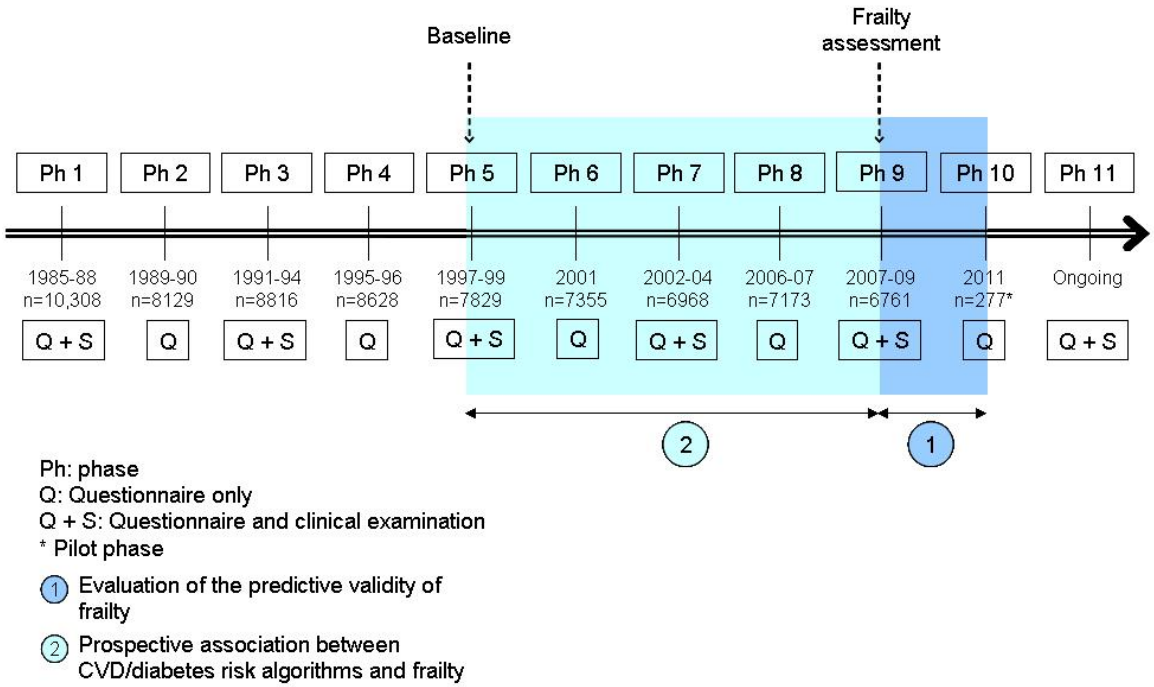
Data collected during phases

Components necessary to construct the phenotype of frailty were measured for the first time at phase 9.

To achieve the objective (ii) of my thesis consisted in validating the phenotype of frailty in the Whitehall II study, data from phase 9 were considered as 'baseline'.

In the literature, CVD and diabetes risk scores were estimated to predict the 10-year risk of CVD and diabetes, respectively. Thus, regarding the objective (iii) of my thesis consisted in examining the predictive capacity of CVD and diabetes risk factors and the corresponding diseases risk algorithms for frailty, I utilised CVD and diabetes risk factors measured at phase 5 in order to respect 10 years of difference between the baseline and the end of follow-up (phase 9).

Figure 3.2. Design specific to this thesis



Data from registries

Mortality registry

Mortality was used as an outcome in the study of the predictive validity of the phenotype of frailty in Section 4.5. A total of 10,297 respondents (99.9%) were successfully traced for mortality through the national mortality register kept by the National Health Service (NHS) Central Register using the NHS identification number assigned to each British citizen. In the present analysis, mortality follow-up began at the measurement of the phenotype of frailty (2007–2009, phase 9) and ended on January 31, 2010.

Hospitalisation registry

Hospitalisation was used as an outcome in studies of the validity of the phenotype of frailty (Chapters 4 and 6). Hospitalisation information was provided by the NHS Information Centre for health and social care.[198] The latter is responsible for managing a data warehouse called Hospital Episode Statistics (HES). The HES dataset has a record-

level form (several observations per patient) and contains details of all admissions to NHS hospitals in England.

Using anonymised patient identifiers, the NHS Information Centre provided us with a tailor-made HES dataset including all admissions of participants of the Whitehall II study from April 1989 to January 2010. It contains 31,881 records and 71 variables, in particular episode start date which allowed to select HES records of participants after taking part in the phase 9 examination. For the purposes of analyses, only information on the first hospital admission after participating in phase 9 has been chosen. After merging the subsample of HES dataset with that of the Whitehall II study, participants recorded in the HES dataset were classified as an ‘incident case of hospitalisation’, and those who were not registered in HES as a ‘non-case of hospitalisation’. Because the HES data were available for England only at the time of this work, participants living outside of England at phase 9 were excluded.

4 Validity of the phenotype of frailty in the Whitehall II study

4.1 Introduction

In this Chapter, three types of validity of the phenotype of frailty were studied: content, concurrent and predictive validity.

4.2 Objectives

The specific objectives to be addressed in this Chapter are:

i. to examine the content validity of the phenotype of frailty

ii. to test the concurrent validity of the phenotype of frailty by examining first univariate associations between frailty and covariates which have been shown to be associated with frailty in the literature and second the relationship between frailty, comorbidity and disability

iii. to test the predictive validity of the phenotype of frailty by examining whether the association between frailty and subsequent hospitalisation was independent from comorbidity, disability, and other covariates.

4.3 Content validity

Content validity pertains to the degree to which the phenotype of frailty fully measures the concept of frailty.

As seen in Section 1.2, the conceptual definition of frailty according to Fried and colleagues is ‘biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes’. The authors operationalised this concept adding five components: exhaustion, low physical activity, low walking speed, low grip strength, and weight loss (Chapter 2). The concept of frailty defined by Fried and colleagues and its operationalisation appear to be consistent as numerous studies have shown that the phenotype of frailty is well associated with biological phenomena (Section 2.4).

4.4 Concurrent validity

4.4.1 Materials and methods

Study population

Among 6,761 respondents at phase 9, 1,395 had missing data on frailty components. In order to have the same study population in Sections 4.4 and 4.5, 197 participants were further excluded as their hospitalisation data from the HES were not available for those living outside of England at the time of this work.

Predictor of interest

Individual components were categorised similarly to Fried and colleagues, as described in Section 2.4, in order to make comparable the prevalence of frailty in the Whitehall II study with that of CHS. However, as described below, some harmonisation was necessary as all components of frailty were not assessed in the Whitehall II study using protocols recommended by Fried and colleagues:

Exhaustion: this component was operationalised as in CHS based on two items drawn from the CES-D scale:[143] 'I felt that everything I did was an effort in the last week' and 'I could not get going in the last week'. If participants answered 'occasionally or moderate amount of the time (3-4 days)' or 'most or all of the time (5-7 days)' to either of these items, they were categorised as being exhausted.

Physical activity: participants reported habitual physical activity from a 20-item questionnaire on frequency and duration of participation in 'mildly energetic' (e.g., weeding, general housework, bicycle repair), 'moderately energetic' (e.g., dancing, cycling, leisurely swimming), and 'vigorous' (e.g., running, hard swimming, playing squash) physical activity.[199] Frequency and duration of each activity were combined to compute hours per week of physical activity. A compendium of activity energy costs was then used to assign each of the 20 physical activities assessed a metabolic equivalent (MET).[200] MET values reflected the intensity of each physical activity, 1 MET being approximately equal to the energy cost of lying quietly. Amount of time spent in activities

with MET values ranging from 3 to 6 was summed to allow calculation of total number of hours per week of moderate physical activity. Similarly, amount of time spent in activities with MET values of 6 or above (e.g., sports) was summed to allow calculation of total hours per week of vigorous physical activity. Using the existing derived variables on physical activity expressed in number of MET per week, a kcal energy expenditure was calculated using a formula from the Compendium of physical activity: Energy expenditure (kcals/week) = MET/week*weight.[200] This formula was then applied for each participant. Low levels of physical activity were denoted by an expenditure of < 383 kcal/week in men and < 270 in women.

Walking time/8-foot: this component is based on usual walking speed over a distance of 8 feet (2.4 meters). Three trials were performed and the maximum of the three scores was used for scoring purposes. Established thresholds to denote risk are based on results for a 15 feet (4.6 meters) walking test that incorporate physical stature as a proxy for stride length. Cut-offs for frailty for walking speed were calculated in order to keep the same magnitude (walking speed cut-off in the Whitehall II study = (8*walking speed cut-off in CHS)/15). Thus, participants were categorised as having slow walking speed when time to walk 8 feet was ≥ 3.73 seconds (for men (women) ≤ 173 (< 159) cm tall or ≥ 3.20 seconds (for taller men and women).

Grip strength: it was assessed with the participant's dominant/preferred hand using the Smedley's hand grip dynamometer, and measured in kilograms. A trained interviewer administered the test, and three trials were performed. The maximum of the three scores was used for scoring purposes. Frailty for grip strength was stratified by sex and BMI, using exact cut-offs given by Fried and colleagues. For men, low grip strength was denoted as: ≤ 29 kg (BMI ≤ 24 kg/m^2), ≤ 30 (BMI 24.1-28), and ≤ 32 (BMI > 28). For women, low grip strength was: ≤ 17 kg (BMI ≤ 23 kg/m^2), ≤ 17.3 (BMI 23.1-26), ≤ 18 (BMI 26.1-29), and ≤ 21 (BMI > 29).

Weight loss: no data were available to assess unintentional weight loss in the last year. Therefore, this component was based on data on weight change between phases 7 and 9. In the Whitehall II study, weight has been measured using a bioimpedance scale. Five-

year relative weight loss was calculated as: K = (weight at phase 7-weight at phase 9)/ weight at phase 7. If the value K was higher than 10% then the weight loss criterion for frailty definition was considered positive (and otherwise negative). The decision to use a higher cut-off than in CHS was based on the following reasons: (1) the period during which the change in weight was measured was longer; (2) weight loss is regarded as ineluctable with ageing even with recommended caloric intake,[201] and (3) in the Women's Health Aging Study-I, in which Fried is a principal investigator, researchers used a cut-off of 10% (Table 2.9).

Classification of frailty status: as in CHS, a total frailty score was calculated by allocating a value of 1 to each of the above component if presents, and 0, if absent, resulting in a range of 0 to 5. Participants were classified as 'frail' if they had at least three of the five frailty components, as 'pre-frail' if they had 1-2, and as 'non-frail' if they had none of these components.[16]

Appendix 3 presents the criteria used to define frailty in the Whitehall II study in comparison with CHS criteria and the percentage for each component of frailty. The match is reasonably good given the different age range of the cohorts.

Outcomes

Comorbidity: participants were asked if they had any longstanding illness, diseases or medical conditions for which they had sought treatment in the last 12 months. The list of diseases has been coded using the International Classification of Diseases version 10 (ICD-10).[202] Comorbidity was defined as self-reported two or more conditions.[16]

Disability: the World Health Organisation (WHO) defines disabilities as an 'umbrella term, covering impairments, activity limitations, and participation restrictions'.[203] Disability was usually estimated using two measurements: basic and instrumental activities of daily living (BADL and IADL) developed by Katz and colleagues and Lawton and Brody, respectively.[79,80]

Items included in these instruments slightly differed in the Whitehall II study compared to the original instruments. Therefore, the versions of BADL and IADL in the Whitehall II study were qualified as 'modified'. Appendix 4 shows these differences.

For both BADL and IADL, participants were asked if they had any difficulties with the listed everyday activities. For each domain of disability, if participants indicated that they had difficulties in one or more activities, they were considered as having BADL or IADL disability.[79,80]

Covariates

The selection of covariates was mostly based on Fried and colleagues' work.[204] They had been shown to be predictive of mortality in the CHS cohort:

Socio-demographic variables comprised the following: sex; age; self-reported ethnicity (White, non-White); education (none, lower secondary, A-levels, university or higher); the socio-economic position (SEP) variable used in this thesis was derived from the British occupational based social class:[205] the category 'high' or 'administrator' groups classes I and II, the category 'intermediate' or 'executive officer' classes IIIN, IIIM, IV, V, and the category 'low' or 'office support staff' class VI);[206] total household income in £/year (< 15,000, 15,000-< 25,000, 25,000-< 50,000, ≥ 50,000) from any source including wages or salary from work, savings or investments, rent or property, pensions, benefits and/or maintenance;[207] marital status (married/cohabitating, other); and number of close relatives and good friends.

Behavioural variables included the following: smoking status (none, stopped smoking before phase 1, stopped smoking during the follow-up between phases 1 and 9, current smoker); daily consumption of fruit and vegetables (yes, no); daily alcohol consumption in units per week; and physical activity (moderate and vigorous) in hours per week. Further details on the definition of the physical activity in the Whitehall II study are described above in this Chapter.

Clinical examination variables were body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and categorised using the WHO

classification:[208] < 25, 25-29.99, and ≥ 30 kg/m^2 (weight was measured to the nearest 0.1 kg on digital Soehnle electronic scales (Leifheit AS, Nassau, Germany) with the study participant in their underwear. Height was measured in bare feet to the nearest 1 mm using a stadiometer with the participant standing erect with head in the Frankfurt plane); systolic and diastolic blood pressure in millimetres of mercury; and mini-mental state examination (MMSE) to assess global cognitive function.

Medical variables included the following information: presence of diabetes mellitus, defined as reported doctor-diagnosed diabetes mellitus or use of diabetes medication; presence of CVD; previous history of hospitalisation, determined using the HES data; and, number of medications.

Statistical analyses

Description of variables

Each variable was described according to its characteristics: arithmetic means and standard deviations (SD) if quantitative variables had a normal distribution, medians and inter-quartile ranges (IQRs) if quantitative variables had not a normal distribution, or frequencies and proportions for qualitative variables.

Univariate analysis

Chi-square, Fisher's exact, Wilcoxon-Mann-Whitney, Cochrane-Armitage trend, and Student's t-tests were used accordingly. Agreement between frailty, comorbidity, and disability was assessed with Cohen's Kappa statistic.

Venn diagram

This diagram was drawn to visualise all possible relations between frailty, comorbidity, and disability.

Multivariable analysis

To determine the concurrent validity of the phenotype of frailty, separate logistic regression models[209] were performed to estimate the strength of association between frailty (frail, pre-frail and non-frail) and comorbidity (yes, no), and BADL/IADL (yes, no), and adjusting for sex and age. This model estimates odds ratios (ORs) and their 95% confidence interval (CI) expressing the strength of the association between an exposure and an outcome.

In logistic regression no assumptions are made about the distributions of the dependent variables. However, two points need to be considered: (1) covariates should not be highly correlated with one another because this can produce inaccurate estimates or the analysis may fail to converge, and (2) sufficient numbers in both categories of the outcome variable are required. Thus, the more covariates, the larger the sample size required.

Descriptive analyses and logistic regression models were performed using SAS version 9.1.

4.4.2 Results

Description of study population and missing data

Of 10,308 study members participating in phase 1, 5,169 were included in the present analysis. Compared with participants alive at phase 9 but excluded (owing to unknown vital status, non participation, missing data on the frailty scale, and living outside of England) (n=4,153), people in the analytic sample (n=5,169) were on average 0.7 years younger, less likely to be female (27.5% versus 39.7%) and of low socio-economic status (3.9% versus 12.4%).

Table 4.1 describes the characteristics of study population. The median age at phase 9 was 65.8 years and 72.6% were men.

Table 4.1. Characteristics of the 5,169 study participants

	N	% / mean (SD) or median (IQR)
Sex		
Men	3750	72.6
Women	1419	27.4
Age (years) in median (IQR)	5169	65.8 (60.9; 70.8)
Ethnicity		
White	4779	92.5
Non-White	390	7.5
Education		
No or lower secondary	2133	42.9
A levels	1334	26.8
University or higher	1509	30.3
Missing	193	-
Socio-economic position		
Low	515	10.0
Intermediate	2214	42.8
High	2440	47.2
Income £/year		
< 15,000	562	11.2
15,000-< 25,000	1097	21.8
25,000-< 50,000	2108	41.9
≥ 50,000	1265	25.1
Missing	137	-
Marital status		
Married/cohabiting	3870	76.0
Other	1223	24.0
Missing	76	-
Number of relatives and friends in median (IQR)	5079	6 (4; 10)
Smoking status		
Never	2688	52.5
Stopped before phase 1	1543	30.1
Stopped during follow-up	536	10.5
Current	356	6.9
Missing	46	-
Daily consumption of fruit and vegetables		
No	1127	21.8
Yes	4038	78.2
Missing	4	-
Daily alcohol consumption level (WHO)		
None	933	18.2
Not risky	3252	63.6

Risky	930	18.2
Missing	54	-
Alcohol consumption (units/week) in median (IQR)	5115	7 (2; 15)
Physical activity (hours/week) in categories		
< 2.5	2208	42.9
≥ 2.5	2940	57.1
Missing	21	-
Physical activity (hours/week) in median (IQR)	5148	3.0 (1.1; 5.6)
BMI (kg/m^2) in categories		
Normal (< 25)	1984	38.4
Overweight ([25-30[)	2214	42.8
Obese (≥ 30)	971	18.8
BMI (kg/m^2) in mean (SD)	5169	26.7 (4.4)
Systolic blood pressure status		
Hypotension/normal	2009	38.9
Prehypertension	2281	44.2
Hypertension	870	16.9
Missing	9	-
Systolic blood pressure (mmHg) in mean (SD)	5160	125.2 (16.1)
Diastolic blood pressure status		
Hypotension/normal	4220	81.8
Prehypertension	758	14.7
Hypertension	182	3.5
Missing	9	-
Diastolic blood pressure (mmHg) in mean (SD)	5160	70.9 (10.1)
MMSE score < 24		
No	5088	99.4
Yes	30	0.6
Missing	51	-
MMSE score in median (IQR)	5118	29 (28; 29)
Diabetes status		
No	3632	70.3
Yes	1537	29.7
Previous history of hospitalisation		
No	2073	40.1
Yes	3096	59.9
Number of medications in median (IQR)	5169	2 (1; 4)
Phenotype of frailty		
Non-frail	3029	58.6
Pre-frail	1993	38.6
Frail	147	2.8
Modified basic ADL ≥1		
No	4713	91.4
Yes	442	8.6

Missing	14	-
Modified instrumental ADL ≥1		
No	4490	87.1
Yes	665	12.9
Missing	14	-
Presence of comorbidity		
No	3382	65.4
Yes	1787	34.6
Hospitalisation after phase 9		
No	4019	77.8
Yes	1150	22.2
Death after phase 9		
No	5131	99.3
Yes	34	0.7
Unknown	4	-

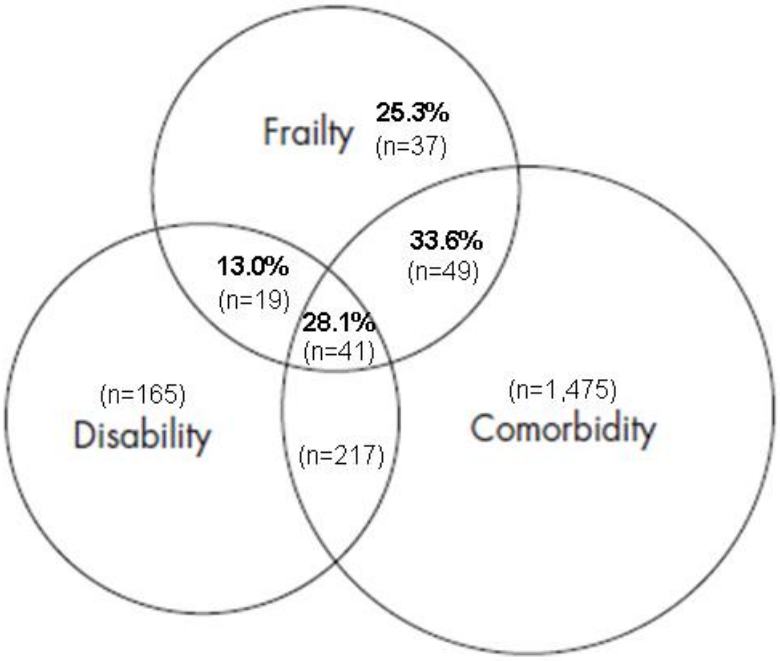
Association between frailty, disability and comorbidity

According to the phenotype of frailty, 2.8% (n=147) of participants were classified as frail, 38.6% as pre-frail, and 58.6% as non-frail. Overall, 8.6% were considered as BADL disabled and 34.6% had comorbidity (Table 4.1). Kappa coefficients was 0.04 (95% CI: 0.03, 0.06) between frailty and comorbidity, 0.17 (95% CI: 0.13, 0.21) between frailty and basic ADL, and 0.11 (95% CI: 0.09, 0.13).

Venn diagram

Overall, 61.1% of participants had none of these conditions. For 38.9% (n=2,003) of those who had at least one of these conditions, a Venn diagram was drawn to represent the extent of overlap of frailty with disability and comorbidity (Figure 4.1). Among those who were frail, 25.3% had neither disability nor comorbidity, 13.0% had disability, 33.6% had comorbidity, and 28.1% had both disability and comorbidity.

Figure 4.1. Association between frailty, disability and comorbidity



Total represented: 2,003 participants who were frail or disabled, or had comorbidity.

Univariate analysis

Tables in Appendices 5, 6, and 7 display results of univariate associations between participants' characteristics (socio-demographic, behavioural, clinical examination, and medical) and frailty, comorbidity, and BADL disability, respectively. Table in Appendix 8 summarises results from these appendices. These tables show that globally the three conditions – frailty, disability, and comorbidity – were associated with same covariates. Those who were frail, disabled or had comorbidity, compared to those without these conditions, were more likely to be women, older, non-White, in a lower socio-economic position, not married or not in partnership, ex-smokers (stopped smoking during the follow-up); have a low daily consumption of fruit and vegetables, low consumption of alcohol, low physical activity, high BMI, diabetes (for frailty and disability), a history of

a previous hospitalisation, and been treated with a higher number of drugs. Low MMSE score, indicating poor cognitive function, was more strongly associated with frailty than with other conditions.

Multivariable analysis

Appendix 9 displays the association between frailty and modified basic and instrumental ADL and comorbidity. Sex- and age-adjusted results show that, in comparison with the non-frail group, the pre-frail and frail groups were 2.2 to 13.9 times more likely to be disabled and 1.4 to 3.2 times more likely to have comorbidity.

4.4.3 Discussion

The prevalence of frailty in the Whitehall II study, according to the phenotype of frailty was 2.8%. This is low compared to that found in the CHS (6.9%),[16] in the Hertfordshire Cohort Study (6.3%),[210] in the English Longitudinal Study of Ageing (approximately 8%).[140] The low prevalence of frailty in the Whitehall II cohort may be mainly explained by the younger age (range 55 to 79 years) of participants compared to that of other studies (≥ 64 years) and the fact that Whitehall II is an occupational cohort. Selection on the basis of being fit enough to work is likely to mean that this cohort was healthier at baseline than the general population. Furthermore, the harmonisation of measurements to match those in previous studies may have been imperfect leading to imprecise determination of frailty prevalence.

Consistent with the literature,[138,152,153,211] in the Whitehall II study, socio-demographic variables were associated with frailty. Although frailty was highly correlated with comorbidity and disability, over 25% of frail participants were without comorbidity/disability. This provides some support for the hypothesis that frailty captures other characteristics unrelated to these conditions.

Criterion validation (e.g., concurrent validation examined here) is the correlation of a scale with some other measure of the trait or disorder under study, ideally, a gold standard which has been used and accepted in the field. Whereas construct validity is used when such a gold standard does not exist; in this case, we relate the new measure – frailty– to a

similar construct. Although their theoretical definitions are clear, their applications appear to be confusing. For example, Fried and colleagues[16] and Gobbens and colleagues[120] tested the concurrent validity of their frailty instruments against adverse health outcomes such as disability and comorbidity. In this thesis, I have followed these examples, which may be questionable. This confusion is also reported in the literature.[106]

4.5 Predictive validity

4.5.1 Materials and methods

Study population

Analytic sample used in this Chapter was the same as in Section 4.4.

Predictor of interest

Frailty status (frail, pre-frail, and non-frail) is defined in Section 4.4.1.

Outcomes

Definitions of mortality (yes, no) and hospitalisation (yes, no) were provided in Section 3.4.

Covariates

The following variables had been used as covariates: sex, age, ethnicity, educational level, socio-economic position, income/year, number of relatives and friends, alcohol status, physical activity, BMI, systolic blood pressure, diastolic blood pressure, MMSE, diabetes status, previous history of hospitalisation, and number of medications. They were described in Section 4.4.1.

Statistical analyses

Univariate analysis

As mortality and hospitalisation are time-to-event data, Kaplan-Meier method[212] and log-rank test[213] were used to determine the difference in survival curves between frailty and mortality and hospitalisation. Time-to-event data comprised following characteristics: (1) case status: death (yes, no), hospitalisation (yes, no); (2) start date: date of phase 9 examination; (3) end date for cases: date of death or date of hospitalisation, for non-cases: January 31, 2010; and (4) duration of follow-up was calculated in months as end date minus start date.

Multivariable analysis

Multivariable survival analyses were performed using the Cox proportional hazards model.[214] Violations of proportional hazards assumptions were explored. This model estimates hazard ratios (HRs) and their 95% CIs expressing the strength of the association between an exposure and a time to event data.

Predictive validity of frailty for mortality was examined after adjustment for sex and age only because of a low number of deaths (n=34).

For hospitalisation, three potential predictors were studied: frailty, disability, and comorbidity performing three following models: model 1: sex and age adjusted; model 2: frailty, comorbidity, and disability were each adjusted for covariates that were associated with hospitalisation with a p-value of 0.20 or less; and, model 3 included frailty, comorbidity, and disability together with the covariates in model 2. Potential interaction terms – frailty*sex, frailty*age, frailty*disability, and frailty*comorbidity – in hospitalisation had p-values > 0.05 negating any necessity to stratify the analyses by sex, age, disability, or comorbidity. The proportional hazards assumption for the Cox model was verified for the phenotype of frailty graphically (1) observing Kaplan-Meier curves (parallel curves were expected) (see below) and (2) log(-log(survival)) versus log of survival time graph (parallel lines were expected) (Appendix 10). This assumption was also tested including in the model a time-dependent covariate frailty*log(follow-up). As the time-dependent variable was not significant (p-value=0.12), this supported the assumption of proportional hazard.

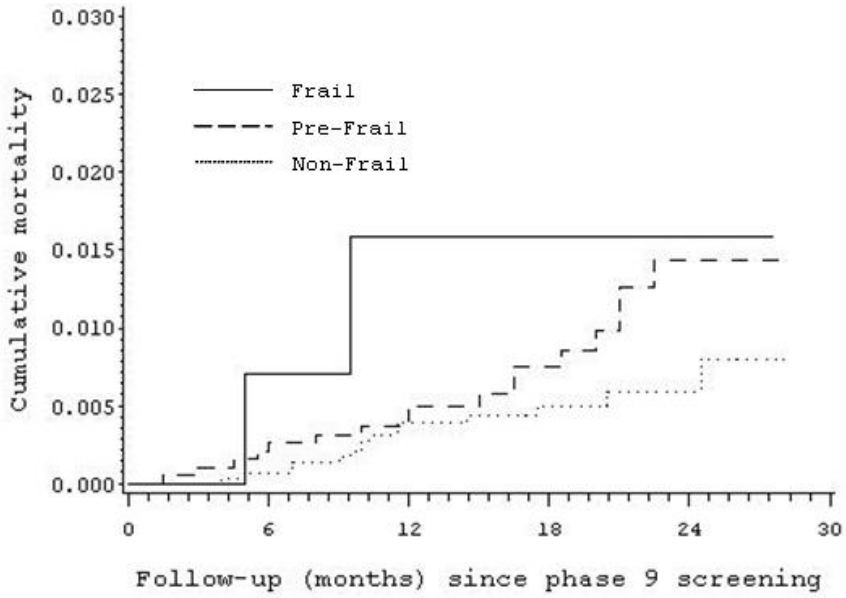
Kaplan-Meier method, log-rank test, and Cox proportional hazards models were performed using SAS version 9.1.

4.5.2 Results

Mortality

After phase 9 examination until January 31, 2010, with a median follow-up of 17.5 months (SD=6.1), 34 (0.7%) participants died (Table 4.1). Unadjusted survival curves showed that frail participants were more likely to die within less than 1 year after phase 9 examination compared to those who were pre-frail or non-frail (Figure 4.2) but this difference did not the statistical significance (log-rank test, p=0.13). After adjusting for sex and age, those who were frail were 4.6 times more likely to die than non-frail participants (Table 4.2).

Figure 4.2. Kaplan-Meier curves showing probability of death according to frailty status



Numbers at risk

Frail: 3-5 components	147	132	93	65	25	-
Pre-frail: 1-2 components	1990	1902	1549	1008	388	-
Non-frail: 0 component	3028	2945	2506	1525	546	-

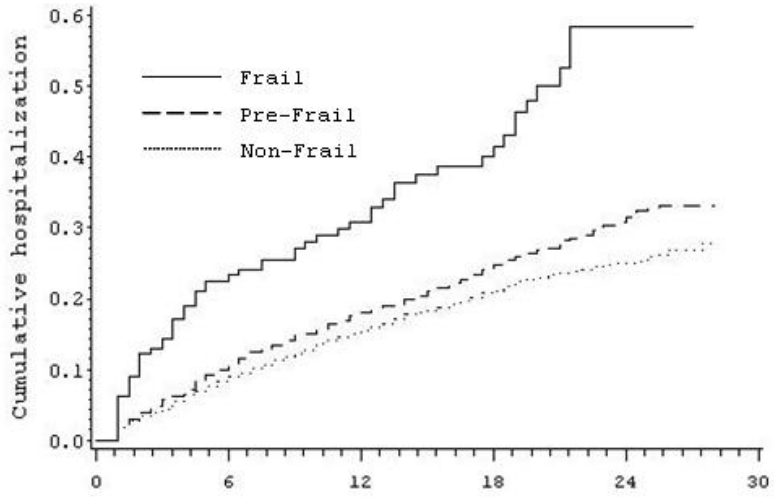
Table 4.2. HRs (95% CIs) for mortality according to the frailty status with a maximum follow-up time of 30 months

	Mortality n(event)=34		
	HR	**95% CI**	**p-value**
Sex and age adjusted			
Frailty			
Non-frail (n=3028)	1	--	--
Pre-frail (n=1990)	1.39	0.68-2.86	0.37
Frail (n=147)	4.64	1.51-14.26	0.007

Hospitalisation

After phase 9 examination until January 31, 2010, 22.2% had been hospitalised at least once (Table 4.1), with a median follow-up of 15.2 months (SD=7.1). Kaplan-Meier curves showed that frail or pre-frail participants were more likely to be hospitalised than non-frail participants after phase 9 examination (Figure 4.3).

Figure 4.3. Kaplan-Meier curves showing probability of hospitalisation according to frailty status



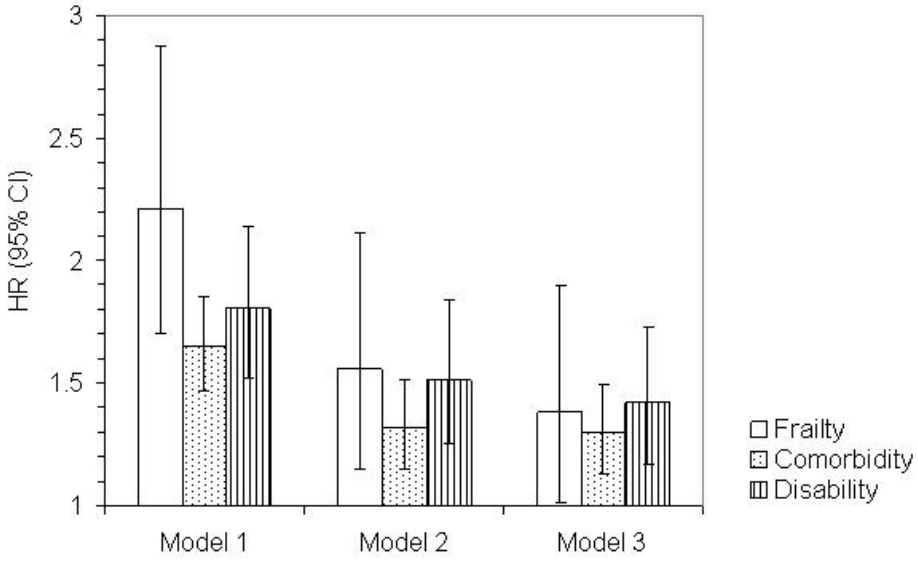
Numbers at risk						
Frail: 3-5 components	147	103	66	38	7	-
Pre-frail: 1-2 components	1993	1697	1226	737	231	-
Non-frail: 0 component	3029	2681	2042	1124	354	-

In univariate analysis, variables associated with hospitalisation with p-values ≤ 0.20 were: sex, age, ethnicity, educational level, socio-economic position, income/year, number of relatives and friends, alcohol consumption, daily consumption of fruit and vegetables, physical activity, BMI, systolic blood pressure, diastolic blood pressure, MMSE, diabetes status, previous history of hospitalisation, and number of medications (Appendix 11).

In age- and sex-adjusted analyses, with the non-frail group as the referent, the frail group had an elevated HR for hospitalisation of 2.40 (95% CI: 1.83, 3.14) while for the pre-frail group it was 1.20 (95% CI: 1.06, 1.35).

High risk of hospitalisation among frail participants persisted after multivariable adjustment (model 2), even after entering in the model comorbidity and disability data (model 3, see Figure 4.4 and Appendix 12).

Figure 4.4. HRs (95% CIs) for hospitalisation according to frailty, comorbidity, and disability status, with a maximum follow-up time of 30 months



Model 1: Adjusted for sex and age.
Model 2: Adjusted for the predictors (frailty, comorbidity, or disability) and the covariates (sex, age, ethnicity, educational level, socio-economic position, income/year, number of relatives & friends, daily consumption of fruits and vegetables, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, mini-mental state examination, diabetes status, previous history of hospitalisation, and number of medications).
Model 3: As model 2 with frailty, comorbidity, and disability mutually adjusted.

4.5.3 Discussion

The findings on concurrent and predictive validity suggest that the phenotype of frailty is a reasonably valid instrument. Results from the concurrent validity showed that frailty was strongly associated with disability, assessed using the modified basic and instrumental ADL, and moderately associated with comorbidity, with respective sex and age-adjusted ORs of 10.3, 13.3 and 2.8. Kiely and colleagues[98] in the MOBILIZE Boston study compared cross-sectional association between disability and frailty measured using the criteria from the study of osteoporotic fractures (SOF)[116] with that of CHS.[16] In a fully adjusted model, they showed that frail participants were 5.4 and 7.7 times more likely to be disabled according to the instrumental ADL definition, in SOF and CHS studies, respectively.

In prospective analyses, the phenotype of frailty was found to predict hospitalisation and the strength of prediction (RR=1.33) was similar to that of basic ADL disability (RR=1.33) and comorbidity (RR=1.25) in a mutually adjusted model. The strength of the prediction was also similar to that found in several other studies: in CHS, it was 1.29;[16] and in the Three-City Study, the corresponding OR was 1.36.[96] In the MOBILIZE Boston study, a stronger association was reported (RR=3.54)[98] whereas in the Women's Health and Aging Studies no association between frailty and hospital admissions was observed (RR=0.67; 95% CI: 0.33; 1.35).[75] In longitudinal studies on frailty, ADL disability is regarded as an adverse outcome of frailty,[16,96,139,215] but researchers seldom distinguish between measurements of frailty, disability and comorbidity.[61] Compared with other studies, the strength of this present work is to be able to adjust for disability and comorbidity in the prediction of hospitalisation by the phenotype of frailty.

These findings provide some justification for the use of this instrument in further analyses in this thesis.

5 Reliability of the phenotype of frailty in the Whitehall II study

5.1 Introduction

Reliability is defined in Chapter 2. Briefly, reliability refers to the consistency of a measure. A measure is reliable if it gives consistent results under consistent conditions. There are several types of reliability.[106] Two types of reliability can be assessed in the Whitehall II study: internal consistency and test-retest reliability. Internal consistency reliability assesses how a set of items are closely related as a group. Test-retest reliability assesses the degree to which test scores are consistent from one test administration to the next.

5.2 Objective

The specific objective addressed in this Chapter is to assess internal consistency and test-retest reliability of the phenotype of frailty in the Whitehall II study.

5.3 Materials and methods

Internal consistency reliability

Study population

Analytic sample used in this Section was described in Chapter 4 (n=5,169).

Statistical analysis

Internal consistency is assessed with Cronbach's alpha. This coefficient represents the average inter-item correlation. As the average increases, Cronbach's alpha increases as well. A reliability coefficient of 0.70 or higher is considered 'acceptable'.[216] The standardised Cronbach's alpha was calculated by the software SAS 9.1.

Test-retest reliability

Study population

After the clinic visit at phase 9, two percent of participants, selected at random from the clinic appointments schedule, were asked to have repeated examinations within 30 days of the visit. Of the 5,169 participants examined in Chapter 4, data from the repeated examinations were available for 182 of them.

Statistical analysis

Because completion of a health survey questionnaire was not requested during the second visit, it was not possible to assess fully the reliability of the phenotype of frailty measure. Thus, its reliability has been approximately evaluated with the following three components – walking speed, grip strength, and weight – measured during the repeated examination. Components measured during the first visit were called 'test' and during the second visit 're-test'. The agreement between test and re-test measures was examined using the Bland-Altman plot.[217] This plot is a graphical method to compare two repeated measures. This is a scatter plot of mean of measurements and the differences plotted on the vertical axis which shows the amount of disagreement between 2 measures. Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the SD of the differences. The presentation of the 95% limits of agreement is for visual judgment of how well two methods of measurement agree.

5.4 Results

Cronbach's alpha

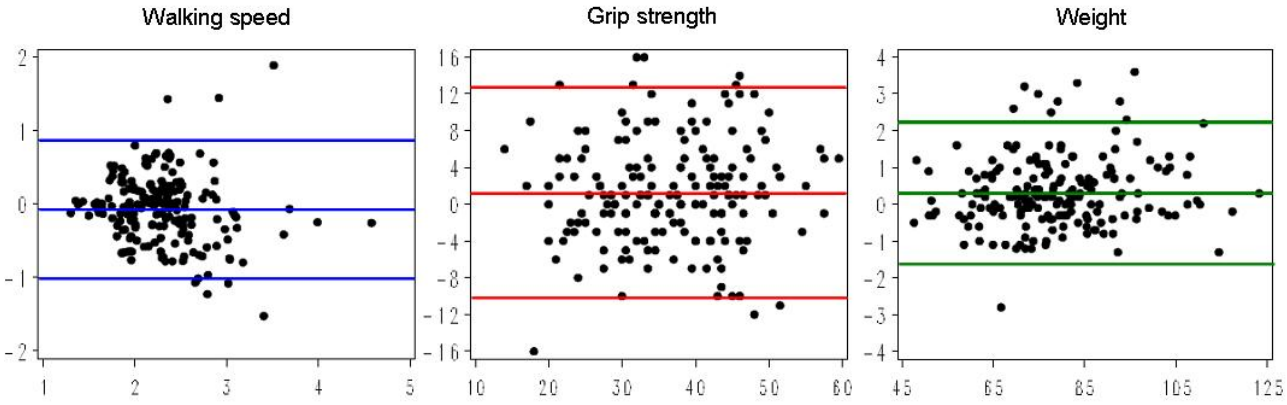
The standardised Cronbach's alpha coefficient was 0.28. This coefficient is low compared with the threshold of an acceptable scale (0.7).

Bland-Altman plot

The distribution of walking speed, grip strength, and weight of test and retest measures was normal (Appendix 13). Agreement between the test and retest values of these components was evaluated by the Bland-Altman approach and shown in Figure 5.1. For these three components, more than 95% of the differences between the test-retest

measures were approximately within the limits of agreement. Number of values outside of the 95% limits was expected to be 9 or less (182 participants * 0.05) and this was the case. In addition, the variability was approximately random and uniform along the range of values.

Figure 5.1. Bland-Altman plots



5.5 Discussion

Internal consistency of the phenotype of frailty was low when compared to psychometric scales measuring a unidimensional concept. The low level of internal consistency was not surprising given that the phenotype of frailty is expected to include multiple items which are heterogeneous, reflecting the complexity of frailty phenomenon.[218] Therefore, a weak internal consistency found in this study should not be regarded as an indication of poor reliability. In fact, the estimation of the internal consistency reliability here was not necessary.

Regarding the test and re-test reliability, as the 95% of differences between test and re-test measures were included within the limits of agreement, walking speed, grip strength, and weight components have been reliably measured.

6 Phenotype of frailty: composite versus single measurements in the Whitehall II study

6.1 Introduction

While it is assumed that the measurement of frailty needs to include multiple components, these may overlap. Using fewer components would be more time- and cost-efficient. Although studies using the phenotype of frailty have generally shown that the greater the number of frailty components used the higher the risk of a given adverse health outcome,[16,75,96,116,193,219] it remains unclear whether all components of the scale contribute to associations with health outcomes or whether some of them are redundant.

6.2 Objectives

Specific objectives addressed in this Chapter were:

i. to test whether the association between the phenotype of frailty and hospitalisation was greater than that of any single component of measure or the additive risk associated with combination of components

ii. to compare the prediction accuracy of multi-component measures of frailty for total hospitalisations with a single-component measure

6.3 Materials and methods

Study population

For the current analyses, the flow of participants through the study is the same as depicted in Chapter 4 (n=5,169).

Exposure and outcome

Exposure variables were the phenotype of frailty and its five individual components described in Section 4.4.1. The outcome variable of interest was hospitalisation.

Statistical analysis

Univariate analysis examining association between participants' characteristics and the phenotype of frailty and its individual components and hospitalisation was performed using Wilcoxon-Mann-Whitney and Chi-square tests and Cochrane-Armitage trend.

Following strategies were adapted for the analyses to respond to the objectives of this Chapter.

First, having ascertained that the proportional hazards assumptions had not been violated, HRs and accompanying 95% CIs for the associations of frailty (and its individual components) with all hospitalisations combined were computed using Cox proportional hazard regression models.[214]

In order to explore whether a single component was responsible for generating the association between the overall frailty scale and the risk of hospitalisation, the cumulative effect of frailty markers in the prediction of hospitalisation was studied by creating a frailty score ranging from 0 (no frailty) to 5. Then, the effect of number and combinations of frailty components on the risk of hospitalisation in two separate models was examined.

A subgroup analysis was conducted among study participants who were negative for a given frailty component to estimate cumulative effects (0 to 4) of other frailty components in the prediction of adverse health outcomes. In all analyses, the reference group was that with no apparent frailty.

To evaluate the predictive power for each individual component and the full frailty scale, Harrell's C concordance statistic was calculated,[220] an equivalent to the area under the curve (AUC) statistic for receiver-operating characteristic (ROC) in survival model. It estimates the concordance between the predicted failure order of a pair of subjects and the observed order. Analytic sample was split into 'derivation' and 'validation' datasets of equal size after stratification by age and sex. Then age- and sex- adjusted models were fitted in the derivation dataset and the performance of the models was evaluated in the validation dataset.[221]

Descriptive analyses and Cox proportional hazards models were performed using SAS version 9.1. Calculations of Harrell's C concordance statistic were performed using Stata version 10.

6.4 Results

Study participants and missing data

In Table 6.1, baseline characteristics of study members according to hospitalisation were reported. Of the 5,169 participants, 22.3% had at least one hospitalisation episode during the follow-up (range 0.03 to 28.13 months; mean=15.17). In comparison with non-hospitalised participants, hospitalised participants were more likely to be older, positive for each frailty components, and classified as frail or pre-frail.

Table 6.1. Baseline characteristics of the 5,169 study participants according to hospitalisation during follow-up

	Hospitalisation n (%)		P-value[a]
	No	Yes	
N	4019	1150	
Age in years (mean (SD))	65.4 (5.8)	67.2 (6.0)	<0.0001
Women	1104 (27.5)	315 (27.4)	0.96
Frailty components			
Exhaustion	402 (10.0)	152 (13.2)	0.002
Low physical activity	875 (21.8)	301 (26.2)	0.002
Slow walking speed	340 (8.5)	163 (14.2)	<0.0001
Low grip strength	373 (9.3)	139 (12.1)	0.005
Weight loss	135 (3.4)	54 (4.7)	0.03
Frailty status			<0.0001
Non-frail	2415 (60.1)	614 (53.4)	
Pre-frail	1517 (37.8)	476 (41.4)	
Frail	87 (2.1)	60 (5.2)	

[a] P-value for heterogeneity except for frailty status where P-value is for trend

Association between single components of frailty and future risk of hospitalisation

Table 6.2 shows the association between individual frailty components and the risk of hospitalisation. All five components were related to hospitalisation, with the age- and sex-adjusted HRs ranging from 1.18 (95% CI: 0.98, 1.41) for grip strength to 1.60 (95% CI: 1.35, 1.90) for walking speed. Some attenuation was apparent following adjustment for other components but the rank order of the strength of association remained unchanged.

Table 6.2. HRs (95% CIs) for the association of individual frailty components with hospitalisation (n=5,169)

	Hospitalisation N (%)		HR [95% CI] Sex- and age- adjusted	HR [95% CI] Fully-adjusted[a]
	No	Yes		
Exhaustion				
No	3617 (90.0)	998 (86.8)	1 (ref)	1
Yes	402 (10.0)	152 (13.2)	1.38 [1.17, 1.64]	1.30 [1.10, 1.55]
Low physical activity				
No	3144 (78.2)	849 (73.8)	1	1
Yes	875 (21.8)	301 (26.2)	1.26 [1.10, 1.44]	1.19 [1.04, 1.36]
Slow walking speed				
No	3679 (91.5)	987 (85.8)	1	1
Yes	340 (8.5)	163 (14.2)	1.60 [1.35, 1.90]	1.52 [1.28, 1.80]
Low grip strength				
No	3646 (90.7)	1011 (87.9)	1	1
Yes	373 (9.3)	139 (12.1)	1.18 [0.98, 1.41]	1.07 [0.89, 1.28]
Weight loss				
No	3884 (96.6)	1096 (95.3)	1	1
Yes	135 (3.4)	54 (4.7)	1.41 [1.07, 1.86]	1.34 [1.02, 1.77]

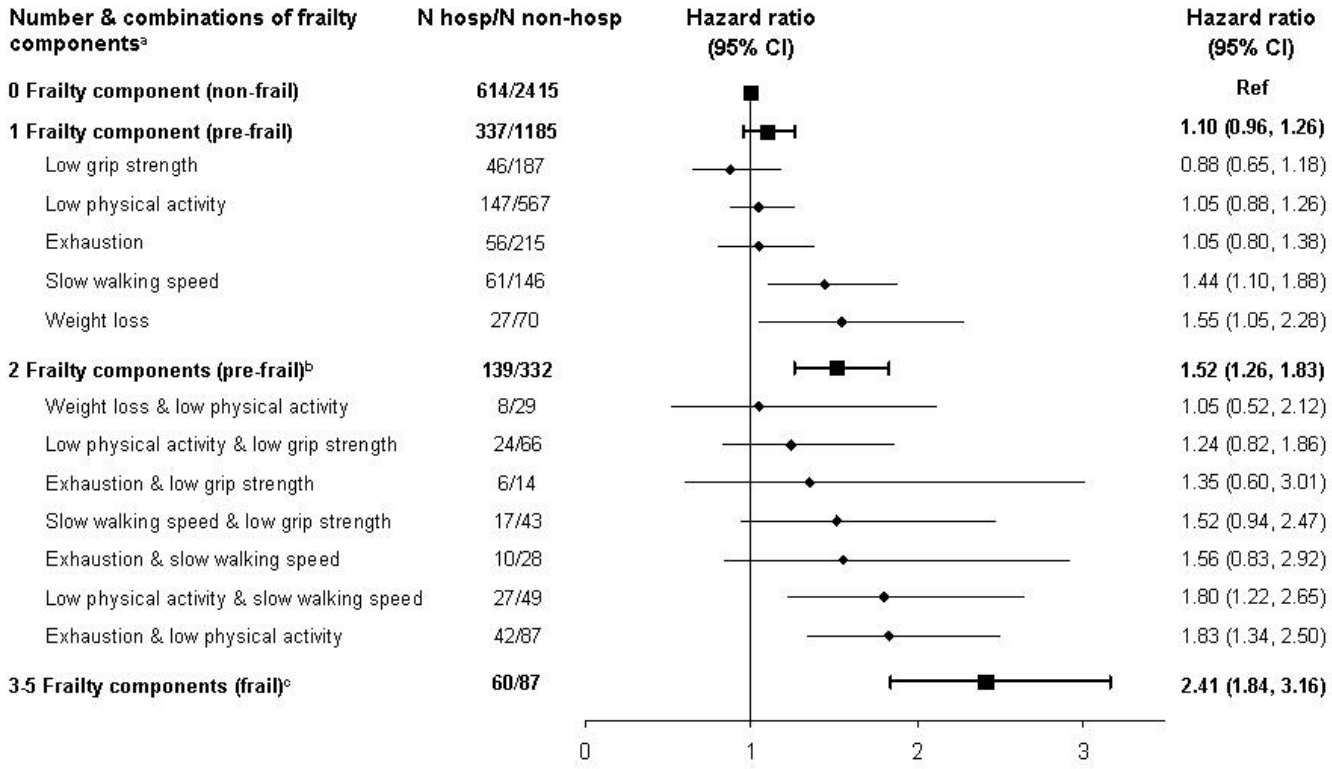
[a] Adjustment for sex, age, exhaustion, physical activity, walking speed, grip strength, and weight loss

Cumulative effect of frailty markers and the risk of hospitalisation

Figure 6.1 shows a dose-response relationship between the risk of hospitalisation and the number frailty components: the HRs for hospitalisation ranged from 1.10 (95% CI: 0.96, 1.26) (any single frailty component) to 2.41 (95% CI: 1.84, 3.16) (3-5 frailty components). Figure 6.1 also displays HRs and their 95% CIs for hospitalisation according to different combinations of indicators included in the frailty scale when the scores were less than 3. Among study members with one frailty component only, the strength and the rank of association of each separate frailty component was largely similar to those reported in Table 6.2 where this estimation was carried out among the study participants with a frailty score of one or more. When examining the possible

combinations of 2 items from the frailty scale, there were very few study members with weight loss; therefore, three combinations were not represented. Two (low physical activity and slow walking speed; exhaustion and low physical activity) of a possible 10 combinations of those with 2 frailty indicators had very similar and strong associations (HRs ranging from 1.80 to 1.83) with hospitalisation.

Figure 6.1. HRs (95% CIs) for the association of combinations of frailty components with subsequent hospitalisation



[a] Results from 2 models: one with different combinations included in the model (diamonds); the other one with number of frailty components included in the model (squares). All analyses were adjusted for age at baseline and sex. The reference group was those with no frailty component.

[b] Three combinations were not reported owing to too few hospitalizations: weight loss & slow walking speed (n=0), weight loss & exhaustion (n=2), and weight loss & low grip strength (n=3).

[c] Owing to low numbers, participants with 3 to 5 frailty components were collapsed.

Table 6.3 presents the results of the association between the number of frailty components with the risk for hospitalisation stratified by the presence of individual frailty components. Within each stratum, a dose-response association between the frailty score and the risk for hospitalisation was still observed.

Table 6.3. HRs (95% CIs) for the association of number of frailty components with hospitalisation, stratified by individual components

	N hosp	N non-hosp	HR [95% CI]		N hosp	N non-hosp	HR [95% CI]
Exhaustion =No	998	3617		Exhaustion =Yes	152	402	
0	614	2415	1 [Ref]	0	56	215	1 [Ref]
1	281	970	1.11 [0.96, 1.28]	1	60	136	1.62 [1.12, 2.33]
2	79	196	1.40 [1.10, 1.77]	2	24	39	2.30 [1.41, 3.74]
3-4	24	36	2.09 [1.39, 3.16]	3-4	12	12	3.72 [1.97, 7.01]
P for trend			0.0001	P for trend			<0.0001
Low PA =No	849	3144		Low PA =Yes	301	875	
0	614	2415	1 [Ref]	0	147	567	1 [Ref]
1	190	618	1.14 [0.96, 1.34]	1	101	231	1.52 [1.17, 1.96]
2	38	101	1.40 [1.01, 1.96]	2	41	64	2.25 [1.58, 3.21]
3-4	7	10	2.22 [1.05, 4.69]	3-4	12	13	3.61 [2.00, 6.55]
P for trend			0.005	P for trend			<0.0001
Slow WS =No	987	3679		Slow WS =Yes	163	340	
0	614	2415	1 [Ref]	0	61	146	1 [Ref]
1	276	1039	1.05 [0.91, 1.21]	1	54	124	1.13 [0.78, 1.63]
2	85	208	1.47 [1.17, 1.85]	2	36	57	1.52 [1.00, 2.30]
3-4	12	17	2.58 [1.46, 4.57]	3-4	12	13	2.46 [1.32, 4.58]
P for trend			0.0004	P for trend			0.004
Low GS =No	1011	3646		Low GS =Yes	139	373	
0	614	2415	1 [Ref]	0	46	187	1 [Ref]
1	291	998	1.15 [1.00, 1.32]	1	50	128	1.58 [1.06, 2.36]
2	89	204	1.61 [1.29, 2.02]	2	33	49	2.56 [1.63, 4.01]
3-4	17	29	2.48 [1.52, 4.03]	3-4	10	9	4.93 [2.47, 9.84]
P for trend			<0.0001	P for trend			<0.0001
Weight loss =No	1096	3884		Weight loss =Yes	54	135	
0	614	2415	1 [Ref]	0	27	70	1 [Ref]
1	310	1115	1.08 [0.94, 1.23]	1	13	45	0.69 [0.35, 1.35]
2	126	287	1.59 [1.31, 1.92]	2	10	13	2.09 [0.99, 4.39]
3-4	46	67	2.33 [1.72, 3.16]	3-4	4	7	1.54 [0.53, 4.49]
P for trend			<0.0001	P for trend			0.19

PA: physical activity; WS: walking speed; GS: grip strength.

Predictive power of single- and multi-component measures for hospitalisation

Harrell's C concordance statistic for individual frailty components and the full frailty scale varied very little: 0.57 (95% CI: 0.55, 0.60) for grip strength and 0.58 (95% CI: 0.56, 0.61) for exhaustion and the full frailty scale. The difference of Harrell's concordance indices between pairs of individual components and the full scale was not statistically significant at conventional levels (all p-values > 0.06; Table 6.4).

Table 6.4. Performance of models in the prediction for hospitalisation including individual components and the phenotype of frailty

Model	Harrell's c statistic [95% CI]	P-value[a]
M1: Age, sex	0.574 [0.549, 0.600]	0.196
M2: M1 + exhaustion (yes/no)	0.583 [0.558, 0.607]	0.401
M3: M1 + low physical activity (yes/no)	0.579 [0.554, 0.605]	0.903
M4: M1 + slow walking speed (yes/no)	0.578 [0.553, 0.604]	0.841
M5: M1 + low grip strength (yes/no)	0.573 [0.548, 0.598]	0.056
M6: M1 + weight loss (yes/no)	0.575 [0.549, 0.600]	0.236
M7: M1 + Fried frailty scale (3-5 versus 0-2)	0.579 [0.554, 0.604]	Ref

[a] P-value comparing the predictive values of M1 to M6 with M7.

6.5 Discussion

The main objective of this study was to examine whether the five components included in the phenotype of frailty scale were equally related to the risk of hospitalisation or whether one single component, or a combination, had the same utility as the full scale.

Although the dose-response relationship between the number of frailty components and the risk of adverse health outcomes[16,75,96,116,193,219] has been previously described, the present results add some novel findings to this literature. First, all five frailty components – exhaustion, low physical activity, slow walking speed, low grip strength, and weight loss – were found to be independently associated with hospitalisation with none of them being redundant. Thus, these analyses support the hypothesis that several components are required to measure frailty.[16,104] These results are also consistent with those from a

previous study[149] where the authors found that slow walking speed was the strongest, and low grip strength the weakest predictor of hospitalisation.

Second, the predictive performance of the individual frailty components was tested and compared with that of the full frailty scale. Harrell's C concordance statistic varied between 0.57 and 0.58 (0.50 indicates that the prediction does not differ from chance), suggesting that neither the components nor the full scale were adequate prediction tools for hospitalisation in the clinical settings.

Third, the absence of difference in predictive performance between individual components and the full scale suggest that measuring only one component of frailty might enable an equally precise prediction of hospitalisation as the full scale, although other analyses conducted in this study did not support this conclusion. Importantly, findings in this Chapter showed that within the group of individuals with a frailty component, those who additionally had other frailty components were up to 4.9 times more likely to experience hospitalisation at follow-up compared with those with no additional frailty components. Thus, the frailty measure seems to stratify risk even within the group of individuals with an individual frailty component.

7 Predictive validity of CVD risk algorithms for frailty in the Whitehall II study

7.1 Introduction

There is increasing evidence to suggest that CVD risk factors measured in midlife predict, in addition to CVD endpoints, a wide range of old-age health outcomes. These include cognitive decline and dementia,[222,223] late-life depression,[224-226] disability,[227] and cancer.[228-231] Although few large-scale prospective studies have examined the association between CVD risk factors and frailty, such a link is plausible for at least two reasons. First, several studies have shown a cross-sectional association between CVD and frailty.[75,77] In one cross-sectional study, subclinical CVD diagnosed using non-invasive testing (carotid ultrasound, ankle-arm index, electrocardiography, echocardiography, and cerebral magnetic resonance imaging) was related to frailty after excluding clinically diagnosed CVD.[60] Second, several individual risk factors included in multi-factorial prediction algorithms of CVD, such as the Framingham score, have been associated with frailty status: high blood pressure,[232] diabetes,[76,232] low HDL cholesterol level,[233,234] and cigarette smoking.[15] In this Chapter, I hypothesised that CVD risk scores would be associated with subsequent frailty. If supported, such an observation would have considerable utility for frailty in clinical practice where such CVD risk scores are routinely administered.

7.2 Objective

The specific objective addressed in this Chapter was to test whether CVD risk scores used to assess 10-year risk of CVD would be associated with subsequent frailty in people without diagnosed CVD at baseline.

In this Chapter, four CVD risk algorithms were investigated: the American Framingham CVD,[235] CHD,[236] and stroke[237] risk scores, and the European SCORE (Systematic Coronary Risk Evaluation).[238]

7.3 Materials and methods

Study population

CVD risk factors measured at phase 5 were utilised to assess the risk of developing frailty at phase 9 when frailty components were first measured.

Outcome of interest

Outcome was the phenotype of frailty as described in Section 4.4.1.

CVD risk factors at baseline

Individual CVD risk factors included in the CVD risk scores were measured as follows:

Total cholesterol was determined by an enzymatic procedure using the automated CHOD-PAP method.

Serum HDL-cholesterol concentrations were measured from the supernatant after precipitation of non-HDL-cholesterol with phosphotungstate.

Systolic blood pressure was measured twice with the Hawksley random zero sphygmomanometer in the sitting position after five minutes' rest. The average of the two readings was used in the present analyses.

Participants reported the medications used in the previous 14 days; responses were coded using the British National Formulary codes.[239] Antihypertensive therapy was based on the use of the following drugs: diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and other antihypertensive drugs.

Current smoking (yes, no) was ascertained by self-report.

Prevalent diabetes mellitus was defined based on reported doctor-diagnosed diabetes mellitus or use of diabetes medication, or when participants had a baseline fasting plasma glucose level greater than 126 mg/dL (> 7.0 mmol/L).[240]

Presence of atrial fibrillation and left ventricular hypertrophy was determined on the electrocardiograms (ECG) using the Minnesota Code:[241] atrial fibrillation is coded as 8-3-1 and left ventricular hypertrophy as 3-1-0.

CVD risk scores at baseline

Four CVD risk score algorithms – the Framingham CVD,[235] CHD,[236] stroke[237] prediction models, and SCORE[238] – were estimated according to the literature. The table in Appendix 14 summarises all components included in the models.

The distribution of the probability of CVD of these algorithms is shown in Appendix 15.

Cardiovascular disease

CVD were classified as non-fatal CHD and stroke, and non-fatal CVD.

Non-fatal CHD events: CHD diagnoses included ischemic heart diseases (international classification of diseases version 9 (ICD-9) codes 410–414 or ICD-10 codes I20–I25)[202,242] which included non-fatal myocardial infarction (MI), angina pectoris, and other forms of ischemic heart disease. Information on non-fatal MI and angina was obtained from several sources. From 1989 onwards the British NHS Hospital Episode Statistics (HES)[198] database has provided reports of participants' diagnoses on discharge and procedure codes for all NHS hospitals in England and Wales. Participants also self-report CHD events in the Whitehall II health survey questionnaires. These are then validated using the study resting electrocardiograms, the HES database, and by contacting general practitioners for confirmation when no other external source exists.

Non-fatal stroke events: non-fatal stroke included first subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and not specified stroke (ICD-10 codes I60–I64), and transient cerebral ischemic attacks (ICD-10 codes G45). The cases were ascertained from participants' general practitioners, information extracted from hospital medical records by study nurses, or data from the NHS HES database obtained after linking the participants' unique NHS identification numbers to this national database. Self-reported stroke cases without clinical verification were excluded.

Non-fatal CVD events: this group includes both non-fatal CHD and stroke cases.

Statistical analyses

Complete data analysis

Each CVD risk factor was described according to the frailty status (frail, pre-frail, and non-frail) depending on its characteristics: arithmetic means and SDs if quantitative variables had a normal distribution, medians and IQRs if quantitative variables had not a normal distribution, or frequencies and proportions for qualitative variables.

The following statistical hypothesis tests were performed for univariate analysis: Student's t-test (if normal distribution) or Mann-Whitney test (if non normal distribution) for quantitative variables, Chi-square test for categorical variables, Cochrane-Armitage trend test for ordered categorical variables.

The associations between these risk factors and frailty were summarised using binary logistic regression analyses with frailty status dichotomised (frail and pre-frail versus non-frail) owing to the low number of frail participants (n=108, 2.8%). As the mean risk scores among men were systematically higher than that among women (p-values for all four scores < 0.0001), these risk scores were transformed into standard scores (mean=0, SD=1) in men and women separately. The ORs of being frail or pre-frail was estimated per one SD increase (higher score greater CVD risk) in the risk scores over the 10-year follow-up. As sex did not modify the relation of the standardised risk scores with frailty at follow-up (all p-values for sex interaction > 0.07), men and women were combined in the analysis.

Following analyses were performed to reach the objective of this Chapter.

In examining the associations between individual risk factors and later frailty, sex-adjusted models were performed and then adjusted for the other risk factors to explore the independent effect of individual CVD risk factors with frailty. Binary logistic regression models were then used to examine the impact of a 1-SD increment in the risk scores on frailty at follow-up.

Association between the CVD risk scores and incident cardiovascular events (CVD, CHD, and strokes) were examined to compare the strength of their associations to that with frailty.

Association between the CVD risk scores and frailty after excluding incident CVD cases was estimated to examine whether the association between the risk scores and frailty was mediated by underlying CVD.[243]

Finally, to explore the extent to which the relationship between the risk scores and frailty was driven by specific CVD risk factors included in the scores, analyses on the risk scores – frailty associations were adjusted individually for each of their risk factors. A greater attenuation in the association after adjustment indicates a greater contribution of that specific risk factor.

Missing data analysis

Analyses above were based on complete data (n=3,895). This cohort represents 52.5% of study members for participants eligible at phase 5 and alive at the end of follow-up (n=7,412). Because the association between the risk scores and frailty could be biased by missing data, I imputed data for missing frailty/pre-frailty status and individual CVD risk factors included in the risk scores. This consists of imputing missing values that is replacing missing values with other values. There are several techniques:

a. Common imputation techniques

Two common approaches for dealing with missing data are:

- mean substitution where missing data values are replaced with the sample mean, and,
- conditional mean imputation where the mean from cases that are similar to the cases with missing values is utilised.

These methods have an important drawback: the imputed values are completely determined by a model applied to the observed data. This tends to decrease variance and

can deform relationships among variables. Another approach consists in imputing multiple times to include some variation into the imputed values. This is possible as they are drawn from a distribution.[244] This technique is called ‘multiple imputation’.

b. Multiple imputation

Multiple imputation provides a ‘complete’ dataset, to which standard complete-data analysis can be applied. It is a method for valid inference from partially observed data using properties derived from the Bayesian method. The main advantage of this approach is, it can be applied whether data are missing at random (MAR, the probability of data being missing does not depend on the unobserved data, conditional on the observed data) or missing not at random (MNAR, the probability of data being missing does depend on the unobserved data, conditional on the observed data).[244,245]

There are different multiple imputation models depending on the missing data pattern. Missing data pattern can be either monotone or arbitrary (Figure 7.1).

When the missing data pattern is monotone, Markov Chain Monte Carlo (MCMC) method is used.

When missing data pattern is arbitrary, following methods are applied:

- multivariable normal approach. Imputed values are drawn from a multivariable normal distribution of all the variables in the imputation model. Therefore, this model is not well suited for categorical variables.

- imputation by chained equations (ICE) approach. This approach generates imputations by performing a series of univariate regression models rather than a single large multivariable normal model. Therefore, this model is well suited for categorical variables.

Figure 7.1. Missing data pattern

Monotone						Arbitrary				
V1	**V2**	**V3**	**V4**	**V5**		**V1**	**V2**	**V3**	**V4**	**V5**
X	X	X	X	X		X	X	.	X	X
X	X	X	X	X		.	X	X	.	.
X	X	X	X			X	.	X	.	X
X	X	X				X	X	.	.	.
X	X					.	X	X	X	.
X						X	X	.	X	.

Missing data pattern in the dataset used in this Chapter was presented in Appendix 16. As it was arbitrary, the ICE approach has been used.

c. ICE approach

i. Theoretical explanation

ICE method generates imputations based on a series of regressions models, one for each variable with missing values. Let's consider x_1, x_2, …, x_k variables with missing data. Imputation values are performed as follows:[244]

Step 1: all variables with missing values are filled in by simple random sampling with replacement from the observed values;

Step 2: x_1 is regressed on all other variables x_2, …, x_k, restricted to individuals with the observed x_1;

Step 3: missing values in x_1 are replaced by simulated draws from the corresponding posterior predictive distribution of x_1;

Step 4: x_2 is regressed on all other variables x_1, x_3, …, x_k, restricted to individuals with the observed x_2;

Step 5: missing values in x_2 are replaced by simulated draws from the corresponding posterior predictive distribution of x_2;

Step 6 and so on: the process is repeated for all other variables with missing values in turn; this is called a cycle.

To obtain stabilised results, the procedure is usually repeated for several cycles (e.g., 10 or 20) to produce a single imputed dataset. An important advantage of ICE approach is to impute different types of variables (continuous, binary, ordered and unordered categorical) using their own imputation model (linear regression for continuous variables, logistic regression for binary variables, ordered logistic regression for ordered variables, and multinomial regression for unordered variables).

ii. Construction of the imputation model

The model includes: (1) all diabetes risk factors included in the risk scores ('partially observed variables'); (2) outcome variable: frailty (frail/pre-frail versus non-frail); and, (3) auxiliary variables: they have to be associated with one or more of the partially observed variables, observed when the partially observed variables are not, and predictive of missingness. These variables are not included in the model of the association between the CVD risk scores and frailty. Here, two auxiliary variables met these criteria: socio-economic position at phase 5 (administrator, executive officer, office support staff), and self-reported general health (excellent or very good, good, fair or poor) (Appendix 17).

Non-normally distributed continuous variables need to be transformed towards normality in the imputation model. After imputation, they are re-transformed back to its original form. Normality of continuous variables was checked in Appendix 18.

iii. Statistical software

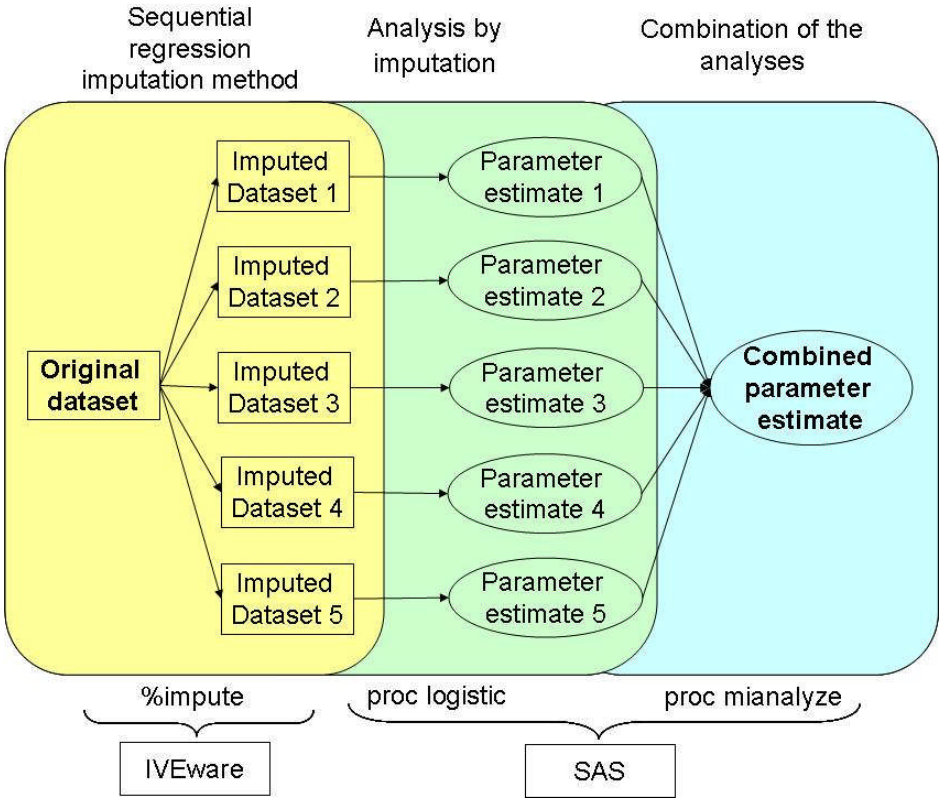
A group of researchers in University of Michigan has developed a SAS callable software application called IVEware (Imputation and Variance Estimation software) using the ICE approach.[246]

Percentage of missing data by variable was calculated basing on study members who both responded to the questionnaire and attended screening examination at baseline (n=7,412) (Appendix 19). Variables with the highest number of missing data were the outcome

variable (frailty) at phase 9 and HDL-cholesterol at phase 5 with percentage > 25%. As this number is relatively high, I decided to run 20 cycles.

Three steps were carried out after obtaining 20 datasets with imputed values: (1) calculating diabetes risk scores from imputed risk factors' values and standardising these probabilities into z-scores to study their 1-SD increment in association with frailty; (2) performing logistic regression model on each of the imputed dataset; and (3) combining the parameter estimates (ORs and their 95% CIs) from each imputed dataset to get a final single set of parameter estimates. Figure 7.2 illustrates the procedure described above.

Figure 7.2. Three steps-procedure to conduct a sensitivity analysis with multiple imputation[a]



[a] This figure is adapted from that presented by Mr Cody Olsen (University of Utah, department of pediatrics) during a biostatistics seminar, October 13, 2011.

Permission to reproduce this figure has been granted by Mr Cody Olsen.

7.4 Results

Complete data analysis

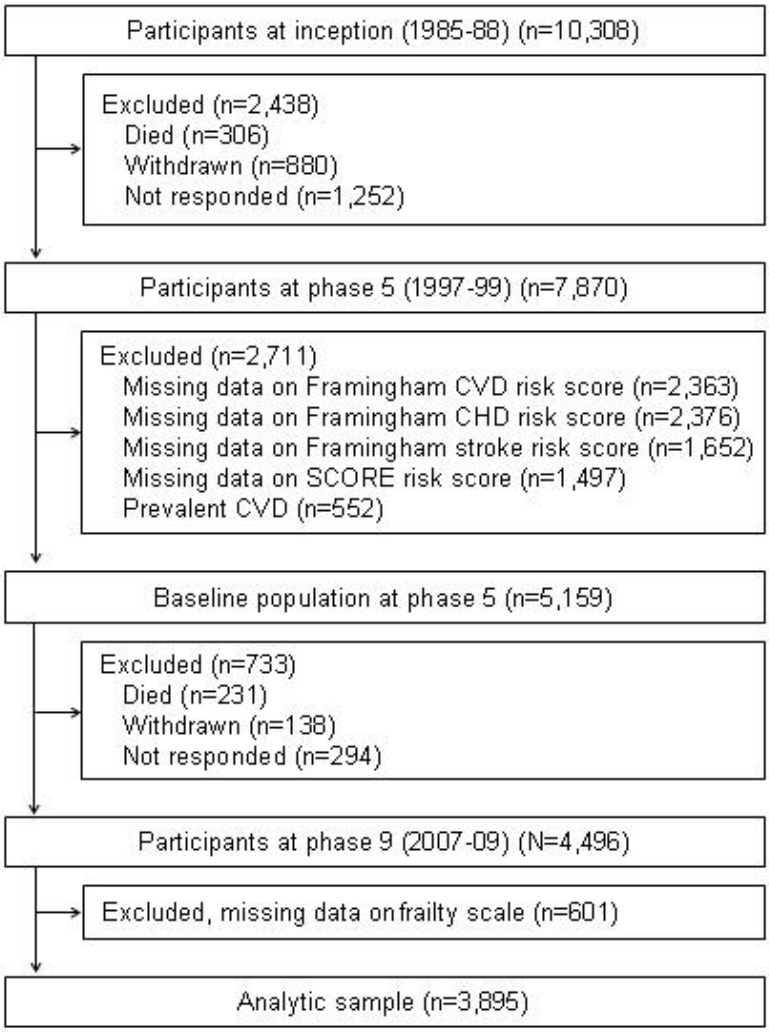
Description of the study participants and missing data

Of the 10,308 study members who participated in phase 1 (1985-1988), 862 had died and 1,447 had dropped out from the study before the start of the data collection at phase 9 (2007-2009). Of the 7,870 participants who attended the phase 5, a total of 3,895

participants (1,037 women) aged 45-69 years at phase 5 constituted the analytic sample (Figure 7.3).

Compared with participants alive at phase 9 but excluded (owing to non participation at phases 5 and 9 and missing data on the CVD risk scores or the frailty scale, (n=4,104)), persons included in the analytic sample (n=3,895) were 0.3 years younger (p=0.01), less likely to be female (26.6% versus 35.3%, $p < 0.0001$), and less likely to be from the lower socioeconomic group (12.4% versus 26.1%, $p < 0.0001$).

Figure 7.3. Flow of study members featured in the present analysis



CVD: cardiovascular disease; CHD: coronary heart disease;
SCORE: Systematic Coronary Risk Evaluation

Table 7.1 shows description of the baseline characteristics of participants according to frailty status at the end of follow-up (on average 10.5 years (SD=0.5) after the measurement of CVD risk scores). Of the 3,895 participants, 2.8% were classified as frail, 37.1% pre-frail, and 60.1% non-frail. In comparison with non-frail participants, frail participants were more likely to be older, female, use antihypertensive treatment, smoke, and have diabetes. Frail participants were also more likely to have experienced a CVD event during the follow-up relative to their non-frail counterparts (16.7 versus 8.5%, p=0.01).

Association between the individual CVD risk factors and frailty

Table 7.2 shows the association between the individual CVD risk factors at baseline and frailty at follow-up. Age, HDL-cholesterol, and smoking status were independently associated with future frailty. Thus, a 1-SD increment in age (5.9 years for men and women) increased the odds of being frail/pre-frail by 12% (OR=1.12; 95% CI: 1.05, 1.20). A 1-SD increment in HDL-cholesterol decreased the odds by 12% (95% CI: 0.83, 0.94), and being a current smoker increased the odds by 40% (95% CI: 1.10, 1.78).

Table 7.1. Characteristics of participants in the analytical sample (n=3,895)

	All	Frailty status at follow-up			P-value[a]
		Not frail	Pre-frail	Frail	
Numbers	3895	2342	1445	108	
Age, years, mean (SD)	55.2 (5.9)	54.9 (5.7)	55.5 (6.1)	57.9 (6.5)	<0.0001
Sex, n (%)					
Male	2858 (73.4)	1926 (77.6)	1023 (67.5)	51 (50.5)	<0.0001
Female	1037 (26.6)	556 (22.4)	492 (32.5)	50 (49.5)	
Total cholesterol, mg/dL	229.23 (40.58)	228.61 (39.50)	230.04 (42.33)	231.63 (40.00)	0.22
HDL cholesterol, mg/dL, mean (SD)	56.65 (15.10)	56.93 (15.23)	56.19 (14.89)	56.77 (15.02)	0.21
Systolic blood pressure, mm Hg	122.7 (16.0)	122.3 (15.7)	123.3 (16.3)	124.5 (16.1)	0.08
Antihypertensive treatment, n (%)					
No	3515 (90.2)	2137 (91.3)	1293 (89.5)	85 (78.7)	<0.0001
Yes	380 (9.8)	205 (8.7)	152 (10.5)	23 (21.3)	
Smoking, n (%)					
No	3593 (92.3)	2185 (93.3)	1313 (90.9)	95 (88.0)	0.006
Yes	302 (7.8)	157 (6.7)	132 (9.1)	13 (12.0)	
Diabetes, n (%)					
No	3755 (96.4)	2273 (97.1)	1381 (95.6)	101 (93.5)	0.01
Yes	140 (3.6)	69 (3.0)	64 (4.4)	7 (6.5)	
Atrial fibrillation, n (%)					
No	3882 (99.7)	2335 (99.7)	1439 (99.6)	108 (100.0)	-
Yes	13 (0.3)	7 (0.3)	6 (0.4)	0	
Left ventricular hypertrophy, n (%)					
No	3667 (94.2)	2214 (94.5)	1356 (93.8)	97 (89.8)	0.10
Yes	228 (5.8)	128 (5.5)	89 (6.2)	11 (10.2)	
Follow-up, years	10.5 (0.5)	10.5 (0.5)	10.5 (0.5)	10.7 (0.5)	0.0003
Incident CVD at follow-up, n (%)					
No	3552 (91.2)	2143 (91.5)	1319 (91.3)	90 (83.3)	0.01
Yes	343 (8.8)	199 (8.5)	126 (8.7)	18 (16.7)	
Incident CHD at follow-up, n (%)					
No	3582 (92.0)	2165 (92.4)	1324 (91.6)	93 (86.1)	0.05
Yes	313 (8.0)	177 (7.6)	121 (8.4)	15 (13.9)	
Incident stroke at follow-up, n (%)					
No	3856 (99.0)	2316 (98.9)	1436 (99.4)	104 (96.3)	0.01
Yes	39 (1.1)	26 (1.1)	9 (0.6)	4 (3.7)	

[a] P for heterogeneity

Table 7.2. Association between individual CVD risk factors at baseline and frailty at 10-year follow-up (n=3,895)

Predictors	N (%)	OR (95% CI) for frailty	
		Adjusted for sex	Fully adjusted[b]
Age, years[a]	3,895	1.14 (1.07, 1.22)	1.12 (1.05, 1.20)
Total cholesterol, mg/dL[a]	3,895	1.03 (0.97, 1.10)	1.01 (0.95, 1.08)
HDL cholesterol, mg/dL[a]	3,895	0.88 (0.82, 0.94)	0.88 (0.83, 0.94)
Systolic blood pressure, mm Hg[a]	3,895	1.09 (1.02, 1.16)	1.04 (0.98, 1.12)
Antihypertensive treatment			
No	3,515 (90.2)	1 (ref)	1 (ref)
Yes	380 (9.8)	1.28 (1.03, 1.58)	1.10 (0.88, 1.37)
Smoking			
No	3,593 (92.2)	1 (ref)	1 (ref)
Yes	302 (7.8)	1.37 (1.08, 1.74)	1.40 (1.10, 1.78)
Diabetes			
No	3,755 (96.4)	1 (ref)	1 (ref)
Yes	140 (3.6)	1.55 (1.10, 2.17)	1.36 (0.96, 1.93)
Atrial fibrillation			
No	3,882 (99.7)	1 (ref)	1 (ref)
Yes	13 (0.3)	1.51 (0.51, 4.50)	1.37 (0.46, 4.13)
Left ventricular hypertrophy			
No	3,667 (94.1)	1 (ref)	1 (ref)
Yes	228 (5.9)	1.25 (0.95, 1.64)	1.17 (0.88, 1.54)

[a] Odds ratio per standard deviation increase.

[b] Model includes all predictors in addition to sex.

Association between CVD risk scores and frailty

Table 7.3 shows the results of analyses of the association of a 1-SD increment in the CVD risk scores with future frailty and cardiovascular events. All risk scores had a similar strength of association with frailty with the ORs ranging from 1.17 (95% CI: 1.10, 1.25) for the Framingham CHD risk score to 1.20 (95% CI: 1.13, 1.28) for the Framingham CVD risk score. As expected, the association of the CVD risk scores was stronger in

relation to predicting CVD events, with ORs ranging from 1.36 (95% CI: 1.15, 1.61) for the Framingham stroke risk score to 1.64 (95% CI: 1.50, 1.80) for the Framingham CVD risk score. The strength of the associations for frailty was not diminished after exclusion of incident CVD cases (Table 7.4).

Table 7.3. ORs (95% CIs) per one sex-specific SD increment in score using four CVD risk algorithms for prediction of frailty and CVD (n=3,895)

	Frail and pre-frail		CVD		
	Number of cases	**OR (95% CI)**	**Outcome**	**Number of cases**	**OR (95% CI)**
Framingham CVD risk score	1553	1.20 (1.13, 1.28)	Any CVD	343	1.64 (1.50, 1.80)
Framingham CHD risk score	1553	1.17 (1.10, 1.25)	CHD	313	1.53 (1.40, 1.68)
Framingham stroke risk score	1553	1.19 (1.12, 1.27)	Stroke	39	1.36 (1.15, 1.61)
SCORE (CVD risk score)	1553	1.18 (1.10, 1.25)	Any CVD	343	1.57 (1.44, 1.71)

Table 7.4. ORs (95% CIs) per one sex-specific SD increment in score using four CVD risk algorithms for prediction of future frailty after excluding incident CVD

CVD risk scores	**OR (95% CI)**
Framingham CVD risk score	1.23 (1.15, 1.32)
Framingham CHD risk score	1.19 (1.11, 1.28)
Framingham stroke risk score	1.22 (1.14, 1.32)
SCORE	1.18 (1.10, 1.27)

CVD risk factors in the association between CVD risk scores and frailty

Table 7.5 shows results of analyses in which the four CVD risk scores as a whole were adjusted for each of their risk factors. The association between risk scores and frailty remained statistically significant after successive adjustments for risk factors suggesting that this association was not driven by any specific risk factor.

Table 7.5. Association between CVD risk scores and frailty

CVD risk scores	OR for frailty (95% CI)
Framingham CVD score	
Unadjusted	1.20 (1.13, 1.28)
Adjusted for[a]	
Age	1.18 (1.09, 1.28)
Total cholesterol	1.22 (1.14, 1.31)
HDL cholesterol	1.21 (1.13, 1.29)
Systolic blood pressure	1.24 (1.15, 1.35)
Antihypertensive treatment	1.20 (1.12, 1.28)
Smoking	1.19 (1.11, 1.27)
Diabetes	1.20 (1.12, 1.28)
Framingham CHD score	
Unadjusted	1.17 (1.10, 1.25)
Adjusted for[a]	
Age	1.13 (1.05, 1.22)
Total cholesterol	1.19 (1.11, 1.27)
HDL cholesterol	1.18 (1.10, 1.27)
Systolic blood pressure	1.18 (1.10, 1.27)
Smoking	1.16 (1.08, 1.24)
Diabetes	1.16 (1.08, 1.24)
Framingham stroke score	
Unadjusted	1.19 (1.12, 1.27)
Adjusted for[a]	
Age	1.15 (1.07, 1.24)
Systolic blood pressure	1.22 (1.13, 1.33)
Antihypertensive treatment	1.18 (1.10, 1.26)
Smoking	1.18 (1.10, 1.26)
Diabetes	1.18 (1.10, 1.26)
Atrial fibrillation	1.19 (1.12, 1.27)
Left ventricular hypertrophy	1.25 (1.15, 1.35)
SCORE	
Unadjusted	1.18 (1.10, 1.25)
Adjusted for[a]	
Age	1.15 (1.05, 1.27)
Total cholesterol	1.19 (1.11, 1.28)
Systolic blood pressure	1.20 (1.11, 1.30)
Smoking	1.16 (1.09, 1.24)

[a] Each CVD risk score was adjusted for individual CVD risk factors.

Missing data analysis

After multiple imputation, ORs for the association between risk factors of CVD and frailty were broadly similar to those with the complete data (Table 7.6). This was also the case for the Framingham CVD, CHD and stroke risk scores, and the SCORE (Table 7.7).

Table 7.6. ORs (95% CIs) for the association between individual components of the CVD risk scores and frailty: complete data versus multiple imputation analysis

	Complete data analysis (n=3,895)	Multiple imputation (n=7,412)
Age, years	1.02 (1.01, 1.03)	1.03 (1.02, 1.04)
Sex		
Male	1 (ref)	1 (ref)
Female	1.74 (1.51, 2.01)	1.78 (1.57, 2.01)
Total cholesterol, mg/dL	1.04 (0.98, 1.10)	1.05 (0.99, 1.11)
HDL cholesterol, mg/dL	0.89 (0.75, 1.05)	0.92 (0.79, 1.07)
Systolic blood pressure, mm Hg	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Diastolic blood pressure, mm Hg	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Antihypertensive treatment		
No	1 (ref)	1 (ref)
Yes	1.32 (1.07, 1.64)	1.42 (1.21, 1.67)
Smoking		
No	1 (ref)	1 (ref)
Yes	1.43 (1.13, 1.81)	1.41 (1.17, 1.70)
Diabetes		
No	1 (ref)	1 (ref)
Yes	1.58 (1.13, 2.21)	1.86 (1.35, 2.55)
Atrial fibrillation		
No	1 (ref)	1 (ref)
Yes	1.30 (0.43, 3.86)	1.35 (0.58, 3.11)
Left ventricular hypertrophy		
No	1 (ref)	1 (ref)
Yes	1.19 (0.91, 1.56)	1.12 (0.89, 1.41)

Table 7.7. ORs (95% CIs) of the association between a 1-SD increment in the CVD risk scores with frailty: complete data versus multiple imputation analysis

	Complete data analysis (n=3,895)	Multiple imputation (n=7,412)
Framingham CVD risk score	1.20 (1.13, 1.28)	1.26 (1.18, 1.33)
Framingham CHD risk score	1.17 (1.10, 1.25)	1.21 (1.15, 1.29)
Framingham stroke risk score	1.19 (1.12, 1.27)	1.22 (1.14, 1.30)
SCORE (CVD risk score)	1.18 (1.10, 1.25)	1.20 (1.14, 1.27)

7.5 Discussion

Main findings

Main findings from this cohort of middle aged individuals were that four different CVD risk scores were associated with an elevated risk of frailty. Thus, one sex-specific SD increment in the risk scores increased the odds of being classified as frail or pre-frail at the end of the 10-year follow-up by 17% to 20%. The strength of this association was not diminished after exclusion of cases of CVD during the follow-up, suggesting that the predictive risk score-frailty associations were not driven by co-morbid CVD (reverse causality). Furthermore, this association was not attributable to any single risk factor included in the risk scores. As far as I am aware, this is the first study to examine the link between scores from CVD risk factor engines and future frailty.

Limitations of the study

This study has some limitations. First, CVD risk at mean age of 55 years was assessed. It remains unclear whether these findings are generalisable to other age groups because at older ages low rather than high levels of some cardiovascular risk factors (total cholesterol, LDL-cholesterol, and systolic blood pressure) are associated with poor health outcome, as assessed by ADL disability, hospitalisation, functional performance, and mortality.[247-249] Second, in relation to CVD prediction, the risk scores are not recommended to be used at older ages (> 75 years); the validity of these scores as risk

markers of frailty should be examined in that age in the future studies. Finally, the study sample consisted of middle-aged civil servants, limiting the generalisability of the present findings. However, these limitations can be compared to the main strength of the study, which resides in the use of prospectively collected data given that previous studies that have examined the association between CVD or its individual risk factors and frailty used cross-sectional data.[60,75,77,232]

Conclusions

Besides the clinical utility of CVD risk scores – Framingham CVD, CHD, stroke, or SCORE – in predicting risk of cardiovascular death and disease, it may be possible that they also help to identify middle-aged persons at risk of frailty. As such, the use of CVD risk scores in clinical practice may also have utility for frailty prediction, although additional predictive markers still need to be identified to improve predictive association and performance.

8 Predictive validity of diabetes risk algorithms for frailty in the Whitehall II study

8.1 Introduction

There is some evidence of a relationship between diabetes and its two mediators – obesity and insulin resistance – and incident frailty[247] and some individual components that denote frailty, such as low grip strength[250,251] and low gait speed.[252]

8.2 Objectives

The specific objectives addressed in this Chapter were:

i. to examine the association between individual diabetes risk factors with frailty.

ii. to examine the predictive capacity of a series of validated diabetes risk algorithms for frailty and compared it to the one for diabetes

In this Chapter, three diabetes risk algorithms were investigated: the Framingham Offspring,[253] the Cambridge,[254] and the Finnish[255] diabetes risk scores.

8.3 Materials and methods

Study population

As for the study of the association between CVD risk scores and frailty in Chapter 7, study members attending phase 5 were included in this Chapter.

Outcome of interest

Outcome was the phenotype of frailty as described in Section 4.4.1.

Diabetes risk factors

Diabetes risk factors necessary to construct three diabetes risk scores included in this Chapter were those included in the CVD risk scores described in Chapter 7 (age, sex,

HDL-cholesterol, systolic/diastolic blood pressure, antihypertensive therapy, smoking status, history of high blood glucose) and other risk factors measured as follows:

Serum triglycerides were determined by enzymatic colorimetric method; BMI calculated and categorised as in Section 4.4.1; waist was taken to be the smallest circumference at/or below the costal margin and measured using a fiberglass tape measure at 600 g tension with the subject in the standing position and still in underwear. Waist circumference categories used were small (< 94 cm in men and 80 cm in women), intermediate (94 to < 102 cm in men and 80 to < 88 cm in women), and high (≥ 102 cm in men and 88 cm in women);[208] self-reported corticosteroid and antidiabetic medications were coded using the British National Formulary codes;[239] parent or sibling history of diabetes and daily consumption of fruit and vegetables were reported by the participants; and physical activity was described as in Section 4.4.1.

Diabetes risk scores

Equations to estimate the 10-year probability of developing diabetes according to the following algorithms were calculated for this thesis: the Framingham Offspring,[253] the Cambridge,[254] and the Finnish[255] diabetes risk scores. The table in Appendix 20 summarises the components of these models. The distribution of the probability of diabetes estimated by these algorithms is shown in Appendix 21.

Type 2 diabetes mellitus

Type 2 diabetes was defined as fasting glucose ≥ 7.0 mmol/L or a 2-hour postload glucose ≥ 11.1 mmol/L, and/or as physician-diagnosed diabetes, and/or use of diabetes medication for those with diagnosed diabetes.[240]

Statistical analyses

Complete data analysis

Each diabetes risk factors at baseline was described according to the frailty status (frail, pre-frail, and non-frail) at 10-year of follow-up using appropriate statistics described in Section 7.3.

As in Chapter 7, owing to the low number of frail participants (n=108, 2.8%), frail and pre-frail categories were combined in further analyses.

Following analyses were performed to reach the objective of this Chapter.

Associations between individual risk factors for diabetes and subsequent frailty were examined using logistic regression adjusted for sex. ORs of being frail or pre-frail were estimated per 1-SD increase (higher score greater diabetes risk) in the risk scores over the 10-year follow-up. Sex modified the relation of the standardised risk score with frailty only for the Cambridge risk score (p-values for sex interaction = 0.03). Therefore, results were presented for men and women combined first, and then stratified by sex for the Cambridge risk score only. To examine the robustness of the association between frailty/pre-frailty and the diabetes risk scores, we conducted several sensitivity analyses: in a study sample excluding incident diabetes cases (sensitivity analysis 1) and in a study sample including prevalent diabetes cases (sensitivity analysis 2). As the variable assessing physical activity is included in both the Finnish score and the Fried's scale, one may expect to observe a strong relationship between this score and frailty. To study the use of the diabetes scores in the prediction of frailty independent of physical activity, I conducted a further sensitivity analysis (3) using the Fried's scale without the physical activity component.

In order to place these effect estimates into context, I also related diabetes risk scores with incident diabetes.

To compare the magnitude of the association between the risk scores with future frailty, 95% CI were calculated around the difference between ORs of the scores 2 by 2 using a 'bias-corrected and accelerated (BCa) bootstrap' method with 2,000 resamplings.[256] This method consists in repeating random sampling with replacement from the original data, to produce random samples of the same size of the original sample, and each provides an

estimate of the difference in ORs. Here, as this process is repeated 2,000 times, 2,000 differences in ORs can be estimated. If these differences in ORs are ordered in increasing value, a bootstrap 95% CI for the differences in ORs would be from the 50th (2.5*20) to the 1950th (97.5*20) largest values. This is known as the 'percentile method'. However, this method can have biases, which can be estimated and corrected for. This corrected method is called BCa bootstrap method.[257]

To evaluate the predictive power for each risk score and to estimate its clinical validity, area under the receiver operating characteristic (ROC) curve (AUC) was calculated.[258]

Finally, to explore the extent to which the relationship between the risk scores and frailty was driven by specific diabetes risk factors included in the scores, analyses on the risk scores–frailty associations were adjusted successively for the individual risk factors one at a time. All analyses were performed using SAS version 9.1.

Missing data analysis

Analyses above were based on complete data (n=2,707). This cohort represents 36.5% of study members for participants eligible at phase 5 and alive at the end of follow-up (n=7,412). Because the association between the risk scores and frailty could be biased by missing data, I imputed data for missing frailty/pre-frailty status and individual diabetes risk factors included in the risk scores using the same procedure described in Section 7.3.

The missing data pattern of the components included in the diabetes risk scores was arbitrary as shown in Appendix 22.

The auxiliary variables associated with the outcome and the response indicator (for the outcome) were socio-economic position at phase 5 and self-reported general health as in Section 7.3 (Appendix 23).

Non-normally distributed continuous variables need to be transformed towards normality in the imputation model. After imputation, they are re-transformed back to its original form. Normality of continuous variables was checked in Appendix 24. Of them, two variables did not have a normal distribution: variable for triglycerides was transformed

into log-scale and variable for the number hours of moderate/vigorous physical activity per week was declared as 'mixed' (categorical and continuous) variable. For a mixed variable, a logistic regression model is used to impute zero versus non-zero status and conditional on imputing a non-zero status, a normal linear regression model is used to impute non-zero values.

Percentage of missing data by variable was calculated basing on study members who both responded to the questionnaire and attended screening examination at baseline (n=7,412) (Appendix 25). Variables with the highest number of missing data were the outcome variable (frailty) at phase 9 and waist circumference at phase 5 with percentage around 25%. As this number is relatively high, I decided to run 20 cycles.

Three steps were carried out after obtaining 20 datasets with imputed values: (1) calculating diabetes risk scores from imputed risk factors' values and standardising these probabilities into z-scores to study their 1-SD increment in association with frailty; (2) performing logistic regression model on each of the imputed dataset; and (3) combining the parameter estimates (ORs and their 95% CIs) from each imputed dataset to get a final single set of parameter estimates (see Figure 7.2).

8.4 Results

Complete data analysis

Description of the study participants and missing data

Of the 10,308 study members who participated in phase 1 (1985-1988), 862 had died and 1,447 had dropped out from the study before the start of the data collection at phase 9 (2007-2009). Of the 7,870 participants who attended the phase 5, a total of 2,707 participants (755 women) aged 45-69 years at phase 5 constituted the analytic sample (Figure 8.1).

Compared with participants alive at phase 9 but excluded (owing to non participation at phases 5 and 9, and missing data on the diabetes risk scores, plasma glucose, or the frailty scale, (n=5,292)), persons included in the analytic sample (n=2,707) were 0.3 years

younger (p=0.005), less likely to be female (27.9% versus 32.7%, $p < 0.0001$), and less likely to be from the lower socioeconomic group (13.0% versus 22.7%, $p < 0.0001$).

Of the 2,707 participants, 2.8% were classified as frail, 37.5% pre-frail, and 59.7% non-frail. Baseline characteristics of participants as a function of frailty status at the end of follow-up (on average 10.5 years, SD=0.5) are detailed in Table 8.1. In comparison with non-frail participants, frail participants were more likely to be older, female, have higher BMI, use antihypertensive treatment, be a current or non-smoker, and less likely to be physically active and consume fruit and vegetables on a daily basis. Frail participants were also more likely to have experienced a diabetes event during the follow-up relative to their non-frail counterparts (13.0% versus 7.4%, p=0.002).

Figure 8.1. Flow of study members featured in the present analysis

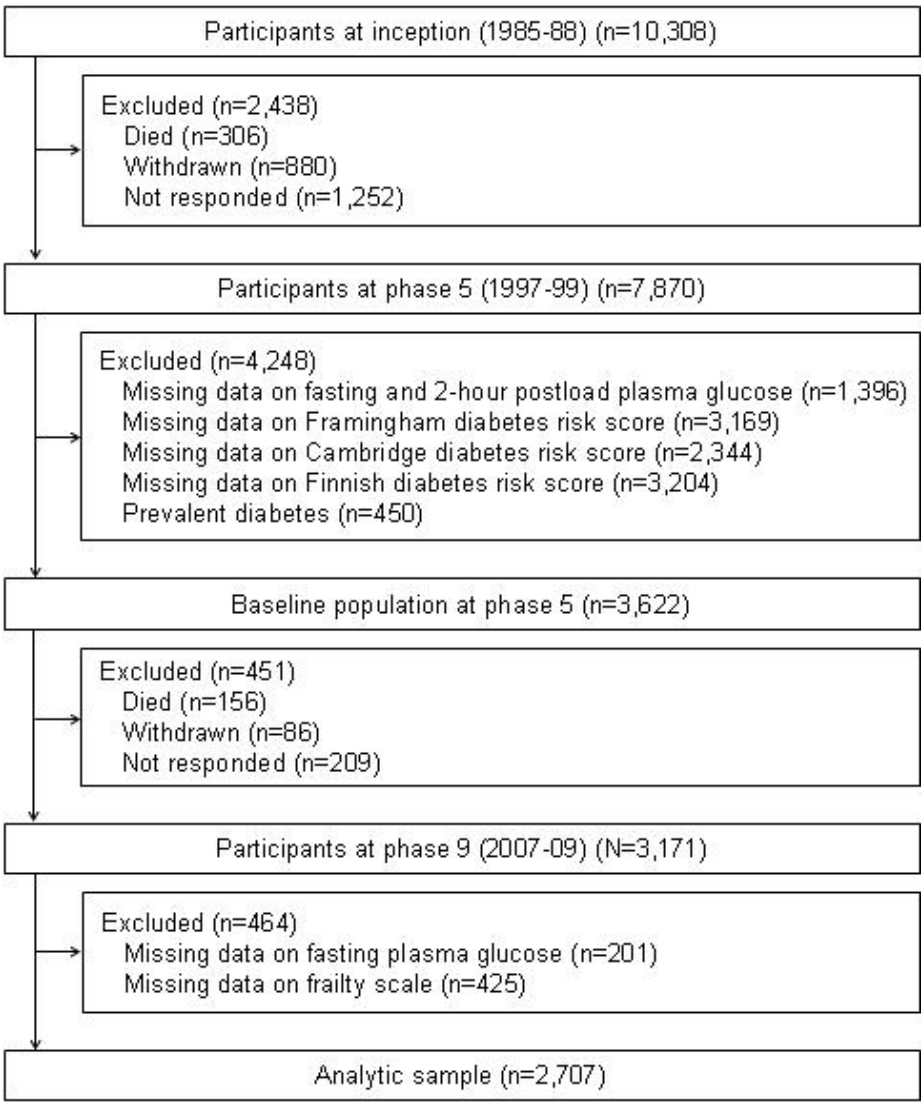


Table 8.1. Characteristics of study participants (n=2,707)

	All	Frailty status at follow-up			P-value[b]
		Not frail	Pre-frail	Frail	
Numbers	2707	1616	1014	77	
Age, years[a]	55.0 (5.9)	54.6 (5.6)	55.4 (6.2)	57.6 (6.2)	<0.0001
Sex, n (%)					
Male	1952 (72.1)	1228 (76.0)	689 (68.0)	35 (45.5)	<0.0001
Female	755 (27.9)	388 (24.0)	325 (32.0)	42 (54.5)	
Parental or siblings history of diabetes, n (%)					
No	2419 (89.4)	1443 (89.3)	907 (89.5)	69 (89.6)	0.99
Yes	288 (10.6)	173 (10.7)	107 (10.5)	8 (10.4)	
Body mass index, kg/m^{2}[a]	25.97 (3.80)	25.81 (3.57)	26.11 (4.01)	27.34 (5.14)	0.001
Waist circumference, cm[a]	90.6 (11.4)	90.3 (11.0)	90.8 (11.6)	92.8 (14.1)	0.07
Systolic blood pressure, mm Hg[a]	121.5 (15.7)	121.3 (15.6)	121.7 (16.0)	124.2 (15.1)	0.24
Diastolic blood pressure, mm Hg[a]	77.1 (10.1)	77.0 (10.0)	77.1 (10.3)	77.1 (11.3)	0.99
Antihypertensive treatment, n (%)					
No	2408 (89.0)	1458 (90.2)	889 (87.7)	61 (79.2)	<0.0001
Yes	299 (11.0)	158 (9.8)	125 (12.3)	16 (20.8)	
Fasting glucose level 100-126 mg/dL, n (%)					
No	2292 (84.7)	1370 (84.8)	856 (84.4)	66 (85.7)	0.94
Yes	415 (15.3)	246 (15.2)	158 (15.6)	11 (14.3)	
HDL cholesterol, mg/dL[a]	56.73 (15.11)	56.89 (15.22)	56.46 (14.99)	56.69 (14.56)	0.53
Triglycerides, geometric mean (geometric SD), mg/dL[a]	100.00 (0.52)	98.28 (63.51)	102.62 (63.71)	101.08 (67.05)	0.11
Corticosteroid treatment, n (%)					
No	2608 (96.3)	1562 (96.7)	972 (95.9)	74 (96.1)	0.56
Yes	99 (3.7)	54 (3.3)	42 (4.1)	3 (3.9)	
Smoking status, n (%)					
Non-smoker	1514 (55.9)	891 (55.1)	575 (56.7)	48 (62.3)	0.005
Ex-smoker	967 (35.7)	610 (37.8)	338 (33.3)	19 (24.7)	
Current smoker	226 (13.0)	115 (7.1)	101 (10.0)	10 (13.0)	
Physical activity ≥ 4 h/week, n (%)					
No	1739 (64.2)	905 (56.0)	764 (75.3)	70 (90.9)	<0.0001
Yes	968 (35.8)	711 (44.0)	250 (24.7)	7 (9.1)	
Daily consumption of fruit and vegetables, n (%)					
No	709 (26.2)	373 (23.1)	307 (30.3)	29 (37.7)	<0.0001
Yes	1998 (73.8)	1243 (76.9)	707 (69.7)	48 (62.3)	
Follow-up, years	10.5 (0.5)	10.5 (0.5)	10.5 (0.5)	10.7 (0.5)	0.03
Incident diabetes at follow-up, n (%)					
No	2466 (91.1)	1497 (92.6)	902 (89.0)	67 (87.0)	0.002
Yes	241 (8.9)	119 (7.4)	112 (11.0)	10 (13.0)	

[a] Figures are means (SD) unless otherwise stated.
[b] P for heterogeneity based on Chi-square test, analysis of variance or Fisher's exact test.

Association between the individual diabetes risk factors and frailty

Table 8.2 presents the association between the risk factors for diabetes and frailty. Older age, abdominal obesity, physical inactivity, and no daily consumption of fruit and vegetables were independently associated with future frailty. Thus, a 1-SD increment in age (5.9 years) increased the odds of being frail/pre-frail by 27% (OR=1.27, 95% CI: 1.17, 1.38); a 1-SD increment in waist circumference (11.4 cm) increased the odds by 24% (95% CI: 1.02, 1.49); participants having a moderate or vigorous physical activity < 4 h/week had 2.5 times (95% CI: 2.08, 2.98) higher odds of frailty than those with ≥ 4 h/week of physical activity; and not having a daily consumption of fruit and vegetables increased the risk of frailty by 50% (95% CI: 1.25, 1.80).

Table 8.2. ORs (95% CIs) for the association between individual components of the diabetes risk scores and frailty (n=2,707)

	N (%)	Adjusted for sex	Fully adjusted
Age, years[a]	2707	1.17 (1.08, 1.27)	1.27 (1.17, 1.38)
Parental/sibling history of diabetes			
No	2419 (89.4)	1 (ref)	1 (ref)
Yes	288 (10.6)	0.95 (0.74, 1.22)	0.83 (0.64, 1.08)
BMI, kg/m2[a]	2707	1.10 (1.01, 1.18)	0.89 (0.75, 1.06)
Waist circumference, cm[a]	2707	1.17 (1.08, 1.27)	1.24 (1.02, 1.49)
Systolic blood pressure, mm Hg[a]	2707	1.05 (0.97, 1.14)	0.98 (0.87, 1.10)
Diastolic blood pressure, mm Hg[a]	2707	1.04 (0.96, 1.12)	1.00 (0.89, 1.13)
Corticoid treatment			
No	2608 (96.3)	1 (ref)	1 (ref)
Yes	99 (3.7)	1.27 (0.85, 1.91)	1.20 (0.79, 1.82)
Current smoking			
No	2481 (91.7)	1 (ref)	1 (ref)
Yes	226 (8.3)	1.42 (1.08, 1.87)	1.25 (0.94, 1.67)
Low physical activity (< 4 h/week)			
No	968 (35.8)	1 (ref)	1 (ref)
Yes	1739 (64.2)	2.41 (2.02, 2.87)	2.49 (2.08, 2.98)
Daily consumption of fruit and vegetables			
No	709 (26.2)	1.57 (1.32, 1.87)	1.50 (1.25, 1.80)
Yes	1998 (73.8)	1 (ref)	1 (ref)
HDL cholesterol, mg/dL[a]	2707	0.89 (0.82, 0.97)	0.94 (0.86, 1.03)
Triglycerides, mg/dL[a]	2707	1.08 (1.00, 1.17)	0.98 (0.90, 1.08)
Fasting glucose, mg/dL[a]	2707	1.04 (0.96, 1.12)	1.03 (0.95, 1.12)

[a] Change per one standard deviation increase.

[b] Model includes all predictors in addition to sex.

Association between diabetes risk scores and frailty

Table 8.3 shows results of the association of a 1-SD increment in the diabetes risk scores and subsequent frailty/pre-frailty and incident diabetes. ORs ranged from 1.05 (95% CI: 0.98, 1.14) for the Framingham Offspring score to 1.27 (95% CI: 1.17, 1.37) for the Finnish score. OR for the Cambridge score was 1.18 (95% CI: 1.09, 1.27).

After stratification by sex, the odds of becoming frail/pre-frail was higher among women (OR=1.30; 95% CI: 1.14, 1.47) than men (OR=1.19; 95% CI: 1.08, 1.32) with the Cambridge risk score.

Table 8.3. ORs (95% CIs) per 1-SD increment in score using three diabetes risk algorithms for frailty and diabetes (n=2,707)

	Frail and pre-frail	Diabetes
Framingham Offspring risk score[a]	1.05 (0.98, 1.14)	1.72 (1.56, 1.90)
Cambridge risk score[a]	1.18 (1.09, 1.27)	1.69 (1.52, 1.88)
Finnish risk score[a]	1.27 (1.17, 1.37)	1.52 (1.38, 1.68)

[a] A 1-SD increase (disadvantage) in the Framingham and Finnish scores was associated with a 4% increase in the probability of developing diabetes. For the Cambridge score, it represented 18%.

The associations between the diabetes scores and frailty/pre-frailty changed slightly after exclusion of incident diabetes cases over the follow-up, inclusion of prevalent diabetes, and modification of the Fried's scale (original scale without physical activity component), but the ranking of their associations with frailty/pre-frailty was maintained (Table 8.4).

Table 8.4. Sensitivity analyses: ORs (95% CIs) per 1-SD increment in score using three diabetes risk algorithms for future frailty

Diabetes risk scores	Main analysis	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
	Study sample (n=2,707)	Study sample excluding incident diabetes cases (n=2,466)	Study sample including prevalent diabetes cases (n=2,824)	Fried's frailty scale excluding physical activity component (n=2,697)
Framingham Offspring	1.05 (0.98, 1.14)	1.07 (0.97, 1.18)	1.09 (1.01, 1.17)	1.06 (0.97, 1.15)
Cambridge	1.18 (1.09, 1.27)	1.14 (1.04, 1.23)	1.18 (1.09, 1.27)	1.23 (1.13, 1.33)
Finnish	1.27 (1.17, 1.37)	1.25 (1.14, 1.36)	1.26 (1.16, 1.37)	1.28 (1.18, 1.39)

Comparison of the strength of the association

a. Differences in ORs

The Finnish score had a significantly stronger association with frailty than the other scores; the differences in ORs were significant in favour for that score, ranging between 0.09 and 0.22 (Table 8.5).

As anticipated, all risk scores were statistically associated with incident diabetes in the study population, with the highest OR for the Framingham risk score [1.72 (95% CI: 1.56, 1.90)] (Tables 8.3 and 8.5).

Table 8.5. Comparison of performances of diabetes risk scores in the prediction of future frailty and diabetes onset

	Δ in OR (95% CI)[a] for frailty comparing the upper and lower tertiles for different diabetes scores	
	Framingham risk score OR=1.05 (0.98, 1.14)	**Cambridge risk score OR=1.18 (1.09, 1.27)**
Framingham risk score OR=1.05 (0.98, 1.14)	—	—
Cambridge risk score OR=1.18 (1.09, 1.27)	Δ = 0.12 (0.02, 0.22)	—
Finnish risk score OR=1.27 (1.17, 1.37)	Δ = 0.22 (0.11, 0.33)	Δ = 0.09 (0.02, 0.17)
	Δ in OR (95% CI)[a] for diabetes comparing the upper and lower tertiles for different diabetes scores	
	Framingham risk score OR=1.72 (1.56, 1.90)	**Cambridge risk score 1.69 (1.52, 1.88)**
Framingham risk score OR=1.72 (1.56, 1.90)	—	—
Cambridge risk score OR=1.69 (1.52, 1.88)	Δ = -0.03 (-0.28, 0.21)	—
Finnish risk score OR=1.52 (1.38, 1.68)	Δ = -0.20 (-0.46, 0.01)	Δ = -0.17 (-0.32, -0.05)

[a] Bias-corrected and accelerated bootstrap (BCa) 95% confidence interval.

b. Comparison of the predictive accuracy

Table 8.6 shows the areas under the curves (AUC) for each diabetes score in the prediction of frailty. The Finnish score had the highest AUC compared with the other scores (0.58 versus 0.53).

In the prediction of diabetes, the Framingham score had the highest AUC [0.76 (0.73, 0.79)].

Table 8.6. Comparisons of the areas under the ROC curves (AUC) and their 95% CIs in the prediction of frailty and diabetes

	Frail and pre-frail		**Diabetes**	
	AUC (95% CI)	**Δ (95% CI)[a]**	**AUC (95% CI)**	**Δ (95% CI)[a]**
Framingham risk score	0.531 (0.509, 0.553)	0.044 (0.022, 0.066)	0.760 (0.727, 0.792)	Ref
Cambridge risk score	0.535 (0.513, 0.557)	0.040 (0.023, 0.057)	0.699 (0.666, 0.732)	0.061 (0.025, 0.097)
Finnish risk score	0.575 (0.553, 0.597)	Ref	0.684 (0.649, 0.718)	0.076 (0.040, 0.112)

Diabetes risk factors in the association between diabetes risk scores and frailty

Table 8.7 presents results of analyses in which the three diabetes risk scores as a whole were adjusted for each of their risk factors. The association between risk scores and frailty remained statistically significant after successive adjustments for risk factors suggesting that this association was not driven by any specific risk factor.

Table 8.7. Association between diabetes risk scores and frailty

Diabetes risk scores	OR (95% CI)
Framingham diabetes score	
Unadjusted	1.05 (0.98, 1.14)
Adjusted for[a]	
Age	1.05 (0.97, 1.13)
Sex	1.06 (0.98, 1.14)
Parental history of diabetes	1.05 (0.97, 1.14)
BMI	1.02 (0.94, 1.11)
Blood pressure > 130/85 mmHg or receiving therapy	1.03 (0.95, 1.11)
HDL-cholesterol	1.03 (0.95, 1.12)
Triglycerides	1.05 (0.97, 1.13)
Fasting glucose	1.09 (0.98, 1.21)
Cambridge diabetes score	
Unadjusted	1.18 (1.09, 1.27)
Adjusted for[a]	
Age	1.14 (1.05, 1.23)
Sex	1.22 (1.13, 1.31)
Parental/sibling history of diabetes	1.19 (1.10, 1.28)
BMI	1.18 (1.07, 1.30)
Antihypertensive therapy	1.16 (1.06, 1.26)
Corticosteroid therapy	1.18 (1.09, 1.28)
Smoking	1.16 (1.07, 1.25)
Finnish diabetes score	
Unadjusted	1.27 (1.17, 1.37)
Adjusted for[a]	
Age	1.25 (1.15, 1.35)
BMI	1.45 (1.28, 1.63)
Waist circumference	1.40 (1.26, 1.54)
Antihypertensive therapy	1.27 (1.17, 1.38)
Physical activity < 4h/week	1.20 (1.11, 1.30)
Daily consumption of fruit and vegetables	1.26 (1.16, 1.36)

[a] Each diabetes risk score was adjusted for individual diabetes risk factors.

Missing data analysis

After multiple imputation, ORs for the association between risk factors of diabetes and frailty were broadly similar to those in the complete data analysis (Table 8.8). This was also the case for the Framingham Offspring, Cambridge, and Finnish risk scores (Table 8.9).

Table 8.8. ORs (95% CIs) for the association between individual components of the diabetes risk scores and frailty: complete data versus multiple imputation analysis

	Complete data analysis (n=2,707)	Multiple imputation (n=7,412)
Age, years	1.03 (1.01, 1.04)	1.03 (1.02, 1.04)
Parental history of diabetes		
No	1 (ref)	1 (ref)
Yes	0.96 (0.73, 1.25)	0.85 (0.71, 1.02)
Sibling history of diabetes at phase 1		
No	1 (ref)	1 (ref)
Yes	0.81 (0.45, 1.45)	0.69 (0.45, 1.05)
Sibling history of diabetes at phase 2		
No	1 (ref)	1 (ref)
Yes	1.57 (1.10, 2.23)	1.25 (0.95, 1.65)
BMI, kg/m2[a]	1.03 (1.01, 1.05)	1.03 (1.01, 1.04)
Waist circumference, cm	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
Systolic blood pressure, mm Hg	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Diastolic blood pressure, mm Hg	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)
Antihypertensive therapy		
No	1 (ref)	1 (ref)
Yes	1.37 (1.08, 1.74)	1.42 (1.22, 1.65)
Corticoid treatment		
No	1 (ref)	1 (ref)
Yes	1.24 (0.83, 1.86)	1.21 (0.91, 1.62)
Current smoking		
No	1 (ref)	1 (ref)
Yes	1.48 (1.12, 1.94)	1.20 (1.10, 1.31)
Past smoking history		
No	1 (ref)	1 (ref)
Yes	0.82 (0.69, 0.96)	0.95 (0.89, 1.00)
Physical activity, h/week	0.83 (0.81, 0.86)	0.81 (0.77, 0.86)
Daily consumption of fruit and vegetables	0.86 (0.81, 0.91)	0.85 (0.81, 0.88)
HDL cholesterol, mg/dL	0.93 (0.77, 1.14)	0.94 (0.82, 1.07)
Triglycerides, mg/dL	1.05 (0.96, 1.15)	1.10 (1.04, 1.17)
Fasting glucose, mg/dL	1.00 (0.85, 1.16)	1.05 (1.00, 1.10)

Table 8.9. ORs (95% CIs) of the association between a 1-SD increment in the diabetes risk scores with frailty: complete data versus multiple imputation analysis

	Complete data analysis (n=2,707)	Multiple imputation (n=7,412)
Framingham risk score	1.05 (0.98, 1.14)	1.11 (1.05, 1.17)
Cambridge risk score	1.18 (1.09, 1.27)	1.17 (1.10, 1.23)
Finnish risk score	1.27 (1.17, 1.37)	1.25 (1.17, 1.33)

8.5 Discussion

Main findings

In this middle aged cohort, several diabetes risk factors that were associated with frailty were identified. In addition, elevated multifactorial diabetes risk scores were found to be associated with an increased risk of subsequent frailty and the Finnish risk score was the strongest predictor.

Results of multiple imputation analysis support the findings from the complete data analysis.

Limitations of the study

This study has some limitations. First, there is no gold standard measure for diabetes prediction and although there are numerous diabetes risk scores,[259-261] they are less known and utilised than the CVD risk scores. The three risk scores tested in this Chapter are widely validated and well known, but several other diabetes prediction algorithms not included in this study exist. Third, as this study sample consisted of middle-aged civil servants, this limits the generalisability of these findings.

Conclusion

In conclusion, all diabetes risk scores were associated with future frailty, in particular the Finnish score. These findings may help to construct an original prediction model to

identify middle-aged persons at risk of frailty as some diabetes risk factors were found to be highly associated with frailty. However, additional predictive markers are still needed to improve predictive association and performance based on diabetes risk factors for clinical practice.

9 Overall discussion

In order to improve the understanding of frailty in elderly population, the present work attempted to answer the following questions: (1) how is frailty currently defined and measured? (2) based on an overview, are there valid and reliable frailty measures which can be used in clinical and research settings? (3) If so, can the validity and reliability be replicated in the Whitehall II study? and (4) to which extent conventional CVD and diabetes risk scores predict frailty 10-years later?

In this Chapter, the principal findings of the present work are first summarised and discussed in light of that from other studies, and then, the limitations of the present study are highlighted. Finally, the directions for future research are outlined.

9.1 Concept of frailty

As highlighted in Chapter 1, there are numerous overlapping definitions of frailty, a recognised geriatric syndrome characterized by age-related declines in functional reserves across an array of physiologic systems leading to a state of high vulnerability to adverse outcomes. However, there is a debate regarding its measurement. Comorbidity and disability are often used as synonyms for frailty and many researchers included comorbidity and disability items in their instruments (Mitnitski and colleagues).[92] For other investigators, frailty can also exist in the absence of comorbidity and disability (Fried and colleagues).[16] Frailty may also reflect the existence of underlying or undiagnosed diseases. However, the concept of frailty is still useful for clinicians and researchers in the context where, among elderly persons, it is difficult to diagnose a disease[262] because the corresponding symptoms can be masked by existing diseases or it becomes difficult distinguishing between new diseases and secondary effects due to frequent polymedication at old age. In addition, atypical presentation of diseases among older elderly can lead to missing diagnosis. If the frailty concept can contribute to capture pre-clinical disease or missed diagnosis then it may have some use.

9.2 Comparison of existing frailty measures

This review provides a comprehensive overview of existing frailty measurements. Two measures developed by Fried and Mitniski/Rockwood groups are remarkable as they have been widely used and tested for validation against adverse health outcomes.

Most general reviews or editorials on frailty have implicitly presented the measure 'phenotype of frailty' developed by Fried group as reference,[10,47,81-90] and a few others[91,93] that of Mitnitski/Rockwood group.[92] Recommendations from other researchers are more nuanced. According to Sternberg and colleagues,[95] the choice depends on the definition and outcomes that best suit the needs of those doing the screening: a researcher in biology may prefer using the phenotype of frailty (Fried group), an administrator the frailty index (Mitnitski/Rockwood group) as its items can derive from an administrative database, and a clinician may prefer a tool developed by Saliba and colleagues[133] as it can help to identify complicated patients. The European, Canadian and American Geriatric Advisory Panel[61] recommends to use a hybrid measure composed of components from both the phenotype of frailty and the frailty index called 'FRAIL' scale. Difficulties in accepting one measure as a gold standard relate to the fact that it is difficult to create a composite measure that would meet all criteria.

One of the aims of this thesis was to examine potential predictors of frailty. To do so, I decided not to create a new frailty instrument but rather to use an existing one. In the context of the absence of a gold standard measure, ideally, the selected instrument must have the highest reliability and validity. As reported in Chapter 2, the phenotype of frailty was selected in this thesis as it has a highest number of external validation, although this instrument has missing information on its reliability. Included components intend to reflect a sensible theoretical framework of frailty by attempting to capture its key characteristics: decline in lean body mass (weight loss), weakness (grip strength), poor endurance (exhaustion and slow walking time), and low activity. Therefore, the operational definition of frailty by Fried and colleagues seems to correspond to the criteria required to be a syndrome, defined as an arbitrary score including multiple and heterogeneous items, reflecting the complexity of clinical phenonemon that cannot be

measured with traditional biometric data.[263] In a different context, this measure has been operationalised as the well-known 'metabolic syndrome', a cluster of 5 risk factors for cardiovascular disease and diabetes; the presence of any 3 of 5 risk factors constitute a diagnosis of metabolic syndrome.[264]

9.3 Phenotype of frailty

The common characteristic captured by all the components included in the phenotype of frailty is sarcopenia. Exhaustion and low physical activity, expression of either muscle weakness or diseases (depression, cancer, infection, sleep disorders, etc), by leading to a prolonged immobility, can cause or deteriorate lean muscle mass loss.[265] Slow walking speed was found to be highly correlated with lower extremity muscle strength (correlation coefficients ranging from 0.19 to 0.50).[266] Both slow walking speed[267] and low grip strength[268] are considered to be useful markers of sarcopenia. Two mechanisms may explain how weight loss leads to sarcopenia, whether the weight loss is intentional or not: (1) the relationship between unintentional weight loss and sacopenia is well known, often caused by an underlying disease;[265] and (2) weight loss seems to be a marker of obesity when weight loss is intentional. Indeed, in our study, among those who lost weight intentionally, 35% of them were obese (7.9% for the unintentional weight loss group and 18.9% for the reference group). Obesity, a well known predictor for type 2 diabetes,[269,270] is recently identified as a risk factor of frailty.[140,154] The underlying mechanism explaining the association between obesity and frailty may be the insulin resistance.[271] It has been suggested that insulin resistance occurring among older persons is due to accumulation of lipid within muscle[272] leading to sarcopenia,[273,274] a core characteristic of frailty. This phenomenon is called 'sarcopenic obesity'.[275]

The overview presented in this thesis and analyses based on the Whitehall II data supported the validity and reliability of the phenotype of frailty developed by Fried group.

Main strengths of this review include its extended evaluation of reliability and validity of each instrument with data extracted from other studies, reflecting its level of their external validation. Furthermore, to date, no article has been published on the extent to which frailty measures have been used by other researchers. This finding might reflect the level

of preference of researchers for a given frailty measurement in the absence of a consensually recognised tool.

The main limitation of this review is probably the use of a unique keyword 'frailty' to identify relevant publications on frailty measurements. One may find such a strategy restrictive, leading to miss some screening tools helping to identify frail elderly. However, all frailty instruments included in previous reviews were also identified in my review, which additionally identified 18 studies[20,109-113,115,117-121,123,124,126-128,131] not included in a previous review;[93] five of them created in 2010 or after.

9.4 Validity of the phenotype of frailty in the Whitehall II study

The phenotype of frailty was found to predict hospitalisation and the strength of prediction was broadly similar to those of basic ADL disability and comorbidity in a mutually adjusted model, indicating an independent role of frailty in the prediction. However, if a more comprehensive measure of comorbidity including many co-occurring comorbid conditions,[276] is used, this could result in frailty not being any longer independently related to subsequent health outcomes. Furthermore, I cannot rule out the possibility that this independent association is explained by early and undiagnosed conditions.

These all three conditions are related to an approximately 1.3-fold increased risk of hospitalisation. The strength of the prediction was also similar to those found in several other studies including the CHS[16] and Three-City[96] studies. However, in the MOBILIZE Boston study, a stronger association between frailty and hospitalisation was reported (RR=3.54)[98] whereas in the Women's Health and Aging Studies no association between frailty and hospital admissions was observed (RR=0.67).[75] Heterogeneity in the measurement of frailty and population characteristics may have contributed to these inconsistencies.

Several findings supported the concept of frailty as a multifactorial syndrome. Consistent with the literature, I found that all five frailty components included in the phenotype of frailty – exhaustion, low physical activity, slow walking speed, low grip strength, and

weight loss – were independently associated with hospitalisation. However, applying statistical tests developed for the assessment of the predictive performance of risk score for clinical practice suggested that the benefit of multi-factorial measurement may be limited. Indeed, Harrell's C concordance statistic varied between 0.57 and 0.58 (0.50 indicates that the prediction does not differ from chance) suggesting that neither the components nor the full scale were adequate prediction tools for hospitalisation. This probably indicates that frailty and its components capture only a very limited range of the conditions leading to hospitalisation.

However, other findings in this thesis supported that the frailty measure seems to stratify risk even within the group of individuals with an individual frailty component. Results from the predictive association (hazard ratio and its 95% CI) and predictive performance (concordance statistic and its 95% CI) seemed contradictory; the first showing that the composite measure was better associated with subsequent hospitalisation than individual components and the second that the composite measure was not sufficiently discriminatory to allow differentiating between frail and not frail elderly at individual level. It has been demonstrated that strong statistical associations between a marker (here frailty) and outcome (here hospitalisation) do not necessarily mean that the marker can discriminate between persons likely to have the outcome and those who do not.[277] Although, the examination of the predictive performance of an instrument is crucial for individual-level prediction and classification for 'personalised medicine', traditional statistical methods such as hazard ratio or odds ratio used by epidemiologists are valuable for characterising population variations in risk and using to target prevention or screening strategies.

A main limitation of this work, shared with many studies in this field of research, is a departure from the original frailty scale. This was particularly the case with weight loss because weight in the previous year was not available in the Whitehall II study. As many studies on frailty, including the Whitehall II, are analyses of existing cohorts primarily set up for other purposes, assessment of frailty components tends to differ between them. Nonetheless, effort should be made to use a standardised definition in the future in order to allow direct comparisons of results between different populations.

Furthermore, as the phenotype of frailty measure was not available at baseline, I could not exclude pre-frail/frail participants. It is likely, however, considering that this was a group of middle-aged participants (mean age: 55.4 years) and the cohort is occupational, the prevalence of frailty/pre-frailty would have been very low. Unavailability of the phenotype of frailty at baseline did not allow estimating the reliability of the frailty change score, a measure estimating the ability of the measure to discriminate between the participants who change a lot and those who change little.

Additionally, because the analytic sample consisted predominantly of white collar workers, this may limit the generalisability of the present findings.

Taken together, these results indicate that a composite measure of frailty proposed by Fried is related to future risk of hospitalisation but shows poor performance as a predictive tool. Much previous work in this domain is based on elderly individuals. That the frailty scale and its individual components were prospectively associated with hospitalisation among the Whitehall II participants aged 55-79 years at baseline, suggests that the measure has appropriate predictive validity in middle and early old age.

9.5 Reliability of the phenotype of frailty in the Whitehall II study

Reliability of the phenotype of frailty was assessed using the internal consistency and test-retest reliability. Because the completion of a health survey questionnaire was not requested during the second visit, it was not possible to assess fully the reliability of the phenotype of frailty. Thus, its reliability has been approximately evaluated with the following three components – walking speed, grip strength, and weight – measured during the repeated examination.

Internal consistency was low (r=0.3) which may be ascribed to the fact that the phenotype of frailty includes multiple components which are heterogeneous. The test-retest reliability of 3 out of 5 components of the phenotype of frailty assessed by the Bland-Altman plot was good.

9.6 Prediction of frailty using CVD risk scores

The main finding from this study was that different CVD risk scores were associated with the risk of frailty: one sex-specific SD increment in the CVD risk scores increased the odds of being classified as frail or pre-frail at the end of the 10-year follow-up by 17% to 20%. This is the first study in its kind.

Although initially designed to predict CVD, the present results suggest that the CVD risk scores also appear to be a predictive marker of general health such as frailty status. Our finding in relation to frailty is in agreement with other studies with other ageing outcomes. All individual risk factors – age, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking, and diabetes – included in CVD scores have also been shown to be associated with cancer,[228-231] which, after CVD, is the second leading cause of death in economically developed countries.[203] In addition, The Framingham CVD risk score was found to be associated with cognitive decline in the Whitehall II study.[222] One plausible mechanism linking risk scores to both CVD and frailty is the presence of atherosclerosis in arteries and related chronic systemic inflammation.[38,278] Atherosclerotic processes can prevent blood flow through the coronary artery causing CVD[278] and through the muscles causing sarcopenia, a clinical feature of frailty.[279]

The proportion of frailty and pre-frailty was higher in women than men (49.8% versus 36.3%, respectively). This is in agreement with previous findings,[104] but opposite to what one might expect for CVD, which is more common in men in late middle-age. In this study, the incidence of CVD was 9.9% in men versus 5.7% in women. A potential explanation for the higher incidence of frailty in women pertain to difference in biology between sexes, with men having greater bone mineral density and muscle mass at old ages.[280,281]

9.7 Prediction of frailty using diabetes risk scores

In this middle aged cohort, several diabetes risk factors were associated with frailty. In addition, elevated multifactorial diabetes risk scores were found to be associated with an increased risk of subsequent frailty: a 1-SD increment in the risk scores increased the

odds of becoming frail or pre-frail by 5% to 27% at the end of the 10-year follow-up. This is also the first study in its kind.

The specific risk factors associated with frailty were waist circumference (a strong correlate of insulin resistance) and two markers of unhealthy behaviours (physical activity less than 4 hours per week and no daily consumption of fruit and vegetables). All these associations are plausible.

First, the link between abdominal obesity and frailty is plausible because increased intramuscular adipose tissue is responsible for insulin resistance,[272] which is a potential contributor to declining muscle strength and quality.[282-286] Moreover, the increase in intramuscular fat in addition to visceral fat has been shown to lead to systemic inflammation with increase in the adipokines such as IL-6, TNF-a, and CRP, that are implicated in the aetiology of insulin resistance,[287-290] frailty,[38] and sarcopenia.[291]

Second, the strong relationship between physical inactivity and subsequent frailty is not surprising either given that it is also one of the five components of Fried's frailty measurement.[16] Inactivity is related to an accelerated loss of lean mass due to a decrease in muscle fibres leading to a low physical capability.[265,292-294]

Third, a plausible mechanism linking fruit and vegetable consumption to frailty may be the antioxidant effect of nutrients included in fruit and vegetables such as carotenoids, vitamins (C, E), and phenolics. These antioxidants have been shown to inhibit lipid peroxidation in vitro particularly that of low-density lipoproteins (LDL)[295-297] responsible for the development of atherosclerosis,[298] the primary cause of cardiovascular diseases which have been shown to be related to frailty in several cross-sectional studies.[60,75,77] Although several prospective studies demonstrated that fruit and vegetables consumption is protective against non-communicable diseases particularly cardiovascular diseases,[299-307] the beneficial effect may not be due to isolated individual antioxidant compounds included in fruit and vegetables, as important meta-analyses of randomised controlled trials failed to show a beneficial effect of vitamins E, C, or b-carotene,[308,309] rather joint effects of known or unknown antioxidants. In addition, one cannot rule out other mechanisms besides the antioxidant effect which explain such associations. Several

researchers support the notion that fruit and vegetables intake is a marker of healthy lifestyle behaviour rather than an aetiological factor of non-communicable diseases as it is highly correlated with other disease risk factors.[310,311]

The strongest prediction of frailty was observed with the Finnish diabetes risk score; this may be due to score composition as the Finnish score included the risk factors listed above that were particularly strongly associated with frailty when analysed separately.

Importantly, the association between the Finnish diabetes score and frailty was not driven by a specific risk factor included in this score. Because physical activity is included in both Finnish score and the phenotype of frailty, it might be possible that this association is mediated by this component. However, a supplementary analysis studying the association with the phenotype of frailty without physical activity showed that this was not the case as the strength of the association remained stable.

The lower predictive preformance of the Cambridge and Framingham risk scores in relation to frailty may be explained by the effect of sex, as the direction of this association was unexpected: old women were more likely to become frail than old men[104] whereas in the prediction of diabetes, sex has a non-significant effect in the Framingham score (β for men= -0.01) and women are at lower risk in the Cambridge score (β for women= -0.88). In addition, three strong predictors (waist circumference, physical activity, and consumption of fruit and vegetables) of frailty were not included in the Cambridge and Framingham risk scores.

Taken together, all diabetes risk scores were associated with future frailty, in particular the Finnish score. Although these findings may help to construct a prediction model to identify middle-aged persons at risk of frailty, additional predictive markers are still needed to substantially improve predictive association and performance based on diabetes risk factors for clinical practice.

The strength of the association between the diabetes risk scores (Cambridge and Finnish, with ORs 1.18 and 1.27) and frailty was quite similar to that with CVD risk scores (OR: 1.18 to 1.20), except the Framingham Offspring diabetes risk score (OR=1.05). As

discussed above, the weaker association of the Framingham Offspring risk score compared to all other CVD or diabetes risk scores in relation to frailty may be explained by the small effect of sex in that score and the absence of strong predictors such as waist circumference, physical activity, and consumption of fruit and vegetables.

9.8 Implications and future research

The literature review included in this thesis highlighted the difficulty in agreeing a consensus on the conceptual definition of frailty in the scientific community. Because the construction of each frailty measure directly depends on the conceptual definition, it is not surprising that to date there is still no gold standard in its measurement. This highlights the importance of future attempts to harmonise and standardise in particular the definition of each component included in frailty instruments, the cut-offs to identify frail, pre-frail, and non-frail individuals (e.g., the phenotype of frailty by Fried group), and the number of deficits and symptoms included in a scale (e.g., the frailty index by Mitnitski/Rockwood group).

Although the CVD and diabetes risk scores were associated with subsequent frailty, further development is needed to improve early identification of individuals at increased risk of frailty. There is clearly room for such development. This is illustrated by two observations. First, in CVD and diabetes risk scores, the direction and the level of some individual risk factors were not in supportive of the prediction of frailty. Second, individual predictors not included in all risk algorithms, such as daily consumption of fruit and vegetables, were strongly associated with frailty. Thus, the frailty risk score should comprise these items.

After identifying pre-frail/frail individuals, it is important first to investigate potential morbidities associated with frailty and to treat them accordingly. Where no disease is diagnosed, then other non-specific interventions may be useful. Evidence from randomized controlled trials suggest that exercise programmes[65] and selected drugs (e.g., dehydroepiandrosterone[66] and testosterone)[67,68] can reverse frailty. High-dose vitamin D has been shown to be also an interesting intervention to prevent frailty as it reduces the risk of fall[72] and fractures.[48] Physical exercises and vitamin D are particularly interesting

interventions at population level due to their positive pleiotropic effects, few adverse health effects, and low costs. These interventions used in the secondary frailty can also be used in the primary frailty as well after identifying individuals at an increased risk of frailty using the CVD and diabetes risk scores examined in this thesis.

9.9 Conclusions

This work suggests that the phenotype of frailty has a reasonable predictive validity in the Whitehall II study and its utility is also supported by previous studies identified in a systematic literature review. Both frailty and pre-frailty mark increased near-term risk of hospitalisation. Existing diseases risk algorithms, in particular that of CVD and diabetes scores, appear to predict subsequent onset of frailty although the clinical utility of these algorithms in identifying those at risk of frailty may be limited. These findings imply that better prevention of cardiovascular and diabetes risk factors in midlife will reduce frailty at older ages.

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Appendices

Appendix 1. Characteristics of frailty instruments utilised in individual studies

Reference/Frailty instrument name	Study name, setting, country	Characteristics of population: N, age (mean (SD); range), % female	Components	Classification	Comment
Subjective frailty instruments					
Strawbridge et al, 1998 [15]: *1994 Frailty Measure*	The Alameda County Study, Prospective cohort, USA	Community-dwelling population N=574 74.0 years; 65+ 57.0%	4 domains: Physical functioning: Sudden loss of balance Weakness in arms Weakness in legs Dizziness when standing up quickly Nutritive functioning: Loss of appetite Unexplained weight loss Cognitive functioning: Difficulty paying attention Trouble finding the right word Difficulty remembering things Forgetting where put something Sensory problems: Difficulty reading a newspaper Difficulty in recognising a friend across the street Difficulty reading signs at night Hearing over the phone Hearing a normal conversation Hearing a conversation in a noisy room	Score for the 6 sensory items: 1: have no difficulty 2: have a little difficulty 3: have some difficulty 4: have a great deal of difficulty. Scores on the other 10 items: 1: rarely or never had the problem in the last 12 months 2: sometimes had the problem 3: often had the problem 4: very often had the problem Participant was considered to have a problem or difficulty for one domain when he/she had a score ≥3 at least 1 of the items. Frail if ≥ 2 domains were considered to have a problem or difficulty.	
Dayhoff et al, 1998 [115]	Subsample of a	Community-dwelling	Performance of ADLs/IADLs using the World	Score range:	Frailty defined as

	larger study examining effects of two exercise interventions, Cross-sectional analysis, USA	participants N=84 Non-frail: 73.2 years (6.0) Frail: 73.5 years (7.9) Age range : 60 to 88 years 85.7%	Health Organisation Assessment of Functional Capacity (14 items, each scored from 1 to 5 (5=unable to perform)) Self-report of perceived health.	14 (self-sufficiency) to 70 (total dependency) Non-frail if score ≤20 & excellent/good health. Frail if score ≥21 & fair/poor health	disability.
Rockwood et al, 1999 [20]: CSHA rules based definition	The Canadian Study of Health and Aging (CSHA), Prospective cohort, Canada	Random sample of community residents N=not reported 65+ %=not available	0: Those who walk without help, perform basic ADL, are continent of bowel and bladder, and are not cognitively impaired 1: Bladder incontinence only 2: One (two if incontinent) or more of needing assistance with mobility or ADL, has cognitive impairment with no dementia, or has bowel or bladder incontinence 3: Two (or three if incontinent) or more of totally dependent for transfers or one or more ADL, incontinent of bowel and bladder, and diagnosis of dementia.	--	Frailty defined as disability or comorbidity.
Steverink et al, 2001 [129]: Groningen frailty indicator (GFI) (manual search)	Cross-sectional study, Netherlands	Hospital inpatients, nursing home residents and community-dwelling elderly N=275 78.0 years (7.0), range=64-99 72.9%	15 items scored 0 or 1: Mobility (4 items) Comorbidity Malnutrition Cognition Vision Hearing Physical energy Loneliness (3 items) Depressed mood Anxiety feelings	Frail if score ≥ 5 out of 15.	Frailty defined as disability or comorbidity. Need further explanation in the GFI construction.
Mitnitski et al, 2002 [92]: Frailty index (FI)	The Canadian Study of Health and Aging (CSHA), Prospective cohort, Canada	Random sample of community residents N=2914 82.0 years (7.4); 65+ 64.4%	20 'deficits' (symptoms, signs, impairments and disabilities)	Impairment index: 0 to 1	No clear cut-off between frail vs non-frail. No standardised number and type of deficits. Frailty defined as disability or

					comorbidity.
Gerdhem et al, 2003 [118]: Subjective Frailty Score	Cross-sectional analysis Sweden	Participants randomly selected from the city files of Malmo N=993 75 years 100%	To make a general assessment of health and appearance within 15 sec from first sight, and transfer this into an arbitrary scale.	Score ranging from 1 (low frailty) to 100 (very frail).	No clear cut-off between frail vs non-frail.
Rockwood et al, 2005 [126]: Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS)	The Canadian Study of Health and Aging (CSHA), Prospective cohort, Canada	Random sample of community residents N=2305	7-point: 1: Very fit 2: Well 3: Well, with treated comorbid disease 4: Apparently vulnerable 5: Mildly frail 6: Moderately frail 7: Severely frail (complete functional dependence on others)	Moderately frail: 6 Severely frail: 7	Frailty defined as disability or comorbidity. Needs a clinical interview.
Cacciatore et al, 2005 [113]: Frailty Staging System Based from Lachs et al, 1990, USA [132]	Osservatorio Geriatrico Regione Campania, Prospective cohort, Italy	Random sample of subjects with/without chronic heart failure, community-dwelling or institutionalised elderly N=1332 75.9 years (6.7) 60%	7 core domains of functioning scored 0 (function is preserved) or 1 (function is lost): BADL disability Mobility (ability to do heavy housework, to walk up and down stairs to the second floor and to walk half a mile) Cognitive function Visual function Hearing function Urinary continence Social support	Class 1: 0 or 1 Class 2: 2 or 3 Class 3: ≥4	Frailty defined as disability.
Amici et al, 2008 [109]: *Marigliano-Cacciafesta Polypathological Scale (MCPS)*	Cross-sectional design, Italy	N=180 79.5 years; 70+ 63.9%	Neurological disorders (5 items) Cardiopathy (4 items) Respiratory disorders (5 items) Renal disorders (4 items) Locomotive apparatus disorders (5 items) Sensory deprivation (5 items) Metabolism and nutritional state (5 items) Cognitive state and mood (5 items) Peripheral vascular system (5 items) Malignant cancerous disorders (5 items) Gastroenteritic disorders (5 items)	Score range: 0 to 245. Polypathology: Slight: <15 Medium: 15-24 Medium-severe: 25-49 Severe: 50-74 Very severe: 75+	Missing information about population characteristics Rationale for weighting scores not explained. Frailty defined as comorbidity. Dose-response effect not shown.
Kanauchi et al, 2008 [122]:	Cross-sectional study,	Hospital inpatients with cardiometabolic risk factors	HRCA Vulnerability Index (2 components): A component includes self-reported	HRCA Vulnerability Index::	Frailty defined as disability.

Based on Morris et al, 1984, USA [137]: Hebrew Rehabilitation Center for Aged (HRCA) Vunerability Index and Saliba et al, 2001, USA [133]: Vulnerable Elders Survey-13 (VES-13)	Japan	N=101 72.9 years (5.1); range 65-85 43.6%	requirements for help in: Preparing meals (score 0 or 1) Taking out the garbage (score 0 or 1) Doing ordinary work around the house (score 0 or 1) Walking up and down stairs (score 0 or 1) Needing to use a cane (score 0 or 1) Needing to use a walker (score 0 or 1) Identifying the current year (score 0 or 1) B component includes self-reported answers for: Leaving their residence (score 0 or 1) Needing help in dressing (score 0 or 1) Having health impediments (score 0 or 1) *VES-13* (13 items): Age (score 0 to 3; 3 if ≥85) Self-reported health (score 0 or 1) Difficulties in physical activities (6 items) (score 0 to 2) ADLs/IADLs (5 items) (score 0 or 4)	Vulnerable if A component score>1 or A component score=1 and B component>0 VES-13 : Score range: 0 to 10 Frail if score ≥3 Participants were frail if they were considered as vulnerable according to the *HRCA Vulnerability Index* or frail according to the *VES-13*	
Gobbens et al, 2010 [120]: Tilburg Frailty Indicator (TFI)	Cross-sectional design, Netherlands	2 random samples of community-dwelling participants Sample 1: n=245, 80.3 years (3.9), 54.7% Sample 2: n=234, 80.2 years (3.7), 59.0%	15 items scored 0 or 1: 8 physical domains: Feeling physically healthy Unexpected weight loss Difficulty in walking Difficulty in maintaining balance Hearing problems Vision problems Lack of strength in hands Physical tiredness 4 psychological domains: Cognition Depressive symptoms Anxiety Coping 3 social domains: Living alone Social relations Social support	Score range: 0 to 15 (15=highest score for frailty)	No clear cut-off between frail vs non-frail.

Objective frailty instruments					
Brown et al, 2000 [112]: *Modified Physical Performance Test (PPT)* Based on Reuben & Siu, 1990, USA [136]: *PPT* and Guralnik et al, 1995, USA [135]	Cross-sectional analysis, USA	Community-dwelling elderly N=107 83 years (4); 77+ %=not available	9 items scored 0 to 4: Lift a 7-pound book to a shelf Put on and remove a jacket Pick up penny from floor Performance of a 360 degrees turn 50-foot walk test Climb one flight of stairs Climb up and down 4 flights of stairs Stand up 5 times from a 16-inch chair Progressive Romberg test	Score range: 0-36 Not frail: 32-36 Mild frailty: 25-32 Moderate frailty: 17-24 Dependent: <17	
Gill et al, 2002 [119] Based on Gill et al, 1995, USA [134]	Primary care practices, Randomised controlled trial, USA	Community-dwelling elderly N=188 Intervention group: n=94, 82.8 years (5.0); 75+, 80% Control group: n=94, 83.5 years (5.2); 75+, 70%	Rapid gait (walking back and forth over a 10-foot (3-m) course as quickly as possible) Single chair stand	Moderately frail if rapid gait>10 s or could not stand from the chair. Severely frail if meet both criteria.	
Klein et al, 2003 [123]: Frailty index	Beaver Dam Eye Study, Prospective cohort, USA	Sample from a private census of the population of Beaver Dam 43+ years	Timed 10-ft walk (score=1 if in the highest quartile, stratified by sex) Handgrip strength (score=1 if in the lowest quartile, stratified by sex) Peak expiratory flow rate (score=1 if in the lowest quartile, stratified by sex) Ability to stand from a sitting position without using arms in one try (score=1 if unable)	Score range: 0 (better) to 4 (worse)	
Bandinelli, 2006 [110]: Short Physical Performance Battery (SPPB) Based on Guralnik et al, 1995, USA [135]	The FRAilty Screening and Intervention trial, Italy	Community-dwelling elderly visiting their primary care physicians N=251 Treatment group: n=126, 76.4 years (3.6), 66% Control group: n=125, 76.4 years (3.4), 60%	3 items scored 0 (unable to perform complete the test) to 4 (highest level of performance): Walking speed over 4 metres 5 timed repeated chair rises Standing balance	Score range: 0 to 12 Frail if ≤9	
Opasich et al, 2010 [124]	Hospital based, study of effect of personalised versus usual physiotherapy, Italy	Patients after receiving a cardiac surgery procedure N=224 Intervention group: n=150, 74.6 years (3.6); 70+,	Balance Performance Oriented Mobility Assessment (BPOMA): assessment of static and dynamic balance Get-Up-and-Go (GUG) test	Non-frail: BPOMA>19 and GUG ≤10s Moderately frail: BPOMA≤19 or GUG	

		40% Control group: n=74, 75 years (3.9); 70+, 45%		>10s Severely frail: BPOMA≤19 and GUG >10s	
Mixed (subjective and objective) frailty instruments					
Speechley & Tinetti, 1991 [128]	Subsample of the Yale Health and Aging Project (YHAP) of the Established Populations for Epidemiologic Study of the Elderly (EPESE) program Prospective cohort, USA	Community dwelling elderly N=336 75+ years	Frail attributes (each item scored 0 or 1): Age ≥80 years Gait/balance abnormalities Infrequent walking for exercise Depressed Taking sedatives Decreased strength in shoulder Decreased strength in knee Lower extremity disability Near vision loss Vigorous attributes (each item scored 0 or 1): Age <80 years Cognitively intact Frequent physical exercise other than walking Good near vision	Score: 0-9 frail attributes 0-4 vigorous attributes Frail: ≤1 vigorous and ≥4 frail attributes. Vigorous: ≥3 vigorous and ≤2 frail attributes. Transitional: neither frail nor vigorous.	
Fried et al, 2001 [16]: Phenotype of Frailty	Cardiovascular Health Study (CHS), Prospective cohort, USA	Community dwelling elderly from 4 US communities N=5317 65+ years 57.9%	5 items, each scored 0 or 1: Unintentional weight loss Self-reported exhaustion Weakness (grip strength) (1 if in the lowest quintile) Slow walking speed (1 if in the highest quintile) Low physical activity (1 if in the lowest quintile)	Score range: 0 to 5 0: frail 1-2: pre-frail ≥3: frail	
Binder et al, 2002 [111]: Physical frailty	Randomised controlled trial, USA	Community-dwelling elderly N=444 83 years (4); 78+ 65.8%	Modified Physical Performance Test score (see Brown et al, 2000) of 18-32 Peak oxygen consumption: 11-18 ml/kg Self-reported difficulty or need for assistance in 2 instrumental ADL or 1 basic ADL	Mild to moderate frailty if ≥2	Instrument contained disability component. Instrument used exclusively to select mild to moderate frailty elderly in randomised controlled trials.
Studenski et al, 2004	Qualitative and	N=not available	Appearance (3 indicators)	Change evaluated after	Needs a clinical

[130]: Clinical Global Impression of Change in Physical Frailty (CGIC-PF)	quantitative instrument development, USA	80.7 years (6.4) 80%	Healthcare utilisation (3 indicators); Medical complexity (3 indicators) Strength (3 objective measures) Balance (3 self-reported+objective measures) Nutrition (3 objective measures) Stamina (2 indicators) Neuromotor (3 objective measures) Mobility (4 objective measures) Perceived health (1 indicator) ADL (4 indicators) Emotional status (2 indicators) Social status (4 indicators)	6 months of follow-up, scored from 1 (worse) to 7 (better).	interview. No clear cut-off between frail vs non-frail. Frailty defined as disability / comorbidity.
Puts et al, 2005 [125]: Static/Dynamic frailty index	Longitudinal Aging Study Amsterdam (LASA), Prospective cohort, Netherlands	Random sample drawn from registers N=1152 Range: 55-85 years 52.3 to 60.0%	Body mass index Peak expiratory flow Cognition Vision and hearing problems (self-reported) Incontinence (self-reported) Sense of mastery (Pearlin & Schooler Mastery scale) Depressive symptoms (CES-D) Physical activity	Static frail if ≥3 components. Dynamic frail if decline or loss ≥3.	Inclusion of one item of disability. Inspired from Fried et al's instrument.
Carriere et al, 2005 [114]: Score-Risk Correspondence for dependency	Epidemiologie de l'Osteoporose (EPIDOS) study, Prospective cohort, France	Random sample drawn from vote-registration or health-insurance membership rolls N=545 Median age (interquartile range): 79 years (76-81); 75+ 100%	Time (years) since baseline evaluation Age (>=74 years) X Time since baseline evaluation Mobility Gait speed<0.78 m/s Time (s) to complete 5 chair stands Perceived health Fear of falling Time (s) to stand in tandem position Body mass index Grip strength Physical activity Education	Score: 25-169 Risk: 0.02-0.99	No clear cut-off between frail vs non-frail.
Rolfson et al, 2006 [127]: Edmonton Frail Scale (EFS) (manual research)	Hospital based, Cross-sectional analysis, Canada	Sample of patients referred for a comprehensive geriatric assessment (CGA) N=158 80.4 years (6.8); 65+	Cognition (drawing a clock) (score 0 to 2) General health status (2 questions each scored 0 to 2) Functional independence (score 0 to 2) Social support (score 0 to 2)	Score 0-17 (17=highest level of frailty)	No clear cut-off between frail vs non-frail. Frailty defined as disability.

		53%	Medication use (2 questions each scored 0 to 1) Nutrition (score 0 to 1) Mood (score 0 to 1) Continence (score 0 to 1) Functional performance (score 0 to 2)		
Ensrud et al, 2008 [116]: Study of Osteoporotic Fractures (SOF) index	Study of Osteoporotic Fractures, Prospective cohort, USA	Community-dwelling elderly from population-based listings in 4 areas of USA N=6701 76.7 years (4.8); 69+ 100%	3 items each scored 0 to 1: Unintentional weight loss (≥5% in 2 years) Inability to rise from a chair 5 times without using arms Reduced energy level (Geriatric Depression Scale)	Robust: 0 Pre-frail:1 Frail: >=2	Inspired from Fried et al's instrument.
Hyde et al, 2010 [121]: FRAIL scale	Health in Men Study, Prospective cohort, Australia	Random sample of community-dwelling elderly from the electoral roll N=3616 76.9 years (3.6); 71+ 0%	5 items each scored 0 to 1: Fatigue (SF-36) Resistance - ability to climb a single flight of stairs (SF-36) Ambulation - ability to walk one block (SF-36) Illnesses - more than 5 (list of 14 diseases) Loss of weight - more than 5% (between 4 to 5 years)	Frail if ≥3	Frailty defined as comorbidity. Inspired from Fried et al's and Mitnitski's instruments.
Freiheit et al, 2010 [117]: Brief Frailty Index	Substudy of the Calgary Cardiac and Cognition (3C) Study Prospective cohort study, hospital-based, Canada	Patients with coronary artery disease 337 70.8 years (5.9); 60+ 27%	5 items each scored 0 to 1: Balance assessment Body mass index Trail-Making Test Part B Geriatric Depression Scale Living alone	Index score range: 0-5 (high score=high risk) 4 categories: 0; 1; 2; ≥3	
Sundermann et al, 2011 [131]: *Comprehensive Assessment of Frailty (CAF)*	Hospital-based, Prospective study, USA	Patients undergoing cardiac surgery N=400 80.1 years (4.0); 74+ 51.5%	Modified Fried et al's phenotype of frailty criteria, each scored 0 or 1: BMI score Exhaustion score Physical activity score Slowness score (walking 4 mm in usual gait speed) Weakness score (grip strength) Physical performance tests, each scored 0 to 4: Standing static Balance Chair rise Put on and remove a jacket	Score range: 1-35 Not frail: 1-10 Moderately frail: 11-25 Severely frail: 25+	Based on Fried et al's and Rockwood et al's instruments.

			Pick up a pen from floor Turn 360 degrees Laboratory tests, each scored 0 to 1: Serum albumin score Forced expiratory volume in 1 second Creatinine score Rockwood et al's CSHA-CFS scored 1 to 7		

'Manual search' characterises an article not referenced by Medline but found in the reference section of selected articles.

Appendix 2. Reliability and validity results for frailty instruments utilised in individual studies

Frailty instrument	Population	Reliability Type: statistical analysis		Validity Type: outcome/statistical analysis	Strength of the association between frailty measure and mortality (estimate with its 95% CI)[d]
Subjective					
Strawbridge et al, 1998 [15]: 1994 Frailty Measure	The Alameda County Study [15]; sample of outpatients from a geriatric practice [312]; the Health Retirement Study [192]	None		**Concurrent validity**: quality of life [15]; cognitive impairment, ADL & IADL [192]/logistic regression **Construct validity**: physical performance measures [312]/Pearson's correlation coefficient	NA
Dayhoff et al, 1998 [115]	Not reported [115]	None		**Construct validity**: balance test & muscle strength [115]/discriminant analysis	NA
Rockwood et al, 1999 [20]: CSHA rules based definition	The CSHA [20]	None		**Predictive validity**: Institutionalisation and mortality [20]/Cox's proportional hazards modelling	**Rockwood**:[20] FU=5 y, RR=3.1 (2.7; 3.6)[a]
Steverink et al, 2001 [129]: Groningen frailty indicator	Hospital inpatients, nursing home residents, and community-dwelling elderly [129]; sample of community dwelling elderly [313]	**Internal consistency**: Cronbach's alpha=0.76 [129]; 0.73 [313]		**Concurrent validity**: MOS SF20 & GHQ [129]/t-test; disability (GARS)/Spearman's rank correlation coefficient **Internal construct validity**: principal component analysis [129] **Construct validity**: TFI & SPQ [313]/Spearman's rank correlation coefficient	NA
Mitnitski et al, 2002 [92]: Frailty index	The CSHA [92,126]; the Cardiovascular Health Study [193]; the Health Retirement Study [192]; a Chinese health survey [314]; the US National Long Term Care Survey [315]; the US Medicare Current Beneficiary Survey [316]; the Chinese longitudinal healthy longevity survey [317,318]; the Mexican Health and Aging	None		**Predictive validity**: mortality [92,126,193,314-316,319-321,321,323,324], hospitalisation [316], institutionalisation [316,320] /Cox's proportional hazards modelling; mortality [317]/multinomial logistic regression; mortality [318]/Weibull hazard regression; mortality, institutionalisation [322]/Kaplan-Meier method **Concurrent validity**: cognitive impairment, ADL & IADL [192]/logistic regression	**Kulminski**:[193] FU range=4 y, RR=1.05 (1.04; 1.06)[b] **Mitnitski**:[92] median FU (death)=2.8 y, RR=1.008 (1.005; 1.011)[b] **Rockwood**:[126] FU range=5.8 y, HR=1.26 (1.24; 1.29)[b] **Goggins**:[314] FU range=10 y, RR=1.28 (1.23; 1.33)[c] **Hastings**:[316] FU range=30 d, RR=1.98 (1.29; 3.05)[a] **Garcia-Gonzalez**:[319] FU range=2 y, HR=6.45 (4.10; 10.14)[a] **Armstrong**:[320] FU range=1 y, HR=1.93 (1.79; 2.08)[a] **Mitnitski**:[321] FU range=12 y, HR=1.03 (1.03; 1.04)[b] **Lucicesare**:[323] FU range=4 y, HR=5.26 (1.05; 26.42)[b]

	Study [319]; home care clients of 8 community Care Access Centres [320]; 7 population-based and 4 clinical/institutional surveys in 4 developed countries [321]; the Gothenburg H-70 cohort study [322]; the Conselice Study of Brain Ageing [323]; the National Population Health Survey of Canada [324]			**Construct validity**: age [92,314]	**Song**:[324] FU range=10 y, RR=1.57 (1.41; 1.74)[a] **Dupre**:[317] FU range=over 3 y; RRR(men)=7.75 (5.54; 10.83)[a]; RRR(women)=10.53 (7.06; 15.70)[a] **Gu**:[318] FU range=3 y; RR(men)=4.56 (2.68; 6.44)[a]; RR(women)=3.84 (1.86; 5.72)[a]
Gerdhem et al, 2003 [118]: Subjective Frailty Score	Sample of participants living in Malmo, Sweden [118]	**Inter-rater reliability**: Spearman rank correlation=0.51 to 0.59 [118]		**Construct validity**: gait, balance, muscle strength, fall [118]/Spearman rank correlation	NA
Rockwood et al, 2005 [126]: CSHA Clinical Frailty Scale	The CSHA [126]; sample of geriatric outpatients [325]	**Inter-rater reliability**: intraclass correlation coefficient=0.97 [126]; weighted kappa=0.68 [325]		**Predictive validity**: mortality [126], institutionalisation [126]/Cox's proportional hazards modelling **Construct validity**: modified MMSE, Cumulative Illness Rating Scale, history of falls, delirium, cognitive impairment or dementia, CSHA rules-based definition of frailty, CSHA Frailty Index, CSHA Function Scale [126]/Pearson or Spearman correlation coefficient; physician version & Phenotype of Frailty [325]/weighted kappa & Kendall's tau correlation	**Rockwood**:[126] FU range=5.8 y, HR=1.30 (1.27; 1.33)[b]
Cacciatore et al, 2005 [113]: Frailty Staging System	Osservatorio Geriatrico Regione Campana [113]	None		**Predictive validity**: mortality [113]/Cox's proportional hazards modelling	**Cacciatore**:[113] FU range=12 y, HR=1.62 (1.08; 2.45)[a]; HR=1.48 (1.04; 2.11)[b]
Amici et al, 2008 [109]: Marigliano-Cacciafesta Polypathological Scale	Sample of patients [109]	None		**Concurrent validity**: Mini nutritional assessment, Tinetti test, Barthel index, global evaluation functional index, geriatric depression scale [109]/ Pearson's correlation coefficient	NA
Kanauchi et al, 2008 [122]: Vulnerable Elderly Survey-13	Patients in nephrology [122]; geriatric outpatients [326]; the Medicare Current Beneficiary Survey [327]	None		**Predictive validity**: mortality [326], fracture [326], cancer diagnosis [327]/logistic regression **Concurrent validity**: WHO quality of life [122]/multi-way ANCOVA	**Ma**:[326] FU range=6 y, OR=1.16 (0.98; 1.37)[b]

Gobbens et al, 2010 [120]: Tilburg Frailty Indicator	Samples of community dwelling elderly [120,313]	**Internal consistency**: Cronbach's alpha=0.73 [120]; 0.79 [313] **Test-retest reliability**: Pearson correlation coefficient=0.79 [120]		**Predictive validity**: disability [120], health care utilisation [120]/linear regression & ROC analyses **Concurrent validity**: disability (GARS) [313]/Spearman's rank correlation coefficient; WHO quality of life [120]/multiple regression analyses **Construct validity**: GFI & SPQ [313]/Spearman's rank correlation coefficient; 15 single TFI components [120]/Pearson's correlation	NA
Objective					
Brown et al, 2000 [112]: Modified Physical Performance Test	Community-dwelling elderly [112]	None		**Construct validity**: obstacle course, Romberg full tandem, Berg balance test, fast gait [112]/ANOVA	NA
Gill et al, 2002 [119]: Physical Frailty Score	Participants living in the municipality of Treviso [328]; the Precipitating Events Project longitudinal study [324,329]	None		**Predictive validity**: mortality [328], ADL [324,329]/Cox's proportional hazards modelling **Concurrent validity**: ADL & IADL [328]/Chi-square test	**Gallucci**:[328] HR and its CI not reported.
Klein et al, 2003 [123]: Frailty index	Sample from a private census of the population of Beaver Dam [123]	**Inter-item consistency**: Spearman and Pearson correlation coefficients=0.31 to 0.52 [123]		**Concurrent validity**: distance visual acuity and contrast sensitivity [123]	NA
Bandinelli, 2006 [110]: Short Physical Performance Battery	Patients recruited by primary care physicians [110]	None		None	NA
Opasich et al, 2010 [124]	Medically stable patients after a cardiac surgery procedure [124]	None		**Concurrent validity**: functional impairment, disability, postsurgery course [124]/2-factor analysis of variance	NA
Mixed					
Speechley & Tinetti, 1991 [128]	The Yale Health and Aging Project cohort [128]	None		**Predictive validity**: falls [128]/Chi-2 test for trend in proportion **Internal construct validity**: principal component analysis [128]	NA
Fried et al, 2001 [16]:	The Cardiovascular Health	None		**Predictive validity**: mortality	**Woods**:[215] mean FU=5.9 y, HR=1.71 (1.48; 1.97)[a]

Phenotype of Frailty	Study [16,147,193]; the MacArthur Study [330]; the Health Retirement Study [192]; Toufen, Taiwan [331]; Sample of women [116]; the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly Boston Study [98]; the Osteoporotic Fractures in Men study [219]; the Study of Osteoporotic Fractures [97]; the Three-City Study [96]; the Hispanic Established Population for the Epidemiological Study of the Elderly [332-335]; the Concord Health and Ageing in Men Project [336]; the Montreal Unmet Needs Study [337]; the Women's Health and Aging Studies I & II [75]; the Women's Health Initiative Observational Study [215]; a nationwide Survey of Health and Living Status of the Elderly in Taiwan [338]; the Canadian Study of Health and Aging [194]; sample of surgical patients [146]			[16,75,96,97,116,193,194,215,219,333,335], fractures [97,116,215], falls [16,98], ADL & IADL [16,75,332], hospitalisation [16], institutionalisation [75,194], idiopathic venous thromboembolism [147]/ Cox's proportional hazards modelling; mortality [330], falls [97,116], ADL & IADL [16,96,116,215], hospitalisation [96,98,215], emergency department visits [98]/logistic regression; MMSE [150]/ general linear mixed model; postoperative complications [146]/logistic regression model **Concurrent validity**: ADL & IADL [98,192]; Bartel index score & depression [331], use of specific health and community services [336]/logistic regression; chronic medical conditions [98], SPPB [98], MMSE [98], Hopkins Verbal Learning Test [98]; Trail Making Test part A & part B [98], Clock-in-a-Box [98], CESD scale [98]/analyse of variance; ADL & IADL, comorbidity [337]/the Cochran-Mantel-Haenszel test; ADL & IADL, comorbidities [338]/one-way ANOVA; health-related quality of life using SF-36 [334]/logistic regression model **Internal construct validity**: latent class analysis [75] **Convergent validity**: Mitnitski's Frailty Index score [194]/Pearson's correlation coefficient	**Bandeen-Roche**:[75] FU range =3 y, HR=6.03 (3.00; 12.08)[a] **Cawthon**:[219] mean FU=4.7 y, HR=2.05 (1.55; 2.72)[a] **Ensrud**:[97] mean FU=9 y, HR=1.82 (1.56; 2.13)[a] **Avila-Funes**:[96] FU range=4 y, HR=1.21 (0.78; 1.87)[a] **Kulminski**:[193] FU range=4 y, RR=1.02 (1.02; 1.03)[b] **Sarkisian**:[330] FU range=9 y, OR=2.1 (1.2; 3.8)[a] **Graham**:[333] FU range=10 y, HR=1.81 (1.41; 2.31)[a] **Fried**:[16] FU range=7 y, HR=1.63 (1.27; 2.08)[a] **Ensrud**:[116] FU range=9 y, HR=2.75 (2.46; 3.07)[a] **Berges**:[335] FU range=10 y, HR(men)=3.04 (2.16; 4.28)[a]; HR(women)=1.92 (1.39; 2.65)[a]
Binder et al, 2002 [111]: Physical frailty	Community-dwelling elderly [111]	**Test-retest reliability** for modified physical performance test=0.96 [111]		None	NA
Studenski et al, 2004 [130]: Clinical Global Impression of Change in Physical Frailty	Sample of 24 patients [130]	**Interrater reliability**: Kendall's multiple-rater concordance coefficient=0.97 [130]		**Face validity**: 6 experts & 46 clinicians [130]	NA
Puts et al, 2005 [125]: Static/Dynamic frailty	The Longitudinal Aging Study Amsterdam [125]	None		**Predictive validity**: performance tests (walking speed, rising from a chair, putting	NA

index				on and taking off a cardigan, and maintaining balance in a tandem stand) & ADL [125]/logistic regression	
Carriere et al, 2005 [114]: Score-Risk Correspondence for dependency	The EPIDOS study [114]	None		**Predictive validity**: 7-year disability [114]/logistic regression	NA
Rolfson et al, 2006 [127]: Edmonton Frail Scale	Sample of patients 65+ years [127]; home care clients of 8 community Care Access Centres [320]; Toufen, Taiwan [331]; Brazilian elderly [339]	**Internal consistency**: Crohnbach's coefficient=0.62 [127] **Inter-rater reliability**: Kappa coefficient=0.77 [127]		**Predictive validity**: mortality [320], institutionalisation [320]/Cox's proportional hazards model; postoperative complications/logistic regression model **Concurrent validity**: comorbidity [331], MMSE [331], incontinence [331], depression [331]/logistic regression **Construct validity**: Barthel Index [127], Rolfson and colleagues' GCIF [127]/Pearson correlation; MMSE score & the Functional independence measure [339]/Spearman's correlation coefficient	**Armstrong**:[320] FU range=1 y, HR=2.49 (2.32; 2.68)[a]
Ensrud et al, 2008 [116]: Study of Osteoporotic Fractures index	Sample of women [116]; the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly Boston Study [98]; community-dwelling outpatients [340]	None		**Predictive validity**: fractures [116], mortality [116], falls [98]/Cox's proportional hazards; falls [116], disability [116], overnight hospitalisation [98], emergency department visits [98]/logistic regression; **Concurrent validity**: ADL & IADL [98]/logistic regression; chronic medical conditions [98], SPPB [98], MMSE [98], Hopkins Verbal Learning Test [98]; Trail Making Test part A & part B [98], Clock-in-a-Box [98], CESD scale [98]/analyses of variance; Older People's quality of life [340]/linear regression analysis	**Ensrud**:[116] FU range=9 y, HR=2.37 (2.14; 2.61)[a]
Hyde et al, 2010 [121]: FRAIL scale	The Health in Men Study [121]	None		**Predictive validity**: Mortality [121]/Cox's proportional hazards model; ADL & IADL [121]/logistic regression model	**Hyde**:[121] FU range=7 y, HR=3.97 (2.89; 5.45)[a]
Freiheit et al, 2010 [117]: Brief Frailty Index	Patients undergoing cardiac catheterisation for coronary artery disease [117]	None		**Predictive validity**: ADL [117], health-related quality of life [117]/Poisson regression model	NA
Sundermann et al, 2011	Patients undergoing elective	None		**Predictive validity**: Mortality	NA

[131]: Comprehensive Assessment of Frailty	cardiac surgery [131]			[131]/Armitage's Trend Test for proportions **Construct validity**: Society of Thoracic Surgeons score & European system for cardiac operative risk evaluation [131]/Spearman's rank correlation	

Abbreviations: (I)ADL: (instrumental)activity of daily living; CI: confidence interval; CSHA: Canadian Study of Health and Aging; FU: follow-up; GARS: Groningen activity restriction scale; GHQ: general health questionnaire; HR: hazard rate; RR: relative risk; MMSE: mini-mental state examination; MOS-SF20: medical outcomes study 20-item short-form; NA: not available; OR: odds ratio; RRR: relative risk ratio; SPQ: Sherbrooke postal questionnaire.

[a] RR calculated for the highest versus lowest category of the frailty score.

[b] RR calculated based on 1-unit increment in the frailty score.

[c] RR calculated based on 10-year increment in the frailty score.

[d] Given that the computation of hazard ratios and odds ratios involves the use of different units and scales of measurement of frailty, they cannot be directly used to make conclusions about which instrument better predicts a given outcome. Nonetheless, they do provide some insights into the value of each scale.

Appendix 3. Frailty-defining criteria: Whitehall II and CHS

	Whitehall II (n=5,366)		CHS (n=5,317) original validation cohort	
	Definition	**%**	**Definition**	**%**
Age (range)	55-79		65-101	
Age class	<65	50.6	<65	0
	65-74	41.0	65-74	67.3
	75-84	8.4	75-84	29.1
	≥85	0	≥85	3.6
Exhaustion	Self-report of either of: 1) felt that everything I did was an effort in the last week, or 2) could not get going in the last week	10.7	Self-report of either of: 1) felt that everything I did was an effort in the last week, or 2) could not get going in the last week	21.3
Low energy expenditure	Whitehall II Time Activity questionnaire: Men: Those with Kcal of PA/week<383 Women: Those with Kcal of PA/week<270	22.8	Short version of the Minnesota Leisure Time Activity questionnaire: Men: Those with Kcal of PA/week<383 Women: Those with Kcal of PA/week<270	24.1
Slowness	Walking 8 feet (2.44 m): Men: Height ≤ 173 cm: ≥ 3.73 sec or height > 173 cm: ≥ 3.20 sec Women: Height ≤ 159 cm: ≥ 3.73 sec or height > 159 cm: ≥ 3.20sec	9.7	Walking 15 feet (4.57 m): Men: Height ≤ 173 cm: ≥ 7sec or height > 173 cm: ≥ 6 sec Women: Height ≤ 159 cm: ≥ 7sec or height > 159 cm: ≥ 6 sec	38.0
Weakness	Grip strength (kg): Men: BMI ≤ 24: ≤ 29 or BMI ≤ 24.1-26: ≤ 30 or BMI ≤ 26.1-28: ≤ 30 or BMI > 28: ≤ 32 Women: BMI ≤ 23: ≤ 17 or BMI ≤ 23.1-26: ≤ 17.3 or BMI ≤ 26.1-29: ≤ 18 or BMI > 29: ≤ 21	9.9	Grip strength (kg): Men: BMI ≤ 24: ≤ 29 or BMI ≤ 24.1-26: ≤ 30 or BMI ≤ 26.1-28: ≤ 30 or BMI > 28: ≤ 32 Women: BMI ≤ 23: ≤ 17 or BMI ≤ 23.1-26: ≤ 17.3 or BMI ≤ 26.1-29: ≤ 18 or BMI > 29: ≤ 21	26.2
Weight loss	Lost ≥10% of previous 5 years' body weight	3.7	Either of: 1) Lost >10 pounds unintentionally in the last year 2) Lost ≥5% of previous year's body weight	7.3
Frailty status	Non-frail	58.6	Non-frail	46.4
	Pre-frail	38.6	Pre-frail	46.7
	Frail	2.8	Frail	6.9

Appendix 4. Basic and instrumental activities of daily living (BADL and IADL) scales

A. BADL scale

Katz BADL (score 0 to 6)	BADL in the Whitehall II study ('modified' Katz BADL), score 0 to 6
Bathing (sponge bath, tub bath, or shower) - Receives either no assistance or assistance in bathing only one part of body	Bathing or showering
Dressing - Gets clothes and dresses without any assistance except for tying shoes.	Dressing, including putting on shoes and socks
Toileting - Goes to toilet room, uses toilet, arranges clothes, and returns without any assistance (may use cane or walker for support and may use bedpan/urinal at nights	Using the toilet, including getting up or down
Transferring - Moves in and out of bed and chair without assistance (may use can or walker)	Getting in or out of bed
Continence - Controls bowel and bladder completely by self (without occasional 'accidents')[a]	--
Feeding - Feeds self without assistance (except for help with cutting meat or buttering bread).	Eating, such as cutting up your food
--	Walking across a room[b]

[a] Question on bowel and bladder continence was not present in the Whitehall II study.

[b] Question on 'walking across a room' was not present in original Katz questionnaire.

B. IADL scale

Lawton and Brody IADL Score 0 to 8	IADL in the Whitehall II study ('modified' Lawton IADL), score 0 to 7
Ability to use telephone	Making telephone calls
Shopping	Shopping for groceries
Food preparation	Preparing a hot meal
Housekeeping	Doing work around the house or garden
Laundry[a]	--
Mode of transportation[a]	--
Responsibility for own medications	Taking medication
Ability to handle finances	Managing money, such as paying bills and keeping track of expenses
--	Using a map to figure out how to get around in a strange place[b]

[a] Questions on laundry and mode of transportation were not present in the Whitehall II study.

[b] Question on 'using a map…' was not present in the original Lawton and Brody questionnaire.

Appendix 5. Characteristics of the 5,169 study participants according to frailty status

	Frailty status				P-value
	Frail (n=147, 2.8%)		Pre-frail/non-frail (n=5022, 97.2%)		
	N	% / Mean (SD) or Median (IQR)	N	% / Mean (SD) or Median (IQR)	
Sex					
Men	79	53.7	3671	73.1	<0.0001[1]
Women	68	46.3	1351	26.9	
Age (years) in median (IQR)	147	69.9 (62.7; 74.3)	5022	64.8 (60.8; 70.7)	<0.0001[2]
Ethnicity					
White	116	78.9	4663	92.9	<0.0001[1]
Non-White	31	21.1	359	7.1	
Education					
No or lower secondary	78	55.7	2055	42.5	0.05[3]
A levels	21	15.0	1313	27.2	
University or higher	41	29.3	1468	30.3	
Missing	7	-	186	-	
Socio-economic position					
Low	38	25.8	477	9.5	<0.0001[3]
Intermediate	67	45.6	2147	42.8	
High	42	28.6	2398	47.8	
Income £/year					
<15,000	42	29.8	520	10.6	<0.0001[3]
15,000-<25,000	42	29.8	1055	21.6	
25,000-<50,000	43	30.5	2065	42.2	
≥50,000	17	10.4	1251	25.6	
Missing	6	-	131	-	
Marital status					
Married/Cohabiting	82	58.2	3788	76.5	<0.0001[1]
Other	59	41.8	1164	23.5	
Missing	6	-	70	-	
Number of relatives and friends in median (IQR)	142	6 (3; 10)	4937	6 (4; 10)	0.26[2]
Smoking status					
Never	83	57.2	2605	52.3	0.06[1]
Stopped before phase 1	30	20.7	1513	30.4	
Stopped during follow-up	21	14.5	515	10.4	
Current	11	7.6	345	6.9	
Missing	2	-	44	-	
Daily consumption of fruit and vegetables					
No	57	38.8	1070	21.3	<0.0001[1]
Yes	90	61.2	3948	78.7	
Missing					
Daily alcohol consumption level (WHO)					
None	60	41.4	873	17.6	<0.0001[3]
Not risky	62	42.7	3190	64.2	
Risky	23	15.9	907	18.2	
Missing	2	-	52	-	

Alcohol consumption (units/week) in median (IQR)	145	2 (0; 12)	4970	7 (2; 15)	<0.0001[2]
Physical activity (hours/week) in categories					
<2.5	140	95.2	2068	41.4	<0.0001[1]
≥2.5	7	4.8	2933	58.6	
Missing	0	-	21	-	
Physical activity (hours/week) in median (IQR)	147	0.3 (0; 0.8)	5001	3.1 (1.3; 5.7)	<0.0001[2]
BMI (kg/m^2) in categories					
Normal (<25)	54	36.7	1930	38.4	0.005[3]
Overweight ([25-30[)	43	29.3	2171	43.2	
Obese (≥30)	50	34.0	921	18.4	
BMI (kg/m^2) in mean (SD)	147	28.1 (6.3)	5022	26.6 (4.3)	0.005[4]
Systolic blood pressure status					
Hypotension/normal	60	41.4	1949	38.9	0.64[3]
Prehypertension	53	36.6	2228	44.4	
Hypertension	32	22.0	838	16.7	
Missing	2	-	7	-	
Systolic blood pressure (mmHg) in mean (SD)	145	125.7 (16.5)	5015	125.2 (16.1)	0.73[4]
Diastolic blood pressure status					
Hypotension/normal	118	81.4	4102	81.8	0.67[3]
Prehypertension	20	13.8	738	14.7	
Hypertension	7	4.8	175	3.5	
Missing	2	-	7	-	
Diastolic blood pressure (mmHg) in mean (SD)	145	69.5 (11.5)	5015	71.0 (10.0)	0.12[4]
MMSE score <24					
No	142	97.3	4946	99.5	0.01[5]
Yes	4	2.7	26	0.5	
Missing	1	-	50	-	
MMSE score in median (IQR)	146	28 (27; 29)	4972	29 (28; 29)	0.005[2]
Diabetes status					
No	90	61.2	3542	70.5	0.02[1]
Yes	57	38.8	1480	29.5	
Previous history of hospitalisation					
No	32	21.8	2041	40.6	<0.0001[1]
Yes	115	78.2	2981	59.4	
Number of medications in median (IQR)	147	4 (2; 7)	5022	2 (1; 4)	<0.0001[2]
Modified basic ADL≥1					
No	86	58.9	4627	92.4	<0.0001[1]
Yes	60	41.1	382	7.6	
Missing	1	-	13	-	
Modified instrumental ADL≥1					
No	65	44.5	4425	88.3	<0.0001[1]
Yes	81	55.5	584	11.7	
Missing	1	-	13	-	
Presence of comorbidity					
No	57	38.8	3325	66.2	<0.0001[1]

Yes	90	61.2	1697	33.8	
Hospitalisation after phase 9					
No	87	59.2	3932	78.3	<0.0001[1]
Yes	60	40.8	1090	21.7	

SD: standard deviation; IQR: interquartile range; WHO: World Health Organisation; BMI: body mass index; MMSE: mini mental state examination; ADL: activity daily living.

1 Chi-square test; *2* Wilcoxon-Mann-Whitney test; *3* Cochrane-Armitage trend test; *4* Student's t-test; *5* Fisher's exact test.

Appendix 6. Characteristics of the 5,169 study participants according to comorbidity status

	Comorbidity				P-value
	Yes (n=1787, 34.6%)		No (n=3382, 65.4%)		
	N	% / Mean (SD) or Median (IQR)	N	% / Mean (SD) or Median (IQR)	
Sex					
Men	1269	71.0	2481	73.4	0.07[1]
Women	518	29.0	901	26.6	
Age (years) in median (IQR)	1787	66.3 (61.7; 72,2)	3382	64.2 (60.5; 69.9)	<0.0001[2]
Ethnicity					
White	1590	89.0	3189	94.3	<0.0001[1]
Non-White	197	11.0	193	5.7	
Education					
No or lower secondary	716	41.7	1417	43.5	0.32
A levels	473	27.5	861	26.4	
University or higher	529	30.8	980	30.1	
Missing	69	-	124	-	
Socio-economic position					
Low	179	10.0	336	9.9	0.71[3]
Intermediate	772	43.2	1442	42.7	
High	836	46.8	1604	47.4	
Income £/year					
<15,000	228	13.1	334	10.2	<0.0001[3]
15,000-<25,000	413	23.7	684	20.8	
25,000-<50,000	729	41.9	1379	41.9	
≥50,000	372	21.3	893	27.1	
Missing	45	-	92	-	
Marital status					
Married/Cohabiting	1312	74.4	2558	76.8	0.06[1]
Other	451	25.6	772	23.2	
Missing	24	-	52	-	
Number of relatives and friends in median (IQR)/mean	1756	6 (4; 10)/7.7	3323	6 (4; 10)/8.3	0.003[2]
Smoking status					
Never	875	49.5	1813	54.0	<0.0001[1]
Stopped before phase 1	560	31.7	983	29.3	
Stopped during follow-up	225	12.7	311	9.3	
Current	107	6.1	249	7.4	
Missing	20	-	26	-	
Daily consumption of fruit and vegetables					
No	383	21.5	744	22.0	0.65[1]
Yes	1402	78.5	2636	78.0	
Missing	2	-	2	-	
Daily alcohol consumption level (WHO)					
None	366	20.7	567	17.0	0.24[3]
Not risky	1062	60.0	2190	65.4	
Risky	341	19.3	589	17.6	

Missing	18	-	36	-	
Alcohol consumption (units/week) in median (IQR)/mean	1769	7 (2; 16)/10.9	3346	7 (2; 15)/10.6	0.09[2]
Physical activity (hours/week) in categories					
<2.5	834	46.9	1374	40.8	<0.0001[1]
≥2.5	946	53.1	1994	59.2	
Missing	7	-	14	-	
Physical activity (hours/week) in median (IQR)	1780	2.8 (0.9; 5.2)	3368	3.3 (1.3; 5.9)	<0.0001[2]
BMI (kg/m^2) in categories					
Normal (<25)	566	31.7	1418	41.9	<0.0001[3]
Overweight ([25-30[)	788	44.1	1426	42.2	
Obese (≥30)	433	24.2	538	15.9	
BMI (kg/m^2) in mean (SD)	1787	27.5 (4.7)	3382	26.2 (4.1)	<0.0001[4]
Systolic blood pressure status					
Hypotension/normal	687	38.6	1322	39.1	0.70[3]
Prehypertension	792	44.4	1489	44.1	
Hypertension	303	17.0	567	16.8	
Missing	5	-	4	-	
Systolic blood pressure (mmHg) in mean (SD)	1782	125.3 (16.0)	3378	125.2 (16.1)	0.74[4]
Diastolic blood pressure status					
Hypotension/normal	1476	82.8	2744	81.2	0.20[3]
Prehypertension	246	13.8	512	15.2	
Hypertension	60	3.4	122	3.6	
Missing	5	-	4	-	
Diastolic blood pressure (mmHg) in mean (SD)	1782	70.5 (10.0)	3378	71.1 (10.1)	0.03[4]
MMSE score <24					
No	1760	99.3	3328	99.5	0.53[1]
Yes	12	0.7	18	0.5	
Missing	15	-	36	-	
MMSE score in median (IQR)/mean	1772	29 (28; 29)/28.4	3346	29 (28; 29)/28.5	0.03[2]
Diabetes status					
No	1140	63.8	2492	73.7	<0.0001[1]
Yes	647	36.2	890	26.3	
Previous history of hospitalisation					
No	505	28.3	1568	46.4	<0.0001[1]
Yes	1282	71.7	1814	53.6	
Number of medications in median (IQR)	1787	4 (2; 6)	3382	1 (0; 3)	<0.0001[2]
Phenotype of frailty					
Non-frail	918	51.4	2111	62.4	<0.0001[3]
Pre-frail	779	43.6	1214	35.9	
Frail	90	5.0	57	1.7	
Modified basic ADL≥1					
No	1524	85.5	3189	94.5	<0.0001[1]
Yes	258	14.5	184	5.5	
Missing	5	-	9	-	
Modified instrumental ADL≥1					
No	1420	79.7	3070	91.0	<0.0001[1]
Yes	362	20.3	303	9.0	
Missing	5	-	9	-	

Hospitalisation after phase 9					
No	1256	70.3	2763	81.7	<0.0001[1]
Yes	531	29.7	619	18.3	

SD: standard deviation; IQR: interquartile range; WHO: World Health Organisation; BMI: body mass index; MMSE: mini mental state examination; ADL: activity daily living.

1 Chi-square test; *2* Mann-Whitney test; *3* Cochrane-Armitage trend test; *4* Student's t-test.

Appendix 7. Characteristics of the 5,155 study participants according to BADL disability status

	Disability (≥ 1 BADL)				P-value
	Yes (n=442, 8.6%)		No (n=4713, 91.4%)		
	N	% / Mean (SD) or Median (IQR)	N	% / Mean (SD) or Median (IQR)	
Sex					
Men	287	64.9	3456	73.3	0.0002[1]
Women	155	35.1	1257	26.7	
Age (years) in median (IQR)	442	66.6 (61.6, 72.6)	4713	64.7 (60.8, 70.6)	<0.0001[2]
Ethnicity					
White	397	89.8	4372	92.8	0.02[1]
Non-White	45	10.2	341	7.2	
Education					
No or lower secondary	208	49.0	1919	42.3	0.0005[3]
A levels	119	28.1	1211	26.7	
University or higher	97	22.9	1409	31.0	
Missing	18	-	174	-	
Socio-economic position					
Low	70	15.8	441	9.4	<0.0001[3]
Intermediate	206	46.6	2003	42.5	
High	166	37.6	2269	48.1	
Income £/year					
<15,000	78	18.4	479	10.4	<0.0001[3]
15,000-<25,000	123	29.0	971	21.2	
25,000-<50,000	138	32.6	1967	42.8	
≥50,000	85	20.0	1177	25.6	
Missing	18	-	119	-	
Marital status					
Married/Cohabiting	299	68.7	3566	76.8	0.0002[1]
Other	136	31.3	1078	23.2	
Missing	7	-	69	-	
Number of relatives and friends in median (IQR)/mean	433	6 (4; 10)/7.6	4633	6 (4; 10)/7.9	0.57[2]
Smoking status					
Never	217	49.5	2466	52.8	0.0004[1]
Stopped before phase 1	119	27.2	1421	30.4	
Stopped during follow-up	72	16.4	464	9.9	
Current	30	6.9	324	6.9	
Missing	4	-	38	-	
Daily consumption of fruit and vegetables					
No	129	29.2	992	21.1	<0.0001[1]
Yes	313	70.8	3717	78.9	
Missing	0	-	4	-	
Daily alcohol consumption level (WHO)					
None	104	24.1	827	17.7	0.04[3]
Not risky	249	57.6	2993	64.1	
Risky	79	18.3	849	18.2	
Missing	10	-	44	-	
Alcohol consumption (units/week) in	432	6 (1; 14)	4669	7 (2; 15)	0.002[2]

median (IQR)					
Physical activity (hours/week) in categories					
<2.5	250	56.6	1950	41.6	<0.0001[1]
≥2.5	192	43.4	2742	58.4	
Missing	0	-	21	-	
Physical activity (hours/week) in median (IQR)	442	1.9 (0.6; 3.9)	4692	3.2 (1.3; 5.8)	<0.0001[2]
BMI (kg/m^2) in categories					
Normal (<25)	106	24.0	1875	39.8	<0.0001[3]
Overweight ([25-30[)	170	38.5	2039	43.3	
Obese (≥30)	166	37.5	799	16.9	
BMI (kg/m^2) in mean (SD)	442	29.0 (5.4)	4713	26.5 (4.2)	<0.0001[4]
Systolic blood pressure status					
Hypotension/normal	164	37.3	1842	39.1	0.23[3]
Prehypertension	192	43.6	2080	44.2	
Hypertension	84	19.1	785	16.7	
Missing	2	-	6	-	
Systolic blood pressure (mmHg) in mean (SD)	440	126.0 (16.3)	4707	125.2 (16.1)	0.32[4]
Diastolic blood pressure status					
Hypotension/normal	352	80.0	3856	81.9	0.41[3]
Prehypertension	72	16.4	685	14.6	
Hypertension	16	3.6	166	3.5	
Missing	2	-	6	-	
Diastolic blood pressure (mmHg) in mean (SD)	440	71.0 (10.2)	4707	70.9 (10.1)	0.85[4]
MMSE score <24					
No	434	99.1	4641	99.5	0.31[5]
Yes	4	0.9	25	0.5	
Missing	4	-	47	-	
MMSE score in median (IQR)/mean	438	29 (28; 29)/28.3	4666	29 (28; 29)/28.5	0.004[2]
Diabetes status					
No	302	68.3	3322	70.5	0.34[1]
Yes	140	31.7	1391	29.5	
Previous history of hospitalisation					
No	125	28.3	1945	41.3	<0.0001[1]
Yes	317	71.7	2768	58.7	
Number of medications in median (IQR)	442	4 (2; 6)	4713	2 (1; 4)	<0.0001[2]
Phenotype of frailty					
Non-frail	157	35.5	2867	60.8	<0.0001[3]
Pre-frail	225	50.9	1760	37.4	
Frail	60	13.6	86	1.8	
Modified instrumental ADL≥1					
No	193	43.7	4297	91.2	<0.0001[1]
Yes	249	56.3	416	8.8	
Presence of comorbidity					
No	184	41.6	3189	67.7	<0.0001[1]
Yes	258	58.4	1524	32.3	
Hospitalisation after phase 9					
No	290	65.6	3720	78.9	<0.0001[1]
Yes	152	34.4	993	21.1	

SD: standard deviation; IQR: interquartile range; WHO: World Health Organisation; BMI: body mass index; MMSE: mini mental state examination; ADL: activity daily living.

1 Chi-square test; *2* Mann-Whitney test; *3* Cochrane-Armitage trend test; *4* Student's t-test; *5* Fisher's exact test.

Appendix 8. Factors significantly associated with frailty, comorbidity, and disability

	Frailty	Comorbidity	Disability (BADL ≥1)
Sex	√	--	√
Age (years)	√	√	√
Ethnicity	√	√	√
Education	√	--	√
Socio-economic position	√	--	√
Income £/year	√	√	√
Marital status	√	--	√
Number of relatives and friends	--	√	--
Smoking status	--	√[b]	√[b]
Daily consumption of fruit and vegetables	√	--	√
Alcohol consumption (units/week)	√[a]	--	√[a]
Physical activity (hours/week)	√	√	√
BMI (kg/m^2)	√	√	√
Systolic blood pressure (mmHg)	--	--	--
Diastolic blood pressure (mmHg)	--	--	--
MMSE score	√	--	--
Diabetes status	√	√	√
Previous history of hospitalisation	√	√	√
Number of medications	√	√	√
Frailty status		√	√
Modified basic ADL≥1	√	√	
Modified instrumental ADL≥1	√	√	√
Comorbidity	√		√
Hospitalisation after phase 9	√	√	√

Directions of the associations:

[a] Participants who had comorbidity and/or were disabled were less likely to consume alcohol.

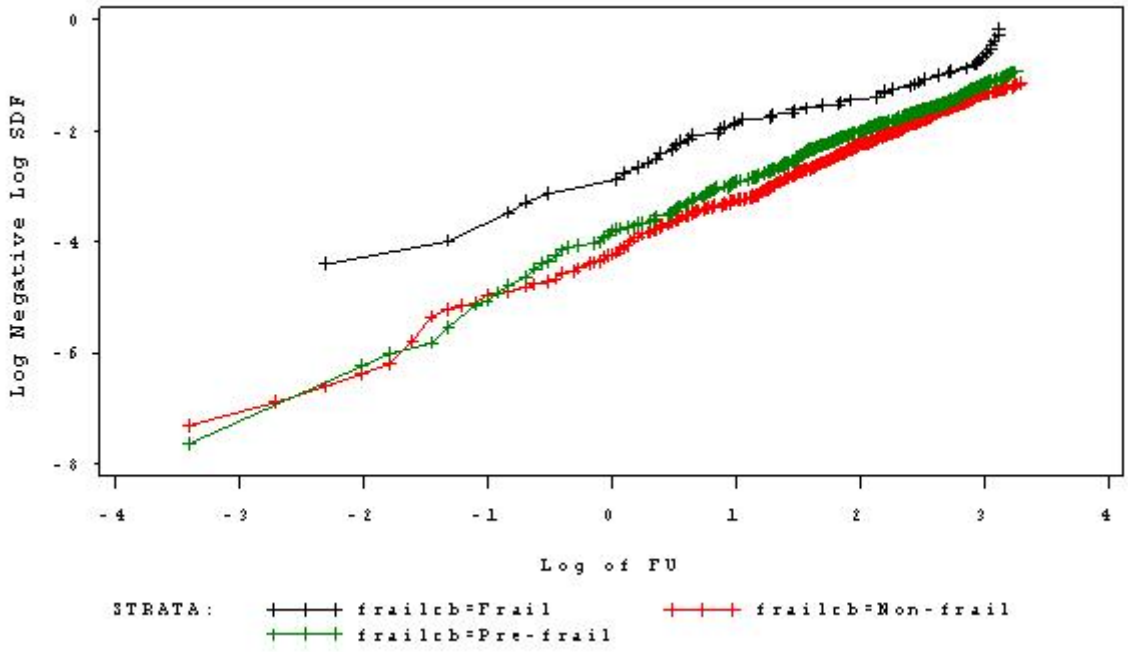
[b] Participants who had comorbidity and/or were disabled were more likely to be a never-smoker or to stop smoking.

Appendix 9. Cross-sectional association between frailty and modified BADL/IADL disability, and comorbidity

	Modified Basic ADL N(Yes)=442			Modified Instrumental ADL N(Yes)=665			Comorbidity N(Yes)=1787		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Unadjusted									
Frailty									
Non-frail (n=3029)	1	--	--	1	--	--	1	--	--
Pre-frail (n=1993)	2.34	1.89-2.89	<0.0001	3.03	2.54-3.63	<0.0001	1.48	1.31-1.66	<0.0001
Frail (n=147)	12.74	8.83-18.39	<0.0001	16.45	11.53-23.45	<0.0001	3.63	2.58-5.10	<0.0001
Sex and age adjusted									
Frailty									
Non-frail (n=3029)	1	--	--	1	--	--	1	--	--
Pre-frail (n=1993)	2.24	1.81-2.78	<0.0001	2.83	2.36-3.39	<0.0001	1.43	1.26-1.61	<0.0001
Frail (n=147)	11.31	7.78-16.42	<0.0001	13.86	9.65-19.89	<0.0001	3.20	2.27-4.52	<0.0001

ADL: activity daily living; CI: confidence interval.

Appendix 10. Verification of proportionality assumption: log(-log(hospitalisation)) on function of log of duration of follow-up



Appendix 11. Characteristics of the 5,169 study participants according to hospitalisation status

	Incident hospitalisation				P-value
	Yes (n=1150, 22.2%)		No (n=4019, 77.8%)		
	N	% / Mean (SD) or median (IQR)	N	% / Mean (SD) or median (IQR)	
Sex					
Men	835	72.6	2915	72.5	0.96[1]
Women	315	27.4	1104	27.5	
Age (years) in median (IQR)	1150	66.8 (62.1; 72.7)	4019	64.4 (60.6; 70.2)	<0.0001[2]
Ethnicity					
White	1025	89.1	3754	93.4	<0.0001[1]
Non-White	113	10.0	265	6.6	
Education					
No or lower secondary	518	46.9	1615	41.7	0.0004[3]
A levels	295	26.7	1039	26.8	
University or higher	291	26.4	1218	31.5	
Missing	46	-	147	-	
Socio-economic position					
Low	130	11.3	385	9.6	0.003[3]
Intermediate	521	45.3	1693	42.1	
High	499	43.4	1941	48.3	
Income £/year					
<15,000	134	12.0	428	10.9	<0.0001[3]
15,000-<25,000	288	25.8	809	20.7	
25,000-<50,000	460	41.3	1648	42.1	
≥50,000	233	20.9	1032	26.3	
Missing	35	-	102	-	
Marital status					
Married/Cohabiting	851	75.1	3019	76.2	0.43[1]
Other	282	24.9	941	23.8	
Missing	17	-	59	-	
Number of relatives and friends in median (IQR)	1128	6 (4; 10)	3951	6 (4; 10)	0.17[2]
Smoking status					
Never	579	50.8	2109	52.9	0.65[1]
Stopped before phase 1	357	31.3	1186	29.8	
Stopped during follow-up	123	10.8	413	10.4	
Current	80	7.0	276	6.9	
Missing	11	-	35	-	
Daily consumption of fruit and vegetables					
No	272	23.7	855	21.3	0.08[1]
Yes	877	76.3	3161	78.7	
Missing	1	-	3	-	
Daily alcohol consumption level (WHO)					
None	242	21.3	691	17.4	0.02[3]
Not risky	695	61.1	2557	64.3	
Risky	200	17.6	730	18.3	
Missing	13	-	41	-	

Alcohol consumption (units/week) in median (IQR)/mean	1137	7 (1; 14)/10.3	3978	7 (2; 16)/10.8	0.01[2]
Physical activity (hours/week) in categories					
<2.5	537	46.9	1671	41.7	0.002[1]
≥2.5	608	53.1	2332	58.3	
Missing	5	-	16	-	
Physical activity (hours/week) in median (IQR)	1145	2.7 (0.9; 5.3)	4003	3.1 (1.3; 5.7)	0.001[2]
BMI (kg/m^2) in categories					
Normal (<25)	424	36.9	1560	38.8	0.26[3]
Overweight ([25-30[)	503	43.7	1711	42.6	
Obese (≥30)	223	19.4	748	18.6	
BMI (kg/m^2) in mean (SD)	1150	26.8 (4.3)	4019	26.6 (4.4)	0.13[4]
Systolic blood pressure status					
Hypotension/normal	460	40.0	1549	38.6	0.10[3]
Prehypertension	518	45.1	1763	44.0	
Hypertension	171	14.9	699	17.4	
Missing	1	-	8	-	
Systolic blood pressure (mmHg) in mean (SD)	1149	124.6 (15.4)	4011	125.4 (16.3)	0.11[4]
Diastolic blood pressure status					
Hypotension/normal	963	83.8	3257	81.2	0.07[3]
Prehypertension	149	13.0	609	15.2	
Hypertension	37	3.2	145	3.6	
Missing	1	-	8	-	
Diastolic blood pressure (mmHg) in mean (SD)	1149	69.9 (10.0)	4011	71.2 (10.1)	0.0002[4]
MMSE score <24					
No	1121	98.8	3967	99.6	0.005[1]
Yes	13	1.2	17	0.4	
Missing	16	-	35	-	
MMSE score in median (IQR)/mean	1134	29 (28; 29)/28.3	3984	29 (28; 29)/28.5	<0.0001[2]
Diabetes status					
No	783	68.1	2849	70.9	0.07[1]
Yes	367	31.9	1170	29.1	
Previous history of hospitalisation					
No	278	24.2	1795	44.7	<0.0001[1]
Yes	872	75.8	2224	55.3	
Number of medications in median (IQR)	1150	3 (1; 5)	4019	2 (1; 4)	<0.0001[2]
Phenotype of frailty					
Non-frail	614	53.4	2415	60.1	<0.0001[3]
Pre-frail	476	41.4	1517	37.8	
Frail	60	5.2	87	2.1	
Modified basic ADL≥1					
No	993	86.7	3720	92.8	<0.0001[1]
Yes	152	13.3	290	7.2	
Missing	5	-	9	-	
Modified instrumental ADL≥1					
No	940	82.1	3550	88.5	<0.0001[1]
Yes	205	17.9	460	11.5	
Missing	5	-	9	-	
Presence of comorbidity					
No	619	53.8	2763	68.8	<0.0001[1]

Yes	531	46.2	1256	31.2

SD: standard deviation; IQR: interquartile range; WHO: World Health Organisation; BMI: body mass index: MMSE: mini mental state examination; ADL: activity daily living.

1 Chi-square test; 2 Mann-Whitney test; 3 Cochrane-Armitage trend test; 4 Student's t-test.

Appendix 12. HRs (95% CI) for hospitalisation according to frailty, comorbidity, and disability status, with a maximum follow-up time of 30 months

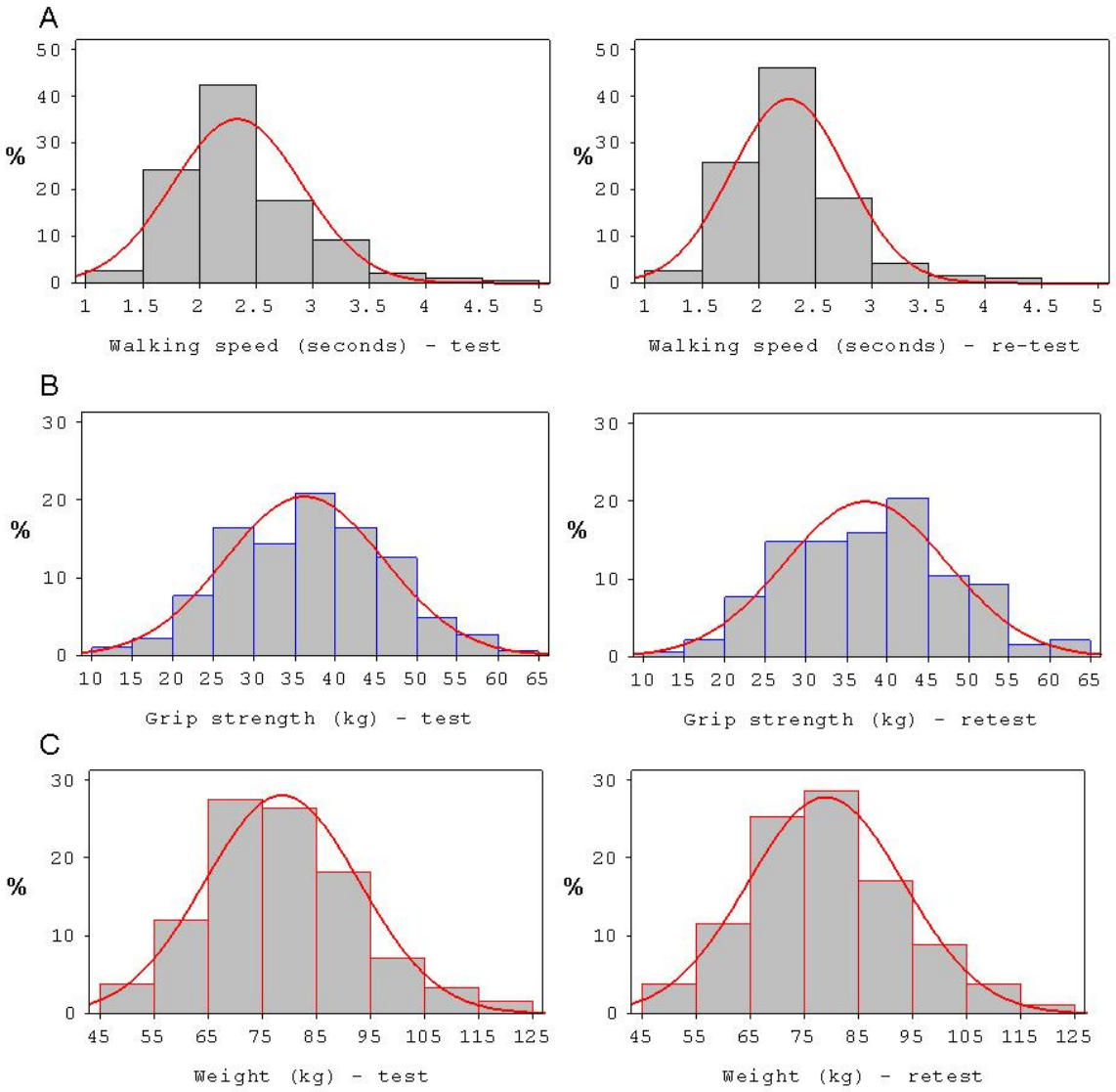
		Hazard ratios (95% CI)		
	n1/n2	**Model 1[1]**	**Model 2[2]**	**Model 3[2]**
Frailty status (yes vs no)	147/5022	2.21 (1.70; 2.88)	1.56 (1.15; 2.11)	1.38 (1.01; 1.89)
Comorbidity (yes vs no)	1787/3382	1.65 (1.47; 1.85)	1.32 (1.15; 1.52)	1.30 (1.13; 1.49)
Disability (yes vs no)	442/4713	1.81 (1.52; 2.14)	1.52 (1.25; 1.84)	1.42 (1.17; 1.73)

1 Model 1: Adjusted for sex and age.

2 Model 2: Adjusted for the predictors (frailty, comorbidity, or disability) and the covariates (sex, age, ethnicity, educational level, socio-economic position, income/year, number of relatives and friends, daily consumption of fruit and vegetables, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, mini-mental state examination, diabetes status, previous history of hospitalisation, and number of medications).

3 Model 3: As model 2 with frailty, comorbidity, and disability mutually adjusted.

Appendix 13. Distribution of walking speed (A), grip strength (B), and weight (C) measured at phase 9 (test) and within 30 days after (retest)

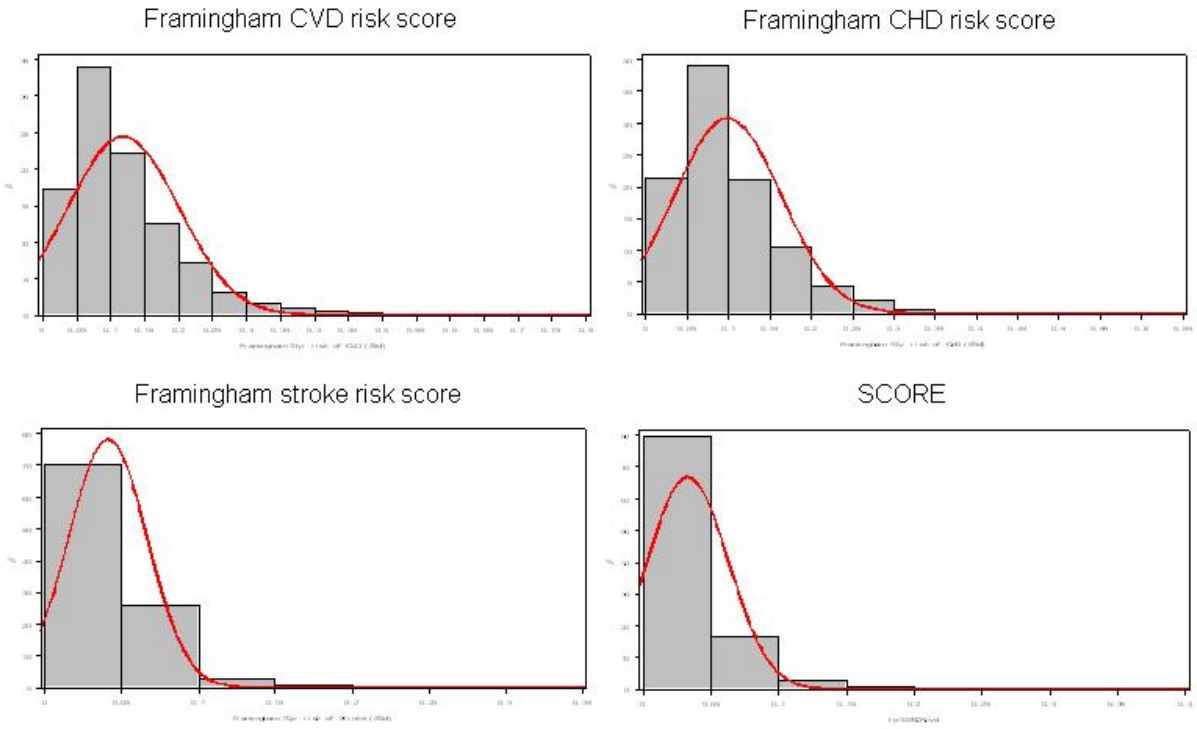


Appendix 14. Composition of the SCORE and Framingham CVD, CHD, and stroke risk algorithms

Score	Country	Sex	Age	Total C	HDL-C	SBP	DBP	AHTD	Smoking	Diabetes	CVD	AF	LVH
Framingham CVD	USA	+	+	+	+	+		+	+	+			
Framingham CHD	USA	+	+	+	+	+	+		+	+			
Framingham stroke	USA	+	+			+		+	+	+	+	+	+
SCORE	Europe	+	+	+		+			+				

Abbreviations: CVD: cardiovascular disease; CHD: coronary heart disease; C: cholesterol; S/DBP: systolic/diastolic blood pressure; AHTD: anti-hypertensive drug; AF: atrial fibrillation; LVH: left ventricular hypertrophy

Appendix 15. Distribution of the probability of developing CVD estimated by 4 CVD risk scores



Appendix 16. Missing data pattern of components included in the CVD risk scores

frailcb22f	TAGE_C	SEX	TANTIHYP	TSMOKE	TSBP	TDBP	TBLCHOL	THDL	tdiab	AFS5	LVHS5	BT123Y
X	X	X	X	X	X	X	X	X	X	X	X	X
X	X	X	X	X	X	X	X	X	X	.	.	X
X	X	X	X	X	X	X	X	X	.	X	X	X
X	X	X	X	X	X	X	X	X	.	.	.	X
X	X	X	X	X	X	X	X	.	X	X	X	X
X	X	X	X	X	X	X	X	.	X	.	.	X
X	X	X	X	X	X	X	X	.	.	X	X	X
X	X	X	X	X	X	X	.	X	X	X	X	X
X	X	X	X	X	X	X	.	.	X	X	X	X
X	X	X	X	X	X	X	.	.	.	X	X	X
X	X	X	X	X	.	.	X	X	X	X	X	X
X	X	X	X	X	.	.	X	X	.	X	X	X
X	X	X	X	X	.	.	X	.	X	X	X	X
X	X	X	X	X	.	.	.	.	X	.	.	X
X	X	X	X	X	.	.	.	.	.	.	.	X
X	X	X	X	.	X	X	X	X	X	X	X	X
X	X	X	X	.	X	X	X	X	.	X	X	X
X	X	X	X	.	.	.	.	.	.	.	.	X
X	X	X	.	X	X	X	X	X	X	X	X	X
X	X	X	.	X	X	X	X	.	X	X	X	X
X	X	X	.	.	X	X	X	X	X	X	X	X
X	X	X	.	.	X	X	X	X	.	X	X	X
X	X	X	.	.	X	X	X	.	X	X	X	X
X	X	X	.	.	X	X	.	.	.	.	.	X
X	X	X	.	.	.	.	.	.	.	.	.	X
.	X	X	X	X	X	X	X	X	X	X	X	X
.	X	X	X	X	X	X	X	X	X	.	.	X
.	X	X	X	X	X	X	X	X	.	X	X	X
.	X	X	X	X	X	X	X	.	X	X	X	X
.	X	X	X	X	X	X	X	.	X	.	.	X
.	X	X	X	X	X	X	X	.	.	X	X	X
.	X	X	X	X	X	X	.	.	X	X	X	X
.	X	X	X	X	X	X	.	.	.	X	X	X
.	X	X	X	X	.	.	X	X	X	X	X	X
.	X	X	X	X	.	.	X	X	.	X	X	X
.	X	X	X	X	.	.	.	.	X	.	.	X
.	X	X	X	X	.	.	.	.	.	X	X	X
.	X	X	X	X	.	.	.	.	.	.	.	X
.	X	X	X	.	X	X	X	X	X	X	X	X
.	X	X	X	.	X	X	X	X	.	X	X	X
.	X	X	X	.	.	.	.	.	X	.	.	X
.	X	X	X	.	.	.	.	.	.	.	.	X
.	X	X	.	X	X	X	X	X	X	X	X	X
.	X	X	.	X	X	X	X	.	X	X	X	X
.	X	X	.	X	X	X	.	.	.	X	X	X
.	X	X	.	X	.	.	.	.	.	.	.	X
.	X	X	.	.	X	X	X	X	X	X	X	X

Appendix 17. Construction of the imputation model to study the association between the CVD risk scores and frailty

1) Probability modeled is frailcb22f='Yes'

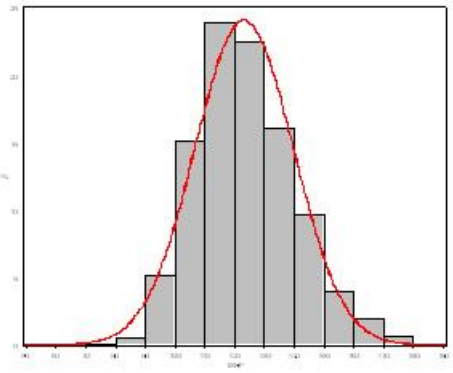
Effect	Point Estimate	95% Wald Confidence Limits		
TAGE_C	1.036	1.023	1.049	
SEX	1.308	1.086	1.574	
TANTIHYP	0.898	0.713	1.131	
TSMOKE	0.773	0.600	0.995	
TSBP	0.999	0.993	1.005	
TDBP	1.002	0.992	1.011	
TBLCHOL	1.010	0.945	1.079	
THDL	0.877	0.724	1.062	
tdiab	1.277	0.901	1.811	
AFS5	1.298	0.432	3.898	
LVHS5	1.192	0.893	1.590	
BT123Y	1.241	0.914	1.683	
TUNITWK0	1.002	0.997	1.007	
tsumill	1.057	0.981	1.138	
TSES	**1.371**	**1.221**	**1.540**	
ETHNIC51	1.116	0.936	1.331	
TNETW	**0.944**	**0.922**	**0.966**	
TGENHLT3	**1.616**	**1.447**	**1.805**	
TREGDIS2	**2.155**	**1.128**	**4.119**	

2) Probability modeled is resp='Yes'

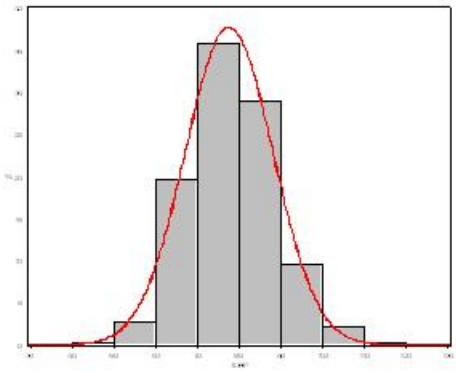
Effect	Point Estimate	95% Wald Confidence Limits		
TAGE_C	0.970	0.957	0.983	
SEX	0.915	0.761	1.102	
TANTIHYP	0.959	0.769	1.197	
TSMOKE	1.617	1.286	2.032	
TSBP	0.998	0.992	1.004	
TDBP	0.997	0.987	1.007	
TBLCHOL	0.934	0.872	1.001	
THDL	0.933	0.767	1.135	
tdiab	0.532	0.400	0.708	
AFS5	0.573	0.224	1.462	
LVHS5	1.054	0.776	1.430	
BT123Y	1.071	0.784	1.464	
TSES	**0.688**	**0.612**	**0.773**	**(auxiliary variable)**
TNETW	1.016	0.991	1.041	
TGENHLT3	**0.794**	**0.713**	**0.884**	**(auxiliary variable)**
TREGDIS2	0.706	0.404	1.236	

Appendix 18. Distribution of continuous variables included in the imputation model in the study of the association between the CVD risk scores and frailty

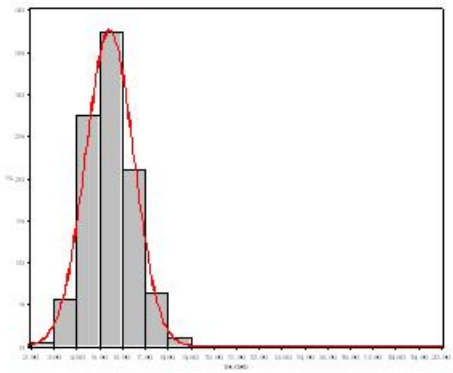
Systolic blood pressure



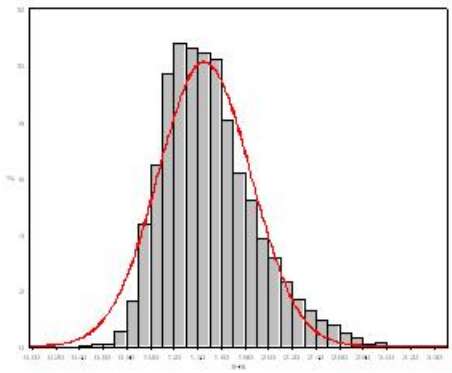
Diastolic blood pressure



Total cholesterol



HDL-cholesterol



Appendix 19. Proportion of missing values for each variable included in the CVD risk scores

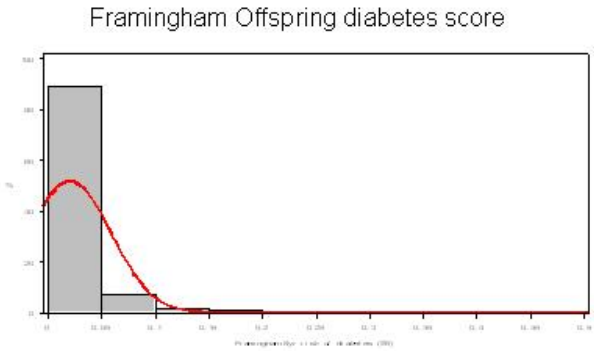
Obs	_NAME_	nmiss1	pmiss
1	STNO_NMiss	0	0.0000
2	TSMOKE_NMiss	580	7.8251
3	TUNITWK0_NMiss	719	9.7005
4	TGENHLT3_NMiss	671	9.0529
5	TANTIHYP_NMiss	66	0.8904
6	TAGE_C_NMiss	0	0.0000
7	TNETW_NMiss	991	13.3702
8	SEX_NMiss	0	0.0000
9	ETHNIC51_NMiss	8	0.1079
10	TBLCHOL_NMiss	1272	17.1614
11	**THDL_NMiss**	**1953**	**26.3492**
12	TDBP_NMiss	1211	16.3384
13	TSBP_NMiss	1211	16.3384
14	AFS5_NMiss	1251	16.8780
15	LVHS5_NMiss	1251	16.8780
16	BT123Y_NMiss	0	0.0000
17	**frailcb22f_NMiss**	**2133**	**28.7777**
18	tsumill_NMiss	41	0.5532
19	TDMWHOTO_NMiss	0	0.0000
20	tdiab_NMiss	1367	18.4431
21	TSES_NMiss	89	1.2008
22	TREGDIS2_NMiss	675	9.1069

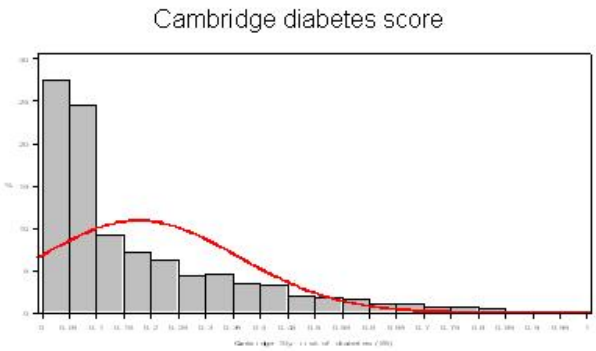
Appendix 20. Composition of the Framingham Offspring, Cambridge, and Finnish diabetes risk algorithms

Study	Year	Country	Age	Sex	PSHD	BMI	WC	SBP	AHT	Steroid	HDL	TG	FG	HHG	Smoking	PA	FV
Framingham	2007	USA	X	X	X	X		X	X		X	X	X				
Cambridge	2000	UK	X	X	X	X			X	X					X		
Finnish	2003	Finland	X			X	X		X					X		X	X

Abbreviations: PSHD: parent/sibling history of diabetes; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; AHT: antihypertensive treatment; HDL-C: HDL-cholesterol; TG: triglycerides; FG: fasting glucose; HHG: history of high blood glucose; PA: physical activity < 4h/wks; FV: daily consumption of fruit and vegetables

Appendix 21. Distribution of the probability of developing diabetes estimated by 3 diabetes risk scores





Appendix 22. Missing data pattern of components included in the diabetes risk scores

frailcb22f	TAGE_C	SEX	DIABPAR	DIABSIB	TANTIHYP	TCRTSDRG	TSMOKE	TSMKPAST	TSPORT	TFRUITVG
X	X	X	X	X	X	X	X	X	X	X
X	X	X	X	X	X	X	X	X	X	--
X	X	X	X	X	X	X	X	X	--	X
X	X	X	X	X	X	X	X	X	X	X
X	X	X	X	X	X	X	X	X	X	--
X	X	X	X	X	X	X	X	X	--	X
X	X	X	X	--	X	X	X	X	X	X
X	X	X	X	--	X	X	X	X	X	--
X	X	X	X	--	X	X	X	X	--	X
X	X	X	X	--	X	X	X	X	X	X
X	X	X	X	--	X	X	X	X	X	--
X	X	X	X	--	X	X	X	X	--	X
X	X	X	X	X	X	X	X	--	X	X
X	X	X	X	X	X	X	X	--	X	--
X	X	X	X	X	X	X	X	--	--	X
X	X	X	X	X	X	X	X	--	--	--
X	X	X	X	X	X	X	X	--	X	X
X	X	X	X	X	X	X	X	--	--	X
X	X	X	X	X	X	X	X	--	--	--
X	X	X	X	--	X	X	X	--	X	X
X	X	X	X	--	X	X	X	--	--	--
X	X	X	X	--	X	X	X	--	X	X
X	X	X	X	--	X	X	X	--	--	X
X	X	X	X	X	X	X	--	X	X	X
X	X	X	X	X	X	X	--	X	X	X
X	X	X	X	X	X	X	--	--	X	X
X	X	X	X	X	X	X	--	--	X	--
X	X	X	X	X	X	X	--	--	--	--
X	X	X	X	X	X	X	--	--	--	--
X	X	X	X	--	X	X	--	--	X	--
X	X	X	X	X	X	X	X	X	X	X
X	X	X	X	X	X	X	X	X	X	X
X	X	X	X	--	X	X	X	X	X	X

Appendix 23. Construction of the imputation model to study the association between the diabetes risk scores and frailty

1) Probability modeled is frailcb22f='Yes'

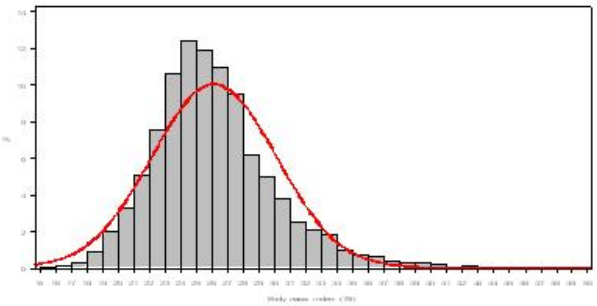
Effect	Point Estimate	95% Wald Confidence Limits	
TAGE_C	1.059	1.040	1.078
SEX	1.157	0.832	1.609
DIABPAR	1.122	0.806	1.563
TBMI	0.977	0.926	1.032
TSBP	0.999	0.992	1.005
TANTIHYP	1.065	0.777	1.460
THDL	0.876	0.649	1.181
TTRIG	0.910	0.797	1.038
TGLUC_F	1.004	0.889	1.134
TCRTSDRG	1.082	0.647	1.810
TSMOKE	1.460	0.385	5.528
TSMKPAST	1.216	0.994	1.488
DIABSIB	1.327	0.702	2.509
TWAIST2	1.009	0.989	1.030
tpdiab	1.238	0.696	2.203
TSPORT	0.840	0.808	0.873
TFRUITVG	0.875	0.806	0.948
TUNITWK0	1.002	0.994	1.010
tsumill	1.039	0.935	1.155
TSES	**1.280**	**1.085**	**1.508**
ETHNIC51	1.048	0.832	1.321
TNETW	0.976	0.945	1.008
TGENHLT3	**1.454**	**1.241**	**1.704**
TREGDIS	0.476	0.180	1.262

2) Probability modeled is resp='Yes'

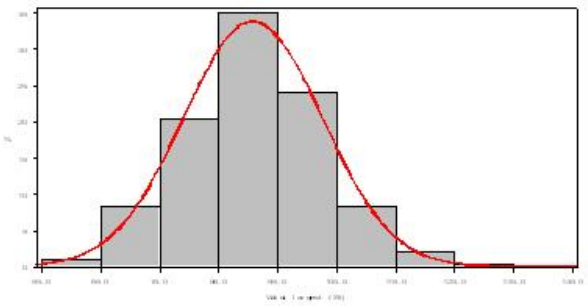
Effect	Point Estimate	95% Wald Confidence Limits		
TAGE_C	1.055	1.038	1.074	
SEX	1.240	0.905	1.699	
DIABPAR	1.113	0.808	1.534	
TBMI	0.978	0.928	1.030	
TSBP	0.998	0.992	1.004	
TANTIHYP	1.029	0.764	1.386	
THDL	0.834	0.626	1.109	
TTRIG	0.907	0.798	1.031	
TGLUC_F	1.024	0.914	1.149	
TCRTSDRG	1.218	0.742	1.998	
TSMOKE	1.172	0.336	4.094	
TSMKPAST	1.238	1.019	1.502	
DIABSIB	1.246	0.673	2.307	
TWAIST2	1.010	0.991	1.030	
tpdiab	1.183	0.677	2.070	
TSPORT	0.842	0.811	0.874	
TFRUITVG	0.885	0.819	0.957	
TSES	**1.308**	**1.118**	**1.529**	**(auxiliary variable)**
TGENHLT3	**1.488**	**1.287**	**1.720**	**(auxiliary variable)**

Appendix 24. Distribution of continuous variables included in the imputation model

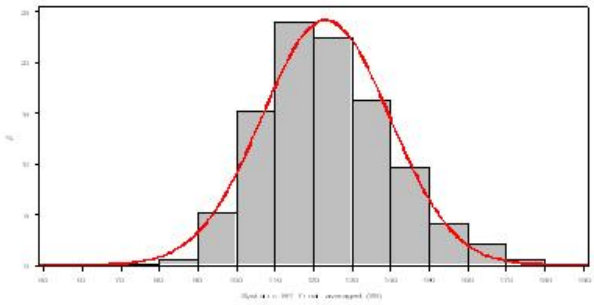
BMI



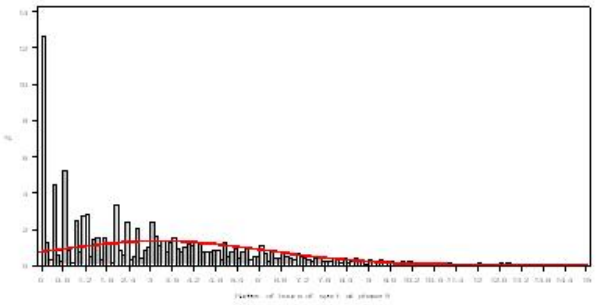
Waist circumference



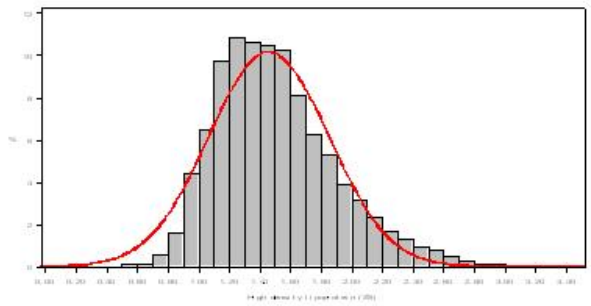
Systolic blood pressure



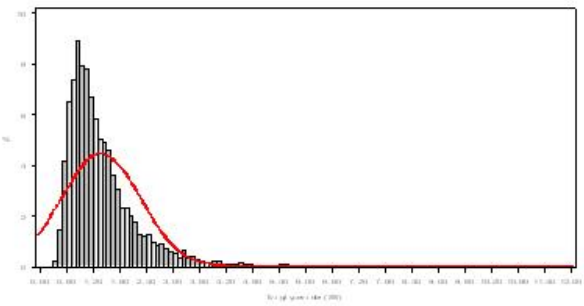
Physical activity



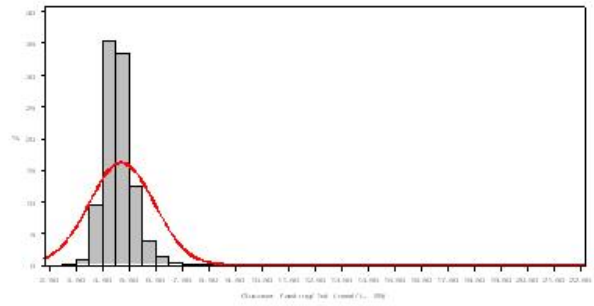
HDL-cholesterol



Triglycerides



Fasting glycaemia



Appendix 25. Proportion of missing values for each variable included in diabetes risk scores

Obs	_NAME_	nmiss1	pmiss
1	STNO_NMiss	0	0.0000
2	**frailcb22f_NMiss**	**1675**	**25.7296**
3	TSBP_NMiss	22	0.3379
4	**TWAIST2_NMiss**	**1583**	**24.3164**
5	TBMI_NMiss	864	13.2719
6	TGLUC_F_NMiss	94	1.4439
7	THDL_NMiss	803	12.3349
8	TTRIG_NMiss	83	1.2750
9	TSMOKE_NMiss	36	0.5530
10	TSMKPAST_NMiss	881	13.5330
11	TCRTSDRG_NMiss	23	0.3533
12	TANTIHYP_NMiss	23	0.3533
13	TAGE_C_NMiss	0	0.0000
14	tpdiab_NMiss	0	0.0000
15	SEX_NMiss	0	0.0000
16	DIABPAR_NMiss	331	5.0845
17	DIABSIB_NMiss	1261	19.3702
18	TSPORT_NMiss	180	2.7650
19	TFRUITVG_NMiss	175	2.6882