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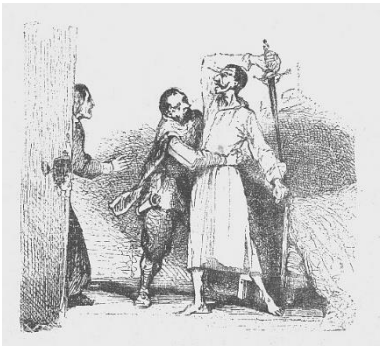
FRAILTY IN AN ELDERLY GENERAL POPULATION



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Summary

Frailty is a term used to describe older people who are more vulnerable to stressors and therefore have a higher risk of death and disability. Frailty is not an irreversible condition and can be reverted with intervention such as physical exercise and nutritional support. Therefore, it can be argued that should be detected early. For this purpose, several frailty scores based on different frailty concepts have been developed. However, to date, none of them is recognized as the "gold standard". One aspect is to diagnose frailty but the other is to prevent the development of this condition. Understanding frailty and its determinants is crucial for prevention and treatment.

Most frailty scores have been studied in their association with mortality. However, there is a gap in the literature concerning their agreement and external validation and discriminative ability.

Diabetes is known as an important determinant of frailty and in addition, they share pathophysiological mechanisms. Frailty is not a static condition and tends to progress with age. However, some individuals can have different accelerated frailty trajectories, and they can even change the trajectory over time. The effect of diabetes over frailty trajectories is scarcely investigated to date.

The main objectives of this Ph.D. thesis were to compare the current operational definitions of frailty and their instruments, through the evaluation of agreement among frailty scores and their predictive/discriminative ability as well as to study the association of between diabetes-related variables and frailty progression.

This Ph.D. thesis provides a direct comparison of the most comprehensive list of frailty

scores examined to date, with state-of-the-art and reproducible methodology, in a well-characterized cohort of the elderly general population.

In the first chapter, a general overview, objectives, and hypotheses of the thesis are presented. Important basic concepts and methods that have been applied throughout the Ph.D. work are described. Also, I describe the study population, the English Longitudinal Study of Ageing (ELSA study).

In the second chapter, the study entitled: “Agreement between 35 Published Frailty Scores in the General Population” is presented as Study I. In this article, I studied the cross-sectional agreement between 35 frailty scores in the ELSA study. I found marked heterogeneity in the degree to which the various scores may over/underestimate frailty and in the agreement on the identification of the same individuals as frail. I concluded that most of the scores cannot be assumed to be interchangeable and that consequently research results based on different scores cannot be compared, pooled or summarised directly.

In the third chapter, the study entitled: “Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer and total mortality in an elderly general population in England: an observational study” is presented as Study II. This study analyses the prospective association and predictive ability of 35 frailty scores in the ELSA study for three relevant outcomes in an elderly population: mortality, cardiovascular disease, and cancer. I demonstrated that all frailty scores were associated with future mortality and that some of them were also associated with later cardiovascular events. However, no relationship with cancer was observed. In addition, the results of this study showed that multidimensional frailty scores may have a stronger and more stable association with mortality and incidence of cardiovascular events. Despite significant associations of frailty scores with mortality outcomes, I found that the added discriminative ability of frailty scores to chronological age may be limited.

In the fourth chapter, the study entitled "Prospective association of baseline diabetes-related variables and frailty trajectories in an elderly general population" is presented as Study III. I studied the baseline diagnosis of diabetes, baseline fasting plasma glucose, and

HbA1c as determinants of frailty trajectories calculated with the three best-performing frailty scores identified in our two previous studies. I found that with 10 years of follow-up, baseline diagnosis of diabetes and baseline levels of HbA1c were associated with frailty trajectories, but not baseline fasting plasma glucose. I concluded that diabetes can be associated with frailty trajectories not only because of common pathophysiological mechanisms but also because of chronic complications related to diabetes. These three studies were based on the analysis of the same population: the ELSA study and included a literature review for identifying frailty scores, a data analysis to calculate scores and multiple imputation techniques to deal with missing data. They follow one another in a logical order of analysis to give answers to the research questions. Finally, in the fifth chapter, I discuss our results and their relevance, particularly in the way this thesis contributes to a better understanding of the concept of frailty and its contribution to knowledge in this field so far. In addition, I discussed the strengths and weaknesses of the analyses presented in this thesis, and I suggest some recommendations derived from the findings of the studies for clinicians and researchers suggesting future directions for research.

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Résumé

La fragilité de la personne âgée est un concept qui permet de décrire les personnes les plus vulnérables aux facteurs de stress, présentant donc un risque plus élevé d'invalidité et de mort. L'état de fragilité n'est pas irréversible et peut être ramené à une certaine condition de robustesse, notamment grâce à l'exercice physique et/ou un soutien nutritionnel. Par conséquent la fragilité devrait être détectée. À cet effet, plusieurs scores de fragilité, basés sur différentes théories, ont été développés. Cependant, à ce jour, aucun d'entre eux n'a été défini comme indicateur de référence. L'approche est double, diagnostiquer les personnes âgées fragiles, mais aussi prévenir l'installation de cette condition. En effet, comprendre l'état de fragilité et ses déterminants sous-jacents est crucial pour sa prévention et son traitement.

La plupart des scores de fragilité ont été étudiés en association avec la mortalité. Cependant, il reste un vide dans la littérature concernant leur fiabilité, leur validation externe et leur capacité discriminante.

Le diabète est connu pour être un des déterminants de la fragilité, et à ce titre ces deux conditions partagent des mécanismes physiopathologiques communs. La fragilité progresse avec l'âge, et n'est pas une condition statique. Ainsi, les trajectoires de fragilité sont très spécifiques des personnes et peuvent être accélérées ou même totalement modifiées avec le temps. L'effet du diabète sur les trajectoires de fragilité est à peine étudié à ce jour.

Les principaux objectifs de cette thèse étaient 1) d'évaluer la concordance entre les différents scores de fragilité et leur capacité prédictive / discriminante; et 2) d'étudier, parmi des déterminants de la fragilité, l'association des variables liées au diabète (glycémie à jeun, HbA1c), avec la progression de la fragilité.

Ce travail a permis la comparaison des scores de fragilité parmi la liste la plus exhaustive des scores existants à ce jour, à l'aide d'une méthodologie de pointe reproductible, dans une cohorte bien caractérisée de la population générale âgée.

Dans le **premier chapitre** de la thèse, une vue d'ensemble du travail, avec ses objectifs et hypothèses, sont présentés. Les concepts de base importants, ainsi que les méthodes qui ont été appliquées tout au long du travail de doctorat sont également décrits. En outre, nous détaillons la population étudiée dans les trois parties de cette thèse. Celle-ci est issue de l'étude longitudinale anglaise sur le vieillissement the English Longitudinal Study of Ageing (ELSA).

Dans le **deuxième chapitre,** l'étude intitulée : **"Agreement between 35 published frailty scores in the general population"** (Concordance entre 35 scores de fragilité publiés dans la population générale) est présentée en tant qu'Étude I. Dans cet article, nous avons réalisé une étude transversale sur la concordance entre 35 scores de fragilité de la cohorte ELSA. Nous avons constaté une hétérogénéité marquée, dans la mesure où les différents scores peuvent sur- ou sous- estimer la fragilité, et difficilement s'accorder sur l'identification des individus dits fragiles. Nous avons conclu que la plupart des paires de scores ne sont pas interchangeables, et que, par conséquent, les résultats de recherche basés sur des scores différents ne peuvent pas être directement comparés, regroupés ou résumés.

Dans le troisième chapitre, l'étude intitulée **"Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer and total mortality in an elderly general population in England: an observational study"** (Analyse comparative de l'association de 35 scores de fragilité avec des événements cardiovasculaires, l'occurrence de cancer et la mortalité totale, dans une population générale âgée en Angleterre: une étude observationnelle) est présentée en tant qu'Étude II. Cette étude analyse l'association prospective et le pouvoir de prédiction de 35 scores de fragilité dans la cohorte ELSA, pour trois paramètres pertinents pour la population âgée: la mortalité, les maladies cardiovasculaires et le cancer. Nous avons démontré que tous les scores de fragilité étaient associés à la mortalité à venir, et que certains d'entre eux étaient également associés à des événements cardiovasculaires ultérieurs. Cependant, aucune relation avec le cancer n'a été observée. De plus, les résultats de cette étude ont montré que les scores de fragilité multidimensionnels peuvent être plus fortement et plus stablement associés à

la mortalité et à l'incidence des événements cardiovasculaires. Malgré des associations significatives entre les scores de fragilité et les résultats de mortalité, nous avons constaté que la capacité discriminante ajoutée des scores de fragilité à l'âge chronologique peut être limitée.

Dans le **quatrième chapitre,** l'étude intitulée **"Prospective association of baseline diabetes related variables and frailty trajectories in an elderly general population"** (Association prospective des variables de référence associées au diabète et des trajectoires de fragilité dans une population générale âgée) est présentée en tant qu'Étude III. Nous avons étudié le diagnostic de référence du diabète, le glucose plasmatique à jeun et l'HbA1c comme déterminants de trajectoires de fragilité, calculées à l'aide des trois scores les plus performants identifiés dans nos deux précédentes études. Grâce à un suivi de la population de 10 ans, nous avons constaté que le diagnostic initial du diabète ainsi que la mesure initiale de l'HbA1c étaient associés aux trajectoires de fragilité, contrairement au glucose plasmatique à jeun. Nous avons conclu que le diabète peut être associé aux trajectoires de fragilité, non seulement à cause de mécanismes physiopathologiques communs, mais aussi en raison de complications chroniques liées à la pathologie.

Ces trois études reposent sur l'analyse de la même population, la cohorte ELSA. Elles incluent une revue de la littérature pour l'identification des scores de fragilité, et une analyse des données pour le calcul des scores à l'aide d'une technique de traitement des données manquantes par une méthode d'imputation multiple. Ces études ont été menées selon un ordre logique d'analyse, pour répondre aux questions de recherche.

Enfin, dans le **cinquième chapitre,** nous discutons de nos résultats et de leur pertinence, notamment la manière dont cette thèse a contribué à une meilleure compréhension du concept de fragilité de la personne âgée. Les forces et des faiblesses des analyses présentées dans cette thèse ont également été discutées dans ce chapitre, de même que la généralisation de nos résultats. Nous avons suggéré quelques recommandations dérivées de ce travail de doctorat, à l'attention de cliniciens et chercheurs.

Zusammenfassung

Frailty (Gebrechlichkeit) ist eine Bezeichnung für ältere Menschen, die anfälliger für Stressfaktoren sind und daher ein erhöhtes Sterberisiko und eine erhöhte Gefahr für Behinderung haben. Gebrechlichkeit ist keine irreversible Erkrankung und kann durch Interventionen wie körperliche Betätigung und Ernährungsunterstützung in einen robusten Zustand zurückversetzt werden. Daher sollte es frühzeitig diagnostiziert werden. Zu diesem Zweck wurden mehrere auf unterschiedlichen Theorien beruhende Frailty-Scores (FS) entwickelt. Bislang wurde jedoch keiner von ihnen als "Goldstandard" definiert. Ein Aspekt besteht darin, die Gebrechlichkeit zu diagnostizieren, aber auch die Entwicklung dieses Zustands zu verhindern. Verständnis der Gebrechlichkeit und der zugrunde liegenden Determinanten dieses Zustands ist entscheidend für die Prävention und Behandlung.

Die meisten Frailty-Scores wurden in ihrer Assoziation mit Mortalität untersucht. Allerdings gibt es in der Literatur eine Lücke in Bezug auf ihre Zuverlässigkeit, externe Validierung und diskriminierende Fähigkeit.

Diabetes ist als eine Determinante der Gebrechlichkeit bekannt und darüber hinaus teilen sie pathophysiologische Mechanismen. Gebrechlichkeit ist keine statische Verfassung sondern neigt dazu, mit dem Alter fortzuschreiten. Einige Individuen können jedoch unterschiedliche beschleunigte Frailty-Trajektorien haben, und sie können sogar den Ablauf im Laufe der Zeit ändern. Die Wirkung von Diabetes auf Frailty-Trajektorien wurde bisher kaum untersucht.

Die Hauptziele dieser Dissertation sind, die Übereinstimmung zwischen Frailty-Scores und ihrer prädiktiven/ diskriminativen Fähigkeit zu untersuchen und unter den Determinanten von Frailty-Scores die Assoziation von Diabetes-bezogenen Variablen mit der Progression der Gebrechlichkeit zu untersuchen.

Diese Doktorarbeit bietet einen direkten Vergleich der vollständigsten Liste von FS, die bis heute untersucht wurden, mit einer modernen und reproduzierbaren Methodik in einer gut charakterisierten Kohorte der älteren Bevölkerung.

Im ersten Kapitel werden ein allgemeiner Überblick, Ziele und Hypothesen der Arbeit vorgestellt. Einige wichtige grundlegende Konzepte und Methoden, die während der gesamten Doktorarbeit angewendet wurden, werden aufgeführt. Außerdem beschreiben wir die Studienpopulation, die englische Longitudinal Study of Aging, für die drei Studien, die Teil dieser Arbeit sind.

Im zweiten Kapitel wird die Studie mit dem Titel **„Agreement between 35 Published Frailty Scores in the General Population“** („Übereinstimmung zwischen 35 veröffentlichten Frailty-Scores in der Allgemeinbevölkerung“) als Studie I vorgestellt. In diesem Artikel untersuchten wir die Querschnittsvereinbarung zwischen 35 FS in der englischen Longitudinal Study of Aging (ELSA). Wir fanden eine ausgeprägte Heterogenität in dem Ausmaß, das die verschiedenen Scores die Gebrechlichkeit über- oder unterschätzen, allerdings stimmten sie darin überein, dieselben Individuen als gebrechlich zu identifizieren. Wir sind zu dem Schluss gekommen, dass die meisten Paare von Scores nicht als austauschbar angesehen werden können und dass folglich Forschungsergebnisse, die auf unterschiedlichen Scores basieren, nicht direkt verglichen oder zusammengefasst werden können.

Im dritten Kapitel wird die Studie mit dem Titel **“Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer and total mortality in an elderly general population in England: an observational study”** („Vergleichende Analyse des Zusammenhangs zwischen 35 Frailty- Scores und kardiovaskulären Ereignissen, Krebs und Gesamtmortalität in einer älteren Bevölkerung in England: eine Beobachtungsstudie“) als Studie II vorgestellt. Diese Studie analysiert die prospektive Assoziation und prädiktive Fähigkeit von 35 Frailty- Scores in der englischen Longitudinal Study of Aging für drei relevante Endpunkte in der älteren Bevölkerung: Mortalität, kardiovaskuläre Erkrankungen und Krebs. Wir zeigten, dass alle Frailty- Scores mit der späteren Sterblichkeit und dass einige von ihnen auch mit späteren kardiovaskulären Ereignissen in Verbindung gebracht werden können. Es wurde jedoch kein Zusammenhang mit Krebs beobachtet. Darüber hinaus zeigten die Ergebnisse dieser Studie, dass multidimensionale Frailty-Scores eine stärkere und stabilere Assoziation mit Mortalität und Inzidenz von kardiovaskulären Ereignissen aufweisen können. Trotz signifikanter Assoziationen

von Frailty-Scores mit Mortalitätsresultaten fanden wir, dass die zusätzliche diskriminative Fähigkeit von Frailty-Scores zum chronologischen Alter begrenzt sein kann.

Im vierten Kapitel wird die Studie mit dem **Titel "Prospective association of baseline diabetes related variables and frailty trajectories in an elderly general population"** („Prospektive Assoziation von diabetesbezogenen Variablen und Frailty- Trajektorien in einer älteren Allgemeinbevölkerung") als Studie III vorgestellt. Wir untersuchten die Baseline Diagnose von Diabetes, Nüchternblutzucker und HbA1c Werte als Determinanten von Frailty- Trajektorien. Diese wurden die mit den drei besten Frailty-Scores berechnet, die in unseren beiden früheren Studien identifiziert wurden. Wir fanden heraus, dass bei der 10-Jahres-Nachuntersuchung die Baseline Diagnose von Diabetes und die HbA1c Werte mit Frailty-Trajektorien assoziiert war, nicht jedoch mit Nüchtern-Plasmaglukose. Wir folgerten, dass Diabetes mit Frailty Trajektorien nicht nur wegen der gemeinsamen pathophysiologischen Mechanismen verbunden sein kann, sondern auch wegen chronischer Komplikationen die im Zusammenhang mit Diabetes stehen.

Die drei Studien basierten auf der Analyse derselben Population: der englischen Longitudinal Study of Aging und umfassten eine Literaturrecherche zur Identifizierung von Frailty-Scores, eine Datenanalyse zur Berechnung von Scores und eine multiple Imputationstechnik von fehlenden Werten. Sie folgen einander in einer logischen Reihenfolge der Analyse, um Antworten auf die Forschungsfragen zu geben.

Schließlich diskutieren wir **im fünften Kapitel** unsere Ergebnisse und ihre Relevanz, insbesondere in Bezug darauf, wie diese These zu einem besseren Verständnis des Konzepts der Gebrechlichkeit und ihres Beitrags zum Wissen auf diesem Gebiet beigetragen hat. Darüber hinaus werden Stärken und Schwächen der in dieser Arbeit vorgestellten Analysen diskutiert, wir werden die Verallgemeinerbarkeit unserer Ergebnisse kommentieren und einige Empfehlungen aus den Ergebnissen der Studien für Kliniker und Forscher vorschlagen, die zukünftige Forschungsrichtungen vorgeben.

Glossary

AUC	Area under the curve
BDE	Beaver Dam Eye Study Index
BFI	Brief Frailty Index
BMI	Body mass index
CASP-19	19-item scale control, autonomy, pleasure, and self-realisation
CGA	Comprehensive Geriatric Assessment
CGAST	Comprehensive Geriatric Assessment Screening Tests
COPD	chronic obstructive pulmonary disease
CSBA	Conselice Study of Brain Aging Score
CVD	cardiovascular disease
EFIP	Evaluative Frailty Index for Physical Activity
EFS	Edmonton Frail Scale
ELSA	English Longitudinal Study of Ageing
FI40	40-item Frailty Index
FI70	70-item Frailty Index (SHARE)
FIBLSA	Frailty Index Beijing Longitudinal Study of Ageing
FiND	Frail Non-Disabled Questionnaire
FS	Frail Scale
FSS	Frailty Staging System
G8	G-8 Geriatric Screening Tool
GFI	Groningen Frailty Indicator
HR	hazard ratio
HRCA	Hebrew Rehabilitation Center for Aged Vulnerability Index
HSF	Health Status Form
IFQ	Inter-Frail Questionnaire
MFS	Modified Frailty Score
MPHF	Modified Phenotype of Frailty

NLTCS	Long Term Care Survey Frailty Index
OR	Odds ratio
PFI	Physical Frailty Index
PHF,	Phenotype of Frailty
RR	relative risk
SDFI	Static/Dynamic Frailty Index
SHARE	Survey of Health, Ageing and Retirement in Europe
SHCFS	Canadian Study of Health and Aging Clinical Frailty Scale
SI	Screening Instrument
SOF	Study of Osteoporotic Fractures
SPPB	Short Physical Performance Battery
SPQ	Sherbrooke Postal Questionnaire
TFI	Tilburg Frailty Indicator
VES13	Vulnerable Elders Survey
WHOAFC	World Health Organization Assessment of Functional Capacity
WHRH	WHOAFC and self-reported health
ZED1	ZutPhen Elderly Study (Physical Activity and Low Energy)
ZED2	ZutPhen Elderly Study (Physical Activity and Weight Loss)
ZED3	ZutPhen Elderly Study (Physical Activity and Low BMI)

Contents

Chapter 1. Introduction

1.1. General introduction

The aim of this thesis is to understand and quantify the impact of the large variety of current operational definitions of frailty.

Due to a decline in fertility and a decrease of mortality, the population of most countries in the world is ageing .[1] Moreover, it is expected that this growth of the elderly population will continue in the next decades and it is projected that the population aged 80 and over will triple by 2030-2050[2].

A consequence of population ageing is that the number of people suffering from chronic diseases such as cancer, bone demineralisation, stroke and dementia will increase.[3] In addition, people present more frequently with multimorbidity, which is defined as two or more chronic diseases in the same individual.[4] As a result, the elderly population has special needs that should be taken into account from today to plan future actions. In addition, the proportion of elderly people with disabilities and with a loss of autonomy, especially after the age of eighty, is already high[5].

The ageing population phenomenon creates new challenges for a country's health systems due to the higher and more prolonged health care needs of older people.[6] In the same way, prevention of ageing related problems is one key measure to help elderly stay healthy and independent.[3]

The concept of frailty is used to describe a subset of older people who are the weakest and most vulnerable to stressors and therefore are at higher risk of poor health outcomes[7]. In addition, frailty has been defined as a state of disturbed homeostasis caused by stressors and leading to an increased risk of falls, disability and premature death[8]. This phenomenon has been distinguished as different from comorbidity and disability, although often overlapping.[9]

In clinical settings, frailty has been used to identify patients who may be at higher risk of death in non-surgical [10] , and surgical patients[11], as well as to identify patients at higher risk for postoperative complications and unplanned hospitalizations.[12] In community dwelling people, frailty is assessed primarily to identify elderly persons who may be at higher risk of falls, fractures, institutionalization and disability.[13]

Frailty is a continuous, dynamic and potentially reversible process[14]. Exercise and nutrition, alone or in combination, are effective interventions that reduce the condition of frailty to a more stable and robust stage[15]. Consequently, it can be argued that frailty should be actively detected as soon as possible.

Although the importance of detecting frailty at an early stage is recognized, there is no consensus on the definition or on which instrument of frailty should be used to assess this condition. In fact, the definition and concepts of frailty diverge among the different groups of experts in the field, with a number of different approaches used to define this condition.

In order to establish a set of diagnostic criteria, many scales have been created, based on different definitions and concepts of frailty. In addition, the instruments also differ in the number, and type of variables as well as in the range and thresholds used to define frailty. This lack of a "gold standard" makes research in the area of frailty difficult, as the results are not comparable because they define frailty differently and therefore identify different subgroups of the population as frail.

1.2. Purpose of the thesis

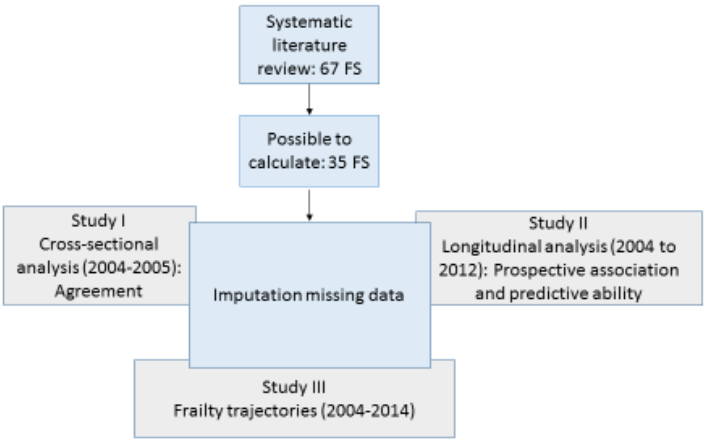
This study focuses on the following research questions:

In a well-characterized cohort of elderly people: participants in the English Longitudinal Study of Ageing and

1. In a cross sectional analysis, which is the agreement between a wide set of frailty scores? (Study I)
2. In a cross sectional analysis, which are the frailty scores that accurate that accurately assess the “true” level of frailty ? (Study I)
3. In a longitudinal analysis, which are the frailty scores that are associated with future total mortality? (Study II)
4. In a longitudinal analysis, are some frailty scores associated with future cardiovascular disease or cancer? (Study II)

5. In a longitudinal analysis, which is the added predictive value of frailty scores over chronological age? (Study II)
6. In a longitudinal trajectory analysis, are diabetesa and biomarkers with frailty trajectories? (Study III)
7. In a longitudinal trajectory analysis, among diabetes ,$HbA_{1c,}$ and fasting plasma glucose, which are the best predcitors of frailty progression? (Study III).

All analyses were performed on the basis of frailty scores identified by a literature review. Multiple imputation was applied to address the presence of missing data on the underlying variables needed to calculate frailty scores



1.3. Core concepts

1.3.1. Healthy ageing

The ageing process is heterogeneous among populations and individuals. Belsky et al studied participants in a birth cohort and found that even before their forties, people of the same chronological age had different degrees of deterioration in their biological age, defined as "declining integrity of multiple organ systems".[16] Kaplan conducted a longitudinal study in a cohort of adults with a 30-year follow-up and identified different health trajectories: those who survived long and in excellent health, others who survived as long as the first case with a persistent decline and finally, people who lived shorter than previous cases but died in good health[17]. Based on the previous observations, healthy ageing was suggested as a condition that corresponds to the subset of people who live long lives with good functioning up to the end of their lives, and frailty could represent the opposite of the concept of healthy ageing.

As mentioned earlier, older adults have a higher risk of multimorbidity [18] and disability[19]. The challenge should not be to prolong life, but rather to ensure that the ageing process is optimal, freeing the elderly from the burden of illness to the extent possible and allowing them to keep a good quality of life. An optimal evolution in the process of ageing is to get older free of disability and disease. Healthy ageing goes further and involves not only disease and disability-free survival, but also living independently, without significant cognitive impairment, with a good quality of life and full participation in society.[20].

1.3.2. Frailty syndrome

Frailty can be considered a geriatric syndrome with reduced reserve and resistance to stressors, resulting in cumulative decline in multiple physiological systems, causing vulnerability to adverse health outcomes, including falls, hospitalization, institutionalization and mortality. This could imply that a common underlying biological process plays a central role in its development[21].

1.3.2.1. Pathophysiology

With ageing there is a natural decline in hormone secretion, such as oestrogens in women, testosterone in men but also growth hormone, and insulin like growth factor-1. A multiple deficit of hormones rather than a single anabolic hormone would be associated with muscle loss, sarcopenia and frailty[21 22]. Lower values in

non-androgenic hormones such as DHEA-S, IGF-1, and its binding globulin 3 (IGFBP-3) have also been associated with progression from non-frail to frail status in men[23]

An additional possible causal agent is a chronic slightly increased systemic inflammation in the elderly. Values of interleukin 1 and 6, tumour necrosis factor alpha and macrophages in older ages are associated with wasting states and a higher risk of disability in already frail persons[24]. Further epidemiologic evidence is reported by a recent study that showed a prospective association between baseline C-reactive protein and frailty status 15 years later[25].

Glucose metabolism deregulation is associated with some components of frailty status such as walking speed in elderly men.[26] The underlying mechanisms of the association between diabetes/insulin resistance and frailty may reside in inflammatory activity and metabolic stressors such as kinases.[27] Also, an increased waist circumference is described as a possible determinant of the association between insulin resistance and frailty, linking frailty to sarcopenic obesity.[28]

1.3.2.2. Conceptual definitions

Definitions of frailty have evolved over the years, first with concepts very close to disability in the elderly [29] and multiple illness.[30] The concept of frailty began to be used to describe vulnerable elderly persons in the 1990s[31 32]. In 1992, Buchner and Wagner defined frailty as a decrease of physiological reserve with a higher risk of disability[33]. Rockwood in 1994 defined frailty as a condition in the elderly population of precarious balance to maintain health and avoid deficits[34]. In 1996, Rockwood et al introduced the multidimensional concept of frailty as a condition independent of the presence of disability. An approach derived from these concepts is to define frailty based on the appearance of deficits and their accumulation, regardless of the type of deficit, as an indicator of biological ageing.[35]

Other quite different conceptual definitions are those from Campbell et al who in 1997 defined frailty as a condition of diminished reserve to the point of achieving the threshold of disease[36]. Fried in 2001 defined frailty as a physiological syndrome based on a cycle linked to undernutrition and sarcopenia causing vulnerability to adverse outcomes centred on physical issues, and clearly independent of comorbidity and disability (Figure 1).[9 31] Despite the success of this definition due to its usability for both researchers and

clinicians, this concept of frailty centred on physical frailty and wasting was criticised because this concept considers just weight loss/underweight as frailty criteria, excluding obesity from these criteria.[37]

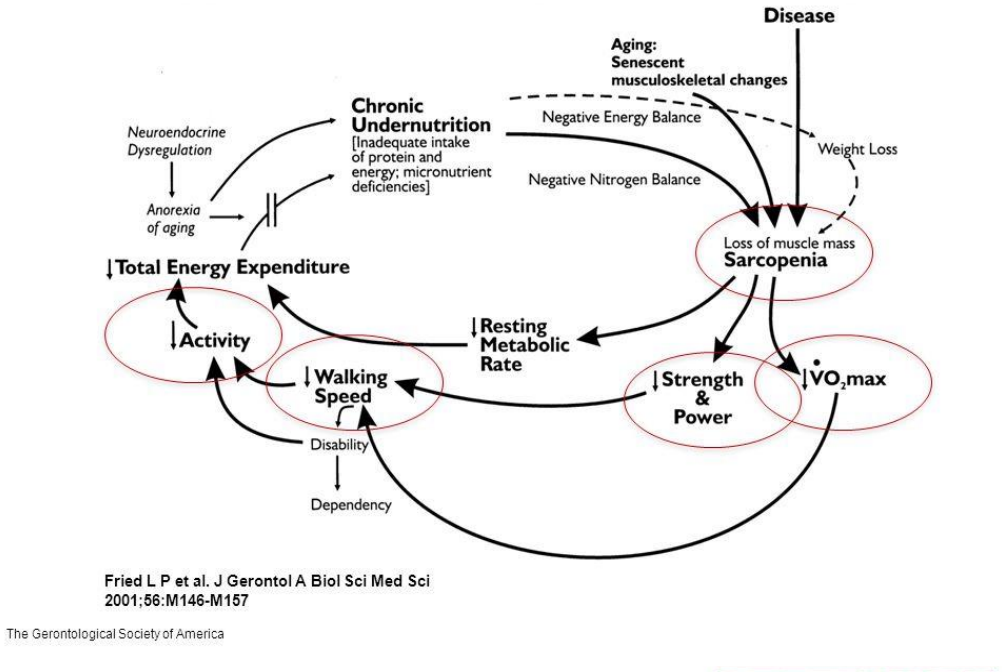
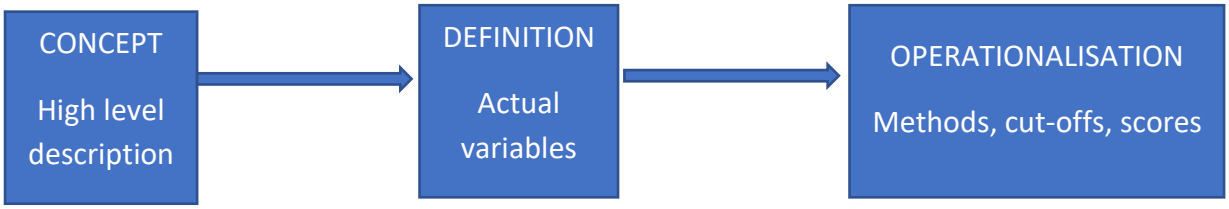


Figure 1. The syndrome of frailty by Fried. Figure extracted from Fried et al[31]

In 2010, Gobbens et al proposed a new definition of the concept of frailty as a dynamic state of loss affecting one or more areas of functioning and increasing the risk of adverse health effects. Their definition is a multidimensional approach based on the following facts: most conceptual definitions agree to describe frailty as a dynamic process, many definitions of operationalization do not exclude disability and comorbidity, and multidimensional scores are feasible in clinical practice[38].

1.3.2.3. Operationalisations of frailty

Operationalisations are a step in the process of putting in practice the concept of frailty in the following structure:



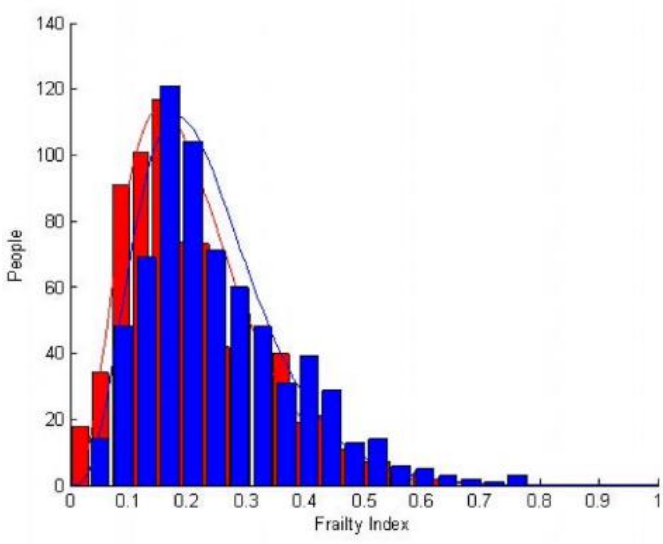
Operationalisation means practical implementation, so going from a concept to a practical tool is operationalisation. This can be done by deriving a score from data analysis but also an expert-designed score ins an operational definition[38] .

One of the points of disagreement is whether to include disability as a variable in the definition of frailty. Some authors consider disability to be an outcome and should not be part of the frailty phenomenon.[39] Others believe that even though disability and frailty are different conditions, they overlap and including disability in the operationalisation definition might improve potential associations with mortality. Therefore, if the latter concept is accepted, disability should be included in the definition.[40]

A first derived definition is **the phenotype of frailty approach** developed by Fried et al[31], which describes frailty as a physiological model including five variables evaluating mainly physical frailty: unintentional weight loss, weakness, exhaustion, slowness and low activity (Figure 1). The score was developed with data from the Cardiovascular Health Study and is by definition categorical, defining frail individuals as the presence of 3 or more components, and pre-frail one or two. This score is the most cited in the literature and the most used in research[41]. Although it is difficult to implement in a clinical setting, it is also widely used by clinicians because of its ease of interpretation[42].

A second derived definition is **the accumulation of the deficit approach** developed by Mitnitski et al [35] , which defines frailty as a diminished response to stress that makes the individual vulnerable and with a higher mortality risk[35]. This condition would be a loss of redundancy, a consequence of an accumulation of deficits[43]. To obtain stability, these scores must include at least 30 variables. Among many other domains, they include physical functioning, disability and comorbidity. They are calculated by summing the number of deficits and dividing the total number of deficits by the number of deficits that were evaluated, giving a continuous scale as output[44]. Although these instruments are less used than the phenotype of frailty score (because of the large number of variables involved in the calculation), it seems that they offer a more accurate risk assessment than other instruments[45].

Figure 2. The accumulation of deficit approach by Mitnitski. Distribution of frailty index in an elderly population at baseline (red) and 18 months later (blue). Figure extracted of Searle et al[46].



A third derived definition is **the multidimensional approach** by Gobbens, which defines frailty as a dynamic state of loss affecting one or more domains of functioning. This approach often includes physical and mental health, cognitive and social domains. However, unlike the accumulation of deficit approach, it does not require the assessing of a long list of variables. Therefore, it is less time-consuming and more feasible in clinical or community settings[38].

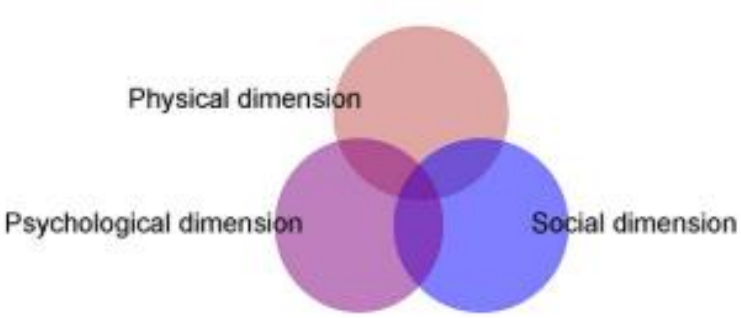


Figure 3. Multidimensional concept of frailty based on the Tilburg Frailty Indicator[47]. Figure extracted from Sieber[21]

With different operationalisation approaches, a plethora of frailty scores have been created. Some of the scores are defined based on subjective information (questionnaires), others collect objective information (physical examination and blood samples) and others have both types of information[41]. Also, frailty scores diverge in the way they define frail by binary, categorical, or, continuous and in their ranges.

Therefore, it can be argued that earlier detection may bring longer term benefits.

1.4. Core methods

1.4.1. Study population: The English Longitudinal Study of Ageing

Many epidemiological cohort studies have been developed around the world to provide information on the elderly population[48]. The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study representative of the older middle aged and elderly English population. The study started in 2002 and is based on participants of the Health Survey of England who were born before 1952 and lived in households. The age range of the sample was from 50 to 100 years and the response of the households to participate was 70%[49].

The information about participants in ELSA is collected at 2-year intervals (waves). Each wave collects data about health determinants, physical and mental health. All waves gather subjective data (questionnaires) including social and psychological factors, behaviour, and cognition. Moreover, waves 2, 4, and 6 also have a physical examination and blood samples (biological markers of disease) (Figure 4). Mortality was evaluated in 2012 and can be studied thanks to a nation-wide registry linked to the ELSA data[49].

ELSA was chosen as the data set for the three studies of this thesis, because of the numerous strengths of ELSA (very comprehensive data on elderly European population, high quality subjective and objective measurements, enabling to answer many research questions concerning frailty and other outcomes). Also, ELSA is a European study, the data are available as open source, with data that are harmonised with the Health and Retirement Study and with the Survey of Health, Ageing, and Retirement in Europe (SHARE) study.

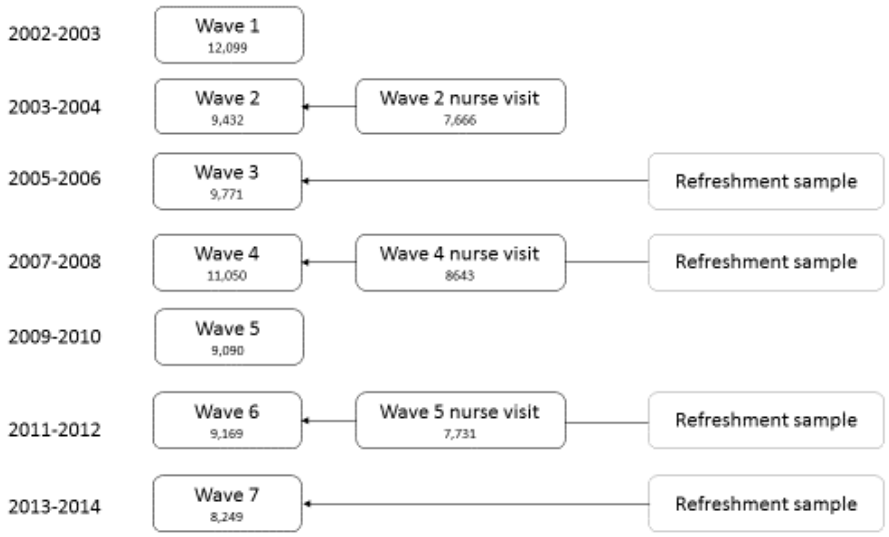


Figure 4. Data collection in ELSA waves 1–7[50]

1.4.2. Quality assessment of health measurement scales applied to frailty instruments

When choosing an instrument to assess health status, it is essential that the instrument can evaluate this condition with minimal measurement error to avoid bias[51]. Marshall et al found that when using unpublished scales, the results were more likely to suffer from bias, reporting more often positive results[52]. There are several reasons for biased results including the use of different scales, a flexible choice of designs and outcomes are chosen with flexibility and a small sample size[51]. If the quality of a health measurement scale needs to be assessed, reliability, validity and feasibility should be analysed[53] Also, discriminative ability can be evaluated with the area under the curve or C statistics[54] When evaluating a scale in a prospective analysis, the choice of a dynamic C statistics is suitable[55]

1.4.2.1. Reliability and agreement

A good instrument for the evaluation of health outcomes should be reproducible in many conditions such as different observers, populations, geographic and time context[56]. Reliability is defined as the ratio of variability of scores in the same subjects. Reliability refers to the ability of a measure to give the same results consistently when it is applied to the same subjects at two different periods of time. This term should be differentiated from agreement, which is one of the subdivisions of reliability and also called inter-rater

reliability. Agreement is defined as a measure of concordance between different instruments assessing the same entity (Figure 5)[57].

Two methods to evaluate agreement

The Cohen's Kappa coefficient evaluates the agreement or disagreement between two observers, who apply the same scale[58]. The calculation is the difference between the observed agreement and the agreement expected by chance. A Kappa equal to 1 is a perfect agreement while a Kappa equal to zero is an agreement by chance. Kappa test evaluates precision of the instrument and not accuracy. Precision refers to the reproducibility of a measure. Accuracy is how this measure is near the truth value. This means that an instrument with a high value of Kappa test could also be a biased instrument. Conversely, Kappa coefficient could be very low even when the agreement is high if the disease is rare[59].

The Bland Altman method is described as an alternative method to measure agreement between two instruments, one a new instrument compared with a gold standard instrument. They should use the same scale and in should be tested in the same population. The differences between the two instruments are plotted in the y-axis against the averages of the two instruments in the x-axis. Then the average of the differences, standard errors and the limits of agreement are calculated. When the differences are not uniform, it is recommended to fit a linear regression[60 61].

1.4.2.2. Validity

Validity refers to the ability of a scale to make valid conclusions based on the objectives for which the scale was created.[62] Validity can be subdivided into four types (Figure 5): face validity -items appear to be relevant to what they are actually measuring[53]-, content validity -the scale has to sample all the relevant content-, construct validity -the experimental demonstration of what a scale is intended to measure[63]- and criterion validity -the correlation of the scale with a "gold standard"[53]-

Content validity can be divided in convergent validity (how close the scale is associated to other variables with the same aim) and discriminative validity (ability of a scale to distinguish individuals who experience the outcome from those who do not experience it)[53].

Discriminative validity can be evaluated with the area under the curve or C statistics[54].

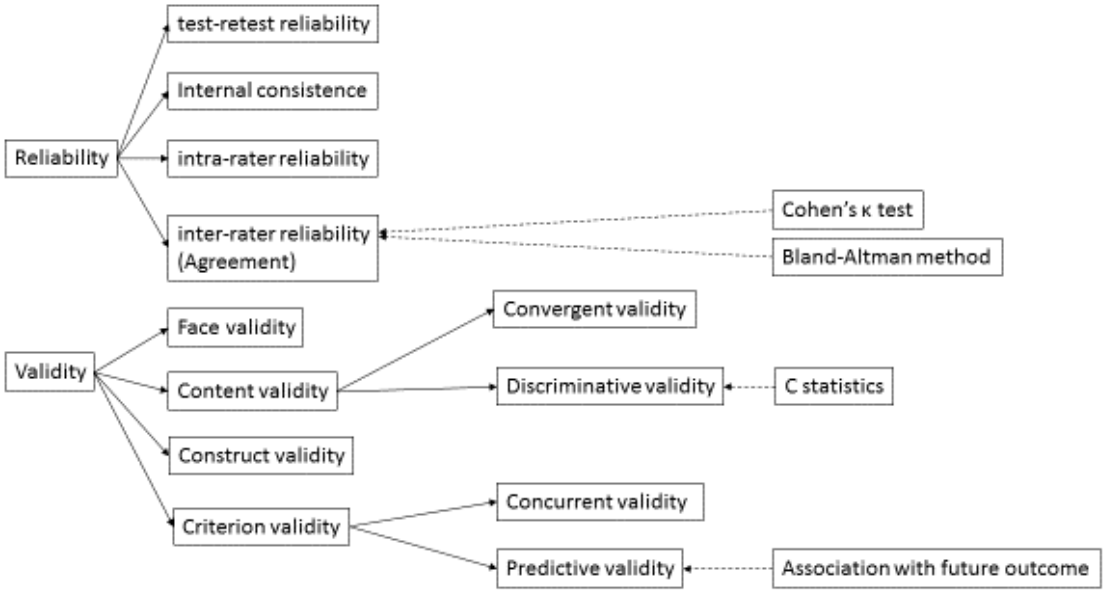


Figure 5. Quality assessment of health measurement scales: reliability and validity

1.5. Objectives

The aim of this thesis was to understand and quantify the impact of the large variety of current operational definitions of frailty on the application of the frailty concept in clinical practice and public health research.

Specific objectives were:

- To study the agreement between a wide set of FS in a well-characterized cohort of elderly people: participants in the English Longitudinal Study of Ageing (ELSA).

- To carry out a comparative external validation of a comprehensive list of frailty scores with regard to three important health outcomes in later life: CVD, cancer, and all-cause mortality, by direct comparison of the strength of associations and of added predictive value, using prospective data from a population-based study in the elderly.

- To evaluate the association of diabetes, fasting plasma glucose (FPG) and HbA1c on long-term frailty trajectories.

The main hypothesis is that current operational definitions through their instruments, will define different subsets of population as frail and there will be also heterogeneity in their performances as frailty instruments.

Chapter 2. Study I

Agreement between 35 Published Frailty Scores in the General Population

GA Aguayo, A-F Donneau, MT Vaillant, A Schritz, OH Franco, S Stranges, L Malisoux, M Guillaume, DR Witte.

American Journal of Epidemiology 2017; 186(4):420-34. doi: 10.1093/aje/kwx061

https://academic.oup.com/aje/article/186/4/420/3868462

2.1. Abstract

In elderly populations, frailty is associated with higher mortality risk. Although many frailty scores (FS) have been proposed, no single FS is considered the gold standard. We aimed to evaluate the agreement between a wide range of FS in the English Longitudinal Study of Ageing (ELSA). Through literature search, we identified 35 FS that could be calculated in ELSA wave 2 (2004-2005). We examined agreement between each FS and the mean of 35 FS, using a modified Bland-Altman model and Cohen's Kappa. Missing data were imputed. Data from 5377 participants (>=60 years) were analysed (44.7% men; 55.3% women). FS showed a widely differing degree of agreement with the mean of all scores and between each pair of scores. Frailty classification also showed a very wide range of agreement (Cohen's Kappa: 0.10-0.83). Agreement was highest amongst FS from accumulation of deficits FS, while accuracy was highest for multidimensional FS. There is marked heterogeneity in the degree to which various FS estimate frailty, and in the identification of the same individuals as frail. Different FS are based on different concepts of frailty and most pairs cannot be assumed to be interchangeable. Research results based on different FS cannot be compared or pooled.

elderly population; frailty scores; agreement; reliability; accuracy; Bland-Altman model; Cohen's kappa coefficient; disability.

Abbreviations: FS, frailty scores; ELSA, English Longitudinal Study of Ageing; M35FS, mean of the 35 analysed frailty scores

2.2. Introduction

Vulnerable elderly individuals are increasingly described in the literature as being frail, i.e. having a decreased ability to recover from an adverse event[9]. Three main approaches have been used to conceptually define frailty.

The first approach is the "phenotype of frailty"[31], which is a physiological model focused mainly on physical frailty and which describes frailty as a phenomenon of "weakness, decreased endurance and slow performance"[31]. This approach regards frailty as separate from disability and comorbidity. The operational definition of this approach defines frailty as the presence of at least 3 out of 5 criteria (pre-frailty: 1 or 2 criteria). The second approach is the "accumulation of deficits"[35], which is based on the accumulation of conditions or disability emphasizing the number rather than the nature of deficits. The operational definition of this approach defines frailty with at least 30 variables[46] and includes disability and comorbidity[64]. The third approach is the "multidimensional model"[65] that defines frailty as a dynamic state of loss affecting one or more areas of functioning such as the cognitive, physical and social domains. Finally, some frailty scores (FS) have been operationalized mainly as the presence of disability.

Frailty is associated with a higher risk of mortality rate, disability, falls, fractures, hospitalization and institutionalization[66] [67]. Some evidence indicates that exercise, caloric and protein support, vitamin D supplementation and reduction of polypharmacy can be effective in preventing progression of frailty and the occurrence of its adverse outcomes[68]. Consequently, it is important to identify frail individuals and individuals at risk at an early stage[66]. However, it remains unclear which tool is best suited for this purpose.

The ability of frailty scores to accurately produce stable and reproducible results has been partially studied[69]. In a systematic review of FS, Bouillon et al[41] found that 7 out of 27 scores had been assessed for both reliability and concurrent or predictive validity. A recent study that assessed validity and reproducibility of 8 commonly used FS in an elderly European general population, found that the prevalence of frailty varied from 6.1% to 43.9%, and that 49.3% of participants were classified as non-frail and 2.4% were classified as frail across all 8 scales[70]. The authors concluded that FS have significant differences regarding validity, feasibility and predictive ability[70].

The absence of consensus on how to conceptually define frailty and the resulting plethora of scales and scores, currently hampers both research in the field and implementation of frailty assessment in clinical practice. In order to enable comparison of studies of frailty performed with different FS, and to facilitate the choice of FS for future studies, it is essential to quantify the degree of agreement between scores and to understand the sources of disagreement.

Based on the hypothesis that different FS may classify different subsets of a population as frail, we set out to study the agreement between a wide set of FS in a well characterized cohort of elderly people, the English Longitudinal Study of Ageing (ELSA) study.

2.3. Methods

2.3.1. Study Population/Design

ELSA is an ongoing cohort based on a large, nationally representative sample of the older middle aged elderly English population. Information about participants is gathered at two-year intervals (waves). All waves include questionnaires concerning health determinants, physical and mental health. In addition, waves 2, 4, and 6 have clinical examination.

Ethical approval was obtained from the Multicenter Research and Ethics Committee. Participants signed informed consent[71]. ELSA data were accessed via the UK data service under data sharing project number 82538.

We carried out a cross-sectional analysis of data from wave 2 (2004-2005) of the ELSA study, as this is the first wave where a comprehensive assessment of frailty indicators was performed. Since not all frailty related variables were measured in participants younger than 60 years, we restricted our analyses to those aged 60 and over.

2.3.2. Identification and selection of FS

A PubMed search of the literature was performed (date range: 1 January 1970 to 31 August 2015) with the following query: "((frailty [Title / Abstract]) AND score [Title / Abstract])". Abstracts were checked for the publication of an original FS. Furthermore, FS were identified based on references from recent reviews articles[39 41 72 73]. Published FS were selected for inclusion if at least 80% of the component variables were available in ELSA wave 2. If one or more underlying variables (maximally 20%) of a score were unobtainable from the data, the FS was calculated based on the available variables and the total score and the cut-off were refitted to the actual number of variables[74]. Variables unavailable due to the ELSA study design were not imputed.

FS were calculated trying to be faithful to the original scores. However, it was necessary to tailor some variables to the data. For some FS, this adaptation was based on previous publications[70]. FS vary in yielding continuous, categorical, or binary outputs; each with different ranges. Each score was rescaled to the interval 0 to 1 by dividing the original score output by the highest possible value for each score. Some scores were additionally inverted ((re- scaled score * -1) +1) to conform to our definition of 0 representing the absence of frailty and 1 its presence.

2.3.3. Missing data

If data from an available underlying variable in ELSA was missing for some participants, multiple imputation was applied[75]. The amount of missing data varied from 0.04 to 24.7%.

The maximum % of missing data was used to decide how many imputations to perform[76]. Therefore, we imputed 30 times, using chained equations (package "Mice"[77]). To obtain optimally plausible values for the scores, imputation was applied to the original underlying variables, and FS were calculated a posteriori using imputed values.

All statistical analyses were performed on the 30 imputed datasets and resulting estimates were pooled according to the Rubin rules[75 78]. All results presented in this paper have been obtained based on the multiple imputation procedure described above.

2.3.4. Statistical analyses

The prevalence of frailty was calculated for each FS prior to re-scaling using the original, published cut-off points. To enable comparisons between scores, the mean, median and standard deviation and all further analyses were calculated on the rescaled scores in the total population and also stratified by sex, age and smoking status.

Agreement was analysed using 3 parallels methods:

1) Modified Bland-Altman model[79]. In the absence of an external gold standard for frailty, we chose the mean of the 35 analysed frailty scores (M35FS) as a global estimate of 'true frailty'. The error (difference between each score and the M35FS) was plotted on the y-axis against the M35FS on the x-axis. Linear regression was used to calculate the dependence of each score's error (over or underestimation) on the severity of frailty, as well as to calculate its limits of agreement. The degree of under/overestimation was estimated at the median of the M35FS (model A).

2) Traditional pairwise Bland-Altman models were built comparing all 595 possible pairs of FS. The error (difference between each score and the mean of the 2 compared FS) was plotted on the y-axis against a rough estimate of the 'true frailty' defined as the mean of the 2 FS on the x-axis. The width of prediction intervals and the absolute error (calculated in the median point on the x-axis) were analysed (model B).

3) Cohen's Kappa (kappa). in order to enable comparisons across all 595 possible pairs of 35 FS in spite of different underlying concepts of frailty, different cut-off points and the absence of a published cut-off point in some cases, kappa was also calculated applying an arbitrary cut-off across all scores (defining the 20% highest scores as 'frail'). In cases where a score category straddled the 20% cut-off level, kappa was calculated using a 20 bootstrap resample procedure, which classified participants from the straddling category randomly as frail/non frail in the proportion necessary to achieve an over-all 20% frailty prevalence. 95%-confidence intervals for kappa were calculated based on Rubin's method for covariance and confidence interval calculation in imputed data. The mean within-imputation variance, the between-imputations variance, the total variance and finally the confidence intervals were calculated[78].

FS were grouped into 4 main operationalization models: 'phenotype of frailty' for scores based mainly on physical functioning variables; 'accumulation of deficits' for scores based on various domains and at least 30 variables; 'multidimensional model' for scores that analyse at least 3 domains of functioning and including less than 30 variables; and 'disability model' for scores based mainly on disability variables. FS were also grouped according to the stated target population: community dwelling or clinical setting.

In addition, to assess agreement with regard to a binary or categorical definition of frailty, kappa was calculated for pairs of FS with a published cut-off level (29 out of 35 FS).

2.4. Results

We analysed data from all 5377 participants aged 60 or over (44.7% men and 55.3% women) who attended the ELSA wave 2 clinical examination.

Sixty-seven original FS were identified through the literature search. Thirty-five of 67 scores (52.2%) could be calculated with ELSA wave 2 data. Web Table 1 shows the list of included and excluded FS. Web Table 2 shows details of all variables for the 35 FS and their adapted version in the ELSA dataset. Table 1 presents the general characteristics of the study population by sex.
Table 2 describes the 35 FS that were analysed in this study[31 46 47 80-109]. The FS with the highest proportion of individual-level missing values was Frailty Index 70 items (40.5%) while WHOAFC & self-reported health and Vulnerable Elders Survey had the lowest proportion of missing values (0.1%). Most of the scores (29 of 35) had published cut-offs to define frailty.

Prevalence as defined by the published cut-offs varied considerably. The mean prevalence of frailty (standard deviation) was 23.1% (19.7) for men (range: 0.8-65.0) and 28.9% (21.9) for women (range 1.0-72.4) (Table 3).

Table 4 shows the mean (SD) FS values after re-scaling to the 0-1 range in the whole population globally as well as stratified by sex, age and smoking status. Across scores women, older participants and smokers/former-smokers were frailer than men, younger participants and never smokers respectively.

Table 5 displays the median kappa values. It also shows the median of prediction interval widths and absolute error of under/overestimation in analyses: based on Model A and model B.

Table 1. General Characteristics of Participants ($n = 5,377$) in Wave 2 of the English Longitudinal Study of Ageing, 2004–2005

Characteristic	Men ($n = 2,401$)		Women ($n = 2,976$)	
	Mean (SD)	%	Mean (SD)	%
Age, years[a]	70.8 (7.6)		71.5 (8.2)[b]	
Body mass index[c,d,e]	27.7 (4.1)		28.0 (5.2)	
Total cognitive score (per point)[d,e,f]	26.7 (6.4)		27.6 (6.7)[b]	
Marital status (currently married)[d,g]		75.0		52.8[b]
Education (no high school qualification)[d,g]		37.3		48.7[b]
Smoking status[d,g]				
Current smoker		12.8		11.9[b]
Former smoker		61.9		43.5[b]
Never smoker		25.4		44.6[b]
Physical activity[d,g,h]				
None (sedentary)		6.6		7.9[b]
Mild		22.7		30.9[b]
Moderate		50.9		48.7[b]
Vigorous		19.8		12.5[b]
Chronic disease[i,j]				
Diabetes		11.4		8.4[b]
Hypertension		46.3		49.6[b]
Myocardial infarction		11.6		4.9[b]
Stroke		6.9		5.8
Cancer		8.4		9.8
Lung disease		8.5		8.4
Arthritis		33.6		50.7[b]
Depression symptoms (CES-D score ≥4)[d,g,k]		25.7		37.1[b]

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; SD, standard deviation.
[a] *P* value was derived from an unpaired *t* test.
[b] $P < 0.05$.
[c] Weight (kg)/height $(m)^2$.
[d] Imputed data.
[e] Linear regression model.
[f] Sum of memory and executive indices; values range from 0 (worst) to 50 (best).
[g] Logistic regression.
[h] Self-reported frequency of mild, moderate, or vigorous activity at least once per week.
[i] *P* value was derived from a χ^2 test.
[j] Self-reported ever diagnosis of the condition.
[k] Assessed by means of the 8-item CES-D.

Table 2. Characteristics of Frailty Scores Calculated among Participants in Wave 2 of the English Longitudinal Study of Ageing , 2004-2005

First Author, Year (Reference No.)	Frailty measure	Country	Model	Aim	Definition of score	Defined variables	Calculated variables	% of Missing data
Klein, 2003 (80)	Beaver Dam Eye Study Index	United States	POF	CD	Continuous	4	4	26.5
Gill, 2002 (81)	Physical Frailty Index	United States	POF	CS	Categorical	2	2	19.1
Cesari, 2014 (82)	FiND Questionnaire	France	POF	CD	Binary	5	5	1.3
Abellan van Kan, 2008 (83)	Frail Scale	France	POF	CS	Categorical	5	5	1.3
Fried, 2001 (31)	Phenotype of Frailty	United States	POF	CD	Categorical	5	5	13.4
Rothman, 2008 (84)	Modified Phenotype of Frailty	United States	POF	CD	Continuous	7	7	15.8
Ensrud, 2007 (85)	Study of Osteoporotic Fractures	United States	POF	CS	Categorical	3	3	14.3
Guralnik, 1994 (86)	Short Physical Performance Battery	United States	POF	CD	Binary	3	3	21.8
Chin, 1999 (87)	ZED (Physical Activity & Low Energy)	Netherlands	POF	CD	Binary	2	2	0.5
Chin, 1999 (87)	ZED (Physical Activity & Weight Loss)	Netherlands	POF	CD	Binary	2	2	0.8
Chin, 1999 (87)	ZED (Physical Activity & Low BMI)	Netherlands	POF	CD	Binary	2	2	4.7
Freiheit, 2010 (88)	Brief Frailty Index	Canada	MD	CS	Binary	5	5	17.3
Hubbard, 2009 (89)	Modified Frailty Score	United Kingdom	MD	CS	Categorical	5	5	21.6
Balducci, 2000 (90)	CGAST	United States	MD	CS	Categorical	9	9	10.4
Ravaglia, 2008 (91)	Conselice Study of Brain Aging Score	Italy	MD	CD	Binary	9	9	23.4
Rolfson, 2006 (92)	Edmonton Frail Scale	Canada	MD	CS	Binary	9	9	12.6
Cacciatore, 2005 (121)	Frailty Staging System	Italy	MD	CS	Categorical	7	7	3.5
Bellera, 2012 (94)	G-8 Geriatric Screening Tool	France	MD	CS	Categorical	8	7	4.2
Steverink, 2001 (95)	Groningen Frailty Indicator	Netherlands	MD	CS	Binary	11	11	14.3
Brody, 1997 (96)	Health Status Form	United States	MD	CD	Continuous	4	4	11.9
Puts, 2005 (97)	Static/Dynamic Frailty Index	Netherlands	MD	CD	Binary	9	9	25.3
Maly, 1997 (98)	Screening Instrument	United States	MD	CD	Binary	6	6	11.3
Hábert, 1996 (96)	Sherbrooke Postal Questionnaire	Canada	MD	CD	Binary	6	6	14.4
Di Bari, 2014 (100)	Inter-Frail Questionnaire	Italy	MD	CD	Binary	10	8	14.8
Gobbens, 2010 (47)	Tilburg Frailty Indicator	Netherlands	MD	CD	Binary	15	15	22.1
Jones, 2004 (101)	Comprehensive Geriatric Assessment	Canada	AOD	CD	Categorical	44	41	35.1
de Vries, 2013 (102)	Evaluative Frailty Index for Physical Activity	Netherlands	AOD	CD	Continuous	50	42	22.8
Searle, 2008 (46)	Frailty Index 40 items	Canada	AOD	CD	Binary	40	37	23.7
Theou, 2013 (103)	Frailty Index 70 items (SHARE)	Canada	AOD	CD	Binary	70	62	40.5

Table 2. Continued

First Author, Year (Reference No.)	Frailty measure	Country	Model	Aim	Definition of score	Defined variables	Calculated variables	% of Missing data
Fang, 2012 (104)	Frailty Index (BLSA)	China	AOD	CD	Continuous	35	29	17.5
Kulminski, 2007 (105)	National Long Term Care Survey Frailty Index	United States	AOD	CD	Continuous	32	26	0.9
Dayhoff, 1998 (106)	WHOAFC & self-reported health	United States	DA	CD	Binary	15	14	0.1
Morris, 1984 (107)	HRCA Vulnerability Index	United States	DA	CD	Binary	10	10	18.9
Rockwood, 2005 (108)	CSHA Clinical Frailty Scale	Canada	DA	CS	Categorical	8	8	0.2
Saliba, 2001 (109)	Vulnerable Elders Survey	United States	DA	CD	Binary	13	12	0.1

Abbreviations: BLSA, Beijing Longitudinal Study of Ageing; BMI, body mass index, CS, Clinical setting; CD, Community-dwelling; CGAST, Comprehensive Geriatric Assessment Screening tests; CSHA, Canadian Study of Health and Aging; DA, disability; AOD, accumulation of deficits; ELSA, English Longitudinal Study of Ageing; FiND, Frail Non-Disabled; HRCA, Hebrew Rehabilitation Center for Aged; MD, Multidimensional; POF, Phenotype of frailty; SHARE, Survey of Health, Ageing and Retirement in Europe; ST, Screening Tests; WHOAFC, World Health Organization Assessment of Functional Capacity; ZED, Zutphen Elderly Study.

Table 3. Prevalence of Frailty Among Participants in Wave 2 of the English Longitudinal Study of Ageing, 2004–2005

Frailty Model and Measure	Published Cutoff	Cutoff Used	Men			Women		
			% Not Frail	% Prefrail	% Frail	% Not Frail	% Prefrail	% Frail
"Phenotype of frailty" model								
Beaver Dam Eye Study Index	None	NA	NA	NA	NA	NA	NA	NA
Physical Frailty Index	>1 and >0	>1 and >0	81.9	14.9	3.2	73.8	20.4	5.8
FIND Questionnaire[a]	≥1	≥1	60.3	NA	39.7	52.3	NA	47.7
Frail Scale	>2; >0	>2; >0	61.5	31.2	7.4	53.1	38.0	8.9
Phenotype of Frailty	≥3; ≥1	≥3; ≥1	11.7	75.8	12.5	6.6	78.6	14.8
Modified Phenotype of Frailty	None	NA	NA	NA	NA	NA	NA	NA
Study of Osteoporotic Fractures	≥2; ≥1	≥2; ≥1	67.6	25.6	6.8	60.4	30.2	9.4
Short Physical Performance Battery	≤9	≤9	35.0	NA	65.0	29.0	NA	71.0
ZED1 (Physical Activity and Low Energy)	>1	>1	96.3	NA	3.7	95.5	NA	4.5
ZED2 (Physical Activity and Weight Loss)	>1	>1	98.1	NA	1.9	97.0	NA	3.0
ZED3 (Physical Activity and Low BMI)	>1	>1	99.2	NA	0.8	99.0	NA	1.0
Multidimensional model								
Brief Frailty Index	≥3	≥3	91.0	NA	9.0	82.8	NA	17.2
Modified Frailty Score	>2; >0	>2; >0	20.0	16.3	63.7	12.9	18.6	68.5
CGAST	>2; >0	>2; >0	17.6	49.0	33.4	12.4	45.9	41.7
Conselice Study of Brain Aging Score	≥3	≥3	47.3	NA	52.7	65.2	NA	34.8
Edmonton Frail Scale	≥8	≥8	96.7	NA	3.3	95.2	NA	4.8
Frailty Staging System	≥4; ≥2	≥4; ≥2	58.2	30.6	11.2	50.6	34.4	15.0
G-8 geriatric screening tool	≤14	≤12	37.9	NA	62.1	27.6	NA	72.4
Groningen Frailty Indicator	≥4	≥4	64.8	NA	35.2	55.9	NA	44.1
Health Status Form	None	NA	NA	NA	NA	NA	NA	NA
Static/Dynamic Frailty Index	≥3	≥3	65.7	NA	34.3	45.7	NA	54.3
Screening Instrument	≥3	≥3	95.6	NA	4.4	92.1	NA	7.9
Sherbrooke Postal Questionnaire	≥2	≥2	81.3	NA	18.7	71.7	NA	28.3
Inter-Frail Questionnaire	≥5	≥5	98.4	NA	1.6	97.2	NA	2.8
Tilburg Frailty Indicator	≥5	≥5	64.1	NA	35.9	53.3	NA	46.7
"Accumulation of deficits" model								
Comprehensive Geriatric Assessment	≥7; ≥13	≥6; ≥12	57.8	30.7	11.5	42.1	40.2	17.7
Evaluative Frailty Index for Physical Activity	None	NA	NA	NA	NA	NA	NA	NA
40-item Frailty Index	>0.2	>0.2	68.8	NA	31.2	56.7	NA	43.3
70-item Frailty Index (SHARE)	≥0.25	≥0.25	74.7	NA	25.3	62.7	NA	37.3
Frailty Index (BLSA)	None	NA	NA	NA	NA	NA	NA	NA
Long Term Care Survey Frailty Index	None	NA	NA	NA	NA	NA	NA	NA

Table continues

Table 3. Continued

Frailty Model and Measure	Published Cutoff	Cutoff Used	Men			Women		
			% Not Frail	% Prefrail	% Frail	% Not Frail	% Prefrail	% Frail
Disability model								
WHOAFC and self-reported health	≥21 or SRH = poor[b]	≥4 or SRH = poor[c]	81.5	NA	18.5	74.1	NA	25.9
HRCA Vulnerability Index	"A" box ≥1 or "A" box = 0 and "B" box ≥0[d]	"A" box ≥1 or "A" box = 0 and "B" box ≥0[d]	73.8	NA	26.2	57.6	NA	42.4
CSHA Clinical Frailty Scale	1–7	≥5	86.8	NA	13.2	83.0	NA	17.0
Vulnerable Elders Survey	≥3	≥2.8	73.9	NA	26.1	63.5	NA	36.5

Abbreviations: BLSA, Beijing Longitudinal Study of Ageing; BMI, body mass index; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSHA, Canadian Study of Health and Aging; FIND, Frail Non-Disabled; HRCA, Hebrew Rehabilitation Center for Aged; NA, not applicable; SHARE, Survey of Health, Ageing and Retirement in Europe; WHOAFC, World Health Organization Assessment of Functional Capacity; ZED, Zutphen Elderly Study.

[a] Frailty calculated as frail + disabled.

[b] Cutoff calculated dividing each variable by 5.

[c] Self-rated health.

[d] "A" box: list of 7 questions; yes = 1, no = 0. "B" box: 2 additional questions; yes = 1, no = 0.

Table 4. Rescaled (0–1) Mean (Standard Deviation)[a] Frailty Scores and *P* Values for Differences[b] Between Frailty Scores, Overall and by Sex, Age, and Smoking Status, Among Participants in Wave 2 of the English Longitudinal Study of Ageing, 2004–2005

Frailty Model and Measure	Total	Sex		Age		Smoking Status		
		Male[c]	Female	≤70 Years[c]	>70 Years	Never Smoker[c]	Ex-Smoker	Current Smoker
"Phenotype of frailty" model								
Beaver Dam Eye Study Index	0.37 (0.27)	0.37 (0.26)	0.38 (0.28)	0.26 (0.23)	0.49 (0.26)[d]	0.35 (0.27)	0.37 (0.27)[d]	0.42 (0.25)[d]
Physical Frailty Index	0.14 (0.27)	0.11 (0.24)	0.16 (0.29)[d]	0.07 (0.19)	0.21 (0.32)[d]	0.13 (0.27)	0.14 (0.27)	0.15 (0.28)
FiND Questionnaire	0.23 (0.23)	0.20 (0.22)	0.25 (0.24)[d]	0.18 (0.20)	0.28 (0.25)[d]	0.21 (0.22)	0.23 (0.23)[d]	0.28 (0.24)[d]
Frail Scale	0.14 (0.20)	0.13 (0.19)	0.16 (0.21)[d]	0.11 (0.17)	0.19 (0.22)[d]	0.13 (0.20)	0.15 (0.20)[d]	0.19 (0.22)[d]
Phenotype of Frailty	0.30 (0.24)	0.27 (0.23)	0.32 (0.24)[d]	0.23 (0.20)	0.38 (0.25)[d]	0.28 (0.23)	0.30 (0.23)[d]	0.34 (0.25)[d]
Modified Phenotype of Frailty	0.33 (0.23)	0.27 (0.23)	0.35 (0.23)[d]	0.25 (0.20)	0.41 (0.24)[d]	0.31 (0.23)	0.33 (0.23)[d]	0.38 (0.24)[d]
Study of Osteoporotic Fractures	0.15 (0.22)	0.13 (0.21)	0.17 (0.23)[d]	0.11 (0.19)	0.20 (0.25)[d]	0.14 (0.22)	0.15 (0.22)	0.19 (0.24)[d]
Short Physical Performance Battery[e]	0.34 (0.19)	0.32 (0.17)	0.35 (0.20)[d]	0.26 (0.15)	0.42 (0.20)[d]	0.33 (0.19)	0.34 (0.19)	0.34 (0.19)
ZED1 (Physical Activity and Low Energy)	0.32 (0.28)	0.29 (0.27)	0.35 (0.28)[d]	0.27 (0.25)	0.38 (0.29)[d]	0.30 (0.27)	0.32 (0.28)[d]	0.39 (0.30)[d]
ZED2 (Physical Activity and Weight Loss)	0.29 (0.25)	0.27 (0.24)	0.31 (0.25)[d]	0.24 (0.21)	0.35 (0.27)[d]	0.29 (0.25)	0.29 (0.24)	0.33 (0.25)[d]
ZED3 (Physical Activity and Low BMI)	0.27 (0.21)	0.24 (0.20)	0.30 (0.22)[d]	0.23 (0.19)	0.31 (0.22)[d]	0.26 (0.21)	0.26 (0.20)	0.33 (0.24)[d]
Multidimensional model								
Brief Frailty Index	0.31 (0.22)	0.27 (0.20)	0.34 (0.23)[d]	0.25 (0.20)	0.37 (0.22)[d]	0.29 (0.22)	0.31 (0.22)	0.36 (0.22)[d]
Modified Frailty Score	0.34 (0.22)	0.32 (0.22)	0.37 (0.22)[d]	0.25 (0.19)	0.45 (0.21)[d]	0.34 (0.22)	0.34 (0.22)	0.38 (0.21)[d]
CGAST	0.22 (0.16)	0.20 (0.12)	0.24 (0.16)[d]	0.19 (0.15)	0.26 (0.16)[d]	0.21 (0.16)	0.23 (0.16)[d]	0.25 (0.17)[d]
Conselice Study of Brain Aging Score	0.32 (0.15)	0.37 (0.15)	0.29 (0.15)[d]	0.26 (0.13)	0.39 (0.15)[d]	0.30 (0.15)	0.34 (0.16)[d]	0.34 (0.15)[d]
Edmonton Frail Scale	0.16 (0.14)	0.15 (0.13)	0.17 (0.14)[d]	0.13 (0.12)	0.20 (0.14)[d]	0.15 (0.13)	0.17 (0.13)[d]	0.19 (0.15)[d]
Frailty Staging System	0.30 (0.22)	0.28 (0.21)	0.16 (0.21)[d]	0.22 (0.19)	0.38 (0.23)[d]	0.28 (0.22)	0.31 (0.22)[d]	0.32 (0.22)[d]
G-8 geriatric screening tool[e]	0.21 (0.14)	0.19 (0.14)	0.23 (0.15)[d]	0.16 (0.12)	0.26 (0.15)[d]	0.20 (0.15)	0.21 (0.14)[d]	0.24 (0.15)[d]
Groningen Frailty Indicator	0.25 (0.16)	0.23 (0.15)	0.26 (0.16)[d]	0.20 (0.14)	0.26 (0.15)[d]	0.23 (0.15)	0.25 (0.15)[d]	0.28 (0.16)[d]
Health Status Form	0.16 (0.20)	0.14 (0.19)	0.17 (0.21)[d]	0.08 (0.14)	0.24 (0.23)[d]	0.14 (0.20)	0.17 (0.21)[d]	0.16 (0.19)
Static/Dynamic Frailty Index	0.34 (0.17)	0.30 (0.23)	0.37 (0.17)[d]	0.27 (0.14)	0.41 (0.17)[d]	0.33 (0.17)	0.33 (0.17)	0.38 (0.17)[d]
Screening Instrument	0.17 (0.17)	0.13 (0.16)	0.19 (0.18)[d]	0.14 (0.16)	0.20 (0.18)[d]	0.16 (0.17)	0.17 (0.17)[d]	0.19 (0.19)[d]
Sherbrooke Postal Questionnaire	0.24 (0.17)	0.22 (0.17)	0.26 (0.18)[d]	0.18 (0.14)	0.30 (0.18)[d]	0.23 (0.17)	0.24 (0.17)	0.25 (0.17)[d]
Inter-Frail Questionnaire	0.22 (0.17)	0.22 (0.16)	0.23 (0.17)[d]	0.16 (0.14)	0.27 (0.17)[d]	0.21 (0.16)	0.22 (0.17)	0.25 (0.17)[d]
Tilburg Frailty Indicator	0.33 (0.18)	0.30 (0.16)	0.35 (0.18)[d]	0.27 (0.15)	0.39 (0.18)[d]	0.32 (0.17)	0.33 (0.17)[d]	0.37 (0.18)[d]
"Accumulation of deficits" model								
Comprehensive Geriatric Assessment	0.18 (0.11)	0.16 (0.11)	0.19 (0.12)[d]	0.15 (0.10)	0.21 (0.12)[d]	0.17 (0.11)	0.18 (0.11)[d]	0.20 (0.12)[d]
Evaluative Frailty Index Physical Activity	0.21 (0.14)	0.19 (0.14)	0.22 (0.15)[d]	0.17 (0.13)	0.26 (0.15)[d]	0.19 (0.14)	0.21 (0.14)[d]	0.24 (0.15)[d]
40-item Frailty Index	0.20 (0.14)	0.17 (0.13)	0.21 (0.14)[d]	0.16 (0.12)	0.23 (0.14)[d]	0.18 (0.14)	0.20 (0.14)[d]	0.22 (0.15)[d]
70-item Frailty Index (SHARE)	0.21 (0.14)	0.18 (0.13)	0.23 (0.15)[d]	0.17 (0.13)	0.25 (0.15)[d]	0.19 (0.14)	0.21 (0.14)[d]	0.24 (0.15)[d]

Table continues

Table 4. Continued

Frailty Model and Measure	Total	Sex		Age		Smoking Status		
		Male[c]	Female	≤70 Years[c]	>70 Years	Never Smoker[c]	Ex-Smoker	Current Smoker
Disability model								
Frailty Index (BLSA)	0.17 (0.13)	0.15 (0.12)	0.18 (0.14)[d]	0.13 (0.11)	0.21 (0.14)[d]	0.16 (0.13)	0.17 (0.13)[d]	0.18 (0.14)[d]
Long Term Care Survey Frailty Index	0.14 (0.11)	0.13 (0.10)	0.14 (0.11)[d]	0.11 (0.09)	0.17 (0.11)[d]	0.13 (0.11)	0.14 (0.10)[d]	0.15 (0.11)[d]
WHOAFC and self-reported health	0.17 (0.20)	0.14 (0.19)	0.19 (0.21)[d]	0.13 (0.19)	0.21 (0.22)[d]	0.15 (0.19)	0.18 (0.21)[d]	0.20 (0.22)[d]
HRCA Vulnerability Index	0.16 (0.18)	0.14 (0.17)	0.18 (0.19)[d]	0.13 (0.16)	0.20 (0.19)[d]	0.14 (0.17)	0.16 (0.18)[d]	0.20 (0.19)[d]
CSHA Clinical Frailty Scale	0.33 (0.22)	0.31 (0.21)	0.34 (0.22)[d]	0.29 (0.19)	0.37 (0.24)[d]	0.31 (0.21)	0.33 (0.22)[d]	0.36 (0.23)[d]
Vulnerable Elders Survey	0.19 (0.20)	0.16 (0.18)	0.22 (0.21)[d]	0.12 (0.16)	0.27 (0.21)[d]	0.18 (0.20)	0.20 (0.20)[d]	0.21 (0.20)[d]

Abbreviations: BLSA, Beijing Longitudinal Study of Ageing; BMI, body mass index; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSHA, Canadian Study of Health and Aging; FIND, Frail Non-Disabled; HRCA, Hebrew Rehabilitation Center for Aged; SHARE, Survey of Health, Ageing and Retirement in Europe; WHOAFC, World Health Organization Assessment of Functional Capacity; ZED, Zutphen Elderly Study.

[a] Standard deviation was calculated according to the rules of Rubin.

[b] Least-squares regression was used for continuous dependent variables.

[c] Reference category.

[d] $P < 0.05$ for women compared with men, older persons (>70 years) compared with younger persons (≤70 years), ex-smokers compared with never smokers, and current smokers compared with never smokers.

* Inverted scale.

Table 5. Cohen's Kappa Coefficients for Agreement Between Frailty Scores and Results of Bland-Altman Model Analysis for Participants in Wave 2 of the English Longitudinal Study of Ageing, 2004–2005

Frailty Model and Measure	Median κ	Width of Prediction Interval		Absolute Error	
		M35FS[a]	PFS[b]	M35FS[a]	PFS[b]
"Phenotype of frailty" model					
Beaver Dam Eye Study Index	0.318	0.747	0.795	0.123	0.140
Physical Frailty Index	0.298	0.732	0.801	0.113	0.135
FIND Questionnaire	0.508	0.415	0.593	0.025	0.058
Frail Scale	0.391	0.421	0.598	0.099	0.090
Phenotype of Frailty	0.402	0.501	0.663	0.048	0.065
Modified Phenotype of Frailty	0.451	0.427	0.624	0.075	0.096
SOF Index	0.254	0.597	0.736	0.089	0.097
Short Physical Performance Battery	0.396	0.499	0.672	0.102	0.113
ZED1 (Physical Activity and Low Energy)	0.363	0.688	0.759	0.067	0.063
ZED2 (Physical Activity and Weight Loss)	0.191	0.760	0.818	0.057	0.061
ZED3 (Physical Activity and Low BMI)	0.195	0.730	0.907	0.050	0.063
Multidimensional model					
Brief Frailty Index	0.316	0.629	0.746	0.073	0.085
Modified Frailty Score	0.293	0.454	0.640	0.076	0.096
CGAST	0.419	0.347	0.552	0.057	0.048
Conselice Study of Brain Aging Score	0.387	0.430	0.600	0.099	0.111
Edmonton Frail Scale	0.454	0.242	0.454	0.092	0.075
Frailty Staging System	0.447	0.500	0.621	0.054	0.068
G-8 geriatric screening tool	0.352	0.355	0.531	0.013	0.064
Groningen Frailty Indicator	0.513	0.280	0.492	0.014	0.065
Health Status Form	0.430	0.485	0.663	0.082	0.072
Static/Dynamic Frailty Index	0.389	0.429	0.612	0.104	0.120
Screening Instrument	0.344	0.479	0.662	0.061	0.053
Sherbrooke Postal Questionnaire	0.305	0.515	0.580	0.015	0.065
Inter-Frail Questionnaire	0.445	0.385	0.699	0.015	0.064
Tilburg Frailty Indicator	0.472	0.339	0.569	0.091	0.111
"Accumulation of deficits" model					
Comprehensive Geriatric Assessment	0.493	0.212	0.424	0.042	0.059
Evaluative Frailty Index for Physical Activity	0.536	0.219	0.462	0.024	0.061
40-item Frailty Index	0.535	0.201	0.450	0.035	0.060
70-item Frailty Index (SHARE)	0.518	0.231	0.468	0.021	0.063
Frailty Index (BLSA)	0.500	0.234	0.449	0.060	0.060
Long Term Care Survey Frailty Index	0.435	0.236	0.440	0.080	0.066
Disability model					
WHOAFC and self-reported health	0.463	0.436	0.616	0.071	0.065
HRCA Vulnerability Index	0.444	0.391	0.589	0.076	0.066
CSHA Clinical Frailty Scale	0.380	0.561	0.721	0.086	0.093
Vulnerable Elders Survey	0.437	0.392	0.602	0.050	0.050

Abbreviations: BLSA, Beijing Longitudinal Study of Ageing; BMI, body mass index; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSHA, Canadian Study of Health and Aging; FIND, Frail Non-Disabled; HRCA, Hebrew Rehabilitation Center for Aged; M35FS, mean of 35 frailty scores; PFS, pair of frailty scores; SHARE, Survey of Health, Ageing and Retirement in Europe; SOF, Study of Osteoporotic Fractures; WHOAFC, World Health Organization Assessment of Functional Capacity; ZED, Zutphen Elderly Study.

[a] Bland-Altman analysis with *x*-axis equal to the M35FS and *y*-axis equal to the difference between each score and M35FS; absolute error was calculated at the median value of the M35FS.

[b] Bland-Altman analysis with *x*-axis equal to the mean of PFS and *y*-axis equal to the difference between each score and the mean of PFS; absolute error was calculated at the median value of the mean of PFS.

Some FS show over or underestimation, which can be seen when the regression line deviates from 0 at the median point of frailty (0.18) (Web Figure 1). The degree of over or underestimation can vary according to frailty level. Some scores show wider prediction intervals than others. On the right side of each Bland Altman, a density plot displays the distribution of the error.

The FS that showed the narrowest prediction interval widths were Frailty Index 40 items with model A and Comprehensive Geriatric Assessment with model B. Both FS belong to the accumulation of deficits model category.

Figure 1 shows a heat map of kappa for all 595 pairs of scores. The scores are grouped by frailty model category and then sorted by each score's median kappa within each category. The highest kappa values was observed in Evaluative Frailty Index for Physical Activity (table 5 and Figure 1).

Kappa values ranged from 0.10 to 0.83 and were > 0.8 for 0.8% of pairs, between 0.6 and 0.8 for 10.4%, of pairs, between 0.4 and 0.6 for 35.3% of pairs, between 0.2 and 0.4 for 45.9% of pairs and <0.2 for 7.6% of pairs (details of estimates and 95% confidence intervals are shown in Web Table 3). For the 29 FS that have a published cut-off, additional results with kappa calculated using these cut-offs are shown in Web Table 4.

Prediction interval widths obtained with model B are plotted as a heat map in Figure 2, grouped by frailty model category. The narrowest median prediction interval widths with model A was found for Frailty Index 40 items (table 5) and with model B for Comprehensive Geriatric Assessment (table 5 and Figure 2). Both FS belong to the accumulation of deficits model.

Figure 3 (grouped by model) shows a heat map of the absolute error calculated with model B. The lowest absolute error with model B was found in Comprehensive Geriatric Assessment Screening Tests and with model A, G-8 Geriatric Screening Tool (table 5). Both FS belong to the multidimensional model (table 5 and Figure 3). Web Figures 2 to 4 show the same analysis of Figures 1 to 3 grouped according to the stated target population. Web Figures 5-11 illustrate heat maps of kappa stratified by sex, age and smoking status. Plots of model B are available in Web appendix.

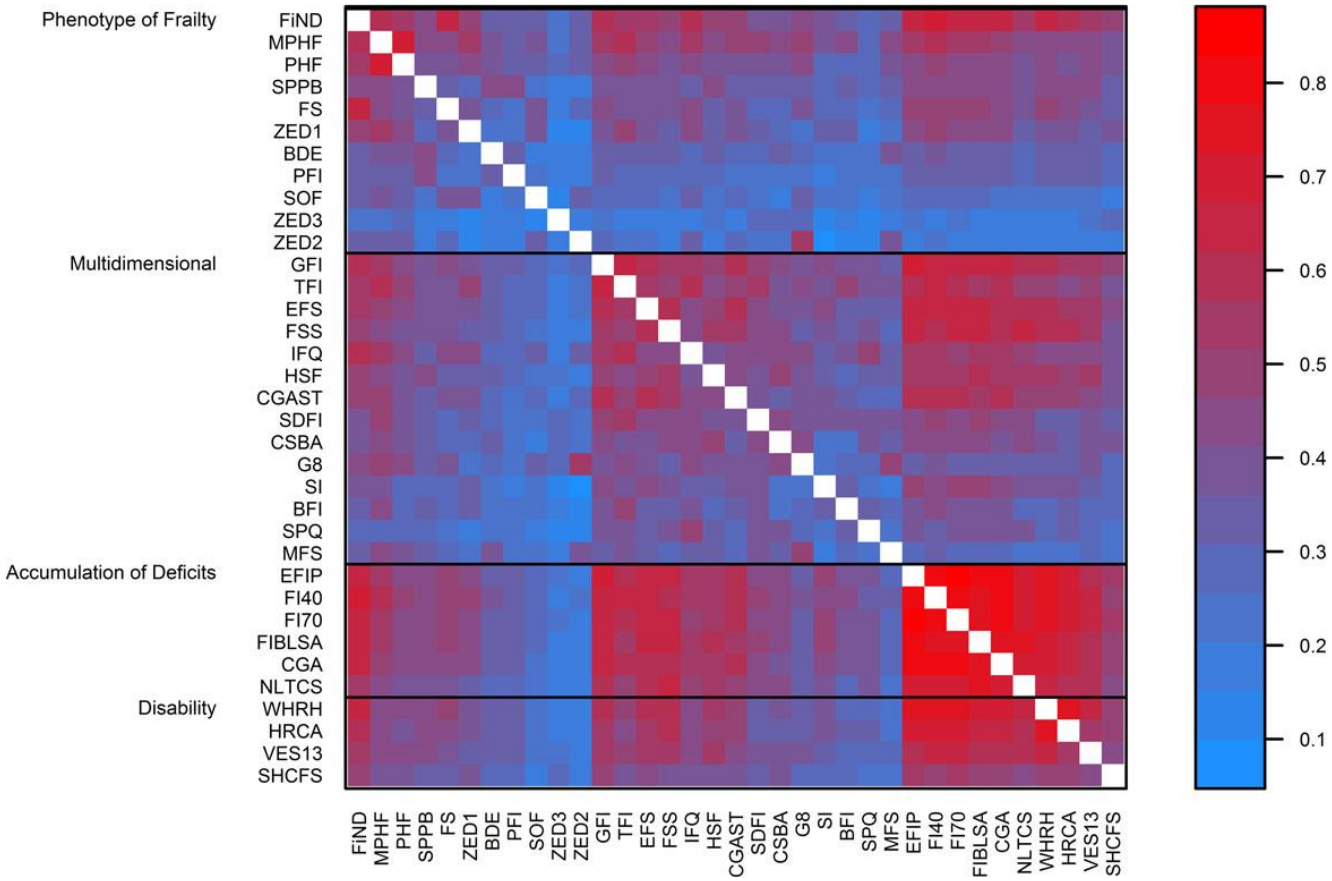


Figure 1. Agreement (calculated with Cohen's κ) between pairs of frailty scores (595 combined pairs of scores) among participants in wave 2 of the English Longitudinal Study of Ageing, 2004–2005. The plot is sorted by frailty model and then from highest (red) to lowest (blue) median value of Cohen's κ coefficient.

BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; MFS, Modified Frailty Score; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; PFI, Physical Frailty Index; FiND, Frail Non-Disabled (FiND) Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 geriatric screening tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; NLTCS, National Long Term Care Survey Frailty Index; PHF, Phenotype of Frailty; MPHF, Modified Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; IFQ, Inter-Frail Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHOAFC, World Health Organization Assessment of Functional Capacity; WHRH, WHOAFC and self-reported health; ZED1, Zutphen Elderly Study (Physical Activity and Low Energy); ZED2, Zutphen Elderly Study (Physical Activity and Weight Loss); ZED3, Zutphen Elderly Study (Physical Activity and Low BMI).

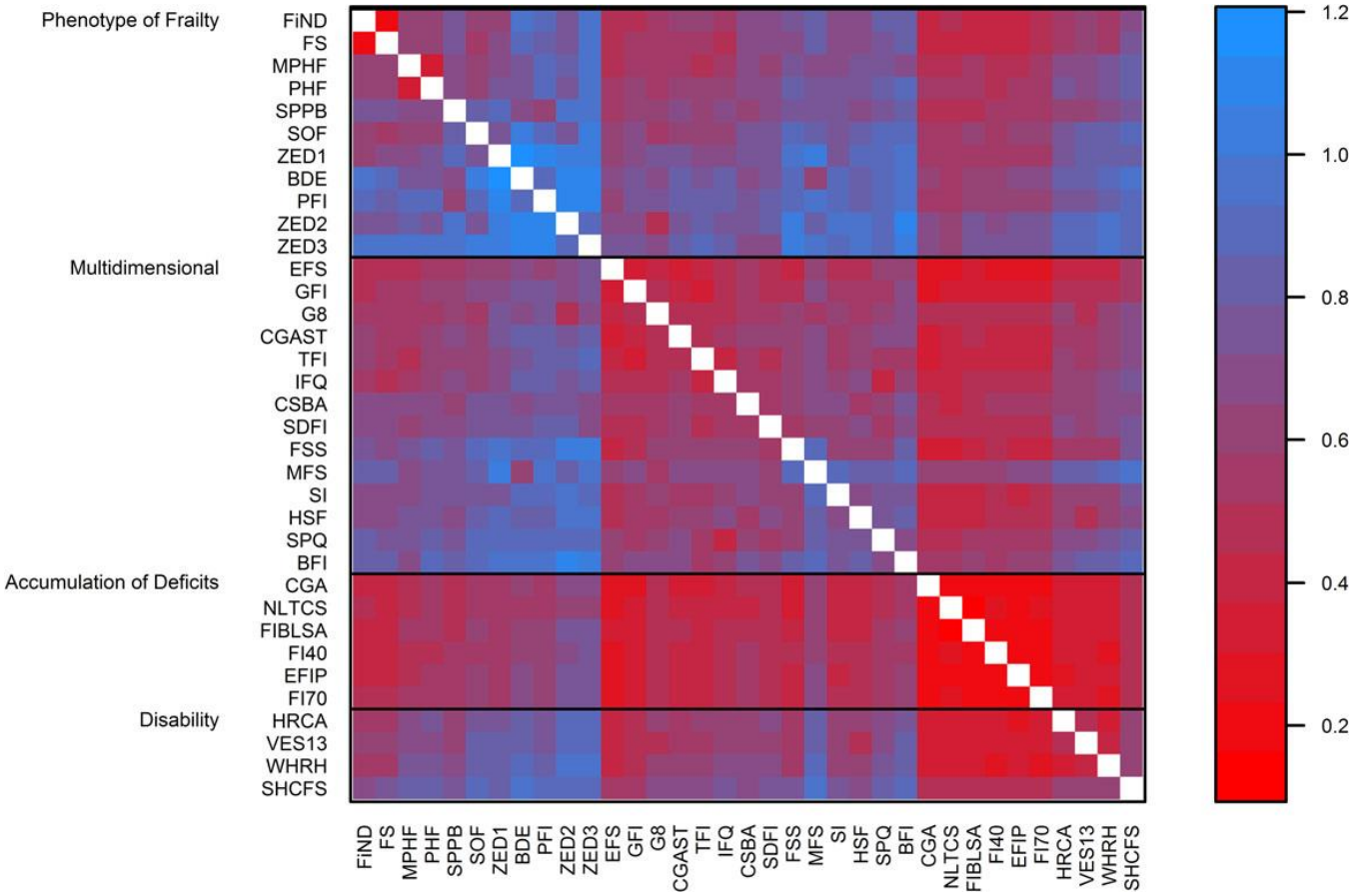


Figure 2. Prediction interval widths obtained with Bland-Altman models for all 595 combined pairs of frailty scores, English Longitudinal Study of Ageing, wave 2 (2004–2005). The narrowest prediction interval widths are shown in red, and the widest are shown in blue. The plot is sorted by frailty model and then by the narrowest prediction interval.

BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; MFS, Modified Frailty Score; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; PFI, Physical Frailty Index; FiND, Frail Non-Disabled (FiND) Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 geriatric screening tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; NLTCS, National Long Term Care Survey Frailty Index; PHF, Phenotype of Frailty; MPHF, Modified Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; IFQ, Inter-Frail Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHOAFC, World Health Organization Assessment of Functional Capacity; WHRH, WHOAFC and self-reported health; ZED1, Zutphen Elderly Study (Physical Activity and Low Energy); ZED2, Zutphen Elderly Study (Physical Activity and Weight Loss); ZED3, Zutphen Elderly Study (Physical Activity and Low BMI).

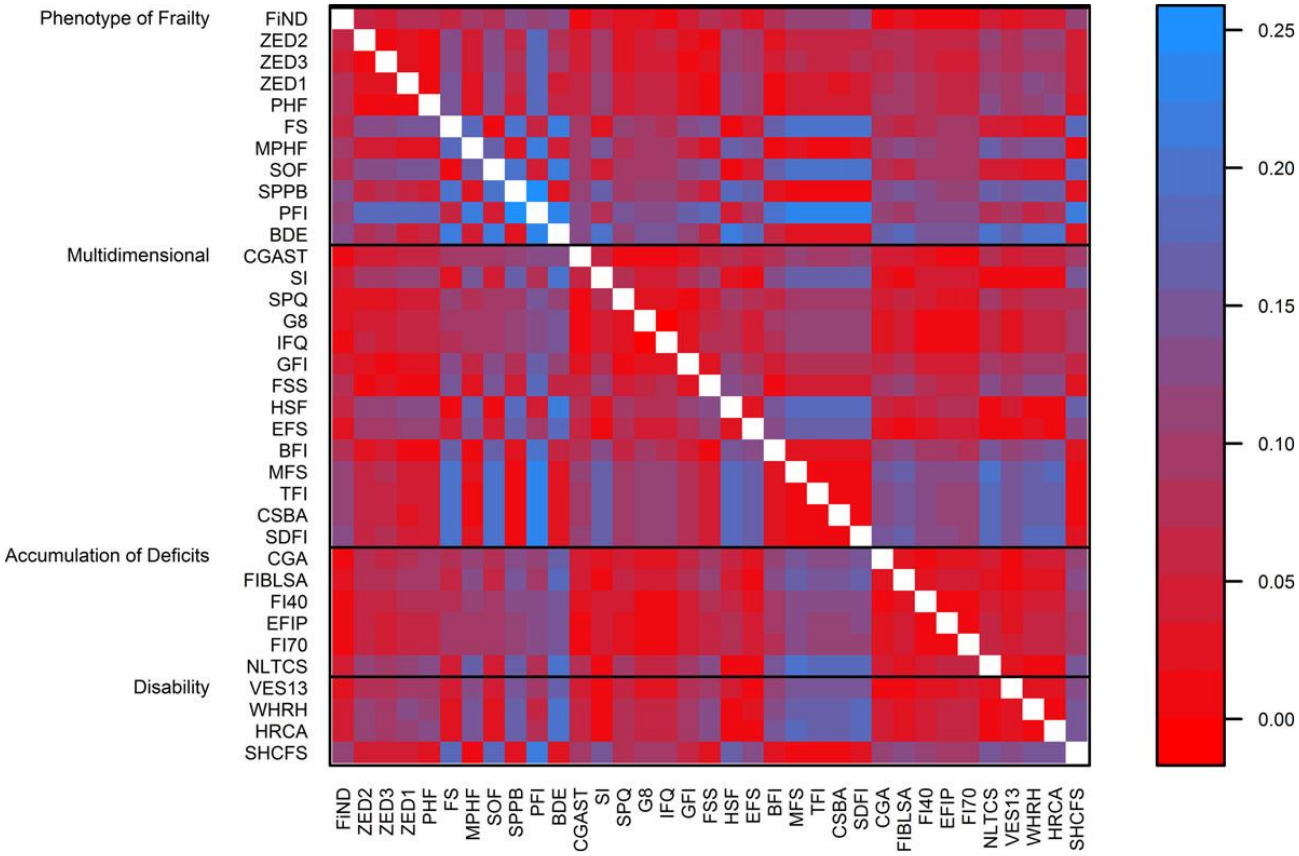


Figure 3. Absolute error (over-/underestimation) of frailty in the median frailty value from the modified Bland-Altman model obtained with all 595 combined pairs of frailty scores, English Longitudinal Study of Ageing, wave 2 (2004–2005). The over-/underestimation is the absolute value of the intercept plus the product of the slope and the median. The intercept and slope are obtained from the Bland-Altman model. The median is calculated as the median value of the mean of 2 frailty scores for each pair. The lowest absolute errors are shown in red, and the highest are shown in blue. The plot is sorted by frailty model and then by the lowest absolute error. BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BDE, Beaver Dam Eye Study Index; MFS, Modified Frailty Score; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; PFI, Physical Frailty Index; FiND, Frail Non-Disabled (FiND) Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 geriatric screening tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; NLTCS, National Long Term Care Survey Frailty Index; PHF, Phenotype of Frailty; MPHF, Modified Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; IFQ, Inter-Frail Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHOAFC, World Health Organization Assessment of Functional Capacity; WHRH,WHOAFC and self-reported health; ZED1, Zutphen Elderly Study (Physical Activity and Low Energy); ZED2, Zutphen Elderly Study (Physical Activity and Weight Loss); ZED3, Zutphen Elderly Study (Physical Activity and Low BMI).

2.5. Discussion

We studied the cross-sectional agreement between 35 FS in an elderly population and found a wide range of agreement. Out of 595 pairs of scores almost 90% had a kappa under 0.6. Our results, based both on traditional and modified Bland-Altman models, indicate that FS belonging to the accumulation of deficits model with many variables have higher median agreement (Figure 1) and narrower prediction interval widths (Figure 2) and that FS belonging to the multidimensional model have lower absolute errors (Figure 3). Our results support our initial hypothesis that different FS classify different subsets of the population as frail.

Using the published cut-off values for each FS, we found very wide variation in the prevalence of frailty, as previously reported by others[70 110-112]. Scores that define solely frail and non-frail categories generally yielded a higher frailty prevalence than scores that also define an intermediate 'pre-frail' state. Even though some variation is to be expected due to the fact that scores have been developed according to different underlying concepts of frailty, our finding of a 70-fold difference between the highest (SPPB: 65.0% in men and 72.4% in women) and the lowest prevalence (ZED3 0.8% in men and 1.0% in women) indicates that published frailty prevalence estimates, and consequently our insight into the magnitude of the frailty problem is dependent to an overwhelming degree on the chosen instrument and cut-off level. Comparisons to prevalence estimates from other populations, such as those published in 2012 in a systematic review[111], therefore need to be undertaken with caution and preferably only between studies using the same instrument.

Our findings also highlight that the general recommendation that scores and their cut-off levels should be recalibrated (by modification of the weights attached to each item and/or revision of the optimal cut-off level) before being applied outside their original population is highly applicable and important in the field of frailty. When we regarded FS on a continuous scale from 0 to 1, the between-score variation was still large, but less pronounced (2.7-fold difference in mean frailty score between the highest (0.35) and the lowest (0.13) score). This indicates that the problem of the wide divergence in prevalence estimates is due in the first place to lack of generalizability of cut-off values across different populations, and in the second place on different characteristics of the scores themselves. The lack of a uniform understanding of what constitutes frailty is what ultimately underlies the large number of different scores to measure it, and the resulting issues when attempting to compare results.

Given the outlined issues with the use of published cut-off levels, we focused our study of agreement on the identification of the 20% frailest individuals. We found that in some cases agreement was as low as 0.1, which with a prevalence of 0.2 means that around 30% of individuals would be classified differently. The highest agreement (0.83) translates into around 6% of individuals being classified differently, at the predefined prevalence of 0.2. Only 11.3% of pairs of scores had a kappa of 0.6 or higher, indicating that only a small minority of score pairs would identify the same individuals as being frail with an acceptable level of consistency. In clinical practice, these low levels of agreement would lead to the selection of largely different people for further examination or treatment, depending on which tool was implemented.

As a summary measure of agreement, kappa has the disadvantage of valuing correct classification of the presence or absence of the condition in equal measure. Judgement of whether or not this is appropriate will depend on the context in which a score is used. If used as part of a sequence of screening steps, sensitivity is likely to be more important than specificity, while if the score is used to guide treatment initiation, specificity will be equally important. Also, in a research context, this measure depends on the prevalence of the condition (with a very low prevalence kappa will be very low, even with a large agreement between raters)[58].

We examined agreement across the entire spectrum of frailty based both on traditional and modified Bland-Altman analyses. Traditional pairwise Bland-Altman models regard the mean of each pair of measures as an indicator of the 'true' value. In our modified Bland-Altman models, we calculated the M35FS, to generate a global indicator of the 'true' level of frailty. Although using the M35FS as a proxy for the 'true' level of frailty makes a number of assumptions, such as assigning equal importance to each of the studied scores, we feel this approach best captures the agreement between each score and the global level of frailty in the absence of an accepted gold standard. The complementary pairwise analyses based on traditional Bland-Altman models largely confirmed the finding of better agreement for FS with numerous variables and lower error for FS from the multidimensional model category (Table 5).

Several scores tended to progressively under or over-estimate at higher levels of 'true' frailty, indicating that they would require not only recalibration of the distribution or cut-off level, but also of the relative weight attached to each underlying variable to avoid giving biased frailty estimates in the ELSA population. Several scores showed remarkably wide prediction intervals, indicating a poor capacity to accurately assess the 'true' level of frailty.

The narrowest prediction intervals were observed for the FS from the accumulation of deficits model category, which were also the FS with the best agreement across all score pairs based on kappa values. In general, scores based on a larger number of variables tended to have narrower prediction intervals and higher over-all agreement; however, with a certain degree of under-estimation in the higher frailty ranges. Scores that are multidimensional tended to have less error at the median point of frailty.

While features such as accuracy, over-all agreement, and bias are important considerations guiding a choice of score for research or clinical practice, practical feasibility is likely to be as important. Although we observed the highest over-all agreement between scores derived from numerous variables, these scores may be difficult to implement in practice due to the high demands on time, expertise and equipment required to obtain a valid and complete set of the necessary data. When we categorized our results by the intended setting (clinical or community-based) in supplementary analyses we observed similar variability in agreement both within and between these two settings (web Figures 2-3). Which score strikes the optimal balance between feasibility and performance is likely to be different in each situation. Our results may help guide these decisions.

The main strengths of the present study are that we analysed agreement between the most comprehensive list of FS examined to date in a large sample representative of an elderly general population, based on data including self-reported and objective measures of determinants and characteristics of frailty. We applied three different approaches to the study of agreement, finding broadly consistent results. In addition, we applied multiple imputation, using a state-of-the art method.

The main limitation is that in the absence of an external gold standard, our analyses of agreement between the continuous scores depended on an internal proxy for 'true' frailty, defined either specifically for each pair of scores, or globally as the M35FS. Our adaptation of some scores to the data available in ELSA may have led to some degree of distortion in comparison to the original score definition. However, this only affects a minority of scores and is unlikely to determine our main findings. Finally, due to the cross-sectional design of the present analysis, we cannot draw conclusions regarding dynamic features of the scores, such as longitudinal stability, or about other aspects such as external validity with regard to frailty outcomes.

Our comparative study of different features of agreement in a wide set of published FS showed marked heterogeneity in the degree to which various FS over/underestimate frailty, and agree in the identification of the same individuals as frail. Different scores are based on different concepts of frailty and most pairs cannot be assumed to be interchangeable. Research results based on different scores cannot be compared, pooled or summarized directly. Our results support a multidimensional concept of frailty that includes many variables.

2.6. Web material

2.6.1. Web table 1

Web Table 1. Included and Excluded Frailty Scores in ELSA Wave 2 (2004-2005)

Score	Author	Year	Publication	% calc	Incl
Armstrong frailty index	Armstrong	2010	Examining three frailty conceptualizations in their ability to predict negative outcomes for home-care clients.	72	No
Brief frailty index (Calgary Cardiac and Cognition study)	Freiheit	2010	Development of a Frailty Index for Patients with Coronary Artery Disease	100	Yes
Chinese Longitudinal Healthy Longevity Survey	Gu	2009	Frailty and Mortality Among Chinese at Advanced Ages	79	No
Clinical Frailty Scale	Rockwood	2005	A global clinical measure of fitness and frailty in elderly people	100	Yes
Clinical Global Impression of Change in Physical Frailty	Studenski	2004	Clinical Global Impression of Change in Physical Frailty: Development of a Measure Based on Clinical Judgment	44	No
Comprehensive assessment of frailty	Sündermann	2011	Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery	61	No
Comprehensive Geriatric Assessment Screening tests	Balducci	2000	Management of Cancer in the Older Person: A Practical Approach	100	Yes
Conselice Study of Brain Aging Score	Ravaglia	2008	Development of an easy prognostic score for frailty outcomes in the aged	100	Yes
CSRG-Frailty Index Score	Rockwood	2014	Frailty Index to Measure Health Status in People with Systemic Sclerosis	64	No
Beaver Dam Eye study score	Klein	2003	Relationship of measures of frailty to visual function: the Beaver Dam Eye Study	100	Yes
WHOAFC & self-reported health	Dayhoff (based on Ferrucci 1991)	1998	Balance and muscle strength as predictors of frailty among older adults	93	Yes
EASY-Care Two-step Older persons Screening	van Kempen	2014	Construct validity and reliability of a two-step tool for the identification of frail older people in primary care	NA	No

Edmonton Frail Scale	Rolfson	2006	Validity and reliability of the Edmonton Frail Scale	100	Yes
Evaluative Frailty Index for Physical Activity	de Vries	2013	Evaluative frailty index for physical activity (EFIP): a reliable and valid instrument to measure changes in level of frailty	84	Yes
Fails and injuries in frail and vigorous community elderly persons	Speechley & Tinetti	1991	Fails and injuries in frail and vigorous community elderly persons	54	No
FI based on ICPC	Drubbel	2013	Prediction of Adverse Health Outcomes in Older People Using a Frailty Index Based on Routine Primary Care Data	78	No
Frail scale	Abellan van Kan	2008	Frailty: Toward a Clinical Definition	100	Yes
Frailty scale(1999)	Rockwood	1999	A brief clinical instrument to classify frailty in elderly people	NA	No
Frailty index of senior mexican adults	García-González	2009	A frailty index to predict the mortality risk in a population of senior Mexican adults	76	No
Frailty index (40 items)	Searle	2008	A standard procedure for creating a frailty index	93	Yes
Frailty Index (Gill)	Gill	2002	A program to prevent functional decline in physically frail, elderly persons who live at home	100	Yes
Frailty index (Opasich)	Opasich	2010	An elderly-centered, personalized, physiotherapy program early after cardiac surgery	71	No
Frailty index of Beijing Longitudinal Study of Ageing	Fang	2012	Frailty in relation to the risk of falls, fractures, and mortality in older Chinese adults: results from the Beijing Longitudinal Study of Aging	80	Yes
Frailty Index-99	Mitnitski	2001	Accumulation of Deficits as a Proxy Measure of Aging	56	No
Frailty Risk Index	Ng	2014	Frailty in Older Persons: Multisystem Risk Factors and the Frailty Risk Index (FRI)	69	No
Frailty Staging System	Cacciatore (based on Lachs 1990	2005	Frailty predicts long-term mortality in elderly subjects with chronic heart failure	100	Yes
Frailty Trait Scale	García-García	2014	A New Operational Definition of Frailty: The Frailty Trait Scale	67	No

Frialty index	Mitnitski	2002	Frailty, fitness and late-life mortality in relation to chronological and biological age	65	No
Frialty index 70 items (Share) based on Mitninski 2001 and Rockwood 2011	Theou (based on Rockwood 2011)	2013	Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans	89	Yes
Frialty index from Comprehensive geriatric assessment (SHARE adaptation)	Jones/Theou	2004	Operationalizing a Frailty Index from a Standardized Comprehensive Geriatric Assessment	93	Yes
Functional assessment screening package	Moore	1996	Screening for common problems in ambulatory elderly: clinical confirmation of a screening instrument	63	No
G-8 geriatric screening tool	Bellera	2012	Screening older cancer patients: first evaluation of the G-8 geriatric screening tool	88	Yes
Gérontopôle Frailty Screening Tool			The integration of frailty into clinical practice: preliminary results from the Gérontopôle	75	No
Groningen Frailty Indicator	Steverink	2001	Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator)	100	Yes
Health Status Form	Brody	1997	Evaluation of a Self-Report Screening Instrument to Predict Frailty Outcomes in Aging Populations	100	Yes
Hebrew Rehabilitation Center for Aged Vulnerability Index	Morris	1984	An Assessment Tool for Use in Identifying Functionally Vulnerable Persons in the Community	100	Yes
Inter-Frail Questionnaire	Di Bari	2014	Screening for Frailty in Older Adults Using a Postal Questionnaire: Rationale, Methods, and Instruments Validation of the INTER-FRAIL Study	80	Yes
Kihon Checklist	Nemoto	2012	Assessment of vulnerable older adults' physical function according to the Japanese Long-Term Care Insurance (LTCI) system and Fried's criteria for frailty syndrome	33	No
Kulminski Frailty Index	Kulminski	2007	Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: results from analyses of the National Long Term Care Survey	81	Yes

Marigliano–Cacciafesta polypathological scale	Amici	2008	The Marigliano–Cacciafesta polypathological scale: A tool for assessing fragility	24	No
MDS-CHESS Scale	Hirdes	2003	The MDS-CHESS Scale: A new measure to predict mortality in institutionalized older people	NA	No
Modified Frailty Score	Hubbard	2009	Characterising frailty in the clinical setting—a comparison of different approaches	100	Yes
Modified Physical performance test	Brown	2000		33	No
Multidimensional Frailty Score for the Prediction of Postoperative Mortality Risk	Kim	2014	Multidimensional Frailty Score for the Prediction of Postoperative Mortality Risk	33	No
Phenotype of frailty	Fried	2001	Frailty in older adults evidence for a phenotype	100	Yes
Phenotype of frailty modified	Rothman	2008	Prognostic Significance of Potential Frailty Criteria	100	Yes
Phenotype of frailty modified-2	Avila-Funes	2009	Cognitive Impairment Improves the Predictive Validity of the Phenotype of Frailty for Adverse Health Outcomes: The Three-City Study	NA	No
Physical frailty	Binder	2002	Effects of Exercise Training on Frailty in Community-Dwelling	33	No
Physical Performance test	Reuben	1990	An objective measure of physical function of elderly outpatients	0	No
Postal screening questionnaire in preventive geriatric care	Barber	1980		66	No
PRISMA-7	Raîche	2008	PRISMA-7: a case-finding tool to identify older adults with moderate to severe disabilities	78	No
Score-Risk Correspondence for dependency	Carrière	2005	Hierarchical components of physical frailty predicted incidence of dependency in a cohort of elderly women	NA	No
Screening Instrument	Maly	1997	The performance of simple instruments in detecting geriatric conditions and selecting community-dwelling older people for geriatric assessment	100	Yes
Self-rated health deficits index	Lucicesare 2010	2010	An index of self-rated health deficits in relation to frailty and adverse outcomes in older adults	50	No

Short Physical Performance Battery	Guralnik	1994	A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission	100	Yes
Static/Dynamic Frailty Index	Puts	2005	Sex differences in the risk of frailty for mortality independent of disability and chronic diseases	100	Yes
Strawbridge questionnaire	Strawbridge	1998	Antecedents of frailty over three decades in an older cohort	56	No
Study of Osteoporotic Fractures	Ensrud	2007	Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women	100	Yes
Subjective Frailty Index	Gerdhem	2003	Bone Mass Cannot Be Predicted by Estimations of Frailty in Elderly Ambulatory Women	0	No
The Frail Non-Disabled (FiND) Questionnaire	Cesari	2014	A Self-Reported Screening Tool for Detecting Community-Dwelling Older Persons with Frailty Syndrome in the Absence of Mobility Disability: The FiND Questionnaire	100	Yes
The Sherbrooke Postal Questionnaire	Hebert	1996	Predictive Validity of a Postal Questionnaire for Screening Community-dwelling Elderly Individuals at Risk of Functional Decline	100	Yes
Tilburg Frailty Indicator	Gobbens	2010	The Tilburg Frailty Indicator: Psychometric Properties	100	Yes
Triage risk screening tool	Meldon	2003	A Brief Risk-stratification Tool to Predict Repeat Emergency Department Visits and Hospitalizations in Older Patients Discharged from the Emergency Department	60	No
Vulnerable Elders Survey	Saliba	2001	The Vulnerable Elders Survey: A Tool for Identifying Vulnerable Older People in the Community	92	Yes
ZutPhen Elderly Study (Physical Activity & Low Energy)	Chin	1999	How to Select a Frail Elderly Population? A Comparison of Three Working Definitions	100	Yes
ZutPhen Elderly Study (Physical Activity & Weight Loss)	Chin	1999	How to Select a Frail Elderly Population? A Comparison of Three Working Definitions	100	Yes

ZutPhen Elderly Study (Physical Activity & Low BMI)	Chin	1999	How to Select a Frail Elderly Population? A Comparison of Three Working Definitions	100	Yes

Abbreviations: % calc, percentage of variables that were possible to calculate with ELSA wave 2; Incl, included in this study.

2.6.2. Web table 2

Supplementary Table 2. Variables of Frailty Scores in ELSA Wave 2 (2004-2005)

Score	Var	Variable name	Original in score	ELSA variables	Miss
BDE	1	walkfrail	Walk test	Walk test	0
BDE	2	f.frail	Peak expiratory flow	Peak expiratory flow	0
BDE	3	frailgrip	Grip	Grip strength	0
BDE	4	rise.frail	Unable to stand	Chair rise	0
BFI	1	sidebyside	Balance: not able to hold a full tandem position.	Balance	0
BFI	2	abnormalBMI	Abnormal BMI	BMI<21|BMI>=30	0
BFI	3	cognbinar	Impaired trail test part B.	Total cognitive index 0-0-5-1	0
BFI	4	depression.cesd	Depression symptoms	CES-D>=4	0
BFI	5	liv.alone	Living alone	Whether has a husband, wife or partner with whom they live	0
CFCS	1	getupgo	Timed get up and go		0
CFCS	2	pa	Low levels of physical activity	Physical activity level	0
CFCS	3	frailgrip	Grip	Grip strength	0
CFCS	4	cognbinar	Cognition	Total cognitive index 0-0-5-1	0
CFCS	5	weight.sc	Weight loss	Weight loss wave 0-wave 2	0
CGA	1	health2	Self-reported health	Self-reported health	0
CGA	2	scoreBMI	BMI	BMI<18.5|BMI>=30	0
CGA	3	medic.chronic	Taking medications for chronic conditions	Adapted medications for hypertension, heart attack, diabetes	0
CGA	4	polypharmacy	Polypharmacy (>2 medications)		0
CGA	5	memory	Cognitive problems	Adapted: prospective memory score	0
CGA	6	multcog			0
CGA	7	lungdis	Chronic lung disease		0
CGA	8	asthma			0
CGA	9	dyslipidemia			0
CGA	10	arthritis	Arthritis		0
CGA	11	osteoporosis			0
CGA	12	cancer			0
CGA	13	heart	Heart attack		0
CGA	14	NA	Stomach or duodenal ulcer	Missing	1
CGA	15	parkinson			0
CGA	16	cataracts			0

CGA	17	stroke	Stroke	Stroke history	0
CGA	18	hipfracture		Hip fractures	0
CGA	19	diabetes	Diabetes		0
CGA	20	bpres	Self-reported high blood pressure		0
CGA	21	hearing	Hearing problems		0
CGA	22	poorvision	Problems with eyesight	Self-reported poor vision	0
CGA	23	incont	Do you have a problem with losing control of urine when you don't want to?	Whether lost urine beyond control in last 12 months	0
CGA	24	NA	Diminished appetite	Missing	1
CGA	25	sleep	Sleep problems		0
CGA	26	Toileting	Toileting	ADL	0
CGA	27	prep.meal	Preparing a hot meal	IADL	0
CGA	28	walkout	Walking 100 meters		0
CGA	29	shop	Shopping	IADL	0
CGA	30	calls	Making telephone calls	IADL	0
CGA	31	medic.take	Need help taking medication	IADL	0
CGA	32	getupchair	Getting up from a chair	Difficulty getting up from chair after sitting long periods	0
CGA	33	walking	Walking around house	**ADL**	0
CGA	34	bath	Bathing	ADL	0
CGA	35	dress	Dressing	ADL	0
CGA	36	eat	Eating	ADL	0
CGA	37	carrying	Lifting 10 lbs	Mobility	0
CGA	38	money	Managing money	IADL	0
CGA	39	climb.stairs	Climbing stairs	Mobility	0
CGA	40	walking	Walking across a room		0
CGA	41	NA	Irritability	Missing	1
CGA	42	pessimism			0
CGA	43	depression.cesd	Feel depressed	CES-D>=4	0
CGA	44	effort	Fatigue	Feel everything is an effort	0
CGAST	1	memory	Mental status	Prospective memory score	0
CGAST	2	depression.cesd	Emotional status/Depression symptoms	CES-D>=4	0
CGAST	3	ADL	ADL	Mean of ADL	0
CGAST	4	IADL	IADL	Mean of IADL	0
CGAST	5	carpet	Home environment	Thigh pile carpet=risk	0
CGAST	6	social.support	Social support	Adapted if participant had no ADL/IADL difficulties=0; if had difficulties and receive help=1; if had difficulties and no receive help=2	0

CGAST	7	reported	Comorbidity	Adapted: Ever reported 2 or more diseases	0
CGAST	8	weight.loss	Nutrition	Weight loss wave 0-wave 2	0
CGAST	9	medic.chronic	Polypharmacy (>2 medications)	Adapted medications for hypertension, heart attack, diabetes	0
CSBA	1	advanced.age	Age>=80		0
CSBA	2	sex.male	Male: gender		0
CSBA	3	pa	Physical inactivity	Physical activity level	0
CSBA	4	medic.chronic	Polypharmacy (>2 medications)	Adapted medications for hypertension, heart attack, diabetes	0
CSBA	5	sensory.deficit	Poor vision or poor hearing		0
CSBA	6	low.BMI	Calf circumference<31 cm	Replaced by BMI<25	0
CSBA	7	IADL	IADL	Mean of IADL	0
CSBA	8	SPPB.scorefrail	Gait and Balance test <=24	Adapted frail defined by SPPB	0
CSBA	9	health2	Self-reported health	Self-reported health	0
DFS	1	walking	Walking between rooms	ADL	0
DFS	2	pulling	Moving around doors	Adapted pulling	0
DFS	3	climb.stairs	Using stairs	Mobility	0
DFS	4	walkout	Walking at least 1/4 mile	Walk outside (walking 100 yards)	0
DFS	5	Toileting	Toileting	ADL	0
DFS	6	bath	Washing and Bathing	ADL	0
DFS	7	dress	Dressing	ADL	0
DFS	8	bed	Getting out of bed	ADL	0
DFS	9	eat	Feeding oneself	ADL	0
DFS	10	stoop	Cutting toenails	Adapted: stoop	0
DFS	11	prep.meal	Preparation of meals	IADL	0
DFS	12	house.garden	Doing heavy housework	IADL	0
DFS	13	NA		Missing	1
DFS	14	carrying	Carrying heavy objects		0
DFS	15	health2	Self-reported health	Self-reported health	0
EFIP	1	bath	Help taking a shower	ADL	0
EFIP	2	dress	Help getting dressed	ADL	0
EFIP	3	bed	Getting out of bed	ADL	0
EFIP	4	NA	Need help for moving in bed	Missing	1
EFIP	5	sitting	Do you need help sitting down from a normal chair?	Difficulty sitting 2 hours	0
EFIP	6	getupchair		Difficulty getting up from chair after sitting long periods	0
EFIP	7	dizziness	Do you feel dizzy when you are standing up?		0

EFIP	8	walking	Walking around house	ADL	0
EFIP	9	walkout		Walk outside (walking 100 yards)	0
EFIP	10	walking.with.aid	Do you use anything (walking stick or frame) to help you walk?		0
EFIP	11	fallingdown		Asked only to>=60 years	0
EFIP	12	Toileting	Toileting	ADL	0
EFIP	13	climb.stairs	Climbing stairs	Mobility	0
EFIP	14	shop	Shopping	IADL	0
EFIP	15	house.garden	House work	IADL	0
EFIP	16	painjoint			0
EFIP	17	ADL	Cut down on usual activity	Mean of ADL	0
EFIP	18	pa	Physical activity		0
EFIP	19	NA	Do you feel nervous or anxious?	Missing	1
EFIP	20	effort		Feel everything is an effort	0
EFIP	21	depression.cesd		CES-D>=4	0
EFIP	22	happy		Feel happy	0
EFIP	23	NA	Do you feel nervous or anxious?	Missing	1
EFIP	24	NA	Are you afraid of falling over?	Missing	1
EFIP	25	orientation	Do you usually know what day and what time of the day it is	MMSE	0
EFIP	26	memory	Do you have difficulty remembering when your appointments are?	Prospective memory score	0
EFIP	27	self.rated.memory	Do you have difficulty remembering names of family members and friends?	Self-rated memory: good, very good and excellent=0; fair=0.5; poor=1	0
EFIP	28	lon	Feel lonely		0
EFIP	29	social.support	When you need help, are there people who are willing and able to help you?	Adapted if participant had no ADL/IADL difficulties=0; if had difficulties and receive help=1; if had difficulties and no receive help=2	0
EFIP	30	friends.help	Are there activities that someone else has taken over for you recently?	How much respondent can rely on these friends if they have a serious problem	0
EFIP	31	social.particip	Are there enough organized activities for you nearby?	Organizational membership	0

EFIP	32	not.use.pub.transp	Do you have problems getting out for organized activities (e.g., problems with transportation to get to them)?	Reasons for not using public transport more often (1st mention)	0
EFIP	33	NA	Do you have enough help from professionals?	Missing	1
EFIP	34	NA	Do you have enough help from professionals?	Missing	1
EFIP	35	health2	How do you rate your health?	Self-reported health	0
EFIP	36	fitness	How do you rate your fitness?	0=sedentary or low; 1=moderate or high	0
EFIP	37	change.h.score	Change in health		0
EFIP	38	medic.take	Need help taking medication	IADL	0
EFIP	39	polypharmacy	Do you take more than 4 medications a day?		0
EFIP	40	NA	Have you had to stay overnight in a hospital unexpectedly in the last 3 months?	Missing	1
EFIP	41	hearing	Do you have difficulty hearing?	Self-reported hearing	0
EFIP	42	poorvision	Problems with eyesight	Self-reported poor vision	0
EFIP	43	NA		Missing	1
EFIP	44	bpres	High blood pressure	Self-reported high blood pressure	0
EFIP	45	heart.disease			0
EFIP	46	diabetes	Diabetes		0
EFIP	47	arthritis	Arthritis		0
EFIP	48	lungdis	Chronic lung disease		0
EFIP	49	incont	Do you have a problem with losing control of urine when you don't want to?	Whether lost urine beyond control in last 12 months	0
EFIP	50	stroke	Stroke	Stroke history	0
EFS	1	cognbinar		Total cognitive index	0
EFS	2	hosp	General health status: admitted in an hospital	Adapted: admitted to hospital for heart problems in the las 6 weeks	0
EFS	3	shealth	Self-assessment general health status 3 categories	Self-rated health	0
EFS	4	disab	Disability	ADL, IADL	0

EFS	5	needhelp	Help received	Adapted if participant had no ADL/IADL difficulties=0; if had difficulties and receive help=1; if had difficulties and no receive help=2	0
EFS	6	reported	Do you use five or more different prescriptions on a regular basis?	Adapted: Ever reported 2 or more diseases	0
EFS	7	medic.take	Need help taking medication	IADL	0
EFS	8	weight	Have you recently lost weight that your closing become looser?	5% lost weight from wave 0 to 2	0
EFS	9	sad	Do you often feel sad or depressed?	Whether respondent felt sad much of the time during the past week or depressed	0
EFS	10	incont	Do you have a problem with losing control of urine when you don't want to?	Whether lost urine beyond control in last 12 months	0
EFS	11	go	Get and go	Unable to chair-rise or gait speed <=0.30m/sec=2; able to Chair rise & gait speed >0.15m/sec=1	0
FI40	1	bath	Bathing	ADL	0
FI40	2	dress	Dressing	ADL	0
FI40	3	bed	Getting out of bed	ADL	0
FI40	4	walking	Walking around house	ADL: Difficulty walking across a room	0
FI40	5	eat	Eating	ADL	0
FI40	6	NA	Grooming	Missing	1
FI40	7	Toileting	Toileting	ADL	0
FI40	8	climb.stairs	Climbing stairs	Mobility	0
FI40	9	carrying	Lifting 10 lbs	Mobility	0
FI40	10	shop	Shopping	IADL	0
FI40	11	house.garden	House work	IADL	0
FI40	12	prep.meal	Preparation of meals	IADL	0
FI40	13	medic.take	Need help taking medication	IADL	0
FI40	14	money	Managing money	IADL	0
FI40	15	weight.loss	Weight loss	Weight loss wave 0-wave 2	0
FI40	16	health2	Self-reported health	Self-reported health	0
FI40	17	change.h.score	Change in health	Changes in self-reported health between wave 0 and wave 2	0
FI40	18	llsill.ord	Stay in bed	Stay in bed	0
FI40	19	ADL	Cut down on usual activity	Mean of ADL	0

FI40	20	walkout		Walk outside (walking 100 yards)	0
FI40	21	effort		Feel everything is an effort	0
FI40	22	depression.cesd	Feel depressed	CES-D>=4	0
FI40	23	happy		Feel happy	0
FI40	24	lon	Feel lonely		0
FI40	25	going	Trouble getting going		0
FI40	26	bpres		Self-reported high blood pressure	0
FI40	27	heart		Heart attack	0
FI40	28	heart.fail			0
FI40	29	stroke	Stroke	Stroke history	0
FI40	30	cancer	Cancer		0
FI40	31	diabetes	Diabetes		0
FI40	32	arthritis	Arthritis		0
FI40	33	lungdis	Chronic lung disease		0
FI40	34	memory	Cognitive problems	Adapted: prospective memory score	0
FI40	35	flowscore	Peak flow	Expiratory flow	0
FI40	36	NA	Shoulder strength	Missing	1
FI40	37	scoreBMI	BMI	BMI<18.5|BMI>=30	0
FI40	38	scoregrip	Grip strength	Grip strength	0
FI40	39	scorewalkusual	Usual walk		0
FI40	40	NA	Rapid pace		1
FI70	1	health2	Self-reported health	Self-reported health	0
FI70	2	hosp	General health status: admitted in an hospital	Adapted: admitted to hospital for heart problems in the las 6 weeks	0
FI70	3	heart	Heart attack		0
FI70	4	stroke	Stroke	Stroke history	0
FI70	5	dyslipidemia			0
FI70	6	diabetes		Diagnosed diabetes or high blood sugar	0
FI70	7	lungdis	Chronic lung disease	History of chronic lung disease	0
FI70	8	asthma		Asthma history	0
FI70	9	llsill.ord	Stay in bed		0
FI70	10	arthritis	Arthritis	Arthritis history	0
FI70	11	osteoporosis		Osteoporosis history	0
FI70	12	cancer		Cancer history	0
FI70	13	bpres		Self-reported high blood pressure	0
FI70	14	NA	Stomach complaints	Missing	1
FI70	15	parkinson			0

FI70	16	cataracts			0
FI70	17	heart_trouble		Adapted 5 heart conditions	0
FI70	18	hipfracture			0
FI70	19	fallingdown			0
FI70	20	sleep	Sleep problems		0
FI70	21	dizziness			0
FI70	22	NA	Swollen legs		1
FI70	23	NA	Stomach complaints		1
FI70	24	incont	Do you have a problem with losing control of urine when you don't want to?	Whether lost urine beyond control in last 12 months	0
FI70	25	respirat			0
FI70	26	NA	Require dentures	Missing	1
FI70	27	NA	Difficulty biting	Missing	1
FI70	28	poorvision	Problems with eyesight	Self-reported poor vision	0
FI70	29	hearing		Self-reported hearing	0
FI70	30	painjoint			0
FI70	31	breath	Breathlessness	MRC respiratory questionnaire	0
FI70	32	climb.stairs	Ability to climb one flight of stairs	Difficulty climbing several flights stairs without resting	0
FI70	33	stoop			0
FI70	34	sitting	Sitting for about 2 hours		0
FI70	35	reacharms			0
FI70	36	pulling			0
FI70	37	carrying			0
FI70	38	walkout	Difficulty walking 100 yards	Difficulty walking 100 yards.	0
FI70	39	pickingup			0
FI70	40	dress	Dressing	ADL	0
FI70	41	walking	Walking across a room		0
FI70	42	getupchair		Difficulty getting up from chair after sitting long periods	0
FI70	43	bath	Help taking a shower	ADL	0
FI70	44	eat	Eating	ADL	0
FI70	45	bed	Getting out of bed	ADL	0
FI70	46	prep.meal	Difficulty preparing a hot meal	ADL	0
FI70	47	Toileting	Toileting	ADL	0
FI70	48	usingmap			0
FI70	49	calls	Making telephone calls	IADL	0
FI70	50	medic.take	Need help taking medication	IADL	0
FI70	51	shop	Shopping	IADL	0
FI70	52	money	Managing money	IADL	0

FI70	53	vigorous	Does vigorous sports or activities		0
FI70	54	moderate	Frequency does moderate sports or activities		0
FI70	55	house.garden	Difficulty doing work around house and garden		0
FI70	56	limitation	Limitation with activities.	ADL&IADL: whether said had none of listed difficulties	0
FI70	57	orientation	Do you usually know what day and what time of the day it is	MMSE	0
FI70	58	NA	Mathematical performance	Missing	1
FI70	59	recalltest		Delayed word recall as % of immediate recall	0
FI70	60	fluencyword		Fluency recoded for Executive Function Index	0
FI70	61	NA	Suicidality	Missing	1
FI70	62	sleep	Sleep problems		0
FI70	63	depression.cesd	Feel depressed	CES-D>=4	0
FI70	64	interest	Interest	Whether respondent enjoyed life much of the time during the past week	0
FI70	65	NA	Appetite	Missing	1
FI70	66	effort	Fatigue	Feel everything is an effort	0
FI70	67	pessimism			0
FI70	68	dothings	Concentration	CASP19 scale: How often can do the things they want to do	0
FI70	69	enjoy		How often enjoys the things they do	0
FI70	70	healthstop	Fear of falling down.	CASP19 scale: How often feels their health stops them doing what they want to do	0
FIBLSA	1	effort	Does not have much energy	Feel everything is an effort	0
FIBLSA	2	NA	Feel less useful	Missing	1
FIBLSA	3	NA	Does not feel a lot of fun in life	Missing	1
FIBLSA	4	happy	Does not feel very happy	Feel happy	0
FIBLSA	5	dothings	Concentration	CASP19 scale: How often can do the things they want to do	0
FIBLSA	6	bpres	Hypertension	Self-reported high blood pressure	0
FIBLSA	7	heart		Heart attack	0
FIBLSA	8	stroke	Stroke	Stroke history	0
FIBLSA	9	NA	TIA	Missing	1

FIBLSA	10	arthritis	Arthritis		0
FIBLSA	11	NA	Thyroid disease	Missing	1
FIBLSA	12	glaucoma	Glaucoma		0
FIBLSA	13	cataracts	Cataracts		0
FIBLSA	14	incont	Incontinence	Whether lost urine beyond control in last 12 months	0
FIBLSA	15	fallingdown		Asked only to>=60 years	0
FIBLSA	16	hipfracture		Asked only to>=60 years	0
FIBLSA	17	NA	Tremor	Missing	1
FIBLSA	18	hearing	Does not hear clearly	Self-reported hearing	0
FIBLSA	19	hearing.aid	Wear a hearing aid		0
FIBLSA	20	walking.with.aid	Use a walking stick	Do you use anything (walking stick or frame) to help you walk?	0
FIBLSA	21	eat	Eating	ADL	0
FIBLSA	22	NA	Grooming	Missing	1
FIBLSA	23	dress	Dressing	ADL	0
FIBLSA	24	bed	Getting out of bed	ADL	0
FIBLSA	25	bath	Bathing	ADL	0
FIBLSA	26	walking	Walking around house	ADL	0
FIBLSA	27	prep.meal	Preparation of meals	IADL	0
FIBLSA	28	money	Managing money	IADL	0
FIBLSA	29	not.use.pub.transp	Need Help taking a bus	Does not take public transport due to health reasons	0
FIBLSA	30	shop	Shopping	IADL	0
FIBLSA	31	walkout		Walk outside (walking 100 yards)	0
FIBLSA	32	climb.stairs	Climbing stairs	Mobility	0
FIBLSA	33	NA	Doing light housework	Missing	1
FIBLSA	34	Toileting	Toileting	ADL	0
FIBLSA	35	cognbinar	Cognition	Total cognitive index 0-0.5-1	0
FIG	1	fast.gait.speed	>10 sec to perform a rapid gait test to 3 meter course and back		0
FIG	2	rise.frail	Unable to stand	Rise outcome	0
FIND	1	walkout	Have you any difficulties at walking 400 meters?	Walk outside (walking 100 yards)	0
FIND	2	climb.stairs	Climbing stairs	Mobility	0
FIND	3	weight.loss	Weight loss wave 0-wave 2	Weight loss wave 0-wave 2	0
FIND	4	effort		Feel everything is an effort	0
FIND	5	pa	Physical activity	Physical activity level	0
FS	1	effort		Feel everything is an effort	0
FS	2	climb	Ability to climb one flight of stairs	Difficulty climbing several flights stairs without resting	0

FS	3	walkout	Difficulty walking 100 yards	Difficulty walking 100 yards.	0
FS	4	alz			0
FS	5	weight.sc	Weight loss	Weight loss wave 0-wave 2	0
FSS	1	disable		Frail=at least one abnormal ADL	0
FSS	2	poor.mobility	Poor mobility ability to do heavy housework, to walk and down stairs and to walk half a mile	Mobility and IADL	0
FSS	3	cognbinar	Cognition	Total cognitive index 0-0.5-1	0
FSS	4	poorvision	Visual function	Self-reported poor vision	0
FSS	5	hearing	Hearing function	Self-reported hearing	0
FSS	6	incont	Do you have a problem with losing control of urine when you don't want to?	Whether lost urine beyond control in last 12 months	0
FSS	7	social.support	Social support	Adapted if participant had no ADL/IADL difficulties=0; if had difficulties and receive help=1; if had difficulties and no receive help=2	0
G8	1	NA	Decline in food intake	Missing	1
G8	2	weight.lossG8	Weight loss during the last 3 months		0
G8	3	mobilg8			0
G8	4	neuropsy			0
G8	5	BMIg8			0
G8	6	polypharmacyg8			0
G8	7	healthg8			0
G8	8	age.g8			0
GFI	1	shop	Shopping	IADL	0
GFI	2	walkout	Difficulty walking 100 yards	Difficulty walking 100 yards.	0
GFI	3	dress		ADL: difficulty Dressing	0
GFI	4	Toileting	Toileting	ADL	0
GFI	5	fitness		0=sedentary or low; 1=moderate or high	0
GFI	6	poorvision	Problems with eyesight	Self-reported poor vision	0
GFI	7	hearing		Self-reported hearing	0
GFI	8	weight.sc		Weight loss wave 0-wave 2	0
GFI	9	reported	Do you take 4 or more different types of medicine?	Ever reported 2 or more diseases	0
GFI	10	memory		Prospective memory score	0
GFI	11	network	Do you sometimes experience an emptiness around you?	Whether the respondent has any friends	0

GFI	12	attention	Do you sometimes miss people around you?	How often respondent feels left out	0
GFI	13	friends.help	Will other people help you if you are in need?	How much respondent can rely on these friends if they have a serious problem	0
GFI	14	sad	In the past 4 weeks did you feel downhearted or sad?	Whether respondent felt sad much of the time during the past week or depressed	0
GFI	15	calm	In the past 4 weeks did you feel calm and relaxed?	Adapted: whether respondent felt their sleep was restless during the past week	0
HRCA	1	prep.meal	Do you prepare your meals yourself?	IADL	0
HRCA	2	carrying	Do you take out the garbage yourself?	Mobility	0
HRCA	3	house.garden	Are you healthy enough to do the ordinary work around the house without help?	IADL	0
HRCA	4	climb.stairs	Climbing stairs	Mobility	0
HRCA	5	walking.with.aid	Do you use a walker or 4-prolonged cane at least some of the time, to get around?	Use of a cane, elbow crutches or walker	0
HRCA	6	wheel.chair	Do you use a wheelchair at least some of the time to get around?	Use of an electric or manual wheel chair, a buggy or scooter	0
HRCA	7	year	Could you please tell me what year it is?	MMSE	0
HRCA	8	social.particip	In the last month, how many days a week have you usually gone out of the house or building in which you live?	Organizational membership	0
HRCA	9	dress	Are you able to dress yourself?	ADL	0
HRCA	10	disab.1_0	How much of the time bad health, sickness or pain stop you from doing things you would like to be doing?	ADL&IADL scale 1-0	0
HSF	1	advanced.age	Age	Age>=80	0
HSF	2	bath	Bathing assistance	ADL	0
HSF	3	medic.take	Need help taking medication	IADL	0
HSF	4	healthstop	Health condition interfere with daily activities	CASP19 scale: How often feels their health stops them doing what they want to do	0

KFI	1	eat	Eating	ADL	0
KFI	2	dress	Dressing	ADL	0
KFI	3	walking	Walking around house	ADL	0
KFI	4	bed	Getting out of bed	ADL	0
KFI	5	bath	Bathing	ADL	0
KFI	6	Toileting	Toileting	ADL	0
KFI	7	calls	Making telephone calls	IADL	0
KFI	8	walkout		Walk outside (walking 100 yards)	0
KFI	9	shop	Shopping	IADL	0
KFI	10	prep.meal	Preparation of meals	IADL	0
KFI	11	NA	Doing light housework	Missing	1
KFI	12	medic.take	Need help taking medication	IADL	0
KFI	13	money	Managing money	IADL	0
KFI	14	arthritis	Arthritis		0
KFI	15	parkinson	Parkinson		0
KFI	16	glaucoma	Glaucoma		0
KFI	17	diabetes	Diabetes		0
KFI	18	NA	stomach problem	Missing	1
KFI	19	heart	History of heart attack	Heart attack	0
KFI	20	bpres	Hypertension	Self-reported high blood pressure	0
KFI	21	stroke	Stroke	Stroke history	0
KFI	22	NA	Flu	Missing	1
KFI	23	hipfracture		Hip fractures	0
KFI	24	NA	Broken bones	Missing	1
KFI	25	incont	Trouble with bladder/bowels	Whether lost urine beyond control in last 12 months	0
KFI	26	alz	Dementia		0
KFI	27	health2	Self-rated health	Self-reported health	0
KFI	28	poorvision	Problems with eyesight	Self-reported poor vision	0
KFI	29	hearing	Hearing	Self-reported hearing	0
KFI	30	hearing.aid	Wear a hearing aid		0
KFI	31	NA	Feet problems	Missing	1
KFI	32	NA	Teeth problems	Missing	1
PHF	1	weight.sc	Weight loss	Weight loss wave 0-wave 2	0
PHF	2	effort	Exhaustion	Feel everything is an effort	0
PHF	3	pa	Physical activity	Physical activity level	0
PHF	4	walkspeed	Walking speed	Measured walking speed	0
PHF	5	gripstrength	Grip strength	Grip strength	0
PHFR	1	weight.sc	Weight loss	Weight loss wave 0-wave 2	0
PHFR	2	effort	Exhaustion	Feel everything is an effort	0
PHFR	3	pa	Physical activity	Physical activity level	0
PHFR	4	walkspeed	Walking speed	Measured walking speed	0
PHFR	5	gripstrength	Grip strength	Grip strength	0

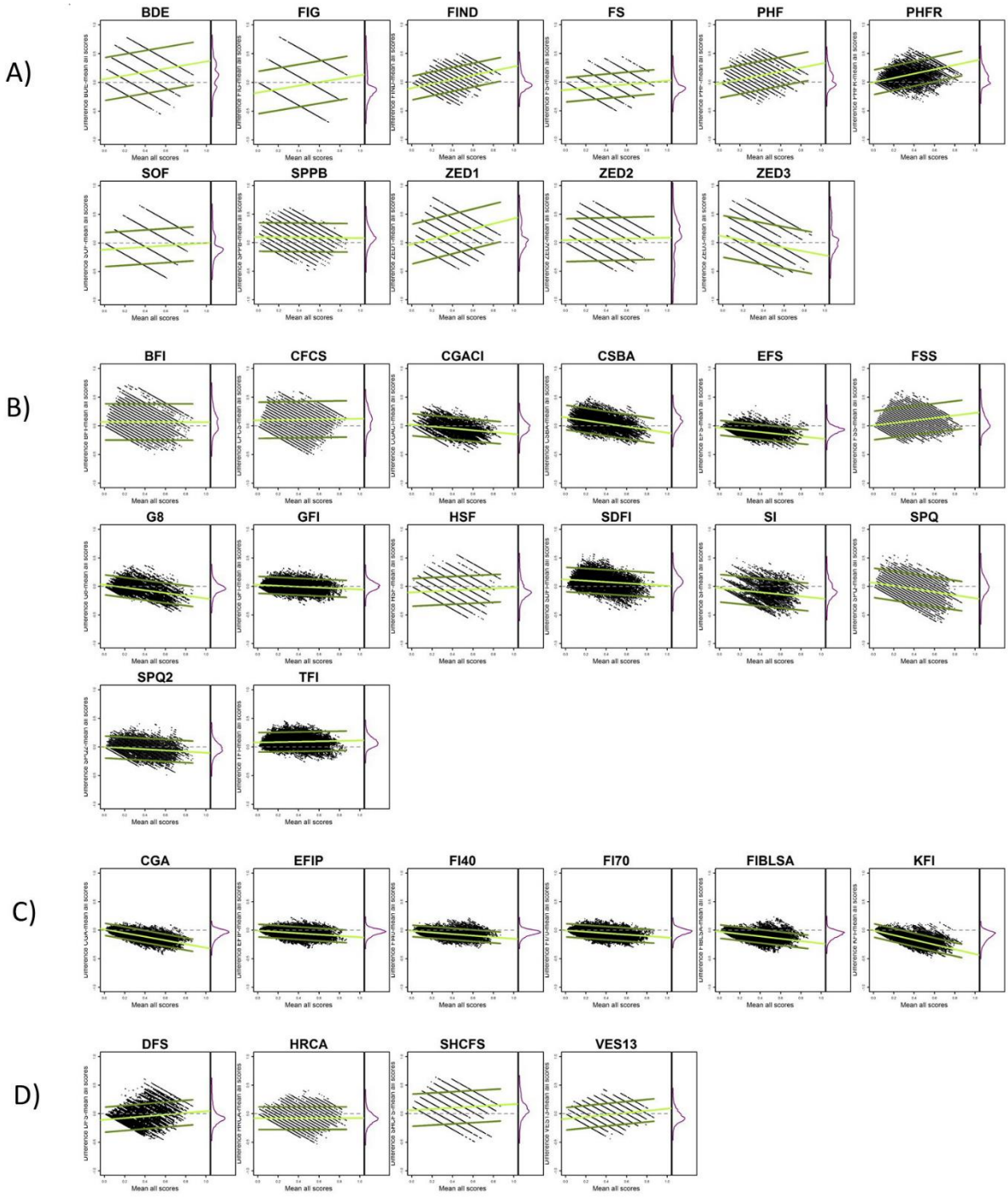
PHFR	6	cognbinar	Cognition	Total cognitive index 0-0-5-1	0
PHFR	7	depression.cesd	Depression symptoms	CES-D>=4	0
SDFI	1	verylow.BMI	BMI less than 23	BMI less than 23	0
SDFI	2	flowscore2	Flow less than 290		0
SDFI	3	cogncat	MMSE<24	Total cognitive index 0-0-5-1	0
SDFI	4	poorvision	Vision capacity	Self-reported poor vision	0
SDFI	5	hearing	Hearing capacity	Self-reported hearing	0
SDFI	6	incont	Incontinence (asking the respondent whether he or she lost urine unintentionally)	Whether lost urine beyond control in last 12 months	0
SDFI	7	CASPoutcontrol	Sense of mastery	CASP19 scale: How often feels what happens to them is out of their control	0
SDFI	8	sad	Depression symptoms	Whether respondent felt sad much of the time during the past week or depressed	0
SDFI	9	pa	Physical activity	pa[palevel==0]<-1 pa[palevel==1]<-0.66 pa[palevel==2]<-0.33 pa[palevel==3]<-0	0
SHCFS	1	sum.ADL	Independent for at least 1 ADL		0
SHCFS	2	goodhealth	Self-perceived health "excellent or very good"		0
SHCFS	3	longillness	Whether has self-reported long-standing illness		0
SHCFS	4	healthwork		Has health problem that limits kind or amount of work	0
SHCFS	5	fitness	How do you rate your fitness?	0=sedentary or low; 1=moderate or high	0
SHCFS	6	sum.IADL		Sum IADL	0
SI	1	depression.cesd	Feels depressed	CES-D>=4	0
SI	2	fallingdown	Falls	Asked only to>=60 years	0
SI	3	incont	Urinary incontinence	Whether lost urine beyond control in last 12 months	0
SI	4	ADL	functional impairment	Mean of ADL	0
SI	5	IADL	IADL	Mean of IADL	0
SI	6	network	Social activities	Whether the respondent has any friends	0
SOF	1	weight.sc	Weight loss	Weight loss wave 0-wave 2	0
SOF	2	effort	Exhaustion	Feel everything is an effort	0
SOF	3	rise.frail	Unable to stand		0

SPBB	1	score.bal.num.inv	Balance	Balance	0
SPBB	2	score.rise.num.inv	Chair rise	Chair rise	0
SPBB	3	walk.inv	Walk test	Walk test	0
SPQ	1	liv.alone	Living alone	Whether has a husband, wife or partner with whom they live	0
SPQ	2	polypharmacy	Polypharmacy (>3 medications)	Polypharmacy (>2 medications)	0
SPQ	3	walking.with.aid	Do you use anything (walking stick or frame) to help you walk?	Do you use anything (walking stick or frame) to help you walk?	0
SPQ	4	poorvision	Problems with eyesight	Self-reported poor vision	0
SPQ	5	hearing	Hear well?	Self-reported hearing	0
SPQ	6	self.rated.memory	Do you have problems with your memory?	Self-rated memory: good, very good and excellent=0; fair=0.5; poor=1	0
SPQ2	1	liv.alone	Living alone	Whether has a husband, wife or partner with whom they live	0
SPQ2	2	poorvision	Problems with eyesight	Self-reported poor vision	0
SPQ2	3	effort	Do you easily get exhausted in daily chores?	Feel everything is an effort	0
SPQ2	4	self.rated.memory	Do you have problems with your memory?	Self-rated memory: good, very good and excellent=0; fair=0.5; poor=1	0
SPQ2	5	NA	Did you have any falls in last 6 months	Missing	1
SPQ2	6	NA	Have you been admitted to hospital or ER in the last 6 months	Missing	1
SPQ2	7	walkout	Do you have Difficulty walking 400 m on a flat surface	Walk outside (walking 100 yards)	0
SPQ2	8	polypharmacy	Do you take 5+ drugs on a regular basis (daily or almost daily)	Polypharmacy (>2 medications)	0
SPQ2	9	weight.loss	Have you lost 3+ kg of weight unintentionally in prior year?	Weight loss wave 0-wave 2	0
SPQ2	10	friends.help	Will other people help you if you are in need?	How much respondent can rely on these friends if they have a serious problem	0
TFI	1	health2		Self-reported health	0
TFI	2	weight.sc	Weight loss	Weight loss wave 0-wave 2	0

TFI	3	difwalk	Do you experience problems in your daily life due to difficulty in walking?	Difficulty walking 1/4 mile unaided: 1=no difficulty=0; 2=some difficulty=0.5; 3=much difficulty=1; 4=unable=1	0
TFI	4	bal	Do you experience problems in your daily life due to difficulty maintaining your balance?	Balance	0
TFI	5	hearing		Self-reported hearing	0
TFI	6	poorvision	Problems with eyesight	Self-reported poor vision	0
TFI	7	strength	Problems due to lack of strength	Grip strength	0
TFI	8	effort		Feel everything is an effort	0
TFI	9	memory		Prospective memory score	0
TFI	10	sad	Do you often feel sad or depressed?	Respondent felt sad much of the time	0
TFI	11	calm	Did you feel calm and relaxed?	Adapted: whether respondent felt their sleep was restless	0
TFI	12	cope	Are you able to cope with problems well?	Feels what happens is out of their control	0
TFI	13	liv.alone	Living alone	Whether has a husband, wife or partner with whom they live	0
TFI	14	lon	Do you sometimes miss having people around you?		0
TFI	15	friends.help		Respondent can rely on these friends if they have problems	0
VES13	1	age.categ	Age <75; 75-84; >85		0
VES13	2	selfrep.health	Self-reported health: fair or poor	Self-reported health: fair or poor	0
VES13	3	stoop			0
VES13	4	carrying	Lifting 10 lbs	Mobility	0
VES13	5	reacharms			0
VES13	6	pickingup			0
VES13	7	walking	Walking around house	ADL: Difficulty walking across a room	0
VES13	8	house.garden	House work	IADL	0
VES13	9	shop	Shopping	IADL	0
VES13	10	money	Managing money	IADL	0
VES13	11	walkout		Walk outside (walking 100 yards)	0
VES13	12	NA		Missing	1
VES13	13	bath	Help taking a shower	ADL	0

ZED1	1	pa	Inactivity	Physical activity level	0
ZED1	2	effort	Low energy	Feel everything is an effort	0
ZED2	0	ZED2st	TOTAL	Physical activity level	0
ZED2	1	pa	Inactivity	Physical activity level	0
ZED2	2	Weight loss	Weight loss	Weight loss wave 0-wave 2	0
ZED3	0	ZED3st	TOTAL		0
ZED3	1	pa	Inactivity	Physical activity level	0
ZED3	2	Very low BMI	BMI less than 23	BMI less than 23	0

Abbreviations: Var, number of variable; Miss, missing variable



2.6.3. Web Figure 1.

The set of Bland-Altman plots show the difference between each of the 35 frailty scores and the average of all 35 scores in ELSA wave 2 (2004-2005). The A) group of panels show the scores based on the phenotype of frailty model, the B) shows those based on the multidimensional model, the C), shows those based on the accumulation of deficits model and the D) shows those based on the disability model.

The smaller panels to the right of each chart show density plot of the differences between each frailty score and the average of all 35 scores. Overestimation or underestimation can be observed when the regression line is lying over than 0 (overestimation) or below 0 (underestimation). Some scores show overestimation or underestimation that increases with higher levels of frailty. The absolute error was measured at the median point of frailty, calculated as the median of the mean of the 35 frailty scores. In the plot, it is shown the distance that separates the upper from the lower prediction interval. Some scores show a narrow distance between prediction intervals while others have a wider distance.

Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.4. Web Table 3

Web Table 3. Cohen's Kappa Estimates and 95% CI in Each Pair of Score scaled to the interval 1 to 0 and with arbitrary cutoff in ELSA Wave 2 (2004-2005)

Pair of score	Estimate	95% lower CI	95% higher CI
BDE_BFI	0.24	0.22	0.26
BDE_CFCS	0.39	0.37	0.41
BDE_CGA	0.32	0.30	0.34
BDE_CGACI	0.27	0.25	0.29
BDE_CSBA	0.33	0.31	0.35
BDE_DFS	0.33	0.31	0.35
BDE_EFIP	0.34	0.32	0.37
BDE_EFS	0.31	0.29	0.34
BDE_FI40	0.37	0.35	0.39
BDE_FI70	0.34	0.32	0.37
BDE_FIBLSA	0.34	0.32	0.36
BDE_FIG	0.31	0.29	0.33
BDE_FIND	0.32	0.30	0.35
BDE_FS	0.27	0.25	0.29
BDE_FSS	0.31	0.29	0.34
BDE_G8	0.28	0.26	0.30
BDE_GFI	0.32	0.30	0.35
BDE_HRCA	0.33	0.31	0.36
BDE_HSF	0.35	0.32	0.37
BDE_KFI	0.31	0.28	0.33
BDE_PHF	0.39	0.37	0.41
BDE_PHFR	0.40	0.38	0.42
BDE_SDFI	0.31	0.28	0.33
BDE_SHCFS	0.28	0.26	0.30
BDE_SI	0.22	0.19	0.24
BDE_SOF	0.19	0.18	0.21
BDE_SPPB	0.41	0.39	0.43
BDE_SPQ	0.25	0.23	0.27
BDE_SPQ2	0.29	0.27	0.31
BDE_TFI	0.35	0.33	0.37
BDE_VES13	0.33	0.31	0.35
BDE_ZED1	0.21	0.19	0.24
BDE_ZED2	0.16	0.14	0.18
BDE_ZED3	0.18	0.16	0.20
BFI_BDE	0.24	0.22	0.26
BFI_CFCS	0.27	0.24	0.29
BFI_CGA	0.38	0.35	0.41
BFI_CGACI	0.35	0.32	0.38
BFI_CSBA	0.24	0.21	0.27

BFI_DFS	0.30	0.27	0.32
BFI_EFIP	0.39	0.36	0.42
BFI_EFS	0.35	0.33	0.38
BFI_FI40	0.43	0.40	0.46
BFI_FI70	0.37	0.34	0.40
BFI_FIBLSA	0.36	0.34	0.39
BFI_FIG	0.23	0.21	0.25
BFI_FIND	0.35	0.32	0.38
BFI_FS	0.26	0.24	0.28
BFI_FSS	0.32	0.30	0.35
BFI_G8	0.27	0.25	0.30
BFI_GFI	0.37	0.34	0.39
BFI_HRCA	0.31	0.29	0.34
BFI_HSF	0.30	0.27	0.33
BFI_KFI	0.29	0.27	0.32
BFI_PHF	0.29	0.27	0.31
BFI_PHFR	0.43	0.41	0.46
BFI_SDFI	0.38	0.35	0.41
BFI_SHCFS	0.28	0.25	0.30
BFI_SI	0.33	0.30	0.35
BFI_SOF	0.20	0.19	0.22
BFI_SPPB	0.32	0.29	0.34
BFI_SPQ	0.32	0.30	0.35
BFI_SPQ2	0.39	0.36	0.42
BFI_TFI	0.48	0.45	0.50
BFI_VES13	0.30	0.27	0.32
BFI_ZED1	0.32	0.29	0.34
BFI_ZED2	0.13	0.10	0.15
BFI_ZED3	0.17	0.15	0.19
CFCS_BDE	0.39	0.37	0.41
CFCS_BFI	0.27	0.24	0.29
CFCS_CGA	0.27	0.24	0.29
CFCS_CGACI	0.30	0.27	0.33
CFCS_CSBA	0.35	0.32	0.37
CFCS_DFS	0.25	0.23	0.28
CFCS_EFIP	0.29	0.26	0.32
CFCS_EFS	0.35	0.32	0.37
CFCS_FI40	0.34	0.31	0.37
CFCS_FI70	0.29	0.26	0.31
CFCS_FIBLSA	0.30	0.27	0.32
CFCS_FIG	0.24	0.22	0.26
CFCS_FIND	0.33	0.31	0.36
CFCS_FS	0.27	0.25	0.29
CFCS_FSS	0.29	0.26	0.31

CFCS_G8	0.47	0.45	0.50
CFCS_GFI	0.32	0.29	0.35
CFCS_HRCA	0.25	0.23	0.28
CFCS_HSF	0.33	0.30	0.35
CFCS_KFI	0.25	0.22	0.28
CFCS_PHF	0.39	0.37	0.42
CFCS_PHFR	0.43	0.40	0.45
CFCS_SDFI	0.37	0.34	0.40
CFCS_SHCFS	0.24	0.21	0.26
CFCS_SI	0.18	0.16	0.21
CFCS_SOF	0.25	0.24	0.27
CFCS_SPPB	0.33	0.31	0.35
CFCS_SPQ	0.25	0.23	0.28
CFCS_SPQ2	0.35	0.32	0.38
CFCS_TFI	0.37	0.35	0.40
CFCS_VES13	0.28	0.25	0.30
CFCS_ZED1	0.21	0.18	0.23
CFCS_ZED2	0.36	0.34	0.38
CFCS_ZED3	0.19	0.16	0.21
CGA_BDE	0.32	0.30	0.34
CGA_BFI	0.38	0.35	0.41
CGA_CFCS	0.27	0.24	0.29
CGA_CGACI	0.57	0.55	0.60
CGA_CSBA	0.40	0.37	0.43
CGA_DFS	0.69	0.66	0.71
CGA_EFIP	0.79	0.77	0.81
CGA_EFS	0.61	0.59	0.64
CGA_FI40	0.79	0.77	0.81
CGA_FI70	0.81	0.79	0.83
CGA_FIBLSA	0.76	0.74	0.78
CGA_FIG	0.31	0.29	0.33
CGA_FIND	0.63	0.60	0.65
CGA_FS	0.46	0.44	0.48
CGA_FSS	0.62	0.59	0.64
CGA_G8	0.32	0.29	0.34
CGA_GFI	0.66	0.64	0.68
CGA_HRCA	0.63	0.61	0.66
CGA_HSF	0.53	0.50	0.56
CGA_KFI	0.72	0.70	0.74
CGA_PHF	0.42	0.39	0.44
CGA_PHFR	0.51	0.48	0.54
CGA_SDFI	0.46	0.43	0.48
CGA_SHCFS	0.47	0.45	0.50
CGA_SI	0.46	0.43	0.49

CGA_SOF	0.25	0.24	0.27
CGA_SPPB	0.41	0.39	0.44
CGA_SPQ	0.37	0.34	0.40
CGA_SPQ2	0.52	0.49	0.54
CGA_TFI	0.59	0.56	0.61
CGA_VES13	0.59	0.57	0.61
CGA_ZED1	0.45	0.42	0.47
CGA_ZED2	0.16	0.13	0.18
CGA_ZED3	0.17	0.15	0.19
CGACI_BDE	0.27	0.25	0.29
CGACI_BFI	0.35	0.32	0.38
CGACI_CFCS	0.30	0.27	0.33
CGACI_CGA	0.57	0.55	0.60
CGACI_CSBA	0.34	0.31	0.37
CGACI_DFS	0.50	0.48	0.53
CGACI_EFIP	0.59	0.56	0.61
CGACI_EFS	0.61	0.58	0.63
CGACI_FI40	0.58	0.56	0.61
CGACI_FI70	0.57	0.54	0.60
CGACI_FIBLSA	0.52	0.50	0.55
CGACI_FIG	0.25	0.23	0.27
CGACI_FIND	0.50	0.48	0.53
CGACI_FS	0.38	0.35	0.40
CGACI_FSS	0.52	0.49	0.55
CGACI_G8	0.41	0.38	0.44
CGACI_GFI	0.58	0.56	0.61
CGACI_HRCA	0.49	0.46	0.51
CGACI_HSF	0.44	0.42	0.47
CGACI_KFI	0.49	0.47	0.52
CGACI_PHF	0.40	0.38	0.43
CGACI_PHFR	0.50	0.47	0.53
CGACI_SDFI	0.38	0.35	0.41
CGACI_SHCFS	0.37	0.34	0.39
CGACI_SI	0.40	0.37	0.42
CGACI_SOF	0.26	0.25	0.28
CGACI_SPPB	0.32	0.29	0.34
CGACI_SPQ	0.26	0.24	0.29
CGACI_SPQ2	0.43	0.40	0.46
CGACI_TFI	0.51	0.49	0.54
CGACI_VES13	0.45	0.42	0.47
CGACI_ZED1	0.38	0.35	0.40
CGACI_ZED2	0.27	0.24	0.30
CGACI_ZED3	0.16	0.14	0.18
CSBA_BDE	0.33	0.31	0.35

CSBA_BFI	0.24	0.21	0.27
CSBA_CFCS	0.35	0.32	0.37
CSBA_CGA	0.40	0.37	0.43
CSBA_CGACI	0.34	0.31	0.37
CSBA_DFS	0.36	0.33	0.39
CSBA_EFIP	0.42	0.39	0.45
CSBA_EFS	0.40	0.37	0.42
CSBA_FI40	0.41	0.38	0.44
CSBA_FI70	0.43	0.40	0.46
CSBA_FIBLSA	0.43	0.40	0.46
CSBA_FIG	0.25	0.23	0.27
CSBA_FIND	0.39	0.36	0.42
CSBA_FS	0.28	0.26	0.30
CSBA_FSS	0.42	0.40	0.45
CSBA_G8	0.42	0.39	0.44
CSBA_GFI	0.45	0.42	0.48
CSBA_HRCA	0.35	0.32	0.38
CSBA_HSF	0.49	0.46	0.52
CSBA_KFI	0.42	0.39	0.45
CSBA_PHF	0.39	0.36	0.41
CSBA_PHFR	0.42	0.39	0.45
CSBA_SDFI	0.44	0.41	0.47
CSBA_SHCFS	0.36	0.34	0.39
CSBA_SI	0.23	0.21	0.26
CSBA_SOF	0.19	0.18	0.21
CSBA_SPPB	0.34	0.32	0.37
CSBA_SPQ	0.38	0.36	0.41
CSBA_SPQ2	0.42	0.40	0.45
CSBA_TFI	0.41	0.38	0.43
CSBA_VES13	0.40	0.37	0.42
CSBA_ZED1	0.27	0.24	0.30
CSBA_ZED2	0.24	0.22	0.27
CSBA_ZED3	0.27	0.25	0.29
DFS_BDE	0.33	0.31	0.35
DFS_BFI	0.30	0.27	0.32
DFS_CFCS	0.25	0.23	0.28
DFS_CGA	0.69	0.66	0.71
DFS_CGACI	0.50	0.48	0.53
DFS_CSBA	0.36	0.33	0.39
DFS_EFIP	0.74	0.71	0.76
DFS_EFS	0.60	0.58	0.63
DFS_FI40	0.74	0.72	0.76
DFS_FI70	0.76	0.73	0.78
DFS_FIBLSA	0.70	0.68	0.73

DFS_FIG	0.33	0.31	0.35
DFS_FIND	0.66	0.63	0.68
DFS_FS	0.47	0.45	0.49
DFS_FSS	0.61	0.58	0.63
DFS_G8	0.32	0.29	0.35
DFS_GFI	0.58	0.55	0.60
DFS_HRCA	0.73	0.70	0.75
DFS_HSF	0.55	0.52	0.58
DFS_KFI	0.65	0.63	0.67
DFS_PHF	0.42	0.40	0.45
DFS_PHFR	0.46	0.43	0.49
DFS_SDFI	0.36	0.33	0.39
DFS_SHCFS	0.51	0.48	0.54
DFS_SI	0.39	0.36	0.41
DFS_SOF	0.23	0.21	0.25
DFS_SPPB	0.43	0.40	0.45
DFS_SPQ	0.30	0.27	0.33
DFS_SPQ2	0.44	0.42	0.47
DFS_TFI	0.47	0.45	0.50
DFS_VES13	0.65	0.63	0.67
DFS_ZED1	0.38	0.35	0.40
DFS_ZED2	0.17	0.15	0.20
DFS_ZED3	0.19	0.17	0.21
EFIP_BDE	0.34	0.32	0.37
EFIP_BFI	0.39	0.36	0.42
EFIP_CFCS	0.29	0.26	0.32
EFIP_CGA	0.79	0.77	0.81
EFIP_CGACI	0.59	0.56	0.61
EFIP_CSBA	0.42	0.39	0.45
EFIP_DFS	0.74	0.71	0.76
EFIP_EFS	0.66	0.64	0.69
EFIP_FI40	0.82	0.80	0.84
EFIP_FI70	0.83	0.81	0.85
EFIP_FIBLSA	0.81	0.79	0.82
EFIP_FIG	0.34	0.32	0.36
EFIP_FIND	0.67	0.64	0.69
EFIP_FS	0.47	0.45	0.49
EFIP_FSS	0.64	0.62	0.67
EFIP_G8	0.35	0.32	0.38
EFIP_GFI	0.70	0.68	0.72
EFIP_HRCA	0.69	0.66	0.71
EFIP_HSF	0.56	0.53	0.59
EFIP_KFI	0.72	0.70	0.74
EFIP_PHF	0.46	0.43	0.48

EFIP_PHFR	0.54	0.51	0.57
EFIP_SDFI	0.46	0.43	0.49
EFIP_SHCFS	0.53	0.51	0.56
EFIP_SI	0.48	0.46	0.51
EFIP_SOF	0.26	0.24	0.28
EFIP_SPPB	0.45	0.43	0.48
EFIP_SPQ	0.39	0.36	0.41
EFIP_SPQ2	0.54	0.51	0.57
EFIP_TFI	0.61	0.58	0.63
EFIP_VES13	0.62	0.59	0.64
EFIP_ZED1	0.46	0.44	0.49
EFIP_ZED2	0.18	0.16	0.21
EFIP_ZED3	0.21	0.19	0.23
EFS_BDE	0.31	0.29	0.34
EFS_BFI	0.35	0.33	0.38
EFS_CFCS	0.35	0.32	0.37
EFS_CGA	0.61	0.59	0.64
EFS_CGACI	0.61	0.58	0.63
EFS_CSBA	0.40	0.37	0.42
EFS_DFS	0.60	0.58	0.63
EFS_EFIP	0.66	0.64	0.69
EFS_FI40	0.67	0.64	0.69
EFS_FI70	0.67	0.64	0.69
EFS_FIBLSA	0.64	0.61	0.66
EFS_FIG	0.31	0.29	0.33
EFS_FIND	0.56	0.53	0.58
EFS_FS	0.40	0.38	0.42
EFS_FSS	0.58	0.56	0.61
EFS_G8	0.40	0.38	0.43
EFS_GFI	0.62	0.59	0.64
EFS_HRCA	0.57	0.54	0.59
EFS_HSF	0.52	0.49	0.54
EFS_KFI	0.60	0.57	0.62
EFS_PHF	0.42	0.40	0.45
EFS_PHFR	0.50	0.47	0.53
EFS_SDFI	0.46	0.43	0.49
EFS_SHCFS	0.45	0.42	0.47
EFS_SI	0.44	0.41	0.47
EFS_SOF	0.26	0.25	0.28
EFS_SPPB	0.40	0.37	0.42
EFS_SPQ	0.31	0.29	0.34
EFS_SPQ2	0.45	0.42	0.48
EFS_TFI	0.55	0.52	0.57
EFS_VES13	0.56	0.54	0.59

EFS_ZED1	0.38	0.36	0.41
EFS_ZED2	0.24	0.21	0.26
EFS_ZED3	0.20	0.18	0.22
FI40_BDE	0.37	0.35	0.39
FI40_BFI	0.43	0.40	0.46
FI40_CFCS	0.34	0.31	0.37
FI40_CGA	0.79	0.77	0.81
FI40_CGACI	0.58	0.56	0.61
FI40_CSBA	0.41	0.38	0.44
FI40_DFS	0.74	0.72	0.76
FI40_EFIP	0.82	0.80	0.84
FI40_EFS	0.67	0.64	0.69
FI40_FI70	0.81	0.79	0.83
FI40_FIBLSA	0.77	0.75	0.79
FI40_FIG	0.34	0.32	0.36
FI40_FIND	0.71	0.69	0.73
FI40_FS	0.50	0.48	0.52
FI40_FSS	0.61	0.58	0.63
FI40_G8	0.39	0.36	0.41
FI40_GFI	0.66	0.64	0.69
FI40_HRCA	0.68	0.65	0.70
FI40_HSF	0.56	0.54	0.59
FI40_KFI	0.69	0.67	0.71
FI40_PHF	0.50	0.47	0.52
FI40_PHFR	0.59	0.57	0.62
FI40_SDFI	0.46	0.44	0.49
FI40_SHCFS	0.51	0.48	0.54
FI40_SI	0.45	0.43	0.48
FI40_SOF	0.29	0.27	0.31
FI40_SPPB	0.46	0.43	0.48
FI40_SPQ	0.36	0.33	0.38
FI40_SPQ2	0.56	0.53	0.59
FI40_TFI	0.64	0.61	0.66
FI40_VES13	0.63	0.61	0.65
FI40_ZED1	0.49	0.46	0.52
FI40_ZED2	0.22	0.19	0.24
FI40_ZED3	0.19	0.17	0.22
FI70_BDE	0.34	0.32	0.37
FI70_BFI	0.37	0.34	0.40
FI70_CFCS	0.29	0.26	0.31
FI70_CGA	0.81	0.79	0.83
FI70_CGACI	0.57	0.54	0.60
FI70_CSBA	0.43	0.40	0.46
FI70_DFS	0.76	0.73	0.78

FI70_EFIP	0.83	0.81	0.85
FI70_EFS	0.67	0.64	0.69
FI70_FI40	0.81	0.79	0.83
FI70_FIBLSA	0.77	0.75	0.79
FI70_FIG	0.34	0.32	0.36
FI70_FIND	0.65	0.63	0.68
FI70_FS	0.47	0.45	0.49
FI70_FSS	0.62	0.60	0.64
FI70_G8	0.35	0.32	0.38
FI70_GFI	0.66	0.64	0.69
FI70_HRCA	0.68	0.66	0.70
FI70_HSF	0.56	0.54	0.59
FI70_KFI	0.69	0.67	0.72
FI70_PHF	0.45	0.43	0.48
FI70_PHFR	0.54	0.51	0.56
FI70_SDFI	0.46	0.43	0.49
FI70_SHCFS	0.53	0.50	0.55
FI70_SI	0.47	0.44	0.49
FI70_SOF	0.26	0.24	0.28
FI70_SPPB	0.44	0.42	0.47
FI70_SPQ	0.36	0.34	0.39
FI70_SPQ2	0.51	0.48	0.54
FI70_TFI	0.58	0.55	0.61
FI70_VES13	0.63	0.61	0.65
FI70_ZED1	0.45	0.43	0.48
FI70_ZED2	0.17	0.15	0.20
FI70_ZED3	0.21	0.18	0.23
FIBLSA_BDE	0.34	0.32	0.36
FIBLSA_BFI	0.36	0.34	0.39
FIBLSA_CFCS	0.30	0.27	0.32
FIBLSA_CGA	0.76	0.74	0.78
FIBLSA_CGACI	0.52	0.50	0.55
FIBLSA_CSBA	0.43	0.40	0.46
FIBLSA_DFS	0.70	0.68	0.73
FIBLSA_EFIP	0.81	0.79	0.82
FIBLSA_EFS	0.64	0.61	0.66
FIBLSA_FI40	0.77	0.75	0.79
FIBLSA_FI70	0.77	0.75	0.79
FIBLSA_FIG	0.34	0.32	0.36
FIBLSA_FIND	0.65	0.63	0.68
FIBLSA_FS	0.47	0.45	0.49
FIBLSA_FSS	0.64	0.62	0.67
FIBLSA_G8	0.35	0.33	0.38
FIBLSA_GFI	0.64	0.61	0.66

FIBLSA_HRCA	0.65	0.63	0.67
FIBLSA_HSF	0.57	0.55	0.60
FIBLSA_KFI	0.75	0.73	0.77
FIBLSA_PHF	0.44	0.42	0.47
FIBLSA_PHFR	0.52	0.49	0.54
FIBLSA_SDFI	0.46	0.44	0.49
FIBLSA_SHCFS	0.48	0.46	0.51
FIBLSA_SI	0.47	0.44	0.49
FIBLSA_SOF	0.26	0.24	0.28
FIBLSA_SPPB	0.45	0.43	0.48
FIBLSA_SPQ	0.39	0.36	0.42
FIBLSA_SPQ2	0.53	0.50	0.55
FIBLSA_TFI	0.57	0.54	0.59
FIBLSA_VES13	0.62	0.60	0.64
FIBLSA_ZED1	0.43	0.41	0.46
FIBLSA_ZED2	0.18	0.16	0.20
FIBLSA_ZED3	0.20	0.18	0.22
FIG_BDE	0.31	0.29	0.33
FIG_BFI	0.23	0.21	0.25
FIG_CFCS	0.24	0.22	0.26
FIG_CGA	0.31	0.29	0.33
FIG_CGACI	0.25	0.23	0.27
FIG_CSBA	0.25	0.23	0.27
FIG_DFS	0.33	0.31	0.35
FIG_EFIP	0.34	0.32	0.36
FIG_EFS	0.31	0.29	0.33
FIG_FI40	0.34	0.32	0.36
FIG_FI70	0.34	0.32	0.36
FIG_FIBLSA	0.34	0.32	0.36
FIG_FIND	0.32	0.30	0.34
FIG_FS	0.24	0.22	0.25
FIG_FSS	0.29	0.27	0.31
FIG_G8	0.24	0.22	0.26
FIG_GFI	0.31	0.29	0.33
FIG_HRCA	0.32	0.30	0.34
FIG_HSF	0.30	0.28	0.32
FIG_KFI	0.30	0.28	0.32
FIG_PHF	0.35	0.33	0.37
FIG_PHFR	0.33	0.31	0.35
FIG_SDFI	0.25	0.23	0.27
FIG_SHCFS	0.27	0.25	0.29
FIG_SI	0.20	0.18	0.22
FIG_SOF	0.21	0.20	0.23
FIG_SPPB	0.42	0.40	0.44

FIG_SPQ	0.22	0.20	0.24
FIG_SPQ2	0.27	0.25	0.29
FIG_TFI	0.30	0.28	0.32
FIG_VES13	0.34	0.32	0.36
FIG_ZED1	0.21	0.19	0.23
FIG_ZED2	0.16	0.14	0.17
FIG_ZED3	0.16	0.14	0.17
FIND_BDE	0.32	0.30	0.35
FIND_BFI	0.35	0.32	0.38
FIND_CFCS	0.33	0.31	0.36
FIND_CGA	0.63	0.60	0.65
FIND_CGACI	0.50	0.48	0.53
FIND_CSBA	0.39	0.36	0.42
FIND_DFS	0.66	0.63	0.68
FIND_EFIP	0.67	0.64	0.69
FIND_EFS	0.56	0.53	0.58
FIND_FI40	0.71	0.69	0.73
FIND_FI70	0.65	0.63	0.68
FIND_FIBLSA	0.65	0.63	0.68
FIND_FIG	0.32	0.30	0.34
FIND_FS	0.63	0.61	0.65
FIND_FSS	0.51	0.48	0.54
FIND_G8	0.45	0.42	0.47
FIND_GFI	0.61	0.58	0.63
FIND_HRCA	0.59	0.56	0.61
FIND_HSF	0.48	0.45	0.50
FIND_KFI	0.55	0.53	0.58
FIND_PHF	0.53	0.51	0.55
FIND_PHFR	0.62	0.59	0.64
FIND_SDFI	0.41	0.38	0.44
FIND_SHCFS	0.49	0.46	0.52
FIND_SI	0.38	0.35	0.40
FIND_SOF	0.34	0.32	0.36
FIND_SPPB	0.42	0.39	0.44
FIND_SPQ	0.30	0.28	0.33
FIND_SPQ2	0.60	0.57	0.63
FIND_TFI	0.56	0.53	0.58
FIND_VES13	0.56	0.54	0.58
FIND_ZED1	0.49	0.47	0.52
FIND_ZED2	0.34	0.32	0.37
FIND_ZED3	0.25	0.23	0.27
FS_BDE	0.27	0.25	0.29
FS_BFI	0.26	0.24	0.28
FS_CFCS	0.27	0.25	0.29

FS_CGA	0.46	0.44	0.48
FS_CGACI	0.38	0.35	0.40
FS_CSBA	0.28	0.26	0.30
FS_DFS	0.47	0.45	0.49
FS_EFIP	0.47	0.45	0.49
FS_EFS	0.40	0.38	0.42
FS_FI40	0.50	0.48	0.52
FS_FI70	0.47	0.45	0.49
FS_FIBLSA	0.47	0.45	0.49
FS_FIG	0.24	0.22	0.25
FS_FIND	0.63	0.61	0.65
FS_FSS	0.37	0.35	0.39
FS_G8	0.37	0.35	0.39
FS_GFI	0.42	0.40	0.45
FS_HRCA	0.45	0.43	0.47
FS_HSF	0.34	0.32	0.36
FS_KFI	0.40	0.38	0.42
FS_PHF	0.39	0.37	0.41
FS_PHFR	0.45	0.43	0.47
FS_SDFI	0.29	0.27	0.31
FS_SHCFS	0.35	0.33	0.37
FS_SI	0.29	0.27	0.31
FS_SOF	0.39	0.38	0.41
FS_SPPB	0.31	0.29	0.33
FS_SPQ	0.23	0.21	0.25
FS_SPQ2	0.45	0.42	0.47
FS_TFI	0.41	0.39	0.43
FS_VES13	0.40	0.38	0.42
FS_ZED1	0.40	0.38	0.42
FS_ZED2	0.31	0.29	0.32
FS_ZED3	0.18	0.16	0.20
FSS_BDE	0.31	0.29	0.34
FSS_BFI	0.32	0.30	0.35
FSS_CFCS	0.29	0.26	0.31
FSS_CGA	0.62	0.59	0.64
FSS_CGACI	0.52	0.49	0.55
FSS_CSBA	0.42	0.40	0.45
FSS_DFS	0.61	0.58	0.63
FSS_EFIP	0.64	0.62	0.67
FSS_EFS	0.58	0.56	0.61
FSS_FI40	0.61	0.58	0.63
FSS_FI70	0.62	0.60	0.64
FSS_FIBLSA	0.64	0.62	0.67
FSS_FIG	0.29	0.27	0.31

FSS_FIND	0.51	0.48	0.54
FSS_FS	0.37	0.35	0.39
FSS_G8	0.33	0.30	0.36
FSS_GFI	0.56	0.53	0.58
FSS_HRCA	0.58	0.56	0.60
FSS_HSF	0.52	0.49	0.55
FSS_KFI	0.63	0.61	0.65
FSS_PHF	0.38	0.36	0.40
FSS_PHFR	0.44	0.42	0.47
FSS_SDFI	0.46	0.43	0.49
FSS_SHCFS	0.40	0.37	0.43
FSS_SI	0.40	0.37	0.43
FSS_SOF	0.22	0.20	0.23
FSS_SPPB	0.38	0.35	0.40
FSS_SPQ	0.38	0.36	0.41
FSS_SPQ2	0.45	0.43	0.48
FSS_TFI	0.48	0.45	0.51
FSS_VES13	0.52	0.49	0.54
FSS_ZED1	0.33	0.30	0.35
FSS_ZED2	0.17	0.15	0.19
FSS_ZED3	0.17	0.15	0.19
G8_BDE	0.28	0.26	0.30
G8_BFI	0.27	0.25	0.30
G8_CFCS	0.47	0.45	0.50
G8_CGA	0.32	0.29	0.34
G8_CGACI	0.41	0.38	0.44
G8_CSBA	0.42	0.39	0.44
G8_DFS	0.32	0.29	0.35
G8_EFIP	0.35	0.32	0.38
G8_EFS	0.40	0.38	0.43
G8_FI40	0.39	0.36	0.41
G8_FI70	0.35	0.32	0.38
G8_FIBLSA	0.35	0.33	0.38
G8_FIG	0.24	0.22	0.26
G8_FIND	0.45	0.42	0.47
G8_FS	0.37	0.35	0.39
G8_FSS	0.33	0.30	0.36
G8_GFI	0.40	0.37	0.42
G8_HRCA	0.32	0.29	0.34
G8_HSF	0.38	0.35	0.41
G8_KFI	0.31	0.28	0.34
G8_PHF	0.44	0.41	0.46
G8_PHFR	0.48	0.45	0.50
G8_SDFI	0.40	0.37	0.42

G8_SHCFS	0.28	0.26	0.31
G8_SI	0.22	0.19	0.24
G8_SOF	0.33	0.32	0.35
G8_SPPB	0.31	0.29	0.34
G8_SPQ	0.28	0.25	0.31
G8_SPQ2	0.46	0.43	0.48
G8_TFI	0.42	0.39	0.45
G8_VES13	0.36	0.34	0.39
G8_ZED1	0.24	0.21	0.26
G8_ZED2	0.56	0.54	0.59
G8_ZED3	0.28	0.26	0.30
GFI_BDE	0.32	0.30	0.35
GFI_BFI	0.37	0.34	0.39
GFI_CFCS	0.32	0.29	0.35
GFI_CGA	0.66	0.64	0.68
GFI_CGACI	0.58	0.56	0.61
GFI_CSBA	0.45	0.42	0.48
GFI_DFS	0.58	0.55	0.60
GFI_EFIP	0.70	0.68	0.72
GFI_EFS	0.62	0.59	0.64
GFI_FI40	0.66	0.64	0.69
GFI_FI70	0.66	0.64	0.69
GFI_FIBLSA	0.64	0.61	0.66
GFI_FIG	0.31	0.29	0.33
GFI_FIND	0.61	0.58	0.63
GFI_FS	0.42	0.40	0.45
GFI_FSS	0.56	0.53	0.58
GFI_G8	0.40	0.37	0.42
GFI_HRCA	0.54	0.51	0.56
GFI_HSF	0.48	0.45	0.50
GFI_KFI	0.59	0.57	0.62
GFI_PHF	0.45	0.43	0.48
GFI_PHFR	0.53	0.50	0.56
GFI_SDFI	0.52	0.49	0.54
GFI_SHCFS	0.51	0.48	0.54
GFI_SI	0.43	0.41	0.46
GFI_SOF	0.26	0.24	0.28
GFI_SPPB	0.41	0.38	0.43
GFI_SPQ	0.37	0.34	0.39
GFI_SPQ2	0.56	0.54	0.59
GFI_TFI	0.64	0.61	0.66
GFI_VES13	0.54	0.51	0.56
GFI_ZED1	0.41	0.38	0.43
GFI_ZED2	0.26	0.24	0.29

GFI_ZED3	0.23	0.20	0.25
HRCA_BDE	0.33	0.31	0.36
HRCA_BFI	0.31	0.29	0.34
HRCA_CFCS	0.25	0.23	0.28
HRCA_CGA	0.63	0.61	0.66
HRCA_CGACI	0.49	0.46	0.51
HRCA_CSBA	0.35	0.32	0.38
HRCA_DFS	0.73	0.70	0.75
HRCA_EFIP	0.69	0.66	0.71
HRCA_EFS	0.57	0.54	0.59
HRCA_FI40	0.68	0.65	0.70
HRCA_FI70	0.68	0.66	0.70
HRCA_FIBLSA	0.65	0.63	0.67
HRCA_FIG	0.32	0.30	0.34
HRCA_FIND	0.59	0.56	0.61
HRCA_FS	0.45	0.43	0.47
HRCA_FSS	0.58	0.56	0.60
HRCA_G8	0.32	0.29	0.34
HRCA_GFI	0.54	0.51	0.56
HRCA_HSF	0.48	0.46	0.51
HRCA_KFI	0.59	0.56	0.61
HRCA_PHF	0.39	0.37	0.41
HRCA_PHFR	0.44	0.42	0.47
HRCA_SDFI	0.35	0.33	0.38
HRCA_SHCFS	0.47	0.44	0.49
HRCA_SI	0.37	0.35	0.40
HRCA_SOF	0.23	0.21	0.25
HRCA_SPPB	0.41	0.39	0.44
HRCA_SPQ	0.32	0.30	0.34
HRCA_SPQ2	0.42	0.39	0.44
HRCA_TFI	0.46	0.43	0.48
HRCA_VES13	0.57	0.55	0.59
HRCA_ZED1	0.36	0.34	0.39
HRCA_ZED2	0.16	0.14	0.18
HRCA_ZED3	0.19	0.16	0.21
HSF_BDE	0.35	0.32	0.37
HSF_BFI	0.30	0.27	0.33
HSF_CFCS	0.33	0.30	0.35
HSF_CGA	0.53	0.50	0.56
HSF_CGACI	0.44	0.42	0.47
HSF_CSBA	0.49	0.46	0.52
HSF_DFS	0.55	0.52	0.58
HSF_EFIP	0.56	0.53	0.59
HSF_EFS	0.52	0.49	0.54

HSF_FI40	0.56	0.54	0.59
HSF_FI70	0.56	0.54	0.59
HSF_FIBLSA	0.57	0.55	0.60
HSF_FIG	0.30	0.28	0.32
HSF_FIND	0.48	0.45	0.50
HSF_FS	0.34	0.32	0.36
HSF_FSS	0.52	0.49	0.55
HSF_G8	0.38	0.35	0.41
HSF_GFI	0.48	0.45	0.50
HSF_HRCA	0.48	0.46	0.51
HSF_KFI	0.54	0.52	0.57
HSF_PHF	0.41	0.38	0.43
HSF_PHFR	0.45	0.42	0.48
HSF_SDFI	0.41	0.38	0.44
HSF_SHCFS	0.41	0.38	0.44
HSF_SI	0.33	0.30	0.36
HSF_SOF	0.21	0.20	0.23
HSF_SPPB	0.42	0.39	0.44
HSF_SPQ	0.34	0.31	0.36
HSF_SPQ2	0.41	0.38	0.44
HSF_TFI	0.46	0.43	0.49
HSF_VES13	0.57	0.54	0.59
HSF_ZED1	0.32	0.29	0.35
HSF_ZED2	0.20	0.17	0.22
HSF_ZED3	0.21	0.18	0.23
KFI_BDE	0.31	0.28	0.33
KFI_BFI	0.29	0.27	0.32
KFI_CFCS	0.25	0.22	0.28
KFI_CGA	0.72	0.70	0.74
KFI_CGACI	0.49	0.47	0.52
KFI_CSBA	0.42	0.39	0.45
KFI_DFS	0.65	0.63	0.67
KFI_EFIP	0.72	0.70	0.74
KFI_EFS	0.60	0.57	0.62
KFI_FI40	0.69	0.67	0.71
KFI_FI70	0.69	0.67	0.72
KFI_FIBLSA	0.75	0.73	0.77
KFI_FIG	0.30	0.28	0.32
KFI_FIND	0.55	0.53	0.58
KFI_FS	0.40	0.38	0.42
KFI_FSS	0.63	0.61	0.65
KFI_G8	0.31	0.28	0.34
KFI_GFI	0.59	0.57	0.62
KFI_HRCA	0.59	0.56	0.61

KFI_HSF	0.54	0.52	0.57
KFI_PHF	0.38	0.35	0.40
KFI_PHFR	0.42	0.39	0.45
KFI_SDFI	0.42	0.39	0.45
KFI_SHCFS	0.45	0.43	0.48
KFI_SI	0.41	0.38	0.43
KFI_SOF	0.22	0.20	0.23
KFI_SPPB	0.39	0.37	0.42
KFI_SPQ	0.37	0.35	0.40
KFI_SPQ2	0.47	0.44	0.50
KFI_TFI	0.47	0.45	0.50
KFI_VES13	0.58	0.55	0.60
KFI_ZED1	0.35	0.32	0.37
KFI_ZED2	0.17	0.14	0.19
KFI_ZED3	0.17	0.15	0.20
PHF_BDE	0.39	0.37	0.41
PHF_BFI	0.29	0.27	0.31
PHF_CFCS	0.39	0.37	0.42
PHF_CGA	0.42	0.39	0.44
PHF_CGACI	0.40	0.38	0.43
PHF_CSBA	0.39	0.36	0.41
PHF_DFS	0.42	0.40	0.45
PHF_EFIP	0.46	0.43	0.48
PHF_EFS	0.42	0.40	0.45
PHF_FI40	0.50	0.47	0.52
PHF_FI70	0.45	0.43	0.48
PHF_FIBLSA	0.44	0.42	0.47
PHF_FIG	0.35	0.33	0.37
PHF_FIND	0.53	0.51	0.55
PHF_FS	0.39	0.37	0.41
PHF_FSS	0.38	0.36	0.40
PHF_G8	0.44	0.41	0.46
PHF_GFI	0.45	0.43	0.48
PHF_HRCA	0.39	0.37	0.41
PHF_HSF	0.41	0.38	0.43
PHF_KFI	0.38	0.35	0.40
PHF_PHFR	0.68	0.66	0.70
PHF_SDFI	0.38	0.35	0.40
PHF_SHCFS	0.40	0.37	0.42
PHF_SI	0.27	0.25	0.30
PHF_SOF	0.33	0.32	0.35
PHF_SPPB	0.40	0.38	0.42
PHF_SPQ	0.26	0.24	0.29
PHF_SPQ2	0.45	0.43	0.48

PHF_TFI	0.48	0.46	0.51
PHF_VES13	0.42	0.40	0.44
PHF_ZED1	0.42	0.39	0.44
PHF_ZED2	0.34	0.32	0.36
PHF_ZED3	0.26	0.24	0.29
PHFR_BDE	0.40	0.38	0.42
PHFR_BFI	0.43	0.41	0.46
PHFR_CFCS	0.43	0.40	0.45
PHFR_CGA	0.51	0.48	0.54
PHFR_CGACI	0.50	0.47	0.53
PHFR_CSBA	0.42	0.39	0.45
PHFR_DFS	0.46	0.43	0.49
PHFR_EFIP	0.54	0.51	0.57
PHFR_EFS	0.50	0.47	0.53
PHFR_FI40	0.59	0.57	0.62
PHFR_FI70	0.54	0.51	0.56
PHFR_FIBLSA	0.52	0.49	0.54
PHFR_FIG	0.33	0.31	0.35
PHFR_FIND	0.62	0.59	0.64
PHFR_FS	0.45	0.43	0.47
PHFR_FSS	0.44	0.42	0.47
PHFR_G8	0.48	0.45	0.50
PHFR_GFI	0.53	0.50	0.56
PHFR_HRCA	0.44	0.42	0.47
PHFR_HSF	0.45	0.42	0.48
PHFR_KFI	0.42	0.39	0.45
PHFR_PHF	0.68	0.66	0.70
PHFR_SDFI	0.48	0.45	0.51
PHFR_SHCFS	0.40	0.37	0.42
PHFR_SI	0.37	0.35	0.40
PHFR_SOF	0.36	0.34	0.38
PHFR_SPPB	0.43	0.40	0.45
PHFR_SPQ	0.30	0.27	0.33
PHFR_SPQ2	0.55	0.52	0.58
PHFR_TFI	0.62	0.59	0.64
PHFR_VES13	0.44	0.41	0.47
PHFR_ZED1	0.54	0.51	0.56
PHF_HSF	0.41	0.38	0.43
PHFR_ZED2	0.33	0.31	0.36
PHFR_ZED3	0.24	0.22	0.26
SDFI_BDE	0.31	0.28	0.33
SDFI_BFI	0.38	0.35	0.41
SDFI_CFCS	0.37	0.34	0.40
SDFI_CGA	0.46	0.43	0.48

SDFI_CGACI	0.38	0.35	0.41
SDFI_CSBA	0.44	0.41	0.47
SDFI_DFS	0.36	0.33	0.39
SDFI_EFIP	0.46	0.43	0.49
SDFI_EFS	0.46	0.43	0.49
SDFI_FI40	0.46	0.44	0.49
SDFI_FI70	0.46	0.43	0.49
SDFI_FIBLSA	0.46	0.44	0.49
SDFI_FIG	0.25	0.23	0.27
SDFI_FIND	0.41	0.38	0.44
SDFI_FS	0.29	0.27	0.31
SDFI_FSS	0.46	0.43	0.49
SDFI_G8	0.40	0.37	0.42
SDFI_GFI	0.52	0.49	0.54
SDFI_HRCA	0.35	0.33	0.38
SDFI_HSF	0.41	0.38	0.44
SDFI_KFI	0.42	0.39	0.45
SDFI_PHF	0.38	0.35	0.40
SDFI_PHFR	0.48	0.45	0.51
SDFI_SHCFS	0.34	0.31	0.37
SDFI_SI	0.38	0.35	0.40
SDFI_SOF	0.22	0.20	0.23
SDFI_SPPB	0.33	0.30	0.36
SDFI_SPQ	0.40	0.38	0.43
SDFI_SPQ2	0.45	0.42	0.48
SDFI_TFI	0.54	0.52	0.57
SDFI_VES13	0.37	0.35	0.40
SDFI_ZED1	0.34	0.32	0.37
SDFI_ZED2	0.21	0.18	0.23
SDFI_ZED3	0.28	0.26	0.30
SHCFS_BDE	0.28	0.26	0.30
SHCFS_BFI	0.28	0.25	0.30
SHCFS_CFCS	0.24	0.21	0.26
SHCFS_CGA	0.47	0.45	0.50
SHCFS_CGACI	0.37	0.34	0.39
SHCFS_CSBA	0.36	0.34	0.39
SHCFS_DFS	0.51	0.48	0.54
SHCFS_EFIP	0.53	0.51	0.56
SHCFS_EFS	0.45	0.42	0.47
SHCFS_FI40	0.51	0.48	0.54
SHCFS_FI70	0.53	0.50	0.55
SHCFS_FIBLSA	0.48	0.46	0.51
SHCFS_FIG	0.27	0.25	0.29
SHCFS_FIND	0.49	0.46	0.52

SHCFS_FS	0.35	0.33	0.37
SHCFS_FSS	0.40	0.37	0.43
SHCFS_G8	0.28	0.26	0.31
SHCFS_GFI	0.51	0.48	0.54
SHCFS_HRCA	0.47	0.44	0.49
SHCFS_HSF	0.41	0.38	0.44
SHCFS_KFI	0.45	0.43	0.48
SHCFS_PHF	0.40	0.37	0.42
SHCFS_PHFR	0.40	0.37	0.42
SHCFS_SDFI	0.34	0.31	0.37
SHCFS_SI	0.29	0.26	0.32
SHCFS_SOF	0.19	0.17	0.21
SHCFS_SPPB	0.36	0.33	0.38
SHCFS_SPQ	0.25	0.23	0.28
SHCFS_SPQ2	0.36	0.33	0.39
SHCFS_TFI	0.40	0.37	0.42
SHCFS_VES13	0.44	0.42	0.47
SHCFS_ZED1	0.36	0.34	0.39
SHCFS_ZED2	0.19	0.16	0.21
SHCFS_ZED3	0.29	0.27	0.31
SI_BDE	0.22	0.19	0.24
SI_BFI	0.33	0.30	0.35
SI_CFCS	0.18	0.16	0.21
SI_CGA	0.46	0.43	0.49
SI_CGACI	0.40	0.37	0.42
SI_CSBA	0.23	0.21	0.26
SI_DFS	0.39	0.36	0.41
SI_EFIP	0.48	0.46	0.51
SI_EFS	0.44	0.41	0.47
SI_FI40	0.45	0.43	0.48
SI_FI70	0.47	0.44	0.49
SI_FIBLSA	0.47	0.44	0.49
SI_FIG	0.20	0.18	0.22
SI_FIND	0.38	0.35	0.40
SI_FS	0.29	0.27	0.31
SI_FSS	0.40	0.37	0.43
SI_G8	0.22	0.19	0.24
SI_GFI	0.43	0.41	0.46
SI_HRCA	0.37	0.35	0.40
SI_HSF	0.33	0.30	0.36
SI_KFI	0.41	0.38	0.43
SI_PHF	0.27	0.25	0.30
SI_PHFR	0.37	0.35	0.40
SI_SDFI	0.38	0.35	0.40

SI_SHCFS	0.29	0.26	0.32
SI_SOF	0.20	0.19	0.22
SI_SPPB	0.26	0.24	0.29
SI_SPQ	0.23	0.21	0.25
SI_SPQ2	0.33	0.31	0.36
SI_TFI	0.41	0.39	0.44
SI_VES13	0.34	0.32	0.37
SI_ZED1	0.34	0.32	0.37
SI_ZED2	0.10	0.08	0.12
SI_ZED3	0.14	0.12	0.16
SOF_BDE	0.19	0.18	0.21
SOF_BFI	0.20	0.19	0.22
SOF_CFCS	0.25	0.24	0.27
SOF_CGA	0.25	0.24	0.27
SOF_CGACI	0.26	0.25	0.28
SOF_CSBA	0.19	0.18	0.21
SOF_DFS	0.23	0.21	0.25
SOF_EFIP	0.26	0.24	0.28
SOF_EFS	0.26	0.25	0.28
SOF_FI40	0.29	0.27	0.31
SOF_FI70	0.26	0.24	0.28
SOF_FIBLSA	0.26	0.24	0.28
SOF_FIG	0.21	0.20	0.23
SOF_FIND	0.34	0.32	0.36
SOF_FS	0.39	0.38	0.41
SOF_FSS	0.22	0.20	0.23
SOF_G8	0.33	0.32	0.35
SOF_GFI	0.26	0.24	0.28
SOF_HRCA	0.23	0.21	0.25
SOF_HSF	0.21	0.20	0.23
SOF_KFI	0.22	0.20	0.23
SOF_PHF	0.33	0.32	0.35
SOF_PHFR	0.36	0.34	0.38
SOF_SDFI	0.22	0.20	0.23
SOF_SHCFS	0.19	0.17	0.21
SOF_SI	0.20	0.19	0.22
SOF_SPPB	0.23	0.21	0.25
SOF_SPQ	0.16	0.14	0.17
SOF_SPQ2	0.32	0.31	0.34
SOF_TFI	0.30	0.29	0.32
SOF_VES13	0.23	0.21	0.24
SOF_ZED1	0.37	0.36	0.39
SOF_ZED2	0.33	0.32	0.35
SOF_ZED3	0.13	0.12	0.15

SPPB_BDE	0.41	0.39	0.43
SPPB_BFI	0.32	0.29	0.34
SPPB_CFCS	0.33	0.31	0.35
SPPB_CGA	0.41	0.39	0.44
SPPB_CGACI	0.32	0.29	0.34
SPPB_CSBA	0.34	0.32	0.37
SPPB_DFS	0.43	0.40	0.45
SPPB_EFIP	0.45	0.43	0.48
SPPB_EFS	0.40	0.37	0.42
SPPB_FI40	0.46	0.43	0.48
SPPB_FI70	0.44	0.42	0.47
SPPB_FIBLSA	0.45	0.43	0.48
SPPB_FIG	0.42	0.40	0.44
SPPB_FIND	0.42	0.39	0.44
SPPB_FS	0.31	0.29	0.33
SPPB_FSS	0.38	0.35	0.40
SPPB_G8	0.31	0.29	0.34
SPPB_GFI	0.41	0.38	0.43
SPPB_HRCA	0.41	0.39	0.44
SPPB_HSF	0.42	0.39	0.44
SPPB_KFI	0.39	0.37	0.42
SPPB_PHF	0.40	0.38	0.42
SPPB_PHFR	0.43	0.40	0.45
SPPB_SDFI	0.33	0.30	0.36
SPPB_SHCFS	0.36	0.33	0.38
SPPB_SI	0.26	0.24	0.29
SPPB_SOF	0.23	0.21	0.25
SPPB_SPQ	0.29	0.27	0.31
SPPB_SPQ2	0.35	0.32	0.37
SPPB_TFI	0.41	0.39	0.44
SPPB_VES13	0.41	0.39	0.44
SPPB_ZED1	0.27	0.25	0.30
SPPB_ZED2	0.19	0.16	0.21
SPPB_ZED3	0.19	0.17	0.21
SPQ_BDE	0.25	0.23	0.27
SPQ_BFI	0.32	0.30	0.35
SPQ_CFCS	0.25	0.23	0.28
SPQ_CGA	0.37	0.34	0.40
SPQ_CGACI	0.26	0.24	0.29
SPQ_CSBA	0.38	0.36	0.41
SPQ_DFS	0.30	0.27	0.33
SPQ_EFIP	0.39	0.36	0.41
SPQ_EFS	0.31	0.29	0.34
SPQ_FI40	0.36	0.33	0.38

SPQ_FI70	0.36	0.34	0.39
SPQ_FIBLSA	0.39	0.36	0.42
SPQ_FIG	0.22	0.20	0.24
SPQ_FIND	0.30	0.28	0.33
SPQ_FS	0.23	0.21	0.25
SPQ_FSS	0.38	0.36	0.41
SPQ_G8	0.28	0.25	0.31
SPQ_GFI	0.37	0.34	0.39
SPQ_HRCA	0.32	0.30	0.34
SPQ_HSF	0.34	0.31	0.36
SPQ_KFI	0.37	0.35	0.40
SPQ_PHF	0.26	0.24	0.29
SPQ_PHFR	0.30	0.27	0.33
SPQ_SDFI	0.40	0.38	0.43
SPQ_SHCFS	0.25	0.23	0.28
SPQ_SI	0.23	0.21	0.25
SPQ_SOF	0.16	0.14	0.17
SPQ_SPPB	0.29	0.27	0.31
SPQ_SPQ2	0.51	0.49	0.54
SPQ_TFI	0.40	0.37	0.43
SPQ_VES13	0.31	0.28	0.33
SPQ_ZED1	0.20	0.18	0.23
SPQ_ZED2	0.15	0.13	0.17
SPQ_ZED3	0.14	0.12	0.16
SPQ2_BDE	0.29	0.27	0.31
SPQ2_BFI	0.39	0.36	0.42
SPQ2_CFCS	0.35	0.32	0.38
SPQ2_CGA	0.52	0.49	0.54
SPQ2_CGACI	0.43	0.40	0.46
SPQ2_CSBA	0.42	0.40	0.45
SPQ2_DFS	0.44	0.42	0.47
SPQ2_EFIP	0.54	0.51	0.57
SPQ2_EFS	0.45	0.42	0.48
SPQ2_FI40	0.56	0.53	0.59
SPQ2_FI70	0.51	0.48	0.54
SPQ2_FIBLSA	0.53	0.50	0.55
SPQ2_FIG	0.27	0.25	0.29
SPQ2_FIND	0.60	0.57	0.63
SPQ2_FS	0.45	0.42	0.47
SPQ2_FSS	0.45	0.43	0.48
SPQ2_G8	0.46	0.43	0.48
SPQ2_GFI	0.56	0.54	0.59
SPQ2_HRCA	0.42	0.39	0.44
SPQ2_HSF	0.41	0.38	0.44

SPQ2_KFI	0.47	0.44	0.50
SPQ2_PHF	0.45	0.43	0.48
SPQ2_PHFR	0.55	0.52	0.58
SPQ2_SDFI	0.45	0.42	0.48
SPQ2_SHCFS	0.36	0.33	0.39
SPQ2_SI	0.33	0.31	0.36
SPQ2_SOF	0.32	0.31	0.34
SPQ2_SPPB	0.35	0.32	0.37
SPQ2_SPQ	0.51	0.49	0.54
SPQ2_TFI	0.60	0.58	0.63
SPQ2_VES13	0.43	0.41	0.46
SPQ2_ZED1	0.42	0.40	0.45
SPQ2_ZED2	0.35	0.32	0.37
SPQ2_ZED3	0.20	0.17	0.22
TFI_BDE	0.35	0.33	0.37
TFI_BFI	0.48	0.45	0.50
TFI_CFCS	0.37	0.35	0.40
TFI_CGA	0.59	0.56	0.61
TFI_CGACI	0.51	0.49	0.54
TFI_CSBA	0.41	0.38	0.43
TFI_DFS	0.47	0.45	0.50
TFI_EFIP	0.61	0.58	0.63
TFI_EFS	0.55	0.52	0.57
TFI_FI40	0.64	0.61	0.66
TFI_FI70	0.58	0.55	0.61
TFI_FIBLSA	0.57	0.54	0.59
TFI_FIG	0.30	0.28	0.32
TFI_FIND	0.56	0.53	0.58
TFI_FS	0.41	0.39	0.43
TFI_FSS	0.48	0.45	0.51
TFI_G8	0.42	0.39	0.45
TFI_GFI	0.64	0.61	0.66
TFI_HRCA	0.46	0.43	0.48
TFI_HSF	0.46	0.43	0.49
TFI_KFI	0.47	0.45	0.50
TFI_PHF	0.48	0.46	0.51
TFI_PHFR	0.62	0.59	0.64
TFI_SDFI	0.54	0.52	0.57
TFI_SHCFS	0.40	0.37	0.42
TFI_SI	0.41	0.39	0.44
TFI_SOF	0.30	0.29	0.32
TFI_SPPB	0.41	0.39	0.44
TFI_SPQ	0.40	0.37	0.43
TFI_SPQ2	0.60	0.58	0.63

TFI_VES13	0.47	0.44	0.49
TFI_ZED1	0.47	0.45	0.50
TFI_ZED2	0.25	0.22	0.27
TFI_ZED3	0.20	0.17	0.22
VES13_BDE	0.33	0.31	0.35
VES13_BFI	0.30	0.27	0.32
VES13_CFCS	0.28	0.25	0.30
VES13_CGA	0.59	0.57	0.61
VES13_CGACI	0.45	0.42	0.47
VES13_CSBA	0.40	0.37	0.42
VES13_DFS	0.65	0.63	0.67
VES13_EFIP	0.62	0.59	0.64
VES13_EFS	0.56	0.54	0.59
VES13_FI40	0.63	0.61	0.65
VES13_FI70	0.63	0.61	0.65
VES13_FIBLSA	0.62	0.60	0.64
VES13_FIG	0.34	0.32	0.36
VES13_FIND	0.56	0.54	0.58
VES13_FS	0.40	0.38	0.42
VES13_FSS	0.52	0.49	0.54
VES13_G8	0.36	0.34	0.39
VES13_GFI	0.54	0.51	0.56
VES13_HRCA	0.57	0.55	0.59
VES13_HSF	0.57	0.54	0.59
VES13_KFI	0.58	0.55	0.60
VES13_PHF	0.42	0.40	0.44
VES13_PHFR	0.44	0.41	0.47
VES13_SDFI	0.37	0.35	0.40
VES13_SHCFS	0.44	0.42	0.47
VES13_SI	0.34	0.32	0.37
VES13_SOF	0.23	0.21	0.24
VES13_SPPB	0.41	0.39	0.44
VES13_SPQ	0.31	0.28	0.33
VES13_SPQ2	0.43	0.41	0.46
VES13_TFI	0.47	0.44	0.49
VES13_ZED1	0.35	0.33	0.38
VES13_ZED2	0.18	0.16	0.20
VES13_ZED3	0.21	0.19	0.23
ZED1_BDE	0.21	0.19	0.24
ZED1_BFI	0.32	0.29	0.34
ZED1_CFCS	0.21	0.18	0.23
ZED1_CGA	0.45	0.42	0.47
ZED1_CGACI	0.38	0.35	0.40
ZED1_CSBA	0.27	0.24	0.30

ZED1_DFS	0.38	0.35	0.40
ZED1_EFIP	0.46	0.44	0.49
ZED1_EFS	0.38	0.36	0.41
ZED1_FI40	0.49	0.46	0.52
ZED1_FI70	0.45	0.43	0.48
ZED1_FIBLSA	0.43	0.41	0.46
ZED1_FIG	0.21	0.19	0.23
ZED1_FIND	0.49	0.47	0.52
ZED1_FS	0.40	0.38	0.42
ZED1_FSS	0.33	0.30	0.35
ZED1_G8	0.24	0.21	0.26
ZED1_GFI	0.41	0.38	0.43
ZED1_HRCA	0.36	0.34	0.39
ZED1_HSF	0.32	0.29	0.35
ZED1_KFI	0.35	0.32	0.37
ZED1_PHF	0.42	0.39	0.44
ZED1_PHFR	0.54	0.51	0.56
ZED1_SDFI	0.34	0.32	0.37
ZED1_SHCFS	0.36	0.34	0.39
ZED1_SI	0.34	0.32	0.37
ZED1_SOF	0.37	0.36	0.39
ZED1_SPPB	0.27	0.25	0.30
ZED1_SPQ	0.20	0.18	0.23
ZED1_SPQ2	0.42	0.40	0.45
ZED1_TFI	0.47	0.45	0.50
ZED1_VES13	0.35	0.33	0.38
ZED1_ZED2	0.12	0.10	0.14
ZED1_ZED3	0.14	0.12	0.16
ZED2_BDE	0.16	0.14	0.18
ZED2_BFI	0.13	0.10	0.15
ZED2_CFCS	0.36	0.34	0.38
ZED2_CGA	0.16	0.13	0.18
ZED2_CGACI	0.27	0.24	0.30
ZED2_CSBA	0.24	0.22	0.27
ZED2_DFS	0.17	0.15	0.20
ZED2_EFIP	0.18	0.16	0.21
ZED2_EFS	0.24	0.21	0.26
ZED2_FI40	0.22	0.19	0.24
ZED2_FI70	0.17	0.15	0.20
ZED2_FIBLSA	0.18	0.16	0.20
ZED2_FIG	0.16	0.14	0.17
ZED2_FIND	0.34	0.32	0.37
ZED2_FS	0.31	0.29	0.32
ZED2_FSS	0.17	0.15	0.19

ZED2_G8	0.56	0.54	0.59
ZED2_GFI	0.26	0.24	0.29
ZED2_HRCA	0.16	0.14	0.18
ZED2_HSF	0.20	0.17	0.22
ZED2_KFI	0.17	0.14	0.19
ZED2_PHF	0.34	0.32	0.36
ZED2_PHFR	0.33	0.31	0.36
ZED2_SDFI	0.21	0.18	0.23
ZED2_SHCFS	0.19	0.16	0.21
ZED2_SI	0.10	0.08	0.12
ZED2_SOF	0.33	0.32	0.35
ZED2_SPPB	0.19	0.16	0.21
ZED2_SPQ	0.15	0.13	0.17
ZED2_SPQ2	0.35	0.32	0.37
ZED2_TFI	0.25	0.22	0.27
ZED2_VES13	0.18	0.16	0.20
ZED2_ZED1	0.12	0.10	0.14
ZED2_ZED3	0.19	0.17	0.21
ZED3_BDE	0.18	0.16	0.20
ZED3_BFI	0.17	0.15	0.19
ZED3_CFCS	0.19	0.16	0.21
ZED3_CGA	0.17	0.15	0.19
ZED3_CGACI	0.16	0.14	0.18
ZED3_CSBA	0.27	0.25	0.29
ZED3_DFS	0.19	0.17	0.21
ZED3_EFIP	0.21	0.19	0.23
ZED3_EFS	0.20	0.18	0.22
ZED3_FI40	0.19	0.17	0.22
ZED3_FI70	0.21	0.18	0.23
ZED3_FIBLSA	0.20	0.18	0.22
ZED3_FIG	0.16	0.14	0.17
ZED3_FIND	0.25	0.23	0.27
ZED3_FS	0.18	0.16	0.20
ZED3_FSS	0.17	0.15	0.19
ZED3_G8	0.28	0.26	0.30
ZED3_GFI	0.23	0.20	0.25
ZED3_HRCA	0.19	0.16	0.21
ZED3_HSF	0.21	0.18	0.23
ZED3_KFI	0.17	0.15	0.20
ZED3_PHF	0.26	0.24	0.29
ZED3_PHFR	0.24	0.22	0.26
ZED3_SDFI	0.28	0.26	0.30
ZED3_SHCFS	0.29	0.27	0.31
ZED3_SI	0.14	0.12	0.16

ZED3_SOF	0.13	0.12	0.15
ZED3_SPPB	0.19	0.17	0.21
ZED3_SPQ	0.14	0.12	0.16
ZED3_SPQ2	0.20	0.17	0.22
ZED3_TFI	0.20	0.17	0.22
ZED3_VES13	0.21	0.19	0.23
ZED3_ZED1	0.14	0.12	0.16
ZED3_ZED2	0.19	0.17	0.21

2.6.5. Web table 4

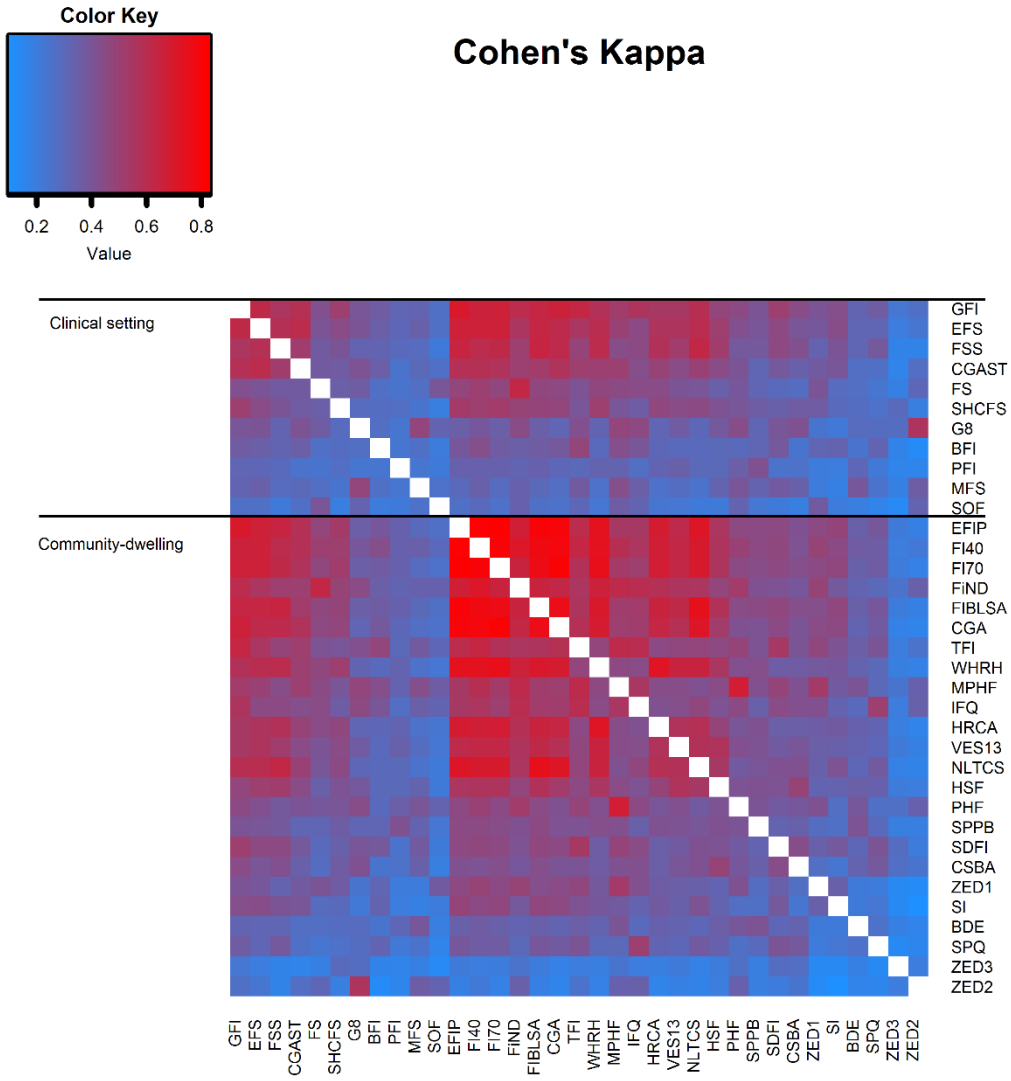
Web table 4. Weighted Cohen's Kappa of Frailty Scores with their Published Cut-offs in ELSA Wave 2 (2004-2005)

score	SPPB	FI40	PHF	SOF	EFS	GFI	TFI	FS	FI70	CGA	BFI	CGAST	CSBA	DFS
SPPB	NA	0.29	0.24	0.13	0.04	0.25	0.29	0.17	0.26	0.25	0.10	0.27	0.40	0.55
FI40	0.29	NA	0.33	0.44	0.13	0.62	0.63	0.55	0.77	0.70	0.33	0.50	0.42	0.90
PHF	0.24	0.33	NA	0.35	0.09	0.31	0.32	0.36	0.30	0.35	0.15	0.35	0.28	0.45
SOF	0.13	0.44	0.35	NA	0.27	0.40	0.43	0.81	0.43	0.46	0.34	0.29	0.29	0.38
EFS	0.04	0.13	0.09	0.27	NA	0.12	0.11	0.26	0.17	0.19	0.25	0.06	0.10	0.12
GFI	0.25	0.62	0.31	0.40	0.12	NA	0.69	0.48	0.62	0.65	0.26	0.51	0.46	0.75
TFI	0.29	0.63	0.32	0.43	0.11	0.69	NA	0.48	0.57	0.61	0.31	0.49	0.46	0.74
FS	0.17	0.55	0.36	0.81	0.26	0.48	0.48	NA	0.56	0.60	0.34	0.34	0.34	0.58
FI70	0.26	0.77	0.30	0.43	0.17	0.62	0.57	0.56	NA	0.73	0.32	0.44	0.43	0.91
CGA	0.25	0.70	0.35	0.46	0.19	0.65	0.61	0.60	0.73	NA	0.34	0.51	0.43	0.79
BFI	0.10	0.33	0.15	0.34	0.25	0.26	0.31	0.34	0.32	0.34	NA	0.17	0.18	0.23
CGAST	0.27	0.50	0.35	0.29	0.06	0.51	0.49	0.34	0.44	0.51	0.17	NA	0.32	0.71
CSBA	0.40	0.42	0.28	0.29	0.10	0.46	0.46	0.34	0.43	0.43	0.18	0.32	NA	0.60
DFS	0.55	0.90	0.45	0.38	0.12	0.75	0.74	0.58	0.91	0.79	0.23	0.71	0.60	NA
FSS	0.25	0.62	0.32	0.41	0.20	0.57	0.52	0.54	0.70	0.72	0.32	0.43	0.48	0.74
HRCA	0.26	0.71	0.28	0.35	0.14	0.52	0.50	0.52	0.72	0.66	0.29	0.41	0.37	0.90
VES13	0.27	0.69	0.29	0.38	0.17	0.55	0.51	0.51	0.75	0.65	0.29	0.39	0.46	0.86
FIG	0.14	0.35	0.22	0.49	0.35	0.30	0.29	0.46	0.41	0.40	0.38	0.17	0.26	0.34
SDFI	0.27	0.47	0.28	0.30	0.09	0.53	0.60	0.33	0.45	0.48	0.25	0.36	0.46	0.58
SPQ	0.18	0.37	0.19	0.27	0.13	0.40	0.47	0.31	0.42	0.45	0.29	0.23	0.43	0.40
SPQ2	0.02	0.07	0.06	0.18	0.35	0.07	0.06	0.16	0.09	0.10	0.19	0.03	0.06	0.06
ZED1	0.04	0.13	0.11	0.28	0.45	0.11	0.10	0.26	0.15	0.18	0.23	0.06	0.10	0.11
ZED2	0.02	0.07	0.07	0.19	0.32	0.07	0.06	0.16	0.08	0.09	0.11	0.04	0.06	0.06
ZED3	0.01	0.02	0.02	0.05	0.13	0.03	0.02	0.04	0.03	0.03	0.05	0.01	0.02	0.02
CFCS	0.29	0.31	0.38	0.23	0.06	0.29	0.35	0.24	0.23	0.25	0.12	0.37	0.30	0.42
SI	0.05	0.17	0.08	0.24	0.39	0.16	0.15	0.25	0.21	0.24	0.27	0.09	0.10	0.14
SHCFS	0.13	0.43	0.21	0.38	0.31	0.38	0.32	0.49	0.52	0.48	0.30	0.22	0.29	0.46
G8	0.30	0.41	0.25	0.24	0.04	0.38	0.41	0.28	0.35	0.35	0.13	0.44	0.37	0.70
FIND	0.17	0.13	0.32	0.08	0.01	0.13	0.13	0.10	0.10	0.10	0.03	0.18	0.11	0.32
Mean	0.20	0.41	0.25	0.32	0.18	0.38	0.38	0.38	0.42	0.42	0.23	0.30	0.31	0.49

Web table 4. Continuation

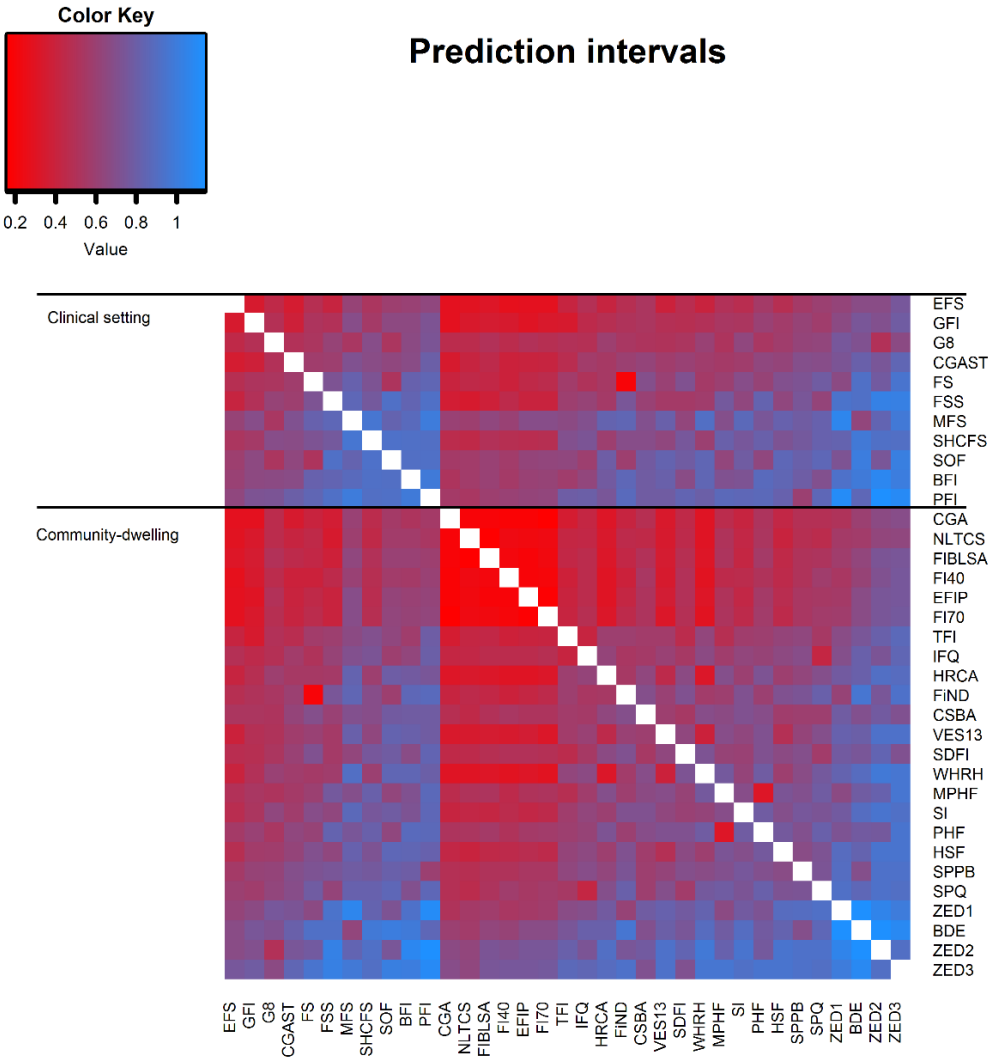
score	HRCA	VES13	FIG	SDFI	SPQ	SPQ2	ZED1	ZED2	ZED3	CFCS	SI	SHCFS	G8
SPPB	0.26	0.27	0.14	0.27	0.18	0.02	0.04	0.02	0.01	0.29	0.05	0.13	0.30
FI40	0.71	0.69	0.35	0.47	0.37	0.07	0.13	0.07	0.02	0.31	0.17	0.43	0.41
PHF	0.28	0.29	0.22	0.28	0.19	0.06	0.11	0.07	0.02	0.38	0.08	0.21	0.25
SOF	0.35	0.38	0.49	0.30	0.27	0.18	0.28	0.19	0.05	0.23	0.24	0.38	0.24
EFS	0.14	0.17	0.35	0.09	0.13	0.35	0.45	0.32	0.13	0.06	0.39	0.31	0.04
GFI	0.52	0.55	0.30	0.53	0.40	0.07	0.11	0.07	0.03	0.29	0.16	0.38	0.38
TFI	0.50	0.51	0.29	0.60	0.47	0.06	0.10	0.06	0.02	0.35	0.15	0.32	0.41
FS	0.52	0.51	0.46	0.33	0.31	0.16	0.26	0.16	0.04	0.24	0.25	0.49	0.28
FI70	0.72	0.75	0.41	0.45	0.42	0.09	0.15	0.08	0.03	0.23	0.21	0.52	0.35
CGA	0.66	0.65	0.40	0.48	0.45	0.10	0.18	0.09	0.03	0.25	0.24	0.48	0.35
BFI	0.29	0.29	0.38	0.25	0.29	0.19	0.23	0.11	0.05	0.12	0.27	0.30	0.13
CGAST	0.41	0.39	0.17	0.36	0.23	0.03	0.06	0.04	0.01	0.37	0.09	0.22	0.44
CSBA	0.37	0.46	0.26	0.46	0.43	0.06	0.10	0.06	0.02	0.30	0.10	0.29	0.37
DFS	0.90	0.86	0.34	0.58	0.40	0.06	0.11	0.06	0.02	0.42	0.14	0.46	0.70
FSS	0.62	0.67	0.43	0.51	0.51	0.11	0.17	0.09	0.03	0.26	0.25	0.50	0.31
HRCA	NA	0.72	0.37	0.40	0.36	0.07	0.13	0.07	0.03	0.24	0.17	0.45	0.38
VES13	0.72	NA	0.42	0.41	0.41	0.09	0.15	0.09	0.03	0.25	0.19	0.51	0.36
FIG	0.37	0.42	NA	0.24	0.29	0.20	0.32	0.19	0.07	0.14	0.28	0.48	0.14
SDFI	0.40	0.41	0.24	NA	0.45	0.05	0.09	0.05	0.02	0.37	0.14	0.26	0.39
SPQ	0.36	0.41	0.29	0.45	NA	0.10	0.09	0.06	0.02	0.20	0.15	0.29	0.22
SPQ2	0.07	0.09	0.20	0.05	0.10	NA	0.33	0.34	0.07	0.03	0.22	0.16	0.02
ZED1	0.13	0.15	0.32	0.09	0.09	0.33	NA	0.44	0.20	0.05	0.27	0.30	0.04
ZED2	0.07	0.09	0.19	0.05	0.06	0.34	0.44	NA	0.23	0.04	0.13	0.16	0.02
ZED3	0.03	0.03	0.07	0.02	0.02	0.07	0.20	0.23	NA	0.01	0.07	0.07	0.01
CFCS	0.24	0.25	0.14	0.37	0.20	0.03	0.05	0.04	0.01	NA	0.05	0.13	0.38
SI	0.17	0.19	0.28	0.14	0.15	0.22	0.27	0.13	0.07	0.05	NA	0.26	0.06
SHCFS	0.45	0.51	0.48	0.26	0.29	0.16	0.30	0.16	0.07	0.13	0.26	NA	0.16
G8	0.38	0.36	0.14	0.39	0.22	0.02	0.04	0.02	0.01	0.38	0.06	0.16	NA
FIND	0.11	0.10	0.04	0.12	0.06	0.01	0.01	0.01	0.00	0.16	0.02	0.05	0.21
Mean	0.38	0.40	0.29	0.32	0.28	0.12	0.18	0.12	0.05	0.22	0.17	0.31	0.26

2.6.6. Web Figure 2



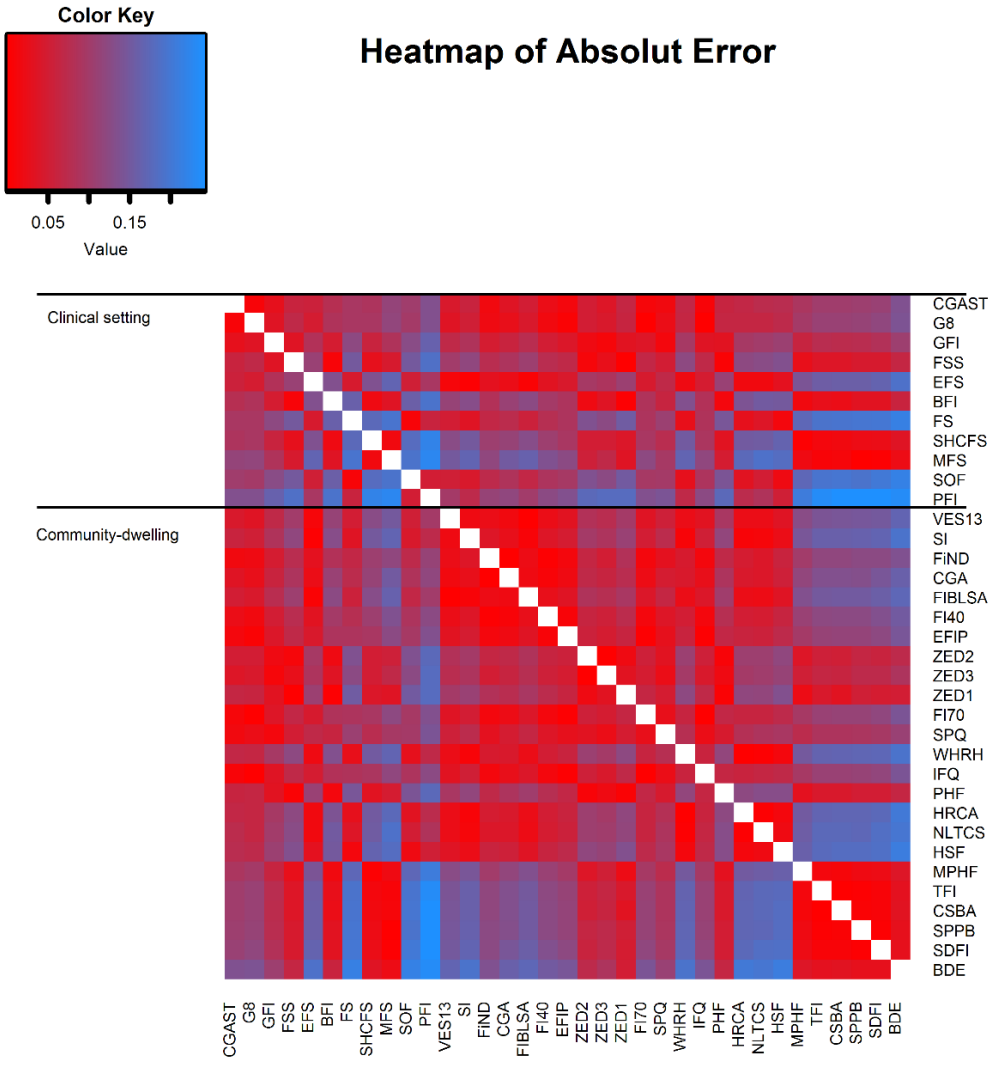
Web Figure 2. Agreement calculated with Cohen's Kappa between each pair of scores (595 combined pairs of scores) in ELSA wave 2 (2004-2005). The plot is sorted by aim of the score (clinical setting versus community-dwelling) and then from highest (red) to lowest (blue) median of Cohen's Kappa coefficients. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.7. Web Figure 3



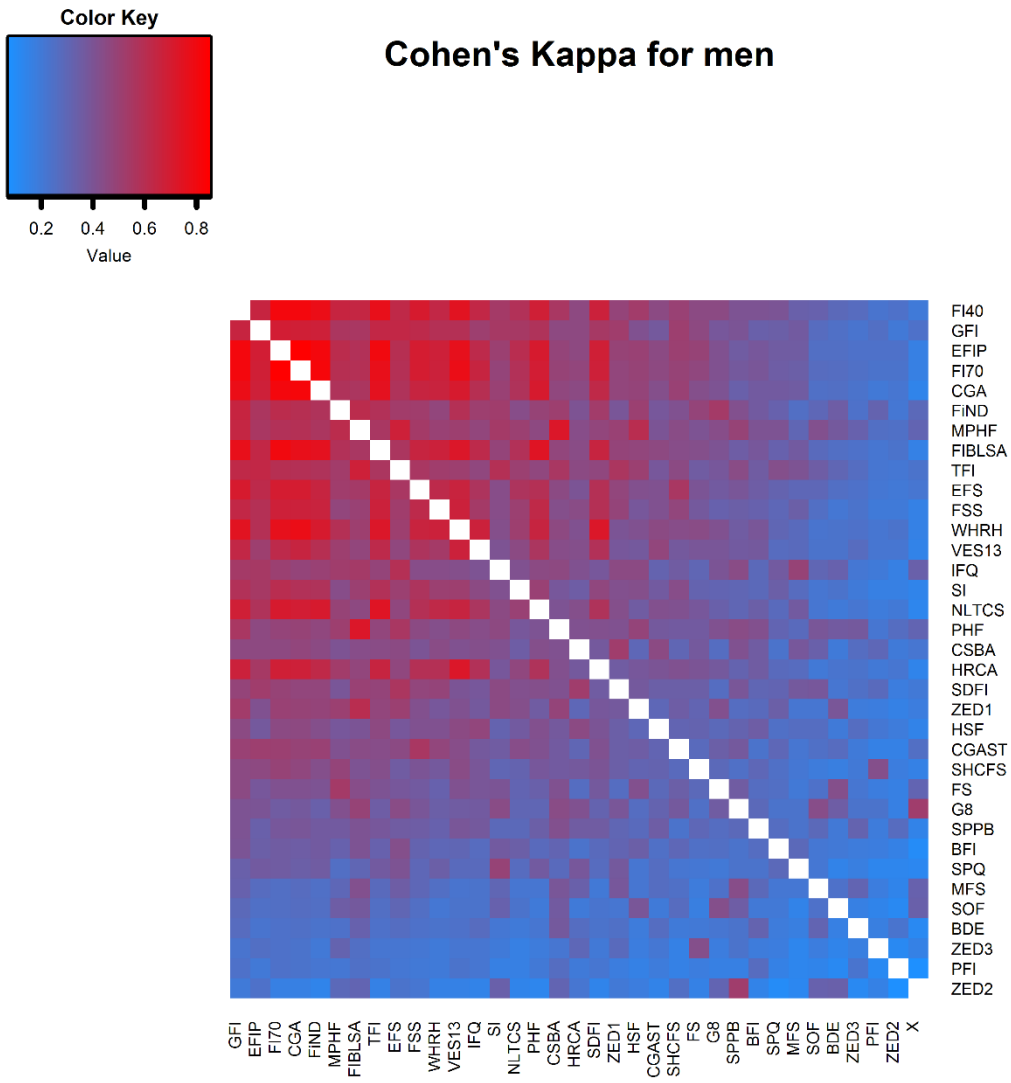
Web Figure 3. Prediction interval widths obtained with the Bland-Altman models for all 595 combined pairs of scores sorted by frailty model and then by prediction interval widths in ELSA wave 2 (2004-2005). In red, the narrowest prediction interval widths and in blue the opposite. The plot is sorted by aim of the score (clinical setting versus community-dwelling) and then by the narrowest prediction interval widths. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.8. Web Figure 4



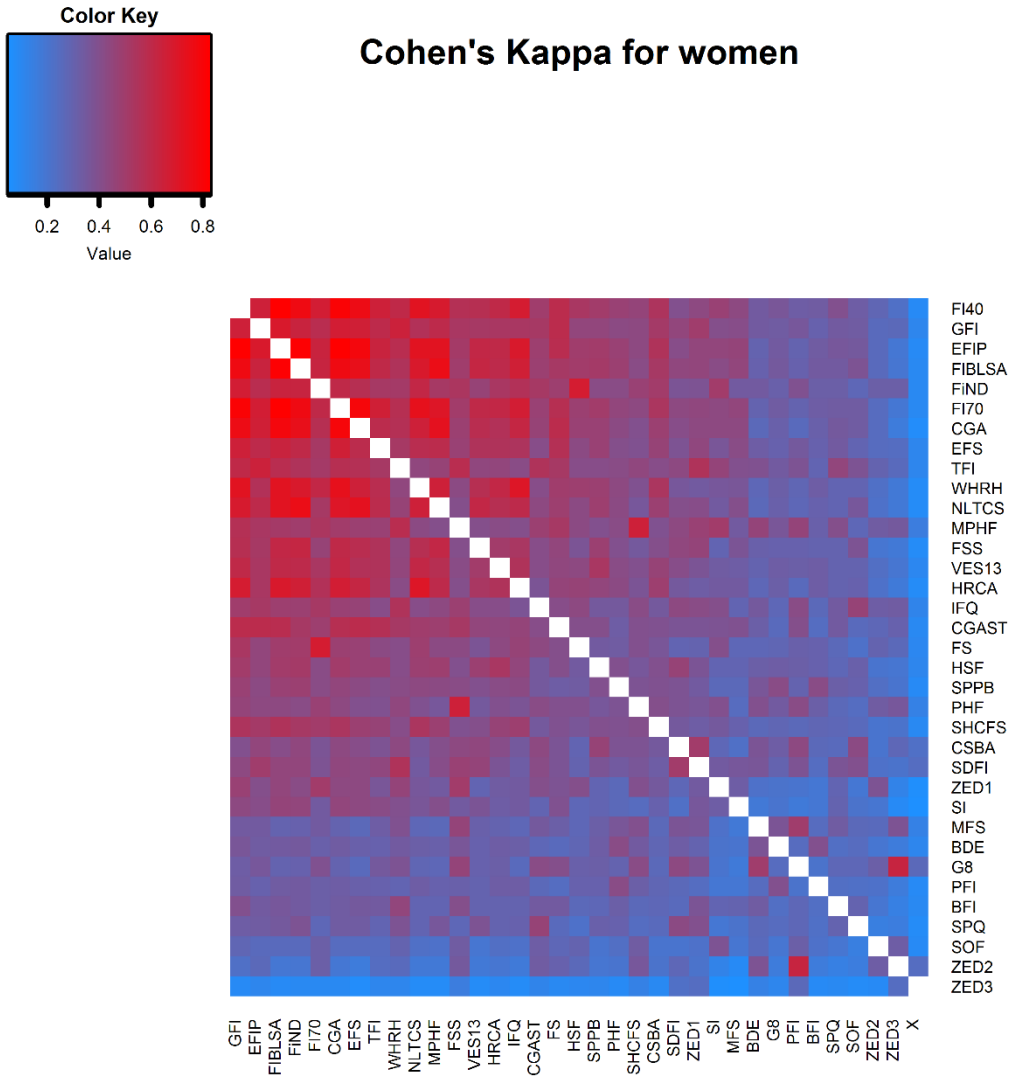
Web Figure 4. Absolute (abs) over/underestimation* of frailty in the median frailty value from the modified Bland Altman model obtained with all 595 combined pairs of scores in ELSA wave 2 (2004-2005). * Over/underestimation= abs [intercept+ (slope*median)] Intercept and slope. The median is calculated as the median of the mean of the mean of the two FS for each pair. The plot is sorted by aim of the score (clinical setting versus community-dwelling) and then by the lowest absolute errors. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.9. Web Figure 5



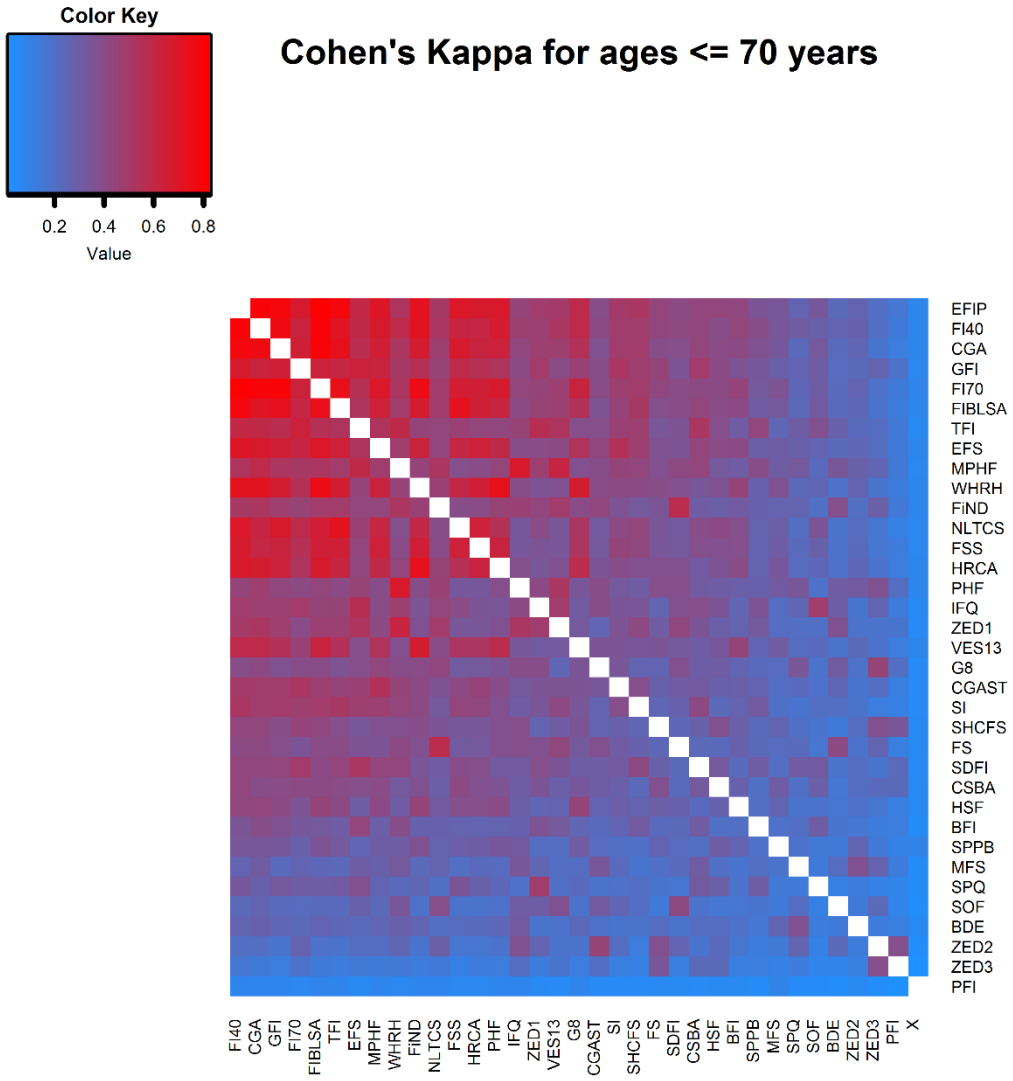
Web Figure 5. Cohen's Kappa in men. Scores are sorted by kappa value. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.10. Web Figure 6



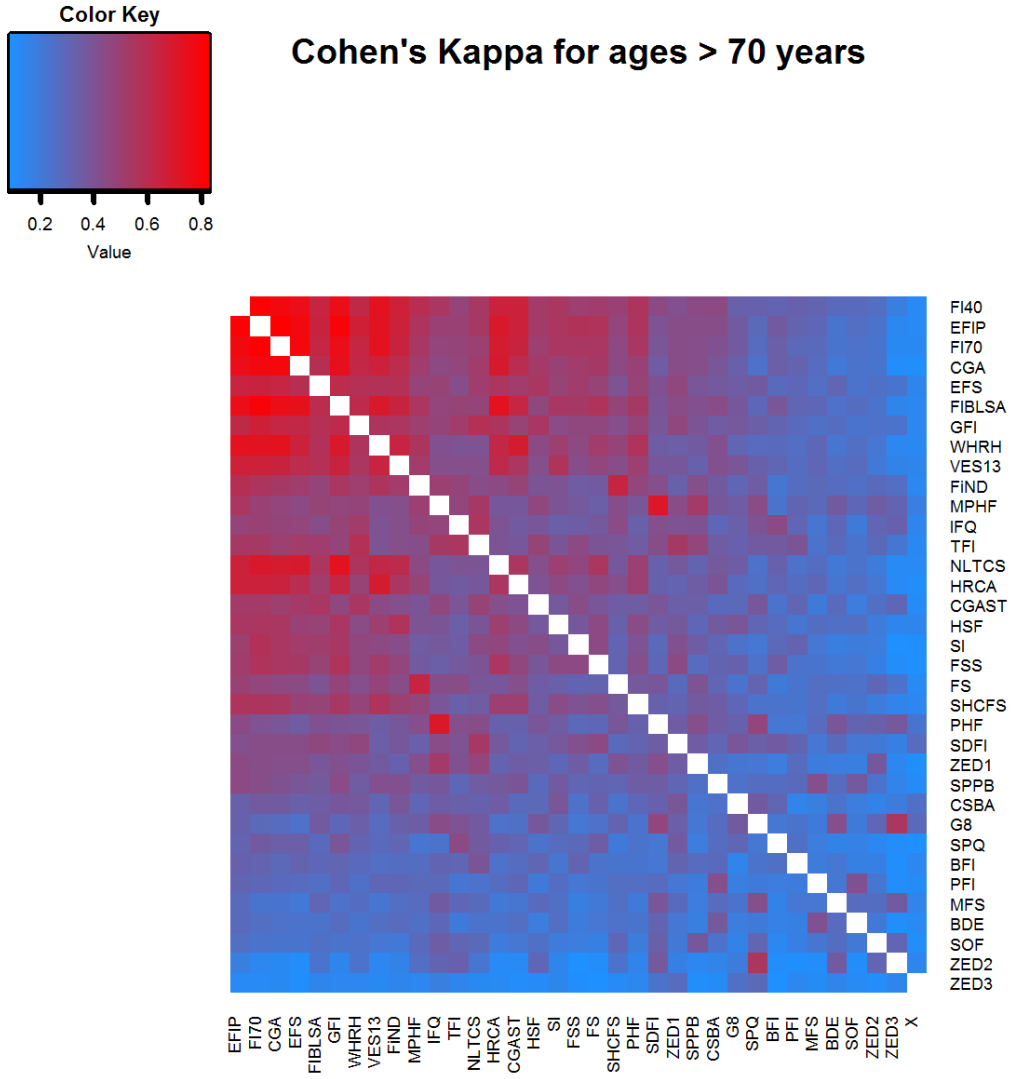
Web Figure 6. Cohen's Kappa in women. Scores are sorted by kappa value. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.11. Web Figure 7



Web Figure 7. Cohen's Kappa in participants aged 70 or less years. Scores are sorted by kappa value. Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

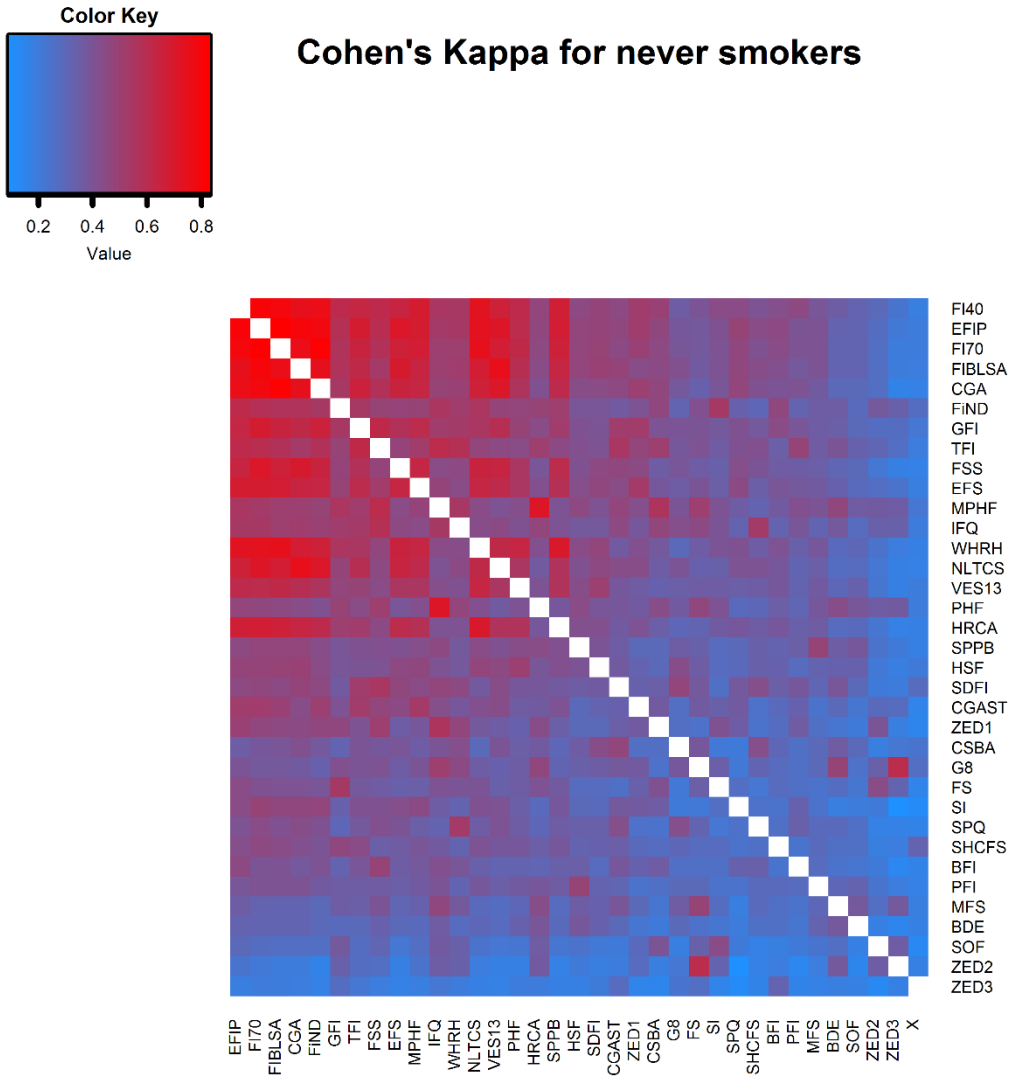
2.6.12. Web Figure 8



Web Figure 8. Cohen's Kappa in participants aged more than 70 years. Scores are sorted by kappa value.

Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

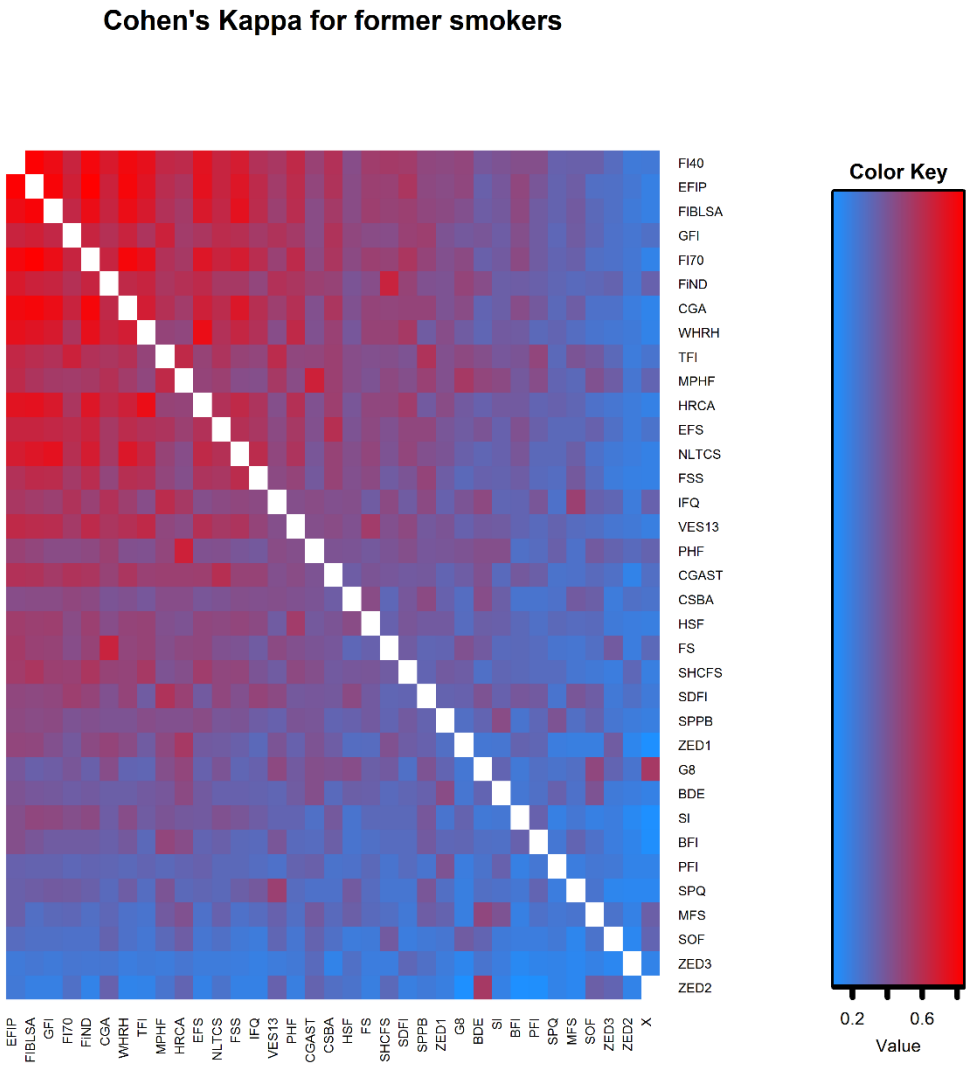
2.6.13. Web Figure 9



Web Figure 9. Cohen's Kappa in never smokers. Scores are sorted by kappa value.

Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

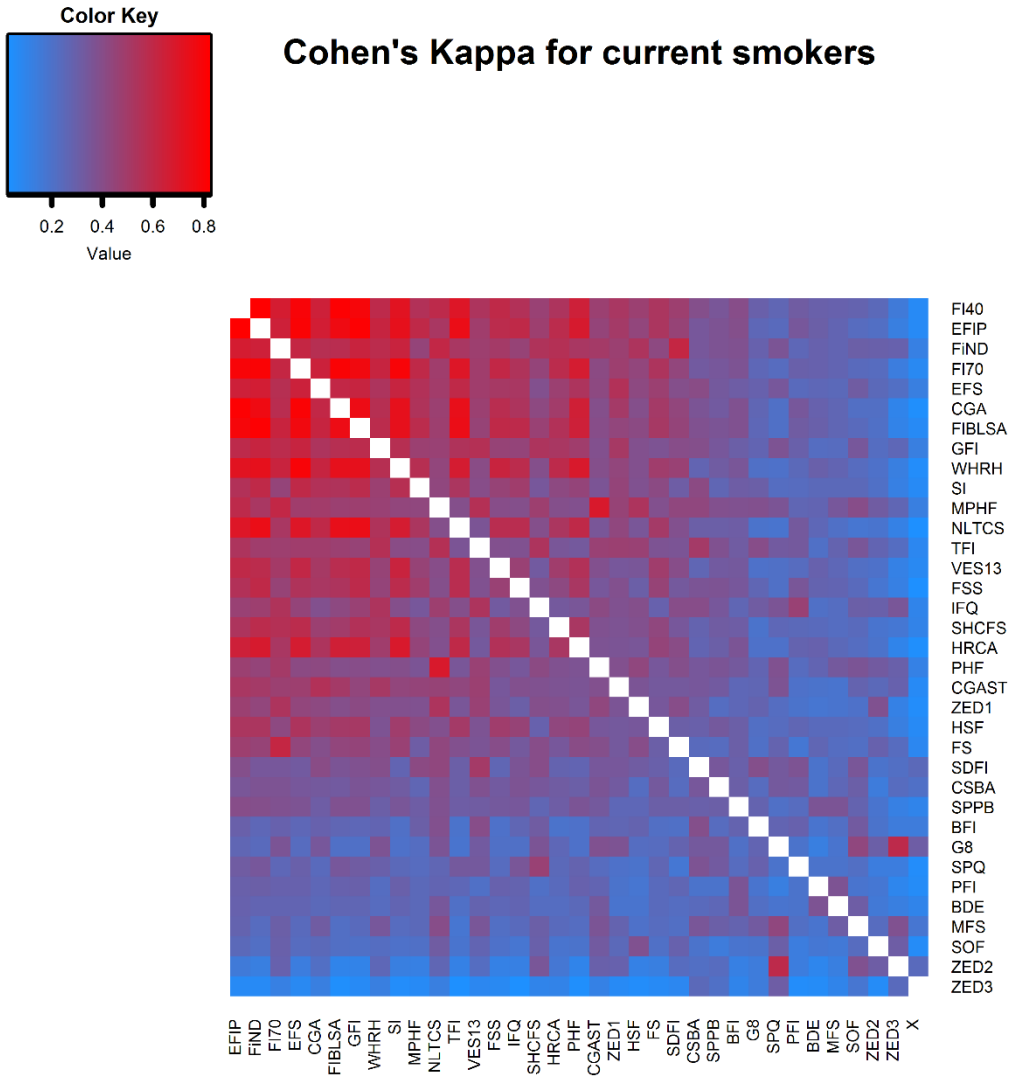
2.6.14. Web Figure 10



Web Figure 10. Cohen's Kappa in former smokers. Scores are sorted by kappa value.

Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

2.6.15. Web Figure 11



Web Figure 11. Cohen's Kappa in current smokers. Scores are sorted by kappa value.

Abbreviations frailty scores: BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, Frailty Index 40 items; FI70, Frailty Index 70 items; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FIND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale.; SI; Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC & self-reported health; ZED1; ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2; ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity & Low BMI).

Chapter 3. Study II

Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer, and total mortality in an elderly general population in England: An observational study

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3.1. Abstract

Background

Frail elderly people experience elevated mortality. However, no consensus exists on the definition of frailty, and many frailty scores have been developed. The main aim of this study was to compare the association between 35 frailty scores and incident cardiovascular disease (CVD), incident cancer, and all-cause mortality. Also, we aimed to assess whether frailty scores added predictive value to basic and adjusted models for these outcomes.

Methods and findings

Through a structured literature search, we identified 35 frailty scores that could be calculated at wave 2 of the English Longitudinal Study of Ageing (ELSA), an observational cohort study. We analysed data from 5,294 participants, 44.9% men, aged 60 years and over. We studied the association between each of the scores and the incidence of CVD, cancer, and all-cause mortality during a 7-year follow-up using Cox proportional hazard models at progressive levels of adjustment. We also examined the added predictive performance of each score on top of basic models using Harrell's C statistic. Using age of the participant as a timescale, in sex-adjusted models, hazard ratios (HRs) (95% confidence intervals) for all-cause mortality ranged from 2.4 (95% CI: 1.7-3.3) to 26.2 (95% CI: 15.4-44.5). In further adjusted models including smoking status and alcohol consumption, HR ranged from 2.3 (95% CI: 1.6-3.1) to 20.2 (95% CI: 11.8-34.5). In fully adjusted models including lifestyle and comorbidity, HR ranged from 0.9 (95% CI: 0.5-1.7) to 8.4 (95% CI: 4.9-14.4). HRs for CVD and cancer incidence in sex-adjusted models ranged from 1.2 (95% CI: 0.5-3.2) to 16.5 (95% CI: 7.8-35.0) and from 0.7 (95% CI: 0.4-1.2) to 2.4 (95% CI: 1.0-5.7), respectively. In sex- and age-adjusted models, all frailty scores showed significant added predictive performance for all-cause mortality, increasing the C statistic by up to 3%. None of the scores significantly improved basic prediction models for CVD or cancer. A source of bias could be the differences in mortality follow-up time compared to CVD/cancer, because the existence of informative censoring cannot be excluded.

Conclusion

There is high variability in the strength of the association between frailty scores and 7-year all-cause mortality, incident CVD, and cancer. With regard to all-cause mortality, some scores give a modest improvement to the predictive ability. Our results show that certain scores clearly outperform others with regard to three important health outcomes in later life. Finally, we think that despite their limitations, the

use of frailty scores to identify the elderly population at risk is still a useful measure, and the choice of a frailty score should balance feasibility with performance.

3.2. Introduction

Although chronological age is the strongest determinant of disease occurrence and mortality, it is increasingly recognised that the process of ageing is heterogeneous[113] due to a combination of differences in lifetime cumulative exposure to determinants of chronic disease and differences in individual susceptibility. The concept of frailty was introduced as a way of identifying individuals who, at a given age, have a particularly fragile health balance and are therefore more vulnerable to rapid health deterioration and early mortality[72]. However, the operationalization of the concept of frailty has been fraught with difficulties, as different groups of researchers and clinicians have expressed diverging views on which characteristics make up frailty and on how these should be assessed individually and in unison.

Considering the type and composition of variables of frailty scores, four main approaches to frailty can be distinguished. First, the “phenotype of frailty” approach describes frailty as a physiological syndrome of diminished resistance to stressors associated with poor health outcomes[31]. Second, the “multidimensional” approach defines frailty as a dynamic process of loss of function in one or more domains, making the individual vulnerable[38]. Third, the “accumulation of deficit” approach counts the number of health problems or deficits to classify the individual as frail[35]. Fourth, we propose a "disability" approach, as frailty scores were created primarily with variables representing a degree of disability. We have included this classification even without a theoretical basis/reference, as these scores are used as frailty scores, although disability is considered by many authors more as a result of frailty or an overlap condition than as an equivalent of frailty[40].

There is no gold standard to measure frailty and many different frailty scores have been created, even within each of the four main approaches[13]. We have previously shown that there is only limited agreement in which individuals will be classified as frail, according to different scores, and that, in consequence, it is impossible to compare the prevalence of frailty or associations with relevant outcomes between studies using different frailty scores directly[114].

To fully assess and compare the performance of different frailty scores, it is also necessary to consider their prospective association and predictive ability for the main conditions that cause the loss of healthy life years and quality of life in an ageing population[115]. Prospective associations were used in this study to investigate frailty scores as risk factors of important outcomes in the elderly population: death or cardiovascular or cancer events[116]. Predictive value was used in this study to determine the ability of frailty scores to discriminate or separate participants who will from those who will not develop an event[54].

Many scores have shown strong associations with all-cause mortality, risk of hospitalization, and disability13, but the knowledge concerning their association with other major causes of ill-health and loss of quality of life, such as cardiovascular disease (CVD) events and cancer, is very limited. In a longitudinal study, Klein et al. found a significant association between frailty and CVD (odds ratio [OR] in men = 1.33 [1.06-1.67]; in women = 1.43 [1.13-1.82]) and a slightly high, although not significant, association between frailty and cancer (OR in men = 1.17 [0.89-1.55]; in women = 1.21 [0.95-1.54])[117]. Another study shows associations between variables that take part of some frailty instruments and cancer incidence[118], but no direct large-scale comparison studies are available.

This comparative analysis is important beyond the fact that this has not been done. Researchers need more information on what frailty scores actually measure and how they can compare or pool results of studies using different frailty scores. Clinicians need more information on the performance of the scores and on the most appropriate instruments in clinical settings. Policy makers need more information on the usefulness of measuring frailty at a population level and how to achieve it with the best instruments.

Therefore, the objective of this study was to carry out a comparative external validation of a comprehensive list of frailty scores with regard to three important health outcomes in later life: CVD, cancer, and all-cause mortality, by direct comparison of the strength of associations and of added predictive value, using prospective data from a population-based study in the elderly. Some of the scales included are composite scales for physical activity or function, grouped as frailty scores for this paper. Our hypothesis was that the marked heterogeneity in approach, type, and composition of frailty scores would translate into heterogeneity in associations and predictive ability, with important health outcomes.

3.3. Methods

3.3.1. Participants, inclusion criteria, and study design

Participants. Data on participants from the English Longitudinal Study of Ageing (ELSA) were used under data-sharing project number 82538. ELSA is an ongoing longitudinal cohort study based on a representative sample of middle-aged and elderly general population 50 years and over living in England[49]. ELSA has extensive subjective and objective information collected in biennial surveys (waves). All waves gathered information concerning physical, cognitive, and psychological health, disability, lifestyle factors, comorbidities, social participation, and social support. Also, even-numbered waves have objective measures: physical functioning assessment and biological sampling[119]. Ethical approval was obtained from the Multicentre Research and Ethics Committee and all participants provided written informed consent[120].

Inclusion criteria. Participants aged 60 or over (because not all frailty-related variables were measured in participants younger than 60 years) who gave permission to link their data with a national mortality register and had a nurse visit in wave 2 were included. The outcomes were measured up to 2012, when mortality data were assessed.

3.3.2. Study design

This is a longitudinal secondary data analysis of ELSA and no formal written analysis plan exists. The analysis was planned in November 2015 during meetings with coauthors. We used the second wave (2004-2005) as baseline because this was the first wave with a clinical examination and laboratory samples. The exposure was the frailty state measured with 35 different frailty scores at baseline, and the follow-up time was from 2004-2005 to 2012.

3.3.3. Frailty scores

A structured search was performed to identify all published original frailty scores. The search strategy has previously been described in detail[114]. The original scores that could be calculated with the ELSA wave 2 data (i.e., those for which at least 80% of the necessary variables were measured) were selected.

Multiple imputation was used to deal with missing data in the underlying measured study variables necessary to calculate the frailty scores. In order to obtain optimally plausible values for the scores, imputation was applied to the original underlying variables, and frailty scores were calculated a posteriori using imputed values.

For preparing an analysis in one single continuous scale, frailty scores were rescaled from 0 (non-frail) to 1 (maximum frail) by dividing the output of each frailty score by the maximum possible value. If the frailty score was defined with a score that gave different weight to some variables, the output was accorded this weight and then rescaled. In addition, some frailty scores had to be inverted to convert the result, according the definition of 0 as non-frail and 1 as maximum frail. Scores were classified into 4 groups depending on their underlying frailty approach: phenotype of frailty (mainly physical functioning variables), multidimensional (at least 2 different dimensions and less than 30 variables), accumulation of deficits (at least 30 variables), and disability (mainly disability variables). A total of 67 original frailty scores were found in the literature search and 35 had at least 80% of variables possible to calculate with the data of ELSA wave 2, and in consequence, they were selected (Table 1). Out of them, 19 had binary cutoffs identifying frail and non-frail individuals, and 10 had categorical cutoffs, additionally identifying an intermediate pre-frail group[114].

Table 1. Frailty scores calculated in participants of ELSA wave 2 (2004-2005)

First Author, Year (Reference No.)	Score name	Abbreviation
	Phenotype of frailty approach	
Klein, 2003[80]	Beaver Dam Eye Study Index	BDE
Cesari, 2014[82]	Frail Non-Disabled (FiND) Questionnaire	FiND
van Kan, 2008[83]	Frail Scale	FS
Rothman, 2008[84]	Modified Phenotype of Frailty	MPHF
Gill, 2002[81]	Physical Frailty Index	PFI
Fried, 2001[31]	Phenotype of Frailty	PHF
Ensrud, 2007[85]	Study of Osteoporotic Fractures	SOF
Guralnik, 1994[86]	Short Physical Performance Battery	SPPB
Chin, 1999[87]	ZED (Physical Activity & Low BMI)	ZED1
Chin, 1999[87]	ZED (Physical Activity & Weight Loss)	ZED2
Chin, 1999[87]	ZED (Physical Activity & Low Energy)	ZED3
	Multidimensional approach	
Freiheit, 2010[88]	Brief Frailty Index	BFI
Balducci, 2000[90]	Comprehensive Geriatric Assessment ST	CGAST
Ravaglia, 2008[91]	Conselice Study of Brain Aging Score	CSBA
Rolfson, 2006[92]	Edmonton Frail Scale	EFS
Cacciatore, 2005[121]	Frailty Staging System	FSS
Bellera, 2012[94]	G-8 Geriatric Screening Tool	G8
Steverink, 2001[95]	Groningen Frailty Indicator	GFI
Brody, 1997[96]	Health Status Form	HSF
Di Bari, 2014[100]	Inter-Frail Questionnaire	IFQ
Hubbard, 2009[89]	Modified Frailty Score	MFS
Puts, 2005[97]	Static/Dynamic Frailty Index	SDFI
Maly, 1997[98] (30)	Screening Instrument	SI
Hébert, 1996[99]	Sherbrooke Postal Questionnaire	SPQ
Gobbens, 2010[47]	Tilburg Frailty Indicator	TFI
	Accumulation of deficits approach	
Jones, 2004[101]	Comprehensive Geriatric Assessment	CGA
de Vries, 2013[102]	Evaluative Frailty Index for Physical Activity	EFIP
Searle, 2008[46]	Frailty Index 40 items	FI40
Theou, 2013[103]	Frailty Index 70 items (SHARE)	FI70
Fang, 2012[104]	Frailty Index (BLSA)	FIBLSA
Kulminski, 2007[105]	Long Term Care Survey Frailty Index	NLTCS
	Disability approach	
Morris, 1984[107]	HRCA Vulnerability Index	HRCA
Rockwood, 2005[108]	CSHA Clinical Frailty Scale	SHCFS
Saliba, 2001[109]	Vulnerable Elders Survey	VES13
Dayhoff, 1998[106]	WHOAFC & self-reported health	WHRH

3.3.4. Missing data

Missing data of some needed variables to calculate frailty scores were observed in 1 (<1.0%) to 3,037 (57.4%) participants. The mechanism of missing data was assumed to be missing at random because the underlying values necessary to calculate frailty scores that were missing for some individuals are likely to depend on observed data in the ELSA data. In other words, missing data did not depend on any unobserved data, but only upon observed data.

Each variable was defined as being of numerical, binary, or categorical type, which defined the appropriate method for imputation. The chained equations approach was chosen because it is a very effective, flexible, and straightforward method to impute data. This method is based on a set of models adapted to the type of missing value; the values are filled first with random sampling, based only on the observed data, and then also based on already imputed data[76 77].

The imputation model was built by selecting the best missing data predictors among the available variables. The imputation model incorporated strong predictors of missing data (cognition, disability) and confounders (age, sex, education, physical activity). Moreover, outcomes were included in the imputation model (mortality, cancer, CVD), but they were not imputed. To optimise the imputed values, the data were ordered from lower to higher percentage of missing data before running the imputation, and a seed was set to allow reproducibility.

We performed 30 imputations to create 30 different data sets. Then, we ran 20 iterations by each of these 30 imputations, sufficient to achieve convergence of the Gibbs sampler. The imputations were assessed by hand (plausible values for imputed data compared to completed data) and by using graphical methods.

3.3.5. Outcomes

We assessed 3 main outcomes: all-cause mortality, CVD, and cancer events. Mortality data linked to ELSA participants was provided by the National Health Service's Central Registry, Southport, UK. For 68 participants, mortality was obtained from other sources (found during ELSA fieldwork or from participants' relatives). Main causes of death were registered as CVD, cancer, diseases of the respiratory system, and other causes. CVD or cancer events were defined by self-report in waves 3-5. A CVD event could be myocardial infarction, heart failure, stroke, or CVD death. A cancer event could be cancer of any type, including cancer

death. For each outcome separately, participants' exposure time was calculated from the participant's age at entry (wave 2 clinical examination: 2004-2005) to participant's age at first event or final censoring (date of mortality assessment: February 2012). Participants lost to follow-up were right-censored at the midpoint between their last visit and the next one. For analysis of CVD and cancer incidence, respective prevalent cases at baseline were excluded.

3.3.6. Definition of covariates/potential confounders

Smoker status was defined as never, previous, or current smoker. The maximum alcohol consumption per day was defined as 0, 1, 2, and >2 units/day. Body mass index (BMI) was defined as a continuous variable calculated as weight (kg)/height $(m)^2$. Self-reported physical activity was defined as time spent in vigorous, moderate, low, and sedentary activity. Diabetes was defined through self-reported medical diagnosis or fasting glucose≥7.0 mmol/L or glycated haemoglobin ≥6.5% [122]. Hypertension was defined from systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively, or self-reported high blood pressure medication[123]. Anaemia was defined as a measured haemoglobin level <13 g/dL (men) and < 12 g/dL (women)[124]. Arthritis was self-reported diagnosis. Neuropsychiatric problems were self-reported diagnoses of: Alzheimer or Parkinson disease, dementia, or psychiatric problems. Cognition was evaluated with a total continuous cognitive index (memory and executive functions)[125]. Self-rated health was defined as excellent, very good, good, fair, or poor. Quality of life was evaluated with the 19-item scale control, autonomy, pleasure, and self-realization (CASP-19) questionnaire[126]. Depression symptoms were assessed with the 8-item Centre for Epidemiologic Study Depression Scale, with cut-off ≥ 4 points[127].

3.3.7. Statistical analysis

We performed two parallel statistical analyses. The first was a continuous analysis with frailty scores rescaled to the range 0 (no frailty) to 1 (frailty). The second was a categorical analysis of frailty scores using cutoffs when they were defined. All data analyses were carried out in R version 3.3.0 using packages `Mice', `lattice', `Survival', mitml', and `survC1'. A p-value of less than 0.05 was considered statistically significant.

Survival analysis. Cox proportional hazards models were fitted for each outcome and independently for each frailty score as a continuous variable. Where a published cut-off level to define frailty was

available, an additional model was run on the binary or categorical frailty classification. For each outcome (all-cause mortality, CVD, and cancer events), 4 models were fitted with progressive levels of adjustment (0-3): model 0: frailty score; model 1: model 0 + sex; model 2: model 1 + smoking status and alcohol consumption; and model 3: model 2 + physical activity, BMI, diabetes, hypertension, CVD, cancer, anaemia, chronic obstructive pulmonary disease (COPD), arthritis, neuropsychiatric problems, depression, cognition, and self-rated health and quality of life. The covariates in each model were chosen because all of them could potentially be confounders, affecting the outcome and/or the exposure. To avoid collinearity issues, the covariates of model 3 were tailored to each frailty score, excluding covariates that were an underlying variable of the score or a highly correlated variable. For CVD and cancer models, CVD and cancer were excluded as covariates (see S1 Table).The proportional hazards assumption was checked by adding a time-covariate interaction in the model. The interaction term was retained in the model if significant[128]. The Cox models were fitted in 30 imputed data sets and the results, including calculated 95% confidence intervals, were pooled according to Rubin's rules[75].

The discrimination ability was assessed with Harrell's C statistic[115] using a calendar time to event scale. Three basic adjusted models: model 1 = age and sex; model 2 = model 1 + age, sex, smoking status, and alcohol; model 3 = model 2 + physical activity, BMI, diabetes, hypertension, CVD, cancer, anaemia, COPD, arthritis, neuropsychiatric problems, depression, cognition, and self-rated health and quality of life were calculated for each outcome. Each frailty score was added to each of these models and improvement of the predictive ability was assessed by evaluating whether the C statistic of the model with the score was significantly higher than in the respective base model. Results are expressed as the difference in C statistics (delta C with 95% confidence intervals) of each model, including a score and its respective base model.

Sensitivity analysis. We performed a sensitivity analysis by excluding all events that occurred during the first year of follow-up with the objective of assessing if pre-existing disease near the date of enrolling could bias the results. For all-cause mortality, all analyses were also performed stratified by sex and age (>70/_70 years).

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (S1 Text).

3.4. Results

Table 2 shows the baseline characteristics of the participants included in the analysis. From 9,432 participants in wave 2 of ELSA, 5,294 (44.9% men) fulfilled the inclusion criteria. Mean age was 71.2 (SD: 8.0) years. The prevalence of CVD and cancer at baseline were 13.7% and 9.3%, respectively. Data from 4,554 participants free of CVD and 4,792 participants free of cancer at baseline were analysed in the respective incidence analyses.

Table 2. Baseline summary characteristics of 5294 participants in ELSA wave 2 (2004-2005)

Mean (SD), age (years)	71.2 (8.0)
No (%) men	2377 (44.9%)
Mean (SD), BMI, (kg/m^2)[1]	27.8 (4.8)
No (%) by weight (underweight/ normal/ overweight/ obesity)[1,2]	148 (2.8%) / 1341 (25.3%) / 2276 (43.0%)/ 1529 (28.9%)
No (%) by smoking status (current/ former/ never)	650 (12.3%) / 2738 (51.7%) / 1906 (36.0%)
No (%) by physical activity (sedentary/ low/ moderate/ vigorous)[1,3]	388 (7.3%) / 1440 (27.2%) / 2624 (49.6%) / 842 (15.9%)
Mean (SD), blood glucose level (mmol/L)[1]	5.3 (1.5)
Mean (SD), blood glycated haemoglobin level (%)[1]	5.7 (0.8)
No (%) with diabetes[1,4]	688 (13.0%)
Mean (SD), systolic/diastolic blood pressure (mm Hg)[1]	137.4 (19.2) / 73.9 (11.2)
No (%) with hypertension[1,5]	2733 (51.6%)
Mean (SD), total cholesterol (mmol/L)[1]	5.8 (1.2)
Mean (SD), LDL cholesterol (mmol/L)[1]	3.5 (1.0)
Mean (SD), HDL cholesterol (mmol/L)[1]	1.5 (0.4)
Mean (SD), triglyceride (mmol/L)[1]	1.8 (1.1)
No (%) of dyslipidemia[1,6]	2171 (41.0%)
No (%) of cardiovascular disease[7]	726 (13.7%)
No (%) of cancer	490 (9.3%)
No (%) of anaemia[1,8]	390 (7.4%)
No (%) of lung disease	1000 (18.9%)
No (%) of arthritis	2276 (43%)
No (%) with depression symptoms[1,9]	1694 (32%)
No (%) by self-rated health (poor/fair/ good/very good/excellent)[1]	401(7.6%) / 1167(22.0%) / 1756 (33.2%) / 1384(26.1%) /586 (11.1%)
Mean (SD), cognitive index (pp)[1,10]	27.1 (6.6)

[1]Imputed data, When data were imputed, SD were calculated according to Rubin's rules.

[2]Underweight: BMI<20, Normal weight: BMI>=20 &<25, Overweight: BMI>=25 &<30, Obesity=BMI>30kg/m2.

[3]Self-reported frequency of at least once a week of: mild / moderate / vigorous activity.

[4]Diabetes defined as self-reported, or fasting glucose ≥7.0 mmol/l, or glycated haemoglobin >=6.5%.

[5]Hypertension defined as systolic >= 140 or diastolic blood pressure >= 90 mm Hg or taking antihypertensive medication.

[6]Dyslipidemia defined as total cholesterol>6.2 mmol or taking medication.

[7]Cardiovascular disease defined as self-reported: myocardial infarction, heart failure, stroke or congestive heart disease.

[8]Haemoglobin lower than 13 g/dl in men and 12 g/dl in women.

[9]Depression defined with >=4 out of 8-item version of the Center for Epidemiological Studies-Depression Scale.

[10]Sum of memory and executive indices, values go from 0 (worst) to 50 (best).

The median follow-up times (Interquartile range) for mortality, CVD, and cancer outcomes were 7.25 (7.00-7.42), 5.83 (5.33-6.08), and 5.83 (5.17-6.08) years, respectively. The numbers of events were 1,144 deaths,

373 incident CVD events, and 425 incident cancer events, translating into a crude mortality rate of 326/10,000 person-years and an incidence rate of 167/10,000 and 184/10,000 person-years for CVD and cancer incidence, respectively. Main causes of death were registered as cancer (32.5%), CVD (35.1%), respiratory (14.8%), and other (17.6%). For the majority of cases, the proportion hazard assumption was not proved. Therefore, all figures and tables show hazard ratios (HRs) at the median follow-up time (3.5 years for mortality and 2.5 years for CVD and cancer events).

3.4.1. All-cause mortality events

Fig 1A and Table 3 show all-cause mortality HRs for frailty scores calculated at median time follow-up (3.5 years) and analysed as continuous variables at different levels of adjustment. The strength of the association between frailty scores and mortality ranged from an HR of 2.4 (95% CI: 1.7-3.3) to 26.2 (95% CI: 15.4-44.5) for those with the highest possible frailty state (rescaled to 1) to the lowest possible frailty state (rescaled to 0), with adjustment for sex.

Adjustments in model 2 slightly attenuated associations for all scores, while retaining statistical significance in all cases. HRs for model 2 ranged from 2.3 (95% CI: 1.6-3.1) to 20.2 (95% CI: 11.8-34.5). Adjustments in model 3 attenuated associations for all scores, retaining statistical significance in 27 out of 35 cases. HRs for model 3 ranged from 0.9 (95% CI: 0.5-1.7) to 8.4 (95% CI: 4.9-14.4).Fig 1B and Table 3 illustrate the same analysis using categorical variables (frailty status).

In sex-adjusted models, HRs ranged from 1.2 (95% CI: 0.9-1.7) to 3.4 (95% CI: 1.4-8.0), with 30 out of 37 cases showing a statistically significant association. Adjustments in model 2 attenuated associations, while retaining statistical significance in 28 out of 37 cases. HRs for model 2 ranged from 1.2 (95% CI: 1.0-1.4) to 3.0 (95% CI: 1.5-6.2). Adjustments in model 3 attenuated associations for all scores, retaining statistical significance in 10 out of 37 cases. HRs for model3 ranged from 0.9 (95% CI: 0.3-2.4) to 2.4 (95% CI: 1.2-4.7). S2 and S3 Tables show HRs for total mortality assessed in yearly intervals, with continuous and categorical analysis, respectively.

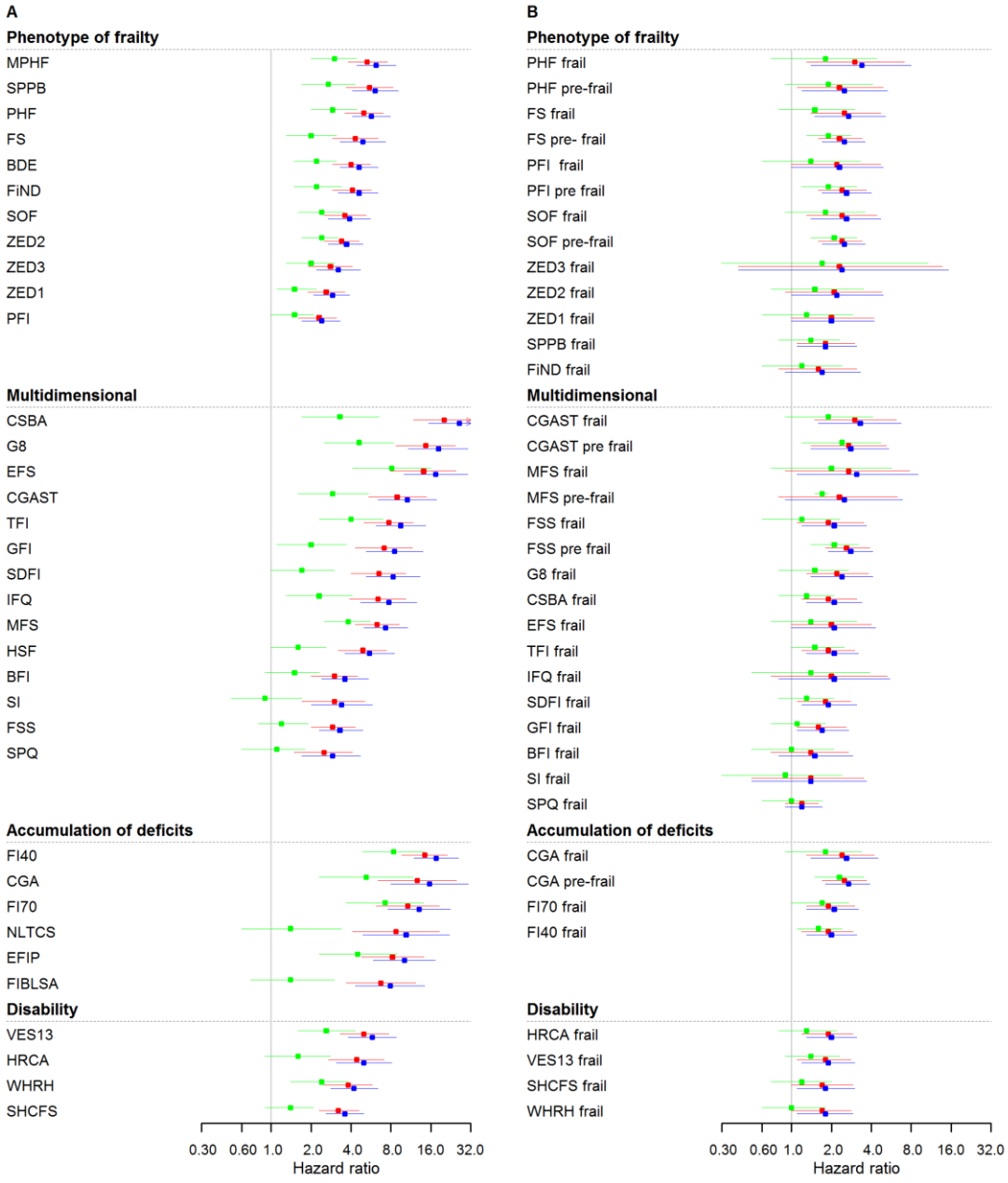

Figure 1. Mortality HRs of frailty scores (*n* = 5,294): Continuous and cutoff analysis. (A) Left panel: continuous analysis; (B) right panel: categorical analysis. Models were fitted using age as timescale, with time 0 = age at entry of study and time 1 = age at event or censoring date. Model 1 in blue: adjusted by sex. Model 2 in red: Model 1 + smoking status, alcohol, and alcohol consumption. Model 3 in green: Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anemia, COPD, arthritis, neuropsychiatric problems, depression, cognition, and self-rated health and quality of life. HRs were at 3.5 years (median follow-up for mortality). BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; COPD, chronic obstructive pulmonary disease; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index (SHARE); FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FiND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HR, hazard ratio; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB,

Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC and self-reported health; ZED1, ZutPhen Elderly Study (Physical Activity

Table 3 Mortality hazard ratios of frailty scores (n=5294) calculated at median time follow-up (3.5 years)

	Continuous analysis					Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]	Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]
Phenotype of frailty approach									
MPHF	5.4 (3.9; 7.6)	6.2 (4.4; 8.7)	5.3 (3.8; 7.5)	3.0 (2.0; 4.4)	PHF frail	3.0 (1.3; 7.2)	3.4 (1.4; 8.0)	3.0 (1.3; 7.1)	1.8 (0.7; 4.4)
SPPB	5.0 (3.3; 7.4)	6.1 (4.1; 9.1)	5.5 (3.7; 8.3)	2.7 (1.7; 4.3)	PHF pre-frail	2.3 (1.1; 5.0)	2.5 (1.2; 5.3)	2.3 (1.1; 4.9)	1.9 (0.9; 4.1)
PHF	5.1 (3.6; 7.1)	5.7 (4.1; 7.9)	5.0 (3.6; 7.0)	2.9 (2.0; 4.4)	FS frail	2.5 (1.4; 4.7)	2.7 (1.5; 5.1)	2.5 (1.4; 4.7)	1.5 (0.8; 3.0)
FS	4.2 (2.8; 6.2)	4.9 (3.3; 7.3)	4.3 (2.9; 6.4)	2.0 (1.3; 3.1)	FS pre- frail	2.3 (1.6; 3.4)	2.5 (1.7; 3.6)	2.3 (1.6; 3.4)	1.9 (1.3; 2.8)
BDE	1.9 (1.4; 2.7)	4.6 (3.3; 6.4)	4.0 (2.9; 5.6)	2.2 (1.5; 3.1)	PFI frail	2.0 (0.9; 4.5)	2.3 (1.0; 4.9)	2.2 (1.0; 4.7)	1.4 (0.6; 3.3)
FiND	3.9 (2.8; 5.5)	4.6 (3.2; 6.4)	4.1 (2.9; 5.7)	2.2 (1.5; 3.4)	PFI pre frail	2.4 (1.6; 3.7)	2.6 (1.7; 4.0)	2.4 (1.6; 3.7)	1.9 (1.2; 3.1)
SOF	3.5 (2.4; 5.0)	3.9 (2.7; 5.6)	3.6 (2.5; 5.2)	2.4 (1.6; 3.6)	SOF frail	2.4 (1.3; 4.3)	2.6 (1.4; 4.7)	2.4 (1.3; 4.4)	1.8 (0.9; 3.6)
ZED2	3.3 (2.5; 4.5)	3.7 (2.7; 4.9)	3.4 (2.5; 4.6)	2.4 (1.7; 3.2)	SOF pre-frail	2.3 (1.6; 3.4)	2.5 (1.7; 3.6)	2.4 (1.6; 3.4)	2.1 (1.4; 3.1)
ZED3	2.6 (1.8; 3.9)	3.2 (2.2; 4.7)	2.8 (1.9; 4.1)	2.0 (1.3; 3.0)	ZED3 frail	2.3 (0.3; 14.8)	2.4 (0.4; 15.2)	2.3 (0.4; 13.7)	1.7 (0.3; 10.7)
ZED1	2.5 (1.9; 3.4)	2.9 (2.1; 3.9)	2.6 (1.9; 3.6)	1.5 (1.1; 2.2)	ZED2 frail	2.1 (0.9; 4.6)	2.2 (1.0; 4.9)	2.1 (0.9; 4.8)	1.5 (0.7; 3.5)
PFI	2.2 (1.6; 3.0)	2.4 (1.7; 3.3)	2.3 (1.6; 3.1)	1.5 (1.0; 2.1)	ZED1 frail	1.9 (0.9; 3.9)	2.0 (1.0; 4.2)	2.0 (1.0; 4.2)	1.3 (0.6; 2.9)
					SPPB frail	1.8 (1.1; 3.0)	1.8 (1.1; 3.1)	1.8 (1.1; 3.0)	1.4 (0.8; 2.3)
					FiND frail	1.6 (0.8; 3.1)	1.7 (0.9; 3.3)	1.6 (0.8; 3.1)	1.2 (0.6; 2.4)
Multidimensional approach									
CSBA	33.4 (20.0; 55.8)	26.2 (15.4; 44.5)	20.2 (11.8; 34.5)	3.3 (1.7; 6.5)	CGAST frail	3.0 (1.5; 6.2)	3.3 (1.6; 6.7)	3.0 (1.5; 6.2)	1.9 (0.9; 4.1)
G8	13.5 (8.1; 22.6)	18.2 (10.8; 30.4)	14.6 (8.7; 24.6)	4.6 (2.5; 8.4)	CGAST pre frail	2.7 (1.4; 5.2)	2.8 (1.4; 5.4)	2.7 (1.4; 5.2)	2.4 (1.2; 4.7)
EFS	13.5 (7.7; 23.5)	17.4 (10.0; 30.3)	14.1 (8.0; 24.8)	8.1 (4.1; 16.0)	MFS frail	1.6 (0.6; 4.7)	3.1 (1.1; 9.0)	2.7 (0.9; 7.8)	2.0 (0.7; 5.7)
CGAST	8.3 (5.0; 13.8)	10.6 (6.4; 17.6)	8.9 (5.4; 14.9)	2.9 (1.6; 5.4)	MFS pre-frail	1.4 (0.5; 3.8)	2.5 (0.9; 6.9)	2.3 (0.8; 6.3)	1.7 (1.5; 1.9)
TFI	6.7 (4.4; 10.2)	9.5 (6.2; 14.6)	7.7 (5.0; 11.8)	4.0 (2.3; 7.0)	FSS frail	2.0 (1.1; 3.5)	2.1 (1.2; 3.7)	1.9 (1.1; 3.5)	1.2 (0.6; 2.3)
GFI	6.7 (4.1; 10.9)	8.5 (5.2; 13.9)	7.1 (4.3; 11.6)	2.0 (1.1; 3.7)	FSS pre frail	2.7 (1.8; 4.0)	2.8 (1.9; 4.1)	2.6 (1.8; 3.9)	2.1 (1.4; 3.2)
SDFI	4.7 (3.0; 7.4)	8.3 (5.2; 13.2)	6.5 (4.0; 10.4)	1.7 (1.0; 3.0)	G8 frail	2.3 (1.3; 3.8)	2.4 (1.4; 4.1)	2.2 (1.3; 3.8)	1.5 (0.8; 2.7)
IFQ	5.8 (3.6; 9.4)	7.7 (4.7; 12.5)	6.4 (3.9; 10.4)	2.3 (1.3; 4.1)	CSBA frail	2.3 (1.5; 3.7)	2.1 (1.3; 3.4)	1.9 (1.2; 3.1)	1.3 (0.8; 2.1)
MFS	6.5 (4.5; 9.5)	7.3 (5.0; 10.7)	6.3 (4.3; 9.2)	3.8 (2.5; 5.6)	EFS frail	1.9 (0.9; 4.0)	2.1 (1.0; 4.3)	2.0 (1.0; 4.0)	1.4 (0.7; 3.1)
HSF	5.1 (3.3; 7.8)	5.5 (3.6; 8.5)	4.9 (3.2; 7.4)	1.6 (1.0; 2.6)	TFI frail	1.9 (1.2; 3.0)	2.1 (1.3; 3.2)	1.9 (1.2; 3.0)	1.5 (1.0; 2.5)
BFI	2.6 (1.7; 3.9)	3.6 (2.4; 5.4)	3.0 (2.0; 4.5)	1.5 (0.9; 2.3)	IFQ frail	1.9 (0.7; 5.1)	2.1 (0.8; 5.5)	2.0 (0.7; 5.3)	1.4 (0.5; 3.9)
SI	2.6 (1.5; 4.5)	3.4 (2.0; 5.8)	3.0 (1.7; 5.1)	0.9 (0.5; 1.7)	SDFI frail	1.7 (1.1; 2.7)	1.9 (1.2; 3.1)	1.8 (1.1; 2.8)	1.3 (0.8; 2.1)
FSS	3.0 (2.1; 4.3)	3.3 (2.3; 4.9)	2.9 (2.0; 4.3)	1.2 (0.8; 1.9)	GFI frail	1.6 (1.0; 2.5)	1.7 (1.1; 2.7)	1.6 (1.1; 2.6)	1.1 (0.7; 1.8)
SPQ	2.2 (1.4; 3.7)	2.9 (1.7; 4.7)	2.5 (1.5; 4.1)	1.1 (0.6; 1.8)	BFI frail	1.3; 0.7; 2.6)	1.5 (0.8; 2.9)	1.4 (0.7; 2.7)	1 (0.5; 2.1)
					SI frail	1.3 (0.5; 3.4)	1.4 (0.5; 3.7)	1.4 (0.5; 3.5)	0.9 (0.3; 2.4)
					SPQ frail	1.2 (0.8; 2.0)	1.2 (0.9; 1.7)	1.2 (1.0; 1.4)	1.0 (0.6; 1.7)
Accumulation of deficits approach									
FI40	10.6 (6.1; 18.3)	17.5 (11.9; 25.8)	14.4 (9.6; 21.4)	8.4 (4.9; 14.4)	CGA frail	2.2 (1.3; 3.9)	2.6 (1.4; 4.5)	2.4 (1.3; 4.2)	1.8 (0.9; 3.4)
CGA	9.7 (5.0; 19.0)	15.6 (8.0; 30.5)	12.6 (6.4; 24.9)	5.2 (2.3; 11.7)	CGA pre-frail	2.4 (1.6; 3.6)	2.7 (1.8; 3.9)	2.5 (1.7; 3.7)	2.3 (1.5; 3.5)
FI70	8.7 (5.1; 14.8)	13.0 (7.6; 22.4)	10.7 (6.2; 18.5)	7.2 (3.7; 14.2)	FI70 frail	1.9 (1.2; 2.9)	2.1 (1.3; 3.2)	1.9 (1.3; 3.0)	1.7 (1.0; 2.7)
NLTCS	9.0 (4.2; 19.0)	10.4 (4.9; 22.1)	8.7 (4.1; 18.6)	1.4 (0.6; 3.4)	FI40 frail	1.8 (1.2; 2.8)	2.0 (1.3; 3.1)	1.9 (1.2; 2.9)	1.6 (1.1; 2.4)
EFIP	7.7 (4.5; 13.2)	10.1 (5.9; 17.3)	8.2 (4.8; 14.2)	4.5 (2.3; 8.9)					
FIBLSA	6.2 (3.4; 11.4)	7.9 (4.3; 14.4)	6.7 (3.7; 12.3)	1.4 (0.7; 3.0)					
Disability approach									
VES13	4.6 (3.0; 7.0)	5.8 (3.8; 8.8)	5.0 (3.3; 7.7)	2.6 (1.6; 4.3)	HRCA frail	1.7 (1.1; 2.7)	2.0 (1.3; 3.1)	1.9 (1.2; 2.9)	1.3 (0.8; 2.2)
HRCA	3.9 (2.4; 6.4)	5.0 (3.1; 8.1)	4.4 (2.7; 7.1)	1.6 (0.9; 2.8)	VES13 frail	1.7 (1.1; 2.7)	1.9 (1.2; 3.0)	1.8 (1.1; 2.8)	1.4 (0.9; 2.3)
WHRH	3.5 (2.3; 5.4)	4.2 (2.8; 6.4)	3.8 (2.5; 5.8)	2.4 (1.4; 3.8)	SHCFS frail	1.7 (1.0; 2.8)	1.8 (1.1; 3.0)	1.7 (1.0; 2.9)	1.2 (0.7; 2.0)
SHCFS	3.2 (2.3; 4.5)	3.6 (2.6; 5.0)	3.2 (2.3; 4.6)	1.4 (0.9; 2.1)	WHRH frail	1.7 (1.0; 2.7)	1.8 (1.1; 2.9)	1.7 (1.0; 2.8)	1.0 (0.6; 1.8)

[1]Model 0= Crude models. [2]Model 1= HR adjusted by sex. [3]Model 2= Model 1 + smoking status and alcohol consumption. 4Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. Models were fitted using age as time scale, with time 0 = age at entry of study and time 1 =age at event or censoring date.

Abbreviations frailty scores: BDE= Beaver Dam Eye Study Index. BFI= Brief Frailty Index. CGA= Comprehensive Geriatric Assessment. CGAST= Comprehensive Geriatric Assessment Screening Tests. CSBA= Conselice Study of Brain Aging Score. EFIP= Evaluative Frailty Index for Physical Activity. EFS= Edmonton Frail Scale. FI40= 40-item Frailty Index. FI70= 70-item Frailty Index (SHARE). FIBLSA= Frailty Index Beijing Longitudinal Study of Ageing. FiND= Frail Non-Disabled Questionnaire. FS= Frail Scale. FSS= Frailty Staging System. G8= G-8 Geriatric Screening Tool. GFI= Groningen Frailty Indicator. HRCA= Hebrew Rehabilitation Center for Aged Vulnerability Index. HSF= Health Status Form. IFQ= Inter-Frail Questionnaire. MFS= Modified Frailty Score. MPHF= Modified Phenotype of Frailty. NLTCS= Long Term Care Survey Frailty Index. PFI= Physical Frailty Index. PHF= Phenotype of Frailty. SDFI=, Static/Dynamic Frailty Index. SHCFS= Canadian Study of Health and Aging Clinical Frailty Scale·. SI= Screening Instrument. SOF= Study of Osteoporotic Fractures. SPPB= Short Physical Performance Battery. SPQ= Sherbrooke Postal Questionnaire. TFI= Tilburg Frailty Indicator. VES13= Vulnerable Elders Survey. WHRH= WHOAFC & self-reported health. ZED1= ZutPhen Elderly Study (Physical Activity & Low Energy). ZED2= ZutPhen Elderly Study (Physical Activity & Weight Loss). ZED3= ZutPhen Elderly Study (Physical Activity & Low BMI).

3.4.2. Cardiovascular events

Fig 2A and S4 Table show HRs for incident CVD for frailty scores analysed as continuous variables. Twenty-three out of thirty-five scores showed a statistically significant association in sex-adjusted models (model 1), ranging from 1.2 (95% CI: 0.5-3.2) to 16.5 (95% CI: 7.8-35.0). Adjustments in model 2 attenuated associations for all scores, retaining statistical significance in 18 out of 35 cases. Further adjustment with model 3 further attenuated associations for all scores, retaining statistical significance in 5 out of 35 cases. The strongest and more stable associations after adjustment with CVD events were seen for scores from the “accumulation of deficits approach” group.

Fig 2B and S4 Table show the analysis performed for incident CVD based on the categorical frailty definitions. Only 6 out of 37 HRs were statistically significant and ranged from 0.6 (95% CI: 0.4-1.0) to 2.7 (1.2-6.3) in sex-adjusted models. The effect of adjustment was a slight attenuation of the associations. S5 and S6 Tables show HR for cardiovascular events assessed in yearly intervals with continuous and categorical analysis, respectively.

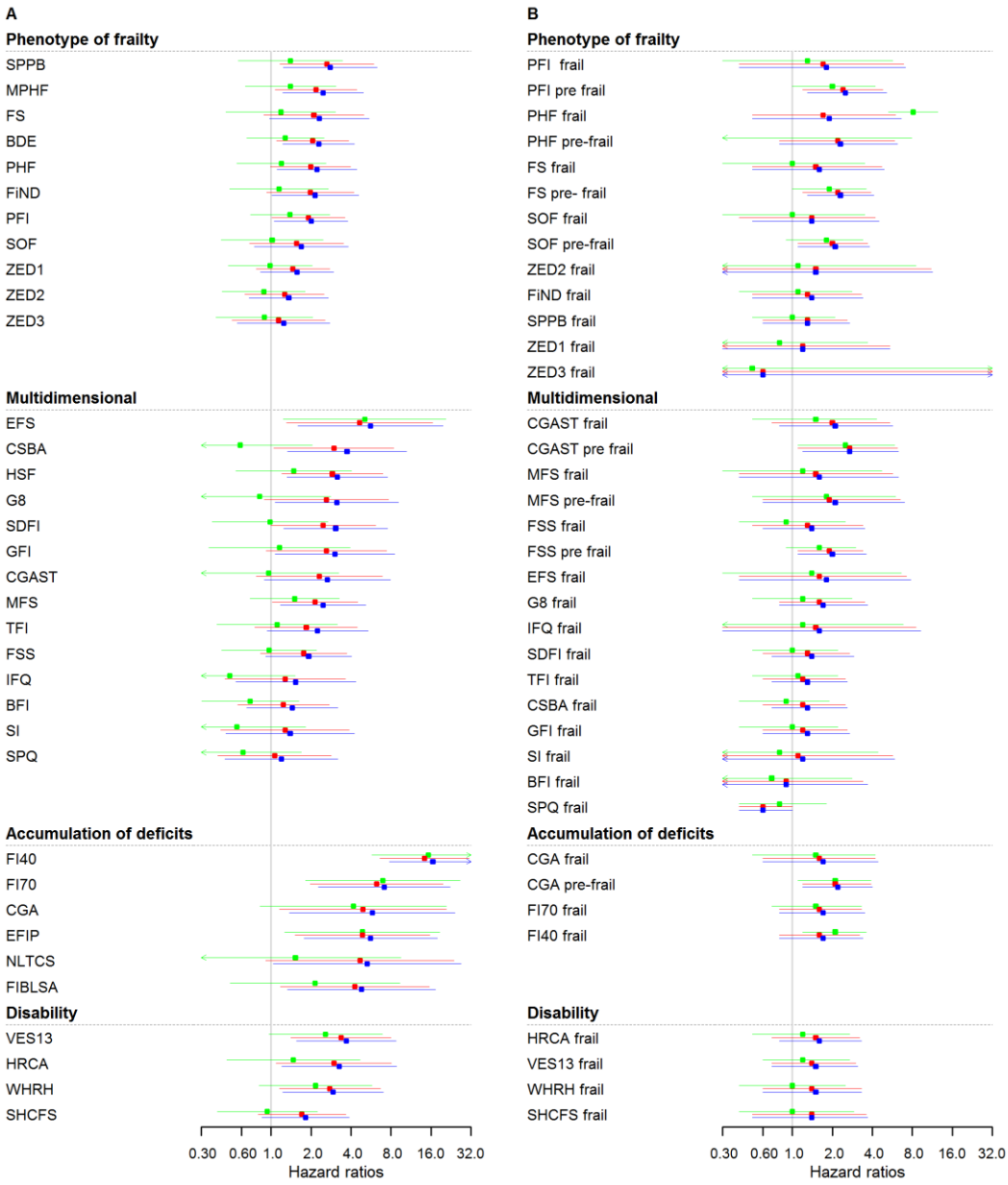

Fig 2. Cardiovascular HRs of frailty scores (n = 4,554): Continuous and cut-off analysis. (A) Left panel: continuous analysis; (B) right panel: categorical analysis. Models were fitted using age as timescale, with time 0 = age at entry of study and time 1 = age at event or censoring date. Model 1 in blue: adjusted by sex. Model 2 in red: Model 1 + smoking status, alcohol, and alcohol consumption. Model 3 in green: Model 2 + physical activity, BMI, diabetes, hypertension cancer, anaemia, COPD, arthritis, neuropsychiatric problems, depression, cognition, and self-rated health and quality of life. HRs were at 2.5 years (median follow-up for CVD events).

BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; COPD, chronic obstructive pulmonary disease; CSBA, Conselice Study of Brain Aging Score; CVD, cardiovascular disease; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index (SHARE); FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FiND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HR, hazard ratio; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index, PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC and self-reported health; ZED1, ZutPhen Elderly Study (Physical Activity and Low Energy); ZED2, ZutPhen Elderly Study (Physical Activity and Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity and Low BMI).

3.4.3. Cancer events

Fig 3 and S7 Table show HRs for incident cancer. Analyses based on continuous scores (Fig 3A) yielded HRs for cancer ranging between 0.7 (95% CI: 0.4-1.2) and 2.4 (95% CI: 1.0-5.7), while most associations (31 out of 35) did not reach statistical significance in sex-adjusted models. Further adjustment (models 2 and 3) attenuated associations for all scores, not retaining any statistical significance. Fig 3B and S7 Table show the results based on categorical frailty classifications, for which most associations did not reach statistical significance; also, with further adjustment (models 2 and 3), no score retained any statistical significance. S8 and S9 Tables show HRs for cancer events assessed in yearly intervals, with continuous and categorical analysis, respectively.

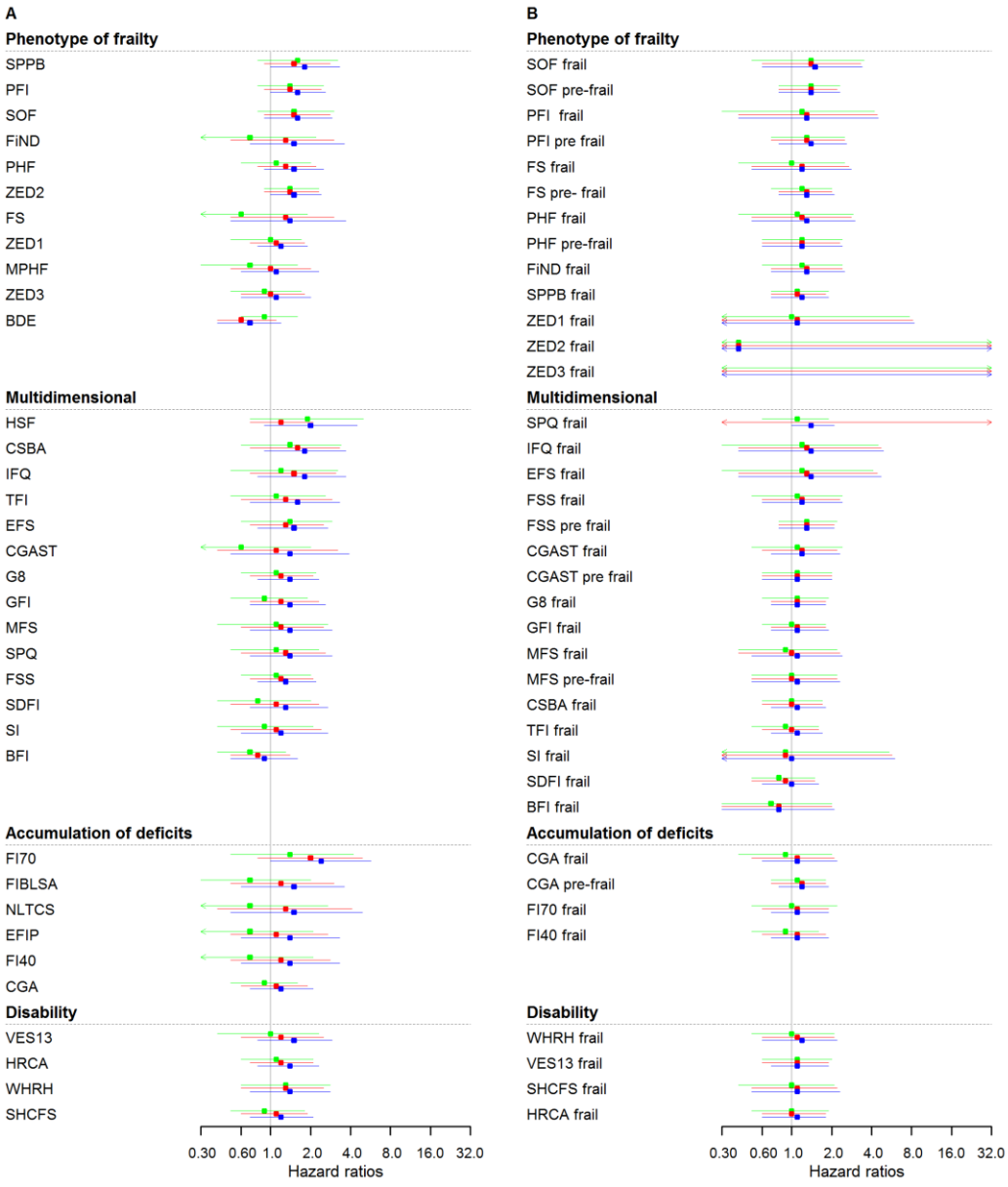

Fig 3. Cancer HRs of frailty scores (*n* = 4,792): Continuous and cut-off analysis. (A) Left panel: continuous analysis; (B) right panel: categorical analysis. Models were fitted using age as timescale, with time 0 = age at entry of study and time 1 = age at event or censoring date. Model 1 in blue: adjusted by sex. Model 2 in red: Model 1 + smoking status, alcohol, and alcohol consumption. Model 3 in green: Model 2 + physical activity, BMI, diabetes, hypertension, CVD, anaemia, COPD, arthritis, neuropsychiatric problems, depression, cognition, and self-rated health and quality of life. HRs were at 2.5 years (median follow-up for cancer events). BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; COPD, chronic obstructive pulmonary disease; CSBA, Conselice Study of Brain Aging Score; CVD, cardiovascular disease; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index (SHARE); FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; FiND, Frail Non-Disabled Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 Geriatric Screening Tool; GFI, Groningen Frailty Indicator; HR, hazard ratio; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; IFQ, Inter-Frail Questionnaire; MFS, Modified Frailty Score; MPHF, Modified Phenotype of Frailty; NLTCS, Long Term Care Survey Frailty Index; PFI, Physical Frailty Index; PHF, Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHRH, WHOAFC and self-reported health; ZED1, ZutPhen Elderly Study (Physical Activity and Low Energy); ZED2, ZutPhen Elderly Study (Physical Activity and Weight Loss); ZED3, ZutPhen Elderly Study (Physical Activity and Low BMI).

3.4.4. Evaluation of discriminative ability

Table 4 shows the discriminative ability of frailty scores for all-cause mortality using Harrell's C statistic. The improvement in prediction for each frailty score analysed as a continuous variable on top of a basic model consisting of age and sex ranged from 0.6% (95% CI: 0.2-0.9) to 3.1% (95% CI: 2.3-3.9) and was statistically significant for all scores. With model 2, improvement was significant in all cases and ranged from 0.4% (95% CI: 0.1-0.7) to 2.5% (95% CI: 1.7-3.2). With further adjusted model 3, improvement was significant in 33 out of 35 cases and ranged from 0.0 (95% CI: −0.4-0.3) to 0.9 (95% CI: 0.5-1.3).

Analyses adding frailty categories to the age and sex basic model gave improvements ranging from 0.1% (95% CI: 0.0-0.2) to 2.1% (95% CI: 1.5-2.6), with all scores showing statistically significant improvement. In most cases, when the predictive value of the different scores was assessed over and above basic models 2, the improvement was attenuated; in most cases, it was also statistically significant.

The C statistic of the basic model for CVD events based only on age and sex was 70.1 (95% CI: 65.7-74.4). None of the continuous scores added predictive performance to this model at a statistically significant level. In analyses of frailty categories, only the G-8 Geriatric Screening Tool (G8) score added statistically significant predictive value (delta C: 1.6 [95% CI: 0.4-2.8]) (S10 Table).
For cancer events, the C statistic of all three basic models was below 60, and all deltas were nonsignificant both in continuous and categorical analyses (S11 Table).

Table 4. Discriminative assessment of mortality models using Harrell's C statistic (n=5294)

	Continuous analysis			Cut-off analysis	
Frailty Score	**Delta (*100) LCI; UCI with 95%CI[1]**	**Delta (*100) LCI; UCI with 95%CI[1]**	**Frailty Score**	**Delta (*100) LCI; UCI with 95%CI[1]**	**Delta (*100) LCI; UCI with 95%CI[1]**
	Model 1	**Model 2**		**Model 1**	**Model 2**
Basic models	**74.3 (72.6; 76.0)[2]**	**75.3 (73.8; 76.9)[2]**	**Basic models**	**74.3 (72.6; 76.0)[2]**	**75.3 (73.8; 76.9)[2]**
			Phenotype of frailty approach		
PHF	2.8 (2.0; 3.7)	2.3 (1.6; 2.9)	PHF frail	1.6 (1.1; 2.2)	1.4 (0.9; 1.9)
MPHF	2.8 (2.0; 3.5)	2.2 (1.6; 2.8)	SOF frail	0.6 (0.3; 1.0)	1.0 (0.6; 1.4)
FiND	2.4 (1.7; 3.1)	1.8 (1.2; 2.4)	FS frail	1.1 (0.6; 1.6)	0.8 (0.4; 1.2)
ZED2	2.3 (1.7; 2.9)	1.9 (1.3; 2.4)	ZED1 frail	0.3 (0.1; 0.6)	0.6 (0.2; 1.0)
FS	2.1 (1.4; 2.7)	1.5 (1.0; 2.1)	PFI pre frail	1.0 (0.5; 1.4)	0.5 (0.2; 0.9)
BDE	2.0 (1.4; 2.6)	1.6 (1.0; 2.1)	SPPB frail	0.7 (0.4; 1.1)	0.5 (0.2; 0.9)
SOF	2.0 (1.3; 2.7)	1.6 (1.1; 2.1)	PHF pre-frail	0.4 (0.2; 0.6)	0.6 (0.2; 1.0)
SPPB	2.0 (1.2; 2.8)	1.6 (1.0; 2.2)	ZED2 frail	0.7 (0.3; 1.2)	0.5 (0.2; 0.8)
ZED1	1.6 (1.0; 2.2)	1.3 (0.8; 1.7)	PFI frail	0.7 (0.3; 1.2)	0.4 (0.1; 0.6)
PFI	1.5 (0.9; 2.0)	1.1 (0.6; 1.6)	FiND frail	0.5 (0.2; 0.9)	0.3 (0.0; 0.5)
ZED3	1.3 (0.8; 1.8)	1.0 (0.5; 1.4)	SOF pre-frail	0.4 (0.1; 0.7)	0.2 (0.0; 0.4)
			FS pre- frail	0.3 (0.1; 0.6)	0.2 (0.0; 0.4)
			ZED3 frail	0.2 (0.0; 0.5)	0.2 (0.0; 0.4)
			Multidimensional approach		
EFS	3.1 (2.3; 3.9)	2.5 (1.7; 3.2)	TFI frail	1.9 (1.3; 2.6)	1.4 (0.9; 2.0)
G8	2.9 (2.0; 3.8)	2.3 (1.6; 2.9)	CGAST frail	1.9 (1.1; 2.6)	1.5 (0.9; 2.0)
CGAST	2.7 (1.8; 3.6)	2.1 (1.5; 2.7)	G8 frail	0.6 (0.2; 1.0)	1.2 (0.6; 1.7)
CSBA	2.5 (1.7; 3.4)	2.0 (1.3; 2.7)	CSBA frail	1.6 (1.0; 2.3)	1.1 (0.6; 1.6)
TFI	2.4 (1.6; 3.1)	1.8 (1.1; 2.4)	SDFI frail	1.6 (1.0; 2.2)	0.9 (0.4; 1.3)
MFS	2.3 (1.6; 3.0)	1.8 (1.2; 2.5)	MFS frail	1.4 (0.8; 1.9)	1.0 (0.5; 1.6)
HSF	2.1 (1.5; 2.7)	1.7 (1.1; 2.3)	GFI frail	1.3 (0.7; 1.9)	0.9 (0.5; 1.3)
GFI	2.1 (1.4; 2.7)	1.6 (1.0; 2.1)	MFS pre-frail	0.8 (0.4; 1.2)	0.7 (0.3; 1.0)
SDFI	2.0 (1.3; 2.6)	1.4 (0.9; 1.9)	EFS frail	1.3 (0.7; 1.8)	0.6 (0.3; 1.0)
IFQ	1.8 (1.2; 2.5)	1.4 (0.8; 1.9)	CGAST pre frail	0.8 (0.3; 1.3)	0.5 (0.1; 0.8)
FSS	1.3 (0.7; 1.9)	1.0 (0.6; 1.5)	SPQ frail	0.4 (0.1; 0.8)	0.3 (0.0; 0.5)
BFI	1.2 (0.6; 1.7)	0.8 (0.5; 1.2)	FSS frail	0.4 (0.1; 0.7)	0.3 (0.1; 0.6)
SI	0.9 (0.5; 1.4)	0.7 (0.3; 1.1)	FSS pre frail	0.4 (0.1; 0.7)	0.2 (0.0; 0.5)
SPQ	0.6 (0.2; 0.9)	0.4 (0.1; 0.7)	BFI frail	0.3 (0.1; 0.6)	0.2 (0.0; 0.4)
			IFQ frail	0.3 (0.0; 0.5)	0.2 (0.0; 0.4)
			SI frail	0.1 (0.0; 0.3)	0.1 (0.0; 0.3)
			Accumulation of deficits approach		
FI40	2.6 (1.8; 3.5)	2.1 (1.4; 2.7)	FI70 frail	2.1 (1.5; 2.6)	1.6 (1.0; 2.1)
FI70	2.5 (1.8; 3.1)	1.9 (1.4; 2.4)	FI40 frail	1.9 (1.3; 2.4)	1.4 (0.8; 2.0)
EFIP	2.0 (1.4; 2.6)	1.5 (1.0; 2.1)	CGA frail	1.2 (0.7; 1.6)	0.9 (0.4; 1.3)
CGA	1.9 (1.3; 2.6)	1.5 (0.9; 2.1)	CGA pre-frail	0.1 (0.0; 0.2)	0.0 (-0.1; 0.1)
FIBLSA	1.6 (1.0; 2.2)	1.2 (0.7; 1.7)			

NLTCS	1.4 (0.9; 2.0)	1.2 (0.7; 1.6)			
			Disability approach		
VES13	2.2 (1.5; 2.9)	1.7 (1.2; 2.3)	HRCA frail	1.7 (1.1; 2.3)	1.3 (0.8; 1.8)
WHRH	1.8 (1.2; 2.3)	1.4 (0.9; 1.9)	VES13 frail	1.5 (0.8; 2.1)	1.1 (0.6; 1.6)
SHCFS	1.8 (1.2; 2.3)	1.4 (0.9; 2.0)	SHCFS frail	1.1 (0.6; 1.6)	0.9 (0.5; 1.3)
HRCA	1.6 (1.2; 2.1)	1.2 (0.8; 1.7)	WHRH frail	1.1 (0.5; 1.7)	0.9 (0.4; 1.3)

Model 1 = age and sex. Model 2 = model 1 + smoking status and maximum alcohol consumption. [1]Delta = percent of improvement adding the frailty score to model. [2]Harrel's C statistic of each model (lower confidence interval; upper confidence interval). BDE= Beaver Dam Eye Study Index; BFI= Brief Frailty Index; CGA= Comprehensive Geriatric Assessment; CGAST= Comprehensive Geriatric Assessment Screening Tests; CSBA= Conselice Study of Brain Aging Score; EFIP= Evaluative Frailty Index for Physical Activity; EFS= Edmonton Frail Scale; FI40= Frailty Index 40 items; FI70= Frailty Index 70 items; FIBLSA= Frailty Index Beijing Longitudinal Study of Ageing; FIND= Frail Non-Disabled Questionnaire; FS= Frail Scale; FSS= Frailty Staging System; G8= G-8 Geriatric Screening Tool; GFI= Groningen Frailty Indicator; HRCA= Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF= Health Status Form; IFQ= Inter-Frail Questionnaire; MFS= Modified Frailty Score; MPHF= Modified Phenotype of Frailty; NLTCS= Long Term Care Survey Frailty Index; PFI= Physical Frailty Index; PHF= Phenotype of Frailty; SDF=, Static/Dynamic Frailty Index; SHCFS= Canadian Study of Health and Aging Clinical Frailty Scale.; SI= Screening Instrument; SOF= Study of Osteoporotic Fractures; SPPB= Short Physical Performance Battery; SPQ= Sherbrooke Postal Questionnaire; TFI= Tilburg Frailty Indicator; VES13= Vulnerable Elders Survey; WHRH= WHOAFC & self-reported health; ZED1= ZutPhen Elderly Study (Physical Activity & Low Energy); ZED2= ZutPhen Elderly Study (Physical Activity & Weight Loss); ZED3= ZutPhen Elderly Study (Physical Activity & Low BMI).

3.4.5. Sensitivity analysis

In sensitivity analyses excluding all events occurring the first year, we observed very similar results compared to those obtained with the total sample, although the strength of the associations was slightly diminished (S12 Table). In sex-stratified analyses for all-cause mortality, men had slightly higher HRs than women. The strongest associations in both sexes were obtained with the “multidimensional approach” (S13 and S14 Tables). In age-stratified analyses (>70/_70 years), HRs for all-cause mortality were much higher in younger participants. However, the pattern of results was similar, with scores from the “multidimensional approach” showing the strongest associations with all-cause mortality in both age strata (S15 and S16 Tables).

3.5. Discussion

Our direct comparison of the association between 35 published frailty scores and three major health outcomes in later life demonstrates that there is great variability in the strength of the prospective association with CVD, cancer, and total mortality. Moreover, the strength of the association also differed between each of the three outcomes. While most scores added predictive ability to both simple and more complex underlying models for total mortality, this was not the case for CVD or cancer.

Our finding of large heterogeneity in the magnitude of the association between different frailty scores and all-cause mortality may be due to the number and selection of variables that make up each score, along with the weight attached to each component variable in the score calculation. This is expected because these scores measure different dimensions of health, are underpinned by significantly different conceptualizations of frailty, and have different objectives of application. Therefore, the choice of a frailty score should also take into account these other aspects such as the target population (patients or general population) and the final objective of frailty assessment (clinical evaluation, research, or public health recommendations).

Interestingly, we observed that for many frailty scores, the proportional hazard assumption was not proved and the association was significantly non-uniform during follow-up time. In most of these cases, HRs for all-cause mortality were lowest directly after baseline and increased subsequently, but in some cases (40-item Frailty Index [FI40]), the opposite pattern was seen, with HRs that decreased over time. While the former set may capture information regarding underlying determinants of longer-term poor health and thus be more interesting in prognostic settings, the latter set can be hypothesized to collect information about existing health problems.

To avoid over-adjustment, the most adjusted models were fitted excluding variables that were underlying variables of frailty scores. We specifically chose these models to investigate whether the score retained an association over and above a comprehensive set of clinical indicators.

Our observation of heterogeneity, not only in the strength of associations but also in the degree of attenuation upon the same sets of adjustments, confirms our earlier observation that different frailty scores cannot be assumed to be interchangeable.

Our finding of a difference between analyses based on continuous scores and categorical classifications of frailty and pre-frailty indicates that the analysis with cutoffs may lead to a loss of information. This observation reflects the well-known loss of information caused by categorization of continuous variables, which assumes that the risk level is uniformly low for all below the given threshold and high for all above the threshold. Although the wish to provide users with a score with clear categories is understandable from a clinical point of view, it should be considered with caution due to the disadvantages. We have previously shown that many individuals are categorised differently by different scores[114]. Moreover, cut-off levels derived from one population may not be applicable in another.

A recent meta-analysis of 24 prospective studies, including 25 different scores, assessed the performance of frailty scores on mortality prediction and found a pooled relative risk (RR) of 1.83 (95% 1.68-1.98) for all-cause mortality based on binary/categorical frailty classifications in elderly populations (≥65 years)[13]. The result of the meta-analysis is similar to our results in the older subgroup and in our analyses based on categorical classifications. The authors found high heterogeneity OR (I^2 statistics heterogeneity index = 95%, $p < 0.001$) and HR/RR (I^2 statistics heterogeneity index = 98%, $p < 0.001$). They attribute this to the different populations, monitoring periods, and concepts of frailty that were included in the meta-analysis. Our study is likely to have less heterogeneous results because it is an analysis in a single data set.

We also found an association between different frailty scores and incident CVD. This was not directly expected, as frailty scores have not been designed for CVD events prediction. Our finding may be explained by the fact that component variables included in the frailty scores are also CVD events. Also, some variables are CVD symptoms and risk factors that could capture pre-existing presentations of CVD. Another explanation is that physicians are possibly less likely to treat CVD risk factors as aggressively in frail patients. In addition, frailty and CVD may share etiological pathways such as chronic low-grade inflammation[129].
There are few prospective studies of the association between frailty scores and incident CVD. Our results expand upon the evidence summarised in a review by Chen[130], which showed a significant cross-sectional association between a binary frailty classification and prevalent CVD in several previous studies[90 117 131]. White et al. reported a statistically significant association (HR: 1.8 [95% CI: 1.4-2.3]) during 30 months of follow-up in a study analysing the Phenotype of Frailty (PHF) score only[132]. Finally, Afilalo et al. demonstrated that to add frailty and disability improves the discrimination of prediction models of mortality in cardiovascular patients[133].

Frailty scores were not associated with incident cancer. As with CVD, frailty scores were not designed for the prediction of cancer. A further possible explanation is that the triggering of a cancer is a process too slow or too heterogeneous to be captured by frailty scores. We found that almost all frailty scores improved the predictive ability of a simple age- and sex-adjusted base model for all-cause mortality. The scores that showed statistically significant added predictive value over and above the most complete base model collect information about weight loss and assess physical functioning, important prognostic determinants, and they are based on relatively few variables, which makes them easily applicable in clinical settings.

However, the magnitude of the added predictive value was modest (up to 3%) and might not be clinically relevant. This could be explained in part because the basic model (age-sex) already had a good predictive ability. Our results showed that frailty scores add predictive ability to chronological age and sex only when the outcome is mortality and are not for the prediction of incident CVD or cancer events. Ensrud et al. compared the mortality predictive ability of 2 scores, the Study of Osteoporotic Fractures (SOF) score and the PHF score, and did not find important differences in the values of the area under the curve (AUC), which were somewhat similar to those obtained by this study[134]. Also, Sourial et al. observed a modest improvement in the mortality predictive ability of age-sex models, adding models including several combinations of frailty scores[135].

Our results also show that frailty scores from the accumulation of deficit and multidimensional families have stronger associations with mortality compared with the phenotype of frailty and disability families. In their meta-analysis, Vermeiren et al. did not report differences in the magnitude of the associations using different frailty approaches[13]. Our study has the clear advantage of making a direct comparison of the predictive performance of the different scores in the same population.

3.5.1. Strengths and limitations

Our study has several strengths. The large set of scores included allows for the comparison between families of scores as well as between individual scores. We performed state-of-the-art multiple imputation to deal with missing data, thereby making optimal use of the available events and follow-up time. We decided to impute underlying variables into their more basic form, which means that we imputed binary, categorical, and continuous variables with different models. Continuous variables were not categorised. The goal was to obtain the most plausible values of frailty scores without losing information. We are convinced that frailty scores with underlying imputed variables give less biased results and increase statistical power and accuracy. With frailty scores that have missing values for some underlying variables, it is likely that a lot of information will be lost. In addition, when some variables have missing data, we cannot rule out a missing at random mechanism. For example, a missing physical examination may be observed more frequently in a frail participant, because he could reject the test for fear of falling. There is strong evidence of the need to impute missing data, especially when the missing mechanism is not totally at random[136]. In addition, our results fill a void especially concerning the scarce information about the relationship between frailty scores and incident CVD and cancer. The results of this study are directly applicable to the general elderly English population and are probably also generalizable to similar populations in other European countries.

A limitation of our analysis was that we had to tailor some variables to calculate certain frailty scores. We based this adaptation on published studies when possible. Another important limitation was the different follow-up duration for total mortality compared to CVD and cancer. Almost 100% of ELSA participants were followed for all-cause mortality based on reliable and objective mortality registries. In contrast, more participants were lost to follow-up with regard to CVD and cancer end points. This could be a source of bias if loss to follow-up was associated both with frailty and with the two outcomes, because participants who were lost to follow-up could be precisely those who experienced a cardiovascular or cancer event. Also, the ascertainment of CVD and cancer was based on self-reports, possibly leading to misclassification due to differential recall. However, in both cases, the most likely impact of these sources of selection would be an underestimation of a true effect rather than identification of a spurious association. Finally, while the ELSA study is a rich source of data and well suited to the study of frailty, we performed a secondary data analysis, which meant that we had to adapt our data analysis to the existing data.

The best performing scores for all-cause mortality using the continuous analysis were multidimensional and accumulation of deficit approach. The multidimensional scores can have few variables, and in consequence, they are easy to apply in a clinical setting. These scores are tailored to capture features related to ill-health in later life over and above the obvious things we can obtain from a simple clinical history, such as polymedication, weight loss, depression symptoms, cognition, and self-reported health. Based on our data, we think that the isolated presence of comorbidity and/or polypharmacy is not enough to evaluate the presence of frailty, which means it is also necessary to measure physical and/or cognitive function.

3.5.2. Conclusions

It seems that while some scores can be regarded as a simple summary indicator for known risk factors, other scores capture other important information, such as self-reported health, medications, cognition, and disability. In our analysis of frailty categories, the best performing scores included physical functioning assessment. Overall, we found that multidimensional frailty scores have the strongest association and largest additional predictive performance for mortality outcomes.

Frailty scores could have been considered clinically useful tools for identifying patients at higher risk of imminent death. However, the observed additional predictive ability for all-cause mortality is low, which

reduces their clinical value for separating individuals who will experience from those who will not experience the outcome.

There are marked differences between scores with regard to their complexity as well as strength and stability of association, with all-cause mortality probably due to a great heterogeneity in the conception of different scores. This means that users of frailty scores should carefully balance the feasibility of measurement with a score's performance. Our results provide evidence to guide clinicians, researchers, and public health practitioners in striking this balance.

We think that future research should focus on the study of the trajectories of frailty scores. Frailty should be assessed with the most adapted instrument for this purpose. This approach could help identify individuals or characteristics of frailty early in time to establish useful interventions in patients and/or the general population.

3.5.3. Acknowledgments

We thank Professor Stephen Senn and François Fays for their contributions to this study.

We gratefully acknowledge the UK Data Archive for supplying the ELSA data. ELSA was developed by a team of researchers based at University College London, the Institute of Fiscal Studies, and the National Centre for Social Research. The data creators or the funders of the data collections and the UK Data Archive do not bear any responsibility for the analyses or interpretations presented here.

3.6. Supporting information

S1 Text. STROBE checklist.

S1 Table. Adjustment covariates for model 3.

S2 Table. Mortality hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis

S3 Table. Mortality hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis.

S4 Table. Cardiovascular events hazard ratios of frailty scores (n = 4,554) calculated at median time follow-up (2.5 years).

S5 Table. Cardiovascular hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis.

S6 Table. Cardiovascular hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis.

S7 Table. Cancer hazard ratios of frailty scores (n = 4,792) calculated at median time follow-up (2.5 years).

S8 Table. Cancer hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis.

S9 Table. Cancer hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis.

S10 Table. Discriminative assessment of cardiovascular models using Harrell's C statistic (n = 4,554).

S11 Table. Discriminative assessment of cancer models using Harrell's C statistic (n = 4,792).

S12 Table. Sensitivity analysis: Mortality hazard ratios of frailty scores (n = 5,253).

S13 Table. Mortality hazard ratios of frailty scores in men (n = 2,377) calculated at median time follow-up (3.5 years).

S14 Table. Mortality hazard ratios of frailty scores in women (n = 2,917) calculated at median time follow-up (3.5 years).

S15 Table. Mortality hazard ratios of frailty scores in participants older than 70 years (n = 2,536) calculated at median time follow-up (3.5 years).

S16 Table. Mortality hazard ratios of frailty scores in participants of 70 years and younger (n = 2,758) calculated at median time follow-up (3.5 years).

S1 Text. STROBE Checklist.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

	Item No.	Recommendation	Paragraph No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-6	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	3	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2	Methods
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA	
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,12,13.	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7	Methods
Bias	9	Describe any efforts to address potential sources of bias	13, 20	Methods
Study size	10	Explain how the study size was arrived at	1,2	Methods

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,13	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	14-19	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	18,20	Methods
		(*c*) Explain how missing data were addressed	8-11	Methods
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	12	Methods
		(*e*) Describe any sensitivity analyses	20	Methods
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2	Results
		(b) Give reasons for non-participation at each stage	2	Results
		(c) Consider use of a flow diagram	NA	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3	Results
		(b) Indicate number of participants with missing data for each variable of interest	8	Methods
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	3	Results
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	3	Results
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-12	Results
		(*b*) Report category boundaries when continuous variables were categorized	NA	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	1	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	2-11	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	20	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3	Acknowledgments

S1 Table. Adjustment covariates for model 3

Table S1. Adjustment covariates for model 3[1]

Score	sex	smoke	Alc	Phy Act	BMI	DM	HTA	CVD	cancer	anaemia	COPD	Arth	Neuro psy	Depr	Cogn	self-rated health	quality of life
BDE	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
BFI	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1
MFS	1	1	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1
CGA	1	1	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1
CGAST	1	1	1	1	0	0	0	1	1	1	0	1	1	0	0	1	1
CSBA	1	1	1	1	0	0	0	1	1	1	0	1	1	0	0	1	1
WHRH	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1
EFIP	1	1	1	0	1	1	0	0	1	1	0	0	0	1	0	0	1
EFS	1	1	1	0	0	0	0	0	1	1	0	0	0	1	0	0	1
FI40	1	1	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1
FI70	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	1
FIBLSA	1	1	1	0	1	1	0	0	1	1	1	1	0	1	0	1	1
PFI	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
FiND	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
FS	1	1	1	0	0	0	0	0	1	1	0	0	0	0	1	1	1
FSS	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1
G8	1	1	1	1	0	0	0	0	1	1	1	1	1	0	1	0	1
GFI	1	1	1	0	0	0	0	0	1	1	1	1	1	1	0	1	1
HRCA	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
HSF	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
NLTCS	1	1	1	0	1	0	0	0	1	1	1	1	0	0	1	0	1
PHF	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
MPHF	1	1	1	0	0	1	1	1	1	1	1	1	1	0	0	1	1
SDFI	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	0
SHCFS	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1
SI	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
SOF	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
SPPB	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
SPQ	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0	1
IFQ	1	1	1	0	0	0	0	0	1	1	1	1	1	1	1	0	1
TFI	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1
VES13	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1
ZED1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
ZED2	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
ZED3	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1

[1]Included in model 3=1/excluded in model 3=0.

Abbreviations: Alcohol=alcohol consumption; HTA= hypertension; CVD= cardiovascular disease; COPD=chronic obstructive pulmonary disease; Neuropsy=neuropsychiatric problems.

S2 Table. Mortality hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis

Table S2. Mortality hazard ratios of frailty scores assessed in intervals from1 to 7 years[1]: age-adjusted model and continuous an

Scores	HR 1 (LCI; UCI)	HR 2 (LCI; UCI)	HR 3 (LCI; UCI)	HR 3.5 (LCI; UCI)	HR 4 (LCI; UCI)	HR 5 (LCI; UCI)	HR 6 (LCI; UCI)	HR 7 (LCI; UCI)
BDE	1.6 (1.2; 2.2)	2.9 (2.1; 4.0)	4.0 (2.9; 5.6)	4.6 (3.3; 6.4)	5.2 (3.7; 7.1)	6.2 (4.5; 8.6)	7.3 (5.2; 10.1)	8.3 (6.0; 11.5)
BFI	1.0 (0.7; 1.5)	2.0 (1.4; 3.0)	3.1 (2.1; 4.6)	3.6 (2.4; 5.4)	4.1 (2.8; 6.2)	5.2 (3.5; 7.8)	6.3 (4.1; 9.4)	7.3 (4.9; 11.0)
CGA	1.9 (1.0; 3.6)	6.0 (3.1; 11.8)	12.0 (6.1; 23.5)	15.6 (8.0; 30.5)	19.5 (10.0; 38.2)	28.5 (14.6; 55.8)	38.9 (19.5; 76.1)	50.5 (25.8; 98.8)
CGAST	2.4 (1.4; 3.9)	5.4 (3.3; 9.0)	8.8 (5.3; 14.6)	10.6 (6.4; 17.6)	12.4 (7.5; 20.6)	16.2 (9.7; 26.9)	20.1 (12.4; 33.5)	24.2 (14.6; 40.2)
CSBA	5.8 (3.4; 9.9)	13.4 (7.9; 22.8)	21.8 (12.8; 37.0)	26.2 (15.4; 44.5)	30.7 (18.1; 52.2)	40.1 (23.6; 68.2)	49.9 (30.7; 84.8)	60.0 (35.3; 102.0)
EFIP	1.8 (1.1; 3.1)	4.7 (2.7; 8.1)	8.2 (4.8; 14.0)	10.1 (5.9; 17.3)	12.1 (7.1; 20.8)	16.5 (9.6; 28.2)	21.1 (12.1; 36.2)	26.1 (15.2; 44.7)
EFS	3.3 (1.9; 5.8)	8.3 (4.7; 14.4)	14.2 (8.1; 24.7)	17.4 (10.0; 30.3)	20.7 (11.9; 36.1)	27.8 (16.0; 48.5)	35.4 (20.7; 61.8)	43.5 (24.9; 75.8)
FI40	22.7 (15.4; 33.5)	19.7 (13.3; 29.0)	18.1 (12.3; 26.6)	17.5 (11.9; 25.8)	17.0 (11.5; 25.1)	16.2 (11.0; 23.9)	15.6 (17.0; 23.0)	15.1 (10.3; 22.3)
FI70	2.4 (1.4; 4.1)	6.1 (3.6; 10.5)	10.6 (6.2; 18.1)	13.0 (7.6; 22.4)	15.6 (9.1; 26.8)	21.1 (12.3; 36.2)	27.1 (15.6; 46.4)	33.3 (19.4; 57.2)
FIBLSA	1.1 (0.6; 2.0)	3.2 (1.8; 5.9)	6.2 (3.4; 11.3)	7.9 (4.3; 14.4)	9.7 (5.3; 17.8)	13.9 (7.6; 25.4)	18.5 (9.7; 33.8)	23.6 (12.9; 43.2)
FiND	1.7 (1.2; 2.4)	2.9 (2.1; 4.1)	4.0 (2.9; 5.6)	4.6 (3.2; 6.4)	5.1 (3.6; 7.1)	6.0 (4.3; 8.5)	7.0 (5.1; 9.8)	7.9 (5.6; 11.1)
FS	1.6 (1.1; 2.4)	3.0 (2.0; 4.5)	4.3 (2.9; 6.4)	4.9 (3.3; 7.3)	5.5 (3.7; 8.2)	6.6 (4.5; 9.9)	7.8 (5.5; 11.6)	8.9 (6.0; 13.3)
FSS	1.0 (0.7; 1.4)	1.9 (1.3; 2.8)	2.9 (2.0; 4.2)	3.3 (2.3; 4.9)	3.8 (2.6; 5.6)	4.7 (3.3; 6.9)	5.7 (3.8; 8.2)	6.6 (4.5; 9.6)
G8	3.3 (2.0; 5.5)	8.5 (5.1; 14.2)	14.7 (8.8; 24.6)	18.2 (10.8; 30.4)	21.8 (13.0; 36.5)	29.5 (17.6; 49.4)	37.8 (21.8; 63.4)	46.7 (27.9; 78.2)
GFI	1.9 (1.2; 3.1)	4.4 (2.7; 7.1)	7.1 (4.3; 11.5)	8.5 (5.2; 13.9)	10.0 (6.1; 16.2)	13.0 (8.0; 21.2)	16.1 (10.0; 26.3)	19.4 (11.9; 31.5)
HRCA	1.1 (0.7; 1.8)	2.6 (1.6; 4.2)	4.2 (2.6; 6.8)	5.0 (3.1; 8.1)	5.9 (3.7; 9.5)	7.7 (4.8; 12.4)	9.6 (5.9; 15.5)	11.5 (7.2; 18.6)
HSF	1.3 (0.8; 1.9)	2.9 (1.9; 4.4)	4.6 (3.0; 7.1)	5.5 (3.6; 8.5)	6.5 (4.3; 9.9)	8.5 (5.5; 12.9)	10.5 (6.5; 16.0)	12.6 (8.3; 19.3)
IFQ	1.6 (1.0; 2.6)	3.8 (2.3; 6.2)	6.3 (3.9; 10.3)	7.7 (4.7; 12.5)	9.0 (5.5; 14.8)	11.9 (7.3; 19.5)	15.0 (9.0; 24.4)	18.1 (11.1; 29.6)
MFS	2.3 (1.6; 3.3)	4.3 (3.0; 6.3)	6.3 (4.3; 9.2)	7.3 (5.0; 10.7)	8.3 (5.7; 12.1)	10.2 (7.0; 14.9)	12.1 (8.3; 17.6)	14.0 (9.6; 20.4)
MPHF	2.0 (1.4; 2.8)	3.7 (2.7; 5.3)	5.4 (3.8; 7.6)	6.2 (4.4; 8.7)	7.0 (5.0; 9.8)	8.5 (6.0; 11.9)	10.0 (7.0; 14.1)	11.5 (8.2; 16.1)
NLTCS	1.0 (0.5; 2.0)	3.6 (1.7; 7.6)	7.8 (3.7; 16.5)	10.4 (4.9; 22.1)	13.4 (6.3; 28.5)	20.6 (9.7; 43.6)	29.1 (13.4; 61.7)	39.0 (18.4; 82.7)
PFI	1.1 (0.8; 1.5)	1.7 (1.2; 2.3)	2.2 (1.6; 3.0)	2.4 (1.7; 3.3)	2.6 (1.9; 3.6)	3.0 (2.2; 4.2)	3.4 (2.6; 4.7)	3.8 (2.7; 5.2)
PHF	1.9 (1.4; 2.7)	3.5 (2.5; 4.9)	5.0 (3.6; 6.9)	5.7 (4.1; 7.9)	6.4 (4.6; 8.9)	7.7 (5.5; 10.8)	9.0 (6.4; 12.6)	10.3 (7.4; 14.4)
SDFI	2.1 (1.3; 3.4)	4.5 (2.8; 7.2)	7.0 (4.4; 11.1)	8.3 (5.2; 13.2)	9.6 (6.0; 15.2)	12.2 (7.7; 19.4)	14.9 (9.6; 23.7)	17.6 (11.1; 28.0)
SHCFS	1.3 (1.0; 1.9)	2.3 (1.6; 3.2)	3.2 (2.3; 4.5)	3.6 (2.6; 5.0)	4.0 (2.8; 5.6)	4.7 (3.4; 6.7)	5.5 (4.0; 7.7)	6.2 (4.4; 8.7)
SI	0.6 (0.4; 1.1)	1.6 (0.9; 2.7)	2.8 (1.6; 4.7)	3.4 (2.0; 5.8)	4.1 (2.4; 6.9)	5.5 (3.2; 9.4)	7.0 (4.1; 12.0)	8.6 (5.0; 14.7)
SOF	1.6 (1.1; 2.2)	2.6 (1.8; 3.7)	3.5 (2.4; 5.0)	3.9 (2.7; 5.6)	4.3 (3.0; 6.2)	5.1 (3.5; 7.3)	5.8 (4.3; 8.3)	6.5 (4.5; 9.3)
SPPB	1.7 (1.2; 2.6)	3.5 (2.3; 5.2)	5.2 (3.5; 7.8)	6.1 (4.1; 9.1)	7.0 (4.7; 10.4)	8.7 (5.8; 13.0)	10.4 (7.0; 15.6)	12.2 (8.2; 18.1)
SPQ	0.6 (0.3; 0.9)	1.4 (0.8; 2.3)	2.3 (1.4; 3.9)	2.9 (1.7; 4.7)	3.4 (2.1; 5.6)	4.5 (2.7; 7.5)	5.7 (3.4; 9.4)	7.0 (4.2; 11.5)
TFI	2.6 (1.7; 4.0)	5.3 (3.5; 8.2)	8.1 (5.3; 12.4)	9.5 (6.2; 14.6)	10.9 (7.1; 16.8)	13.8 (9.0; 21.1)	16.6 (10.9; 25.5)	19.5 (12.7; 30.0)
VES13	1.4 (0.9; 2.1)	3.1 (2.0; 4.7)	4.9 (3.2; 7.4)	5.8 (3.8; 8.8)	6.8 (4.5; 10.3)	8.7 (5.7; 13.2)	10.7 (6.8; 16.3)	12.8 (8.4; 19.4)
WHRH	1.3 (0.9; 2.0)	2.5 (1.7; 3.8)	3.7 (2.4; 5.5)	4.2 (2.8; 6.4)	4.8 (3.2; 7.2)	5.9 (3.9; 8.9)	7.0 (4.8; 10.6)	8.1 (5.4; 12.2)
ZED1	1.2 (0.9; 1.6)	1.9 (1.4; 2.6)	2.6 (1.9; 3.5)	2.9 (2.1; 3.9)	3.2 (2.4; 4.3)	3.7 (2.8; 5.1)	4.3 (3.2; 5.8)	4.8 (3.6; 6.5)
ZED2	1.7 (1.2; 2.3)	2.6 (1.9; 3.5)	3.3 (2.5; 4.5)	3.7 (2.7; 4.9)	4.0 (3.0; 5.4)	4.6 (3.4; 6.2)	5.2 (4.0; 6.9)	5.7 (4.2; 7.6)
ZED3	1.0 (0.7; 1.5)	1.9 (1.3; 2.9)	2.8 (1.9; 4.1)	3.2 (2.2; 4.7)	3.6 (2.4; 5.3)	4.4 (3.0; 6.4)	5.1 (3.6; 7.5)	5.9 (4.0; 8.7)

[1]Hazard ratios calculated from age at baseline to age at the end of the interval. BDE= Beaver Dam Eye Study Index.

S3 Table. Mortality hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis

Scores	HR1 (LCI; UCI)	HR2 (LCI; UCI)	HR3 (LCI; UCI)	HR3.5 (LCI; UCI	HR4 (LCI; UCI)	HR5 (LCI; UCI)	HR6 (LCI; UCI)	HR7 (LCI; UCI)
BFI frail	0.7 (0.5; 0.9)	1.1 (0.6; 1.8)	1.4 (0.7; 2.5)	1.5 (0.8; 2.9)	1.6 (1.8; 3.3)	1.8 (0.9; 4.0)	2.1 (0.9; 4.7)	2.3 (0.9; 5.4)
CGA frail	1.1 (0.9; 1.5)	1.8 (1.2; 2.7)	2.3 (1.4; 3.9)	2.6 (1.4; 4.5)	2.8 (2.7; 5.1)	3.2 (1.4; 6.2)	3.6 (1.8; 7.3)	4.0 (1.5; 8.4)
CGA pre-frail	1.2 (1.0; 1.4)	1.9 (1.4; 2.5)	2.4 (1.7; 3.5)	2.7 (1.8; 3.9)	2.9 (2.5; 4.4)	3.3 (1.7; 5.3)	3.8 (1.3; 6.1)	4.1 (1.4; 7.0)
CGAST frail	1.7 (1.2; 2.3)	2.4 (1.4; 4.2)	3.1 (1.6; 5.9)	3.3 (1.6; 6.7)	3.6 (4.2; 7.6)	4.0 (1.6; 9.2)	4.5 (1.9; 10.7)	4.9 (2.3; 12.3)
CGAST pre frail	1.4 (1.0; 1.9)	2.0 (1.3; 3.4)	2.6 (1.4; 4.7)	2.8 (1.4; 5.4)	3.0 (3.4; 6.0)	3.4 (1.4; 7.2)	3.7 (1.7; 8.4)	4.1 (1.9; 9.6)
CSBA frail	1.1 (0.9; 1.3)	1.6 (1.1; 2.2)	1.9 (1.3; 3.0)	2.1 (1.3; 3.4)	2.3 (2.2; 3.7)	2.6 (1.3; 4.4)	2.8 (1.6; 5.0)	3.0 (1.3; 5.6)
EFS frail	1.6 (1.2; 2.2)	1.9 (1.1; 3.2)	2.0 (1.0; 4.0)	2.1 (1.0; 4.3)	2.1 (3.2; 4.6)	2.3 (1.0; 5.2)	2.3 (1.0; 5.7)	2.4 (2.2; 6.2)
FI40 frail	1.1 (0.9; 1.4)	1.6 (1.1; 2.2)	1.9 (1.3; 2.8)	2.0 (1.3; 3.1)	2.2 (2.2; 3.4)	2.4 (1.3; 3.9)	2.6 (1.5; 4.4)	2.8 (1.4; 4.9)
FI70 frail	1.2 (1.0; 1.4)	1.6 (1.2; 2.2)	1.9 (1.3; 2.9)	2.1 (1.3; 3.2)	2.2 (2.2; 3.5)	2.4 (1.3; 4.1)	2.7 (1.5; 4.6)	2.8 (1.4; 5.1)
FiND frail	1.0 (0.7; 1.3)	1.3 (0.8; 2.2)	1.6 (0.9; 3.0)	1.7 (0.9; 3.3)	1.8 (2.2; 3.7)	2.0 (0.9; 4.4)	2.2 (1.0; 5.0)	2.4 (1.3; 5.6)
FS frail	1.3 (1.0; 1.7)	1.9 (1.2; 3.1)	2.5 (1.4; 4.4)	2.7 (1.5; 5.1)	3.0 (3.1; 5.7)	3.4 (1.4; 7.0)	3.8 (1.8; 8.2)	4.2 (1.7; 9.4)
FS pre- frail	1.1 (1.0; 1.4)	1.8 (1.3; 2.3)	2.3 (1.6; 3.2)	2.5 (1.7; 3.6)	2.7 (2.3; 4.0)	3.1 (1.6; 4.8)	3.5 (1.2; 5.5)	3.8 (1.4; 6.2)
FSS frail	0.9 (0.7; 1.1)	1.4 (0.9; 2.2)	1.9 (1.1; 3.2)	2.1 (1.2; 3.7)	2.3 (2.2; 4.3)	2.7 (1.1; 5.3)	3.1 (0.5; 6.2)	3.4 (1.1; 7.2)
FSS pre frail	1.2 (1.0; 1.4)	1.9 (1.4; 2.5)	2.5 (1.7; 3.6)	2.8 (1.9; 4.1)	3.0 (2.5; 4.6)	3.5 (1.7; 5.6)	4.0 (1.5; 6.5)	4.5 (1.4; 7.5)
G8 frail	1.3 (1.0; 1.6)	1.8 (1.2; 2.7)	2.2 (1.4; 3.7)	2.4 (1.4; 4.1)	2.6 (2.7; 4.5)	2.9 (1.4; 5.3)	3.2 (1.7; 6.1)	3.4 (1.6; 6.8)
GFI frail	1.0 (0.8; 1.2)	1.3 (1.0; 1.9)	1.6 (1.1; 2.4)	1.7 (1.1; 2.7)	1.9 (1.9; 3.0)	2.1 (1.1; 3.5)	2.3 (1.3; 3.9)	2.4 (1.2; 4.3)
HRCA frail	1.1 (0.9; 1.3)	1.5 (1.1; 2.1)	1.8 (1.2; 2.8)	2.0 (1.3; 3.1)	2.1 (2.1; 3.4)	2.3 (1.2; 3.9)	2.5 (1.5; 4.4)	2.7 (1.3; 4.9)
IFQ frail	1.3 (0.8; 2.0)	1.7 (0.8; 3.5)	1.9 (0.8; 4.9)	2.1 (0.8; 5.5)	2.2 (3.5; 6.2)	2.4 (0.8; 7.4)	2.5 (1.7; 8.6)	2.7 (2.0; 9.7)
MFS frail	1.5 (0.9; 2.4)	2.2 (1.0; 4.9)	2.8 (1.5; 7.6)	3.1 (1.1; 9.0)	3.4 (4.9; 10.3)	3.9 (1.1; 13.1)	4.3 (1.2; 15.9)	4.7 (2.4; 18.7)
MFS pre-frail	1.2 (0.8; 1.9)	1.8 (0.8; 3.8)	2.3 (0.9; 5.9)	2.5 (0.9; 6.9)	2.7 (3.8; 7.9)	3.1 (0.9; 10.0)	3.5 (1.0; 12.1)	3.8 (1.9; 14.2)
PFI frail	1.0 (0.7; 1.4)	1.6 (0.9; 2.8)	2.0 (1.0; 4.2)	2.3 (1.0; 4.9)	2.5 (2.8; 5.7)	2.9 (1.0; 7.1)	3.2 (1.2; 8.5)	3.6 (1.4; 10.0)
PFI pre frail	1.1 (0.9; 1.4)	1.8 (1.3; 2.5)	2.3 (1.6; 3.5)	2.6 (1.7; 4.0)	2.8 (2.5; 4.4)	3.3 (1.6; 5.4)	3.7 (1.2; 6.3)	4.1 (1.4; 7.2)
PHF frail	1.5 (1.0; 2.2)	2.4 (1.2; 4.5)	3.1 (1.4; 6.9)	3.4 (1.4; 8.0)	3.7 (4.5; 9.2)	4.3 (1.4; 11.6)	4.8 (1.7; 14.0)	5.3 (2.2; 16.4)
PHF pre-frail	1.1 (0.8; 1.5)	1.7 (1.0; 3.1)	2.2 (1.1; 4.6)	2.5 (1.2; 5.3)	2.7 (3.1; 6.1)	3.1 (1.1; 7.6)	3.5 (1.4; 9.1)	3.9 (1.5; 10.6)
SDFI frail	1.0 (0.8; 1.2)	1.4 (1.0; 2.0)	1.8 (1.2; 2.8)	1.9 (1.2; 3.1)	2.1 (2.0; 3.4)	2.4 (1.2; 4.1)	2.6 (1.5; 4.6)	2.8 (1.2; 5.2)
SHCFS frail	1.2 (0.9; 1.5)	1.5 (1.0; 2.2)	1.7 (1.1; 2.8)	1.8 (1.1; 3.0)	1.9 (2.2; 3.3)	2.1 (1.1; 3.7)	2.2 (1.2; 4.1)	2.3 (1.5; 4.5)
SI frail	0.7 (0.5; 1.1)	1.0 (0.5; 2.1)	1.3 (0.5; 3.1)	1.4 (0.5; 3.7)	1.5 (2.1; 4.2)	1.7 (0.5; 5.2)	1.9 (0.6; 6.2)	2.1 (1.1; 7.2)
SOF frail	1.3 (1.0; 1.7)	1.9 (1.2; 3.0)	2.4 (1.4; 4.2)	2.6 (1.4; 4.7)	2.8 (3.0; 5.2)	3.1 (1.4; 6.3)	3.4 (1.6; 7.3)	3.7 (1.7; 8.2)
SOF pre-frail	1.3 (1.1; 1.5)	1.8 (1.4; 2.4)	2.3 (1.6; 3.2)	2.5 (1.7; 3.6)	2.7 (2.4; 4.0)	3.0 (1.6; 4.6)	3.3 (1.1; 5.3)	3.6 (1.5; 5.9)
SPPB frail	1.0 (0.8; 1.2)	1.4 (0.9; 2.0)	1.7 (1.1; 2.8)	1.8 (1.1; 3.1)	2.0 (2.0; 3.4)	2.2 (1.1; 4.0)	2.4 (1.3; 4.6)	2.6 (1.2; 5.1)
SPQ frail	0.7 (0.6; 0.8)	0.9 (0.8; 1.2)	1.2 (0.9; 1.5)	1.2 (0.9; 1.7)	1.3 (1.2; 1.8)	1.5 (0.9; 2.1)	1.6 (0.1; 2.3)	1.7 (0.8; 2.6)
TFI frail	1.1 (0.9; 1.4)	1.6 (1.1; 2.2)	1.9 (1.3; 2.9)	2.1 (1.3; 3.2)	2.2 (2.2; 3.6)	2.5 (1.3; 4.1)	2.7 (1.6; 4.7)	2.9 (1.4; 5.2)
VES13 frail	1.0 (0.8; 1.2)	1.4 (1.0; 2.0)	1.7 (1.1; 2.7)	1.9 (1.2; 3.0)	2.0 (2.0; 3.3)	2.3 (1.1; 3.8)	2.5 (1.4; 4.3)	2.7 (1.2; 4.8)
WHRH frail	1.1 (0.9; 1.3)	1.4 (1.0; 2.1)	1.7 (1.1; 2.6)	1.8 (1.1; 2.9)	1.9 (2.1; 3.1)	2.1 (1.1; 3.6)	2.2 (1.2; 4.0)	2.4 (1.3; 4.4)
ZED1 frail	1.4 (1.0; 2.0)	1.7 (1.0; 3.0)	1.9 (1.0; 3.8)	2.0 (1.0; 4.2)	2.1 (3.0; 4.5)	2.2 (1.0; 5.2)	2.3 (1.9; 5.7)	2.4 (2.0; 6.3)
ZED2 frail	1.5 (1.1; 2.2)	1.9 (1.0; 3.4)	2.1 (1.0; 4.4)	2.2 (1.0; 4.9)	2.2 (3.4; 5.3)	2.4 (1.0; 6.1)	2.5 (1.9; 6.9)	2.6 (2.2; 7.6)
ZED3 frail	1.1 (0.5; 2.4)	1.7 (0.4; 6.7)	2.2 (0.4; 12.1)	2.4 (0.4; 15.2)	2.6 (6.7; 18.5)	3.0 (0.4; 25.6)	3.4 (1.3; 33.4)	3.8 (2.4; 41.9)

[1]Hazard ratios calculated from age at baseline to age at the end of the interval.

S4 Table. Cardiovascular events hazard ratios of frailty scores (n = 4,554) calculated at median time follow-up (2.5 years).

Table S4. Cardiovascular hazard ratios of frailty scores (n=4554) calculated at median time follow-up (2.5 years)

	Continuous analysis					Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]	Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]
Phenotype of frailty approach									
SPPB	2.5 (1.1; 5.5)	2.8 (1.2; 6.3)	2.6 (1.2; 5.9)	1.4 (0.6; 3.4)	PFI frail	1.7 (0.4; 6.7)	1.8 (0.4; 7.1)	1.7 (0.4; 6.9)	1.3 (0.4; 5.7)
MPHF	2.3 (1.1; 4.6)	2.5 (1.2; 5.0)	2.2 (1.1; 4.4)	1.4 (0.6; 3.1)	PFI pre frail	2.4 (1.2; 4.8)	2.5 (1.2; 5.1)	2.4 (1.2; 4.8)	2.0 (1.2; 4.2)
FS	2.1 (0.9; 5.1)	2.3 (1.0; 5.5)	2.1 (0.9; 5.0)	1.2 (0.5; 3.1)	PHF frail	1.8 (0.5; 6.2)	1.9 (0.5; 6.6)	1.7 (0.5; 6.0)	8.1 (5.3; 12.4)
BDE	2.2 (1.2; 4.1)	2.3 (1.2; 4.2)	2.1 (1.1; 3.8)	1.3 (0.7; 2.5)	PHF pre-frail	2.2 (0.8; 5.9)	2.3 (0.8; 6.2)	2.2 (0.8; 5.9)	0.1 (0.0; 7.9)
PHF	2.1 (1.0; 4.1)	2.2 (1.1; 4.4)	2.0 (1.0; 4.0)	1.2 (0.6; 2.6)	FS frail	1.5 (0.5; 4.8)	1.6 (0.5; 4.9)	1.5 (0.5; 4.7)	1.0 (0.5; 3.5)
FiND	2.0 (0.9; 4.2)	2.1 (1.0; 4.5)	2.0 (0.9; 4.2)	1.1 (0.5; 2.7)	FS pre- frail	2.2 (1.2; 4.0)	2.3 (1.2; 4.1)	2.2 (1.2; 3.9)	1.9 (1.2; 3.6)
PFI	1.9 (1.0; 3.5)	2.0 (1.1; 3.8)	1.9 (1.0; 3.6)	1.4 (0.7; 2.8)	SOF frail	1.4 (0.4; 4.3)	1.4 (0.4; 4.5)	1.4 (0.4; 4.2)	1.0 (0.4; 3.5)
SOF	1.6 (0.7; 3.6)	1.7 (0.7; 3.8)	1.6 (0.7; 3.5)	1.0 (0.4; 2.5)	SOF pre-frail	2.0 (1.1; 3.7)	2.1 (1.1; 3.8)	2.0 (1.1; 3.7)	1.8 (1.1; 3.4)
ZED1	1.4 (0.8; 2.7)	1.6 (0.8; 3.0)	1.5 (0.8; 2.8)	1.0 (0.5; 2.0)	ZED2 frail	1.5 (0.2; 11.2)	1.5 (0.2; 11.3)	1.5 (0.2; 11.1)	1.1 (0.2; 8.5)
ZED2	1.3 (0.7; 2.6)	1.4 (0.7; 2.7)	1.3 (0.6; 2.5)	0.9 (0.4; 1.8)	FiND frail	1.3 (0.5; 3.3)	1.4 (0.5; 3.4)	1.3 (0.5; 3.3)	1.1 (0.5; 2.8)
ZED3	1.1 (0.5; 2.5)	1.2 (0.6; 2.8)	1.1 (0.5; 2.5)	0.9 (0.4; 2.1)	SPPB frail	1.3 (0.6; 2.6)	1.3 (0.6; 2.7)	1.3 (0.6; 2.6)	1.0 (0.6; 2.1)
					ZED1 frail	1.2 (0.2;5.4)	1.2 (0.3; 5.4)	1.2 (0.2;5.4)	0.8 (0.2; 3.7)
					ZED3 frail	0.6 (0.0; 363.5)	0.6 (0.0; 382.6)	0.6 (0.0; 430.5)	0.5 (0.0; 314.9)
Multidimensional approach									
EFS	4.7 (1.3; 16.5)	5.6 (1.6; 19.6)	4.6 (1.3; 16.4)	5.1 (1.2; 20.7)	CGAST frail	2.0 (0.7; 5.3)	2.1 (0.7; 5.7)	2.0 (0.7; 5.4)	1.5 (0.7; 4.3)
CSBA	4.3 (1.6; 11.5)	3.7 (1.3; 10.4)	3.0 (1.1; 8.4)	0.6 (0.2; 2.0)	CGAST pre frail	2.7 (1.2; 6.2)	2.7 (1.2; 6.3)	2.7 (1.2; 6.2)	2.5 (1.2; 5.9)
HSF	2.9 (1.2; 7.0)	3.1 (1.3; 7.5)	2.9 (1.2; 6.9)	1.5 (0.5; 4.0)	MFS frail	1.6 (0.4; 6.1)	1.6 (0.4; 6.3)	1.5 (0.4; 5.7)	1.2 (0.4; 4.7)
G8	2.7 (0.9; 7.8)	3.1 (1.1; 9.1)	2.6 (0.9; 7.6)	0.8 (0.2; 2.8)	MFS pre-frail	2.0 (0.6; 6.8)	2.1 (0.6; 7.0)	1.9 (0.6; 6.5)	1.8 (0.6; 6.0)
SDFI	2.1 (0.9; 5.1)	3.1 (1.3; 7.5)	2.5 (1.0; 6.1)	1.0 (0.4; 2.7)	FSS frail	1.3 (0.5; 3.4)	1.4 (0.5; 3.5)	1.3 (0.5; 3.4)	0.9 (0.5; 2.5)
GFI	2.6 (0.9; 7.3)	3.0 (1.1; 8.5)	2.6 (0.9; 7.4)	1.2 (0.3; 3.9)	FSS pre frail	2.0 (1.1; 3.5)	2.0 (1.1; 3.6)	1.9 (1.1; 3.4)	1.6 (1.1; 3.0)
CGAST	2.3 (0.8; 6.7)	2.7 (0.9; 7.9)	2.3 (0.8; 6.9)	1.0 (0.3; 3.2)	EFS frail	1.7 (0.4; 7.5)	1.8 (0.4; 7.8)	1.6 (0.4; 7.2)	1.4 (0.4; 6.6)
MFS	2.3 (1.1; 4.9)	2.5 (1.2; 5.1)	2.1 (1.0; 4.5)	1.5 (0.7; 3.3)	G8 frail	1.6 (0.8; 3.5)	1.7 (0.8; 3.7)	1.6 (0.8; 3.5)	1.2 (0.8; 2.8)
TFI	1.9 (0.8; 4.4)	2.2 (0.9; 5.4)	1.8 (0.8; 4.5)	1.1 (0.4; 3.1)	IFQ frail	1.5 (0.3; 8.8)	1.6 (0.3; 9.2)	1.5 (0.3; 8.5)	1.2 (0.3; 6.8)
FSS	1.8 (0.8; 3.7)	1.9 (0.9; 4.0)	1.8 (0.8; 3.7)	1.0 (0.4; 2.2)	SDFI frail	1.3 (0.6; 2.6)	1.4 (0.6; 2.9)	1.3 (0.6; 2.7)	1.0 (0.6; 2.2)
IFQ	1.3 (0.5; 3.7)	1.5 (0.5; 4.3)	1.3 (0.5; 3.6)	0.5 (0.2; 1.5)	TFI frail	1.3 (0.6; 2.5)	1.3 (0.6; 2.6)	1.2 (0.6; 2.5)	1.1 (0.6; 2.2)
BFI	1.2 (0.5; 2.6)	1.4 (0.7; 3.2)	1.2 (0.6; 2.7)	0.7 (0.3; 1.6)	CSBA frail	1.4 (0.7; 2.7)	1.3 (0.7; 2.6)	1.2 (0.7; 2.5)	0.9 (0.7; 1.9)
SI	1.2 (0.4; 3.6)	1.4 (0.5; 4.2)	1.3 (0.4; 3.9)	0.6 (0.2; 1.8)	GFI frail	1.2 (0.6; 2.6)	1.3 (0.6; 2.7)	1.2 (0.6; 2.6)	1.0 (0.6; 2.2)
SPQ	1.0 (0.4; 2.8)	1.2 (0.5; 3.2)	1.1 (0.4; 2.8)	0.6 (0.2; 1.7)	SI frail	1.1 (0.2; 5.7)	1.2 (0.2; 5.9)	1.1 (0.2; 5.7)	0.8 (0.2; 4.4)
					BFI frail	0.9 (0.2; 3.4)	0.9 (0.2; 3.7)	0.9 (0.2; 3.4)	0.7 (0.2; 2.8)
					SPQ frail	1.0 (0.4; 2.1)	0.6 (0.4; 1.0)	0.6 (0.4; 1.0)	0.8 (0.4; 1.8)
Accumulation of deficits approach									
FI40	12.7 (6.0; 26.8)	16.5 (7.8; 35.0)	14.3 (6.6; 30.9)	15.2 (5.8; 40.3)	CGA frail	1.5 (0.6; 4.0)	1.7 (0.6; 4.4)	1.6 (0.6; 4.2)	1.5 (0.6; 4.2)
FI70	5.1 (1.6; 15.9)	7.1 (2.3; 22.2)	6.2 (2.0; 19.6)	6.9 (1.8; 26.3)	CGA pre-frail	2.1 (1.1; 3.7)	2.2 (1.1; 4.0)	2.1 (1.1; 3.9)	2.1 (1.1; 3.9)
CGA	4.1 (1.0; 17.1)	5.8 (1.4; 24.2)	4.9 (1.2; 20.9)	4.2 (0.8; 20.8)	FI70 frail	1.6 (0.8; 3.2)	1.7 (0.8; 3.5)	1.6 (0.8; 3.3)	1.5 (0.8; 3.3)
EFIP	4.6 (1.5; 14.6)	5.6 (1.8; 17.8)	4.9 (1.5; 15.6)	4.9 (1.3; 18.6)	FI40 frail	1.5 (0.8; 3.1)	1.7 (0.8; 3.4)	1.6 (0.8; 3.2)	2.1 (0.8; 3.6)
NLTCS	4.7 (0.9; 23.7)	5.3 (1.0; 26.8)	4.7 (0.9; 23.8)	1.5 (0.2; 9.4)					
FIBLSA	4.0 (1.1; 14.5)	4.8 (1.3; 17.2)	4.3 (1.2; 15.5)	2.1 (0.5; 9.3)					
Disability approach									
VES13	3.1 (1.3; 7.4)	3.7 (1.6; 8.7)	3.4 (1.4; 8.0)	2.6 (1.0; 6.9)	HRCA frail	1.4 (0.7; 3.0)	1.6 (0.7; 3.3)	1.5 (0.7; 3.2)	1.2 (0.7; 2.7)
HRCA	2.7 (1.0; 7.3)	3.3 (1.2; 8.8)	3.0 (1.1; 8.1)	1.5 (0.5; 4.7)	VES13 frail	1.4 (0.7; 2.9)	1.5 (0.7; 3.1)	1.4 (0.7; 3.0)	1.2 (0.7; 2.7)
WHRH	2.5 (1.1; 6.1)	2.9 (1.2; 7.0)	2.8 (1.2; 6.6)	2.2 (0.8; 5.8)	WHRH frail	1.4 (0.6; 3.2)	1.5 (0.6; 3.3)	1.4 (0.6; 3.3)	1.0 (0.6; 2.5)
SHCFS	1.7 (0.8; 3.6)	1.8 (0.9; 3.9)	1.7 (0.8; 3.7)	0.9 (0.4; 2.2)	SHCFS frail	1.4 (0.5; 3.6)	1.4 (0.5; 3.7)	1.4 (0.5; 3.6)	1.0 (0.5; 2.9)

[1]Model 0= Crude models. [2]Model 1= HR adjusted by sex. [3]Model 2= Model 1 + smoking status and alcohol consumption. [4]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life.

S5 Table. Cardiovascular hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis

Table S5. Cardiovascular hazard ratios of frailty scores assessed in intervals from1 to 7 years[1]: age-adjusted model and continuousl analysis

Scores	HR1 (LCI; UCI)	HR2 (LCI; UCI)	HR2.5 (LCI; UCI)	HR3 (LCI; UCI)	HR4 (LCI; UCI)	HR5 (LCI; UCI)	HR6 (LCI; UCI)	HR7 (LCI; UCI)
BDE	0.7 (0.4; 1.2)	1.7 (0.9; 3.1)	2.2 (1.2; 4.1)	2.8 (1.5; 5.3)	4.2 (2.3; 7.8)	5.6 (3.1; 10.5)	7.2 (3.9; 13.4)	8.9 (4.8; 16.4)
BFI	0.2 (0.1; 0.5)	0.8 (0.4; 1.7)	1.2 (0.5; 2.6)	1.7 (0.8; 3.6)	2.8 (1.3; 6.1)	4.2 (1.7; 9.1)	5.8 (2.7; 12.6)	7.7 (3.5; 16.7)
CGA	0.2 (0.1; 1.0)	2.0 (0.5; 8.4)	4.1 (1.0; 17.1)	7.2 (1.7; 30.3)	17.9 (4.3; 74.9)	36.2 (8.4; 151.2)	64.2 (15.3; 268.5)	104.3 (24.9; 436.2)
CGAST	0.2 (0.1; 0.6)	1.3 (0.4; 3.8)	2.3 (0.6; 6.7)	3.6 (1.2; 10.8)	7.7 (2.6; 22.9)	13.8 (3.8; 40.9)	22.1 (7.4; 65.7)	33.0 (11.1; 98.1)
CSBA	0.7 (0.3; 1.9)	2.7 (0.0; 7.4)	4.3 (1.9; 11.5)	6.1 (2.3; 16.6)	10.9 (4.0; 29.4)	17.0 (7.4; 45.9)	24.4 (9.0; 66.0)	33.2 (12.3; 89.8)
EFIP	0.4 (0.1; 1.3)	2.6 (0.8; 8.1)	4.6 (1.3; 14.6)	7.4 (2.3; 23.4)	15.7 (4.9; 49.5)	28.0 (8.1; 88.5)	45.0 (14.2; 142.3)	67.2 (21.2; 212.6)
EFS	0.3 (0.1; 1.2)	2.5 (0.7; 8.7)	4.7 (1.2; 16.5)	7.9 (2.3; 27.8)	18.0 (5.1; 63.3)	34.1 (8.7; 119.8)	57.5 (16.4; 201.7)	89.3 (25.5; 313.5)
FI40	17.9 (8.5; 37.8)	13.8 (17.5; 29.2)	12.7 (37.8; 26.8)	11.9 (5.6; 25.1)	10.7 (5.0; 22.5)	9.8 (29.2; 20.7)	9.2 (4.3; 19.3)	8.6 (4.1; 18.2)
FI70	0.5 (0.2; 1.5)	2.9 (0.9; 9.0)	5.1 (1.5; 15.9)	8.1 (2.6; 25.2)	16.9 (5.4; 52.4)	29.7 (9.0; 92.5)	47.3 (15.2; 147.1)	70.0 (22.5; 217.7)
FIBLSA	0.3 (0.1; 1.1)	2.1 (0.6; 7.7)	4.0 (1.1; 14.5)	6.7 (1.9; 24.2)	15.1 (4.2; 54.5)	28.4 (7.7; 102.4)	47.5 (13.2; 171.2)	73.4 (20.3; 264.5)
FiND	0.5 (0.2; 1.0)	1.4 (0.7; 2.9)	2.0 (1.0; 4.2)	2.6 (1.2; 5.6)	4.1 (2.0; 8.8)	5.9 (2.9; 12.5)	7.9 (3.7; 16.7)	10.0 (4.7; 21.3)
FS	0.5 (0.2; 1.2)	1.5 (0.6; 3.5)	2.1 (1.2; 5.1)	2.9 (1.2; 6.8)	4.5 (1.9; 10.7)	6.5 (3.5; 15.4)	8.7 (3.7; 20.6)	11.1 (4.7; 26.3)
FSS	0.4 (0.2; 0.8)	1.2 (0.6; 2.5)	1.8 (0.8; 3.7)	2.4 (1.1; 5.0)	3.9 (1.8; 8.1)	5.6 (2.5; 11.8)	7.6 (3.6; 16.0)	9.9 (4.7; 20.8)
G8	0.3 (0.1; 0.8)	1.5 (0.5; 4.5)	2.7 (0.8; 7.8)	4.2 (1.4; 12.2)	8.6 (2.9; 24.9)	14.9 (4.5; 43.3)	23.4 (8.1; 68.1)	34.3 (11.8; 99.8)
GFI	0.3 (0.1; 0.9)	1.6 (0.6; 4.4)	2.6 (0.9; 7.3)	4.0 (1.4; 11.2)	7.8 (2.8; 21.9)	13.1 (4.4; 36.8)	20.1 (7.2; 56.3)	28.8 (10.3; 80.6)
HRCA	0.4 (0.2; 1.1)	1.7 (0.6; 4.6)	2.7 (1.1; 7.3)	3.9 (1.5; 10.5)	7.0 (2.6; 18.9)	11.0 (4.6; 29.7)	16.0 (5.9; 43.0)	21.8 (8.1; 58.8)
HSF	0.5 (0.2; 1.1)	1.9 (0.8; 4.5)	2.9 (1.1; 7.0)	4.2 (1.8; 10.1)	7.4 (3.1; 17.8)	11.5 (4.5; 27.6)	16.6 (6.9; 39.6)	22.4 (9.4; 53.6)
IFQ	0.2 (0.1; 0.5)	0.8 (0.3; 2.3)	1.3 (0.5; 3.7)	2.0 (0.7; 5.7)	3.9 (1.4; 10.9)	6.4 (2.3; 18.1)	9.8 (3.5; 27.5)	13.8 (4.9; 39.0)
MFS	0.5 (0.3; 1.1)	1.6 (0.8; 3.4)	2.3 (1.1; 4.9)	3.1 (1.5; 6.5)	5.0 (2.4; 10.4)	7.2 (3.4; 15.0)	9.6 (4.6; 20.2)	12.4 (5.9; 25.9)
MPHF	0.5 (0.3; 1.0)	1.6 (0.8; 3.2)	2.3 (1.0; 4.6)	3.0 (1.5; 6.1)	4.9 (2.4; 9.8)	7.0 (3.2; 14.0)	9.4 (4.7; 18.9)	12.1 (6.0; 24.3)
NLTCS	0.2 (0.0; 1.0)	2.1 (0.4; 10.8)	4.7 (1.0; 23.7)	8.8 (1.7; 44.9)	24.2 (4.7; 123.1)	52.8 (10.8; 269.0)	100.0 (19.6; 509.6)	171.7 (33.7; 874.6)
PFI	0.7 (0.4; 1.4)	1.5 (0.8; 2.8)	1.9 (1.4; 3.5)	2.2 (1.2; 4.2)	3.0 (1.6; 5.7)	3.8 (2.8; 7.1)	4.6 (2.4; 8.6)	5.3 (2.8; 10.1)
PHF	0.5 (0.2; 1.0)	1.4 (0.7; 2.9)	2.1 (1.0; 4.1)	2.8 (1.4; 5.5)	4.3 (2.2; 8.7)	6.2 (2.9; 12.4)	8.3 (4.2; 16.5)	10.6 (5.3; 21.1)
SDFI	0.4 (0.2; 1.0)	1.4 (0.6; 3.4)	2.1 (1.0; 5.1)	2.9 (1.2; 7.1)	5.0 (2.1; 12.0)	7.5 (3.4; 18.0)	10.4 (4.3; 25.0)	13.7 (5.7; 33.1)
SHCFS	0.4 (0.2; 0.8)	1.2 (0.5; 2.5)	1.7 (0.8; 3.6)	2.3 (1.1; 5.0)	3.8 (1.8; 8.1)	5.6 (2.5; 11.9)	7.6 (3.6; 16.2)	9.9 (4.6; 21.1)
SI	0.1 (0.0; 0.4)	0.7 (0.2; 2.1)	1.2 (0.4; 3.6)	1.8 (0.6; 5.6)	3.7 (1.2; 11.2)	6.4 (2.1; 19.3)	9.9 (3.3; 30.0)	14.4 (4.7; 43.7)
SOF	0.4 (0.2; 0.9)	1.1 (0.5; 2.6)	1.6 (0.9; 3.6)	2.1 (0.9; 4.7)	3.2 (1.4; 7.3)	4.5 (2.6; 10.2)	6.0 (2.7; 13.5)	7.6 (3.4; 17.1)
SPPB	0.5 (0.2; 1.2)	1.7 (0.8; 3.8)	2.5 (1.2; 5.5)	3.3 (1.5; 7.5)	5.4 (2.4; 12.1)	7.9 (3.8; 17.7)	10.7 (4.8; 24.0)	13.9 (6.2; 31.1)
SPQ	0.2 (0.1; 0.4)	0.7 (0.2; 1.7)	1.0 (0.4; 2.8)	1.5 (0.6; 4.0)	2.8 (1.1; 7.4)	4.5 (1.7; 11.8)	6.6 (2.5; 17.3)	9.1 (3.4; 23.9)
TFI	0.3 (0.1; 0.8)	1.2 (0.5; 2.9)	1.9 (0.8; 4.4)	2.6 (1.1; 6.2)	4.4 (1.9; 10.6)	6.7 (2.9; 16.0)	9.4 (4.0; 22.5)	12.6 (5.3; 30.0)
VES13	0.5 (0.2; 1.2)	2.0 (0.9; 4.8)	3.1 (1.2; 7.4)	4.5 (1.9; 10.6)	7.9 (3.3; 18.6)	12.2 (4.8; 28.7)	17.4 (7.4; 41.0)	23.4 (9.9; 55.4)
WHRH	0.5 (0.2; 1.3)	1.8 (0.7; 4.2)	2.5 (1.3; 6.1)	3.5 (1.4; 8.3)	5.6 (2.3; 13.4)	8.1 (4.2; 19.4)	11.0 (4.6; 26.4)	14.3 (6.0; 34.2)
ZED1	0.4 (0.2; 0.8)	1.1 (0.6; 2.0)	1.4 (0.8; 2.7)	1.9 (1.0; 3.5)	2.8 (1.5; 5.2)	3.8 (2.0; 7.1)	4.9 (2.6; 9.2)	6.0 (3.2; 11.4)
ZED2	0.3 (0.2; 0.7)	0.9 (0.5; 1.8)	1.3 (0.7; 2.6)	1.7 (0.9; 3.4)	2.6 (1.3; 5.2)	3.7 (1.8; 7.3)	4.8 (2.4; 9.6)	6.1 (3.1; 12.1)
ZED3	0.2 (0.1; 0.5)	0.8 (0.3; 1.7)	1.1 (0.5; 2.5)	1.5 (0.7; 3.4)	2.5 (1.1; 5.6)	3.7 (1.7; 8.2)	5.1 (2.3; 11.3)	6.6 (3.0; 14.7)

[1]Hazard ratios calculated from age at baseline to age at the end of the interval.

S6 Table. Cardiovascular hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis

Table S6. Cardiovascular hazard ratios of frailty scores assessed in intervals from1 to 7 years[1]: age-adjusted model and categorical analysis

Scores	HR1 (LCI; UCI)	HR2 (LCI; UCI)	HR2.5 (LCI; UCI)	HR3 (LCI; UCI)	HR4 (LCI; UCI)	HR5 (LCI; UCI)	HR6 (LCI; UCI)	HR7 (LCI; UCI)
BFI frail	0.3 (0.2; 0.7)	0.7 (0.2; 2.4)	0.9 (0.2; 3.7)	1.1 (0.3; 5.1)	1.6 (0.3; 8.7)	2.0 (0.5; 13.1)	2.5 (0.3; 18.4)	3.0 (0.4; 24.4)
CGA frail	0.6 (0.3; 1.0)	1.0 (0.3; 3.0)	1.7 (0.3; 4.4)	2.0 (0.6; 6.0)	2.9 (0.6; 9.8)	3.7 (0.6; 14.2)	4.6 (0.6; 19.3)	5.5 (0.0; 24.9)
CGA pre-frail	0.8 (0.6; 1.0)	1.0 (0.6; 2.9)	2.2 (0.6; 4.0)	2.7 (0.8; 5.3)	3.8 (0.8; 8.1)	4.9 (0.5; 11.2)	6.1 (0.8; 14.7)	7.3 (0.9; 18.4)
CGAST frail	0.8 (0.5; 1.3)	1.3 (0.5; 4.0)	2.1 (0.5; 5.7)	2.5 (0.8; 7.6)	3.4 (0.8; 11.9)	4.3 (0.7; 17.0)	5.2 (0.8; 22.6)	6.2 (0.0; 28.9)
CGAST pre frail	1.0 (0.7; 1.6)	1.6 (0.7; 4.5)	2.7 (0.7; 6.3)	3.3 (1.0; 8.3)	4.5 (1.0; 12.8)	5.7 (1.8; 17.8)	6.9 (1.0; 23.4)	8.1 (1.5; 29.5)
CSBA frail	0.7 (0.5; 1.0)	1.0 (0.5; 2.1)	1.3 (0.5; 2.6)	1.5 (0.7; 3.2)	1.8 (0.7; 4.3)	2.2 (0.3; 5.5)	2.5 (0.7; 6.7)	2.7 (0.1; 7.9)
EFS frail	1.2 (0.5; 2.5)	2.5 (0.5; 5.9)	1.8 (0.5; 7.8)	1.9 (1.2; 9.7)	2.2 (1.2; 13.9)	2.4 (1.9; 18.2)	2.6 (1.2; 22.8)	2.8 (1.9; 27.6)
FI40 frail	0.8 (0.5; 1.1)	1.1 (0.5; 2.6)	1.7 (0.5; 3.4)	1.9 (0.8; 4.2)	2.5 (0.8; 6.0)	3.0 (0.4; 7.9)	3.5 (0.8; 9.9)	3.9 (0.6; 11.9)
FI70 frail	0.8 (0.6; 1.2)	1.2 (0.6; 2.7)	1.7 (0.6; 3.5)	1.9 (0.8; 4.3)	2.4 (0.8; 6.0)	2.9 (0.4; 7.8)	3.3 (0.8; 9.6)	3.7 (0.7; 11.5)
FiND frail	0.6 (0.4; 1.0)	1.0 (0.4; 2.5)	1.4 (0.4; 3.4)	1.6 (0.6; 4.4)	2.0 (0.6; 6.5)	2.5 (0.4; 8.8)	2.9 (0.6; 11.3)	3.3 (0.5; 14.0)
FS frail	0.5 (0.3; 1.0)	1.0 (0.3; 3.3)	1.6 (0.3; 4.9)	2.0 (0.5; 6.8)	2.7 (0.5; 11.3)	3.5 (0.6; 16.6)	4.4 (0.5; 22.9)	5.2 (0.3; 30.0)
FS pre- frail	0.8 (0.6; 1.1)	1.1 (0.6; 3.0)	2.3 (0.6; 4.1)	2.8 (0.8; 5.4)	3.9 (0.8; 8.2)	5.1 (0.5; 11.5)	6.3 (0.8; 15.0)	7.5 (0.0; 18.8)
FSS frail	0.6 (0.3; 0.9)	0.9 (0.3; 2.5)	1.4 (0.3; 3.5)	1.7 (0.6; 4.6)	2.3 (0.6; 7.1)	2.8 (0.4; 10.0)	3.4 (0.6; 13.1)	4.0 (0.5; 16.5)
FSS pre frail	0.8 (0.6; 1.1)	1.1 (0.6; 2.7)	2.0 (0.6; 3.6)	2.4 (0.8; 4.5)	3.2 (0.8; 6.6)	4.0 (0.4; 8.9)	4.9 (0.8; 11.4)	5.7 (0.7; 13.9)
G8 frail	0.8 (0.5; 1.2)	1.2 (0.5; 2.8)	1.7 (0.5; 3.7)	2.0 (0.8; 4.6)	2.6 (0.8; 6.7)	3.1 (0.4; 8.8)	3.7 (0.8; 11.1)	4.2 (0.8; 13.4)
GFI frail	0.6 (0.4; 0.9)	0.9 (0.4; 2.1)	1.3 (0.4; 2.7)	1.5 (0.6; 3.4)	1.9 (0.6; 4.8)	2.3 (0.3; 6.3)	2.7 (0.6; 7.8)	3.1 (0.1; 9.5)
HRCA frail	0.8 (0.5; 1.1)	1.1 (0.5; 2.5)	1.6 (0.5; 3.3)	1.8 (0.8; 4.1)	2.3 (0.8; 5.7)	2.8 (0.4; 7.5)	3.2 (0.8; 9.2)	3.6 (0.5; 11.1)
IFQ frail	1.0 (0.4; 2.4)	2.4 (0.4; 6.6)	1.6 (0.4; 9.2)	1.8 (1.0; 12.1)	2.1 (1.0; 18.5)	2.4 (1.12; 25.7)	2.6 (1.0; 33.7)	2.9 (1.6; 42.3)
MFS frail	0.6 (0.3; 1.3)	1.3 (0.3; 4.3)	1.6 (0.3; 6.3)	2.0 (0.6; 8.6)	2.7 (0.6; 14.2)	3.3 (0.8; 20.9)	4.0 (0.6; 28.7)	4.7 (0.3; 37.5)
MFS pre-frail	0.8 (0.4; 1.5)	1.5 (0.4; 4.8)	2.1 (0.4; 7.0)	2.5 (0.8; 9.4)	3.3 (0.8; 15.2)	4.2 (0.9; 22.1)	5.1 (0.8; 29.9)	5.9 (0.8; 38.6)
PFI frail	0.7 (0.3; 1.4)	1.4 (0.3; 4.8)	1.8 (0.3; 7.1)	2.2 (0.7; 9.9)	2.9 (0.7; 16.4)	3.7 (0.9; 24.4)	4.5 (0.7; 33.7)	5.3 (0.8; 44.2)
PFI pre frail	1.0 (0.7; 1.4)	1.4 (0.7; 3.7)	2.5 (0.7; 5.1)	3.1 (1.0; 6.5)	4.2 (1.0; 9.8)	5.3 (1.6; 13.4)	6.4 (1.0; 17.3)	7.5 (1.7; 21.5)
PHF frail	0.6 (0.3; 1.2)	1.2 (0.3; 4.3)	1.9 (0.3; 6.6)	2.4 (0.6; 9.2)	3.3 (0.6; 15.7)	4.4 (0.9; 23.8)	5.5 (0.6; 33.3)	6.6 (0.3; 44.3)
PHF pre-frail	0.8 (0.4; 1.3)	1.3 (0.4; 4.2)	2.3 (0.4; 6.2)	2.8 (0.8; 8.5)	4.0 (0.8; 13.9)	5.3 (0.8; 20.5)	6.6 (0.8; 28.0)	7.9 (0.2; 36.6)
SDFI frail	0.6 (0.4; 0.9)	0.9 (0.4; 2.2)	1.4 (0.4; 2.9)	1.6 (0.6; 3.6)	2.1 (0.6; 5.1)	2.5 (0.3; 6.6)	2.9 (0.6; 8.3)	3.3 (0.2; 10.0)
SHCFS frail	0.7 (0.4; 1.1)	1.1 (0.4; 2.8)	1.4 (0.4; 3.7)	1.6 (0.7; 4.7)	2.0 (0.7; 6.9)	2.4 (0.4; 9.2)	2.8 (0.7; 11.7)	3.1 (0.8; 14.4)
SI frail	0.5 (0.2; 1.3)	1.3 (0.2; 4.1)	1.2 (0.2; 5.9)	1.3 (0.5; 8.0)	1.7 (0.5; 13.0)	2.0 (0.8; 18.8)	2.4 (0.5; 25.5)	2.7 (0.1; 33.0)
SOF frail	0.5 (0.3; 0.9)	0.9 (0.3; 3.1)	1.4 (0.3; 4.5)	1.8 (0.5; 6.1)	2.4 (0.5; 9.9)	3.1 (0.6; 14.5)	3.8 (0.5; 19.7)	4.5 (0.1; 25.6)
SOF pre-frail	0.7 (0.5; 1.0)	1.0 (0.5; 2.8)	2.1 (0.5; 3.8)	2.5 (0.7; 5.0)	3.4 (0.7; 7.5)	4.4 (0.5; 10.3)	5.4 (0.7; 13.4)	6.4 (0.8; 16.7)
SPPB frail	0.6 (0.4; 0.9)	0.9 (0.4; 2.1)	1.3 (0.4; 2.7)	1.5 (0.6; 3.3)	1.9 (0.6; 4.6)	2.2 (0.3; 6.0)	2.6 (0.6; 7.4)	2.9 (0.1; 8.8)
SPQ frail	0.5 (0.4; 0.6)	0.6 (0.4; 0.9)	0.6 (0.4; 1.0)	0.6 (0.5; 1.2)	0.7 (0.5; 1.4)	0.7 (0.1; 1.5)	0.8 (0.5; 1.7)	0.8 (0.9; 1.9)
TFI frail	0.7 (0.5; 1.0)	1.0 (0.5; 2.1)	1.3 (0.5; 2.6)	1.5 (0.7; 3.2)	1.9 (0.7; 4.4)	2.2 (0.3; 5.6)	2.5 (0.7; 6.8)	2.8 (0.1; 8.1)
VES13 frail	0.7 (0.5; 1.0)	1.0 (0.5; 2.4)	1.5 (0.5; 3.1)	1.7 (0.7; 3.9)	2.2 (0.7; 5.5)	2.7 (0.3; 7.2)	3.1 (0.7; 9.0)	3.5 (0.4; 10.8)
WHRH frail	0.8 (0.5; 1.2)	1.2 (0.5; 2.6)	1.5 (0.5; 3.3)	1.7 (0.8; 4.1)	2.0 (0.8; 5.7)	2.4 (0.4; 7.3)	2.7 (0.8; 8.9)	3.0 (0.6; 10.6)
ZED1 frail	0.8 (0.4; 1.8)	1.8 (0.4; 4.1)	1.2 (0.4; 5.4)	1.3 (0.8; 6.8)	1.4 (0.8; 9.6)	1.6 (0.6; 12.6)	1.7 (0.8; 15.7)	1.8 (0.1; 19.0)
ZED2 frail	0.7 (0.2; 1.9)	1.9 (0.2; 7.4)	1.5 (0.2; 11.3)	1.8 (0.7; 16.0)	2.3 (0.7; 27.8)	2.8 (0.16; 42.6)	3.3 (0.7; 60.5)	3.8 (0.4; 81.3)
ZED3 frail	0.1 (0.0; 3.4)	3.4 (0.0; >99.9)	0.6 (0.0; >99.9)	0.9 (0.1; >99.9)	1.5 (0.1; >99.9)	2.2 (1.0; >99.9)	3.0 (0.1; >99.9)	4.0 (0.1; >99.9)

Hazard ratios calculated from age at baseline to age at the end of the interval.

S7 Table. Cancer hazard ratios of frailty scores (n = 4,792) calculated at median time follow-up (2.5 years)

Table S7. Cancer hazard ratios of frailty scores (n=4792) calculated at median time follow-up (2.5 years)

	Continuous analysis					Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]	Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]
Phenotype of frailty approach									
SPPB	1.8 (0.8; 3.9)	1.8 (1.0; 3.3)	1.5 (0.8; 2.8)	1.6 (0.8; 3.2)	SOF frail	1.4 (0.6; 3.2)	1.5 (0.6; 3.4)	1.4 (0.1; 3.3)	1.4 (0.5; 3.5)
SOF	1.5 (0.9; 2.7)	1.6 (0.9; 2.9)	1.5 (0.9; 2.8)	1.5 (0.8; 3.0)	SOF pre-frail	1.3 (0.8; 2.2)	1.4 (0.8; 2.3)	1.3 (0.1; 2.2)	1.4 (0.8; 2.3)
PHF	1.7 (1.0; 2.9)	1.6 (1.0; 2.6)	1.4 (1.0; 2.4)	1.4 (0.8; 2.5)	PFI frail	1.2 (0.4; 4.2)	1.3 (0.4; 4.5)	1.2 (0.1; 4.4)	1.2 (0.3; 4.2)
ZED2	1.5 (0.9; 2.3)	1.5 (1.0; 2.4)	1.4 (0.9; 2.3)	1.4 (0.9; 2.3)	PFI pre frail	1.3 (0.7; 2.5)	1.4 (0.8; 2.6)	1.3 (0.1; 2.5)	1.3 (0.7; 2.5)
MPHF	1.3 (0.8; 2.2)	1.5 (0.9; 2.5)	1.3 (0.8; 2.2)	1.1 (0.6; 2.0)	FS frail	1.2 (0.5; 2.7)	1.2 (0.5; 2.8)	1.2 (0.1; 2.7)	1.0 (0.4; 2.5)
FS	1.3 (0.7; 2.3)	1.4 (0.7; 2.6)	1.2 (0.7; 2.3)	0.9 (0.5; 1.9)	FS pre- frail	1.3 (0.8; 2.0)	1.3 (0.8; 2.1)	1.3 (0.1; 2.0)	1.2 (0.7; 2.0)
FiND	1.3 (0.8; 2.2)	1.4 (0.8; 2.3)	1.2 (0.8; 2.1)	1.1 (0.6; 2.2)	PHF frail	1.2 (0.5; 2.8)	1.3 (0.5; 3.0)	1.2 (0.0; 2.8)	1.1 (0.4; 3.9)
PFI	1.2 (0.7; 2.0)	1.3 (0.8; 2.2)	1.2 (0.7; 2.1)	1.1 (0.6; 2.0)	PHF pre-frail	1.2 (0.6; 2.3)	1.2 (0.6; 2.4)	1.2 (0.0; 2.3)	1.2 (0.6; 2.4)
ZED1	1.1 (0.7; 1.7)	1.2 (0.8; 1.9)	1.1 (0.7; 1.8)	1.0 (0.5; 1.7)	FiND frail	1.2 (0.6; 2.4)	1.3 (0.7; 2.5)	1.2 (0.0; 2.4)	1.2 (0.6; 2.4)
ZED3	1.0 (0.6; 1.7)	1.1 (0.6; 2.0)	1.0 (0.6; 1.8)	0.9 (0.5; 1.7)	SPPB frail	1.1 (0.7; 1.8)	1.2 (0.7; 1.9)	1.1 (0.1; 1.8)	1.1 (0.7; 1.9)
BDE	0.7 (0.4; 1.2)	0.7 (0.4; 1.2)	0.6 (0.4; 1.1)	0.9 (0.6; 1.6)	ZED1 frail	1.1 (0.1; 8.2)	1.1 (0.1; 8.4)	1.1 (0.1; 8.2)	1.0 (0.1; 8.7)
					ZED2 frail	0.5 (0.2; 1.1)	0.4 (0.0; 42.6)	0.5 (0.2; 1.1)	0.4 (0.0; 42.3)
					ZED3 frail	0.6 (0.0; >99.9)	0 (0; >99.9)	0 (0; >99.9)	0 (0; >99.9)
Multidimensional approach									
EFS	2.0 (0.8; 4.8)	2.4 (1.0; 5.7)	2.0 (0.8; 4.9)	1.4 (0.5; 4.2)	SPQ frail	1.1 (0.7; 1.9)	1.4 (1.0; 2.1)	1.1 (0.9; 1.4)	1.1 (0.6; 2.9)
G8	1.9 (0.8; 4.3)	2.0 (0.9; 4.5)	1.2 (0.8; 2.1)	1.9 (0.7; 5.0)	IFQ frail	1.3 (0.4; 4.5)	1.4 (0.4; 4.9)	1.4 (0.8; 2.5)	1.2 (0.3; 4.5)
CGAST	1.5 (0.7; 3.2)	1.8 (0.9; 3.7)	1.6 (0.7; 3.3)	1.4 (0.6; 3.4)	EFS frail	1.3 (0.4; 4.4)	1.4 (0.4; 4.7)	1.3 (0.4; 4.4)	1.2 (0.3; 4.1)
GFI	1.5 (0.7; 3.2)	1.8 (0.8; 3.7)	1.5 (0.7; 3.1)	1.2 (0.5; 3.2)	FSS frail	1.2 (0.6; 2.3)	1.2 (0.6; 2.4)	1.2 (0.2; 2.3)	1.1 (0.5; 2.4)
IFQ	1.3 (0.6; 2.8)	1.6 (0.7; 3.3)	1.3 (0.6; 2.9)	1.1 (0.5; 2.6)	FSS pre frail	1.3 (0.8; 2.1)	1.3 (0.8; 2.1)	1.3 (0.2; 2.1)	1.3 (0.8; 2.2)
TFI	1.2 (0.6; 2.4)	1.5 (0.8; 2.9)	1.2 (0.6; 2.5)	1.0 (0.4; 2.3)	CGAST frail	1.2 (0.6; 2.2)	1.2 (0.7; 2.3)	1.2 (0.0; 2.2)	1.1 (0.5; 2.4)
CSBA	2.4 (1.1; 5.2)	1.4 (0.6; 3.3)	1.1 (1.1; 2.7)	0.7 (0.2; 2.1)	CGAST pre frail	1.1 (0.6; 2.0)	1.1 (0.6; 2.0)	1.1 (0.0; 2.0)	1.1 (0.6; 2.0)
SPQ	1.2 (0.6; 2.4)	1.4 (0.7; 2.9)	1.3 (0.6; 2.6)	1.1 (0.5; 2.3)	G8 frail	1.1 (0.7; 1.7)	1.1 (0.7; 1.8)	1.1 (0.1; 1.8)	1.1 (0.6; 1.9)
FSS	1.3 (0.7; 2.2)	1.4 (0.8; 2.3)	1.2 (0.7; 2.1)	1.1 (0.6; 2.1)	GFI frail	1.1 (0.7; 1.8)	1.1 (0.7; 1.9)	1.1 (0.5; 1.8)	1.0 (0.6; 1.8)
SDFI	0.9 (0.5; 1.8)	1.3 (0.7; 2.7)	1.1 (0.5; 2.3)	0.8 (0.4; 2.0)	MFS frail	0.8 (0.3; 1.9)	1.1 (0.5; 2.4)	0.8 (0.0; 2.3)	0.9 (0.4; 2.2)
SI	1.0 (0.5; 2.1)	1.2 (0.6; 2.7)	1.1 (0.5; 2.4)	0.9 (0.4; 2.1)	MFS pre-frail	0.9 (0.4; 1.9)	1.1 (0.5; 2.3)	0.9 (0.0; 2.2)	1.0 (0.5; 2.2)
MFS	1.0 (0.6; 2.1)	1.2 (0.7; 2.1)	1.1 (0.6; 1.9)	0.9 (0.5; 1.6)	CSBA frail	1.2 (0.8; 2.0)	1.1 (0.7; 1.8)	1.0 (0.6; 1.7)	1.0 (0.6; 1.7)
HSF	1.1 (0.5; 2.1)	1.1 (0.6; 2.3)	1.0 (0.5; 2.0)	0.7 (0.3; 1.6)	TFI frail	1.0 (0.6; 1.6)	1.1 (0.7; 1.7)	1.0 (0.8; 1.2)	0.9 (0.5; 1.6)
BFI	0.8 (0.5; 1.4)	0.9 (0.5; 1.6)	0.8 (0.5; 1.4)	0.7 (0.4; 1.3)	SI frail	0.9 (0.1; 5.6)	1.0 (0.2; 6.0)	0.9 (0.2; 5.7)	0.9 (0.1; 6.4)
					SDFI frail	0.9 (0.5; 1.5)	1.0 (0.6; 1.6)	0.9 (0.0; 1.5)	0.8 (0.5; 1.5)
					BFI frail	0.7 (0.3; 2.0)	0.8 (0.3; 2.1)	0.7 (0.2; 2.0)	0.7 (0.3; 2.0)
Accumulation of deficits approach									
FI70	1.2 (0.5; 2.7)	1.5 (0.7; 3.6)	1.3 (0.5; 3.0)	0.7 (0.2; 2.2)	CGA frail	1.0 (0.5; 2.0)	1.1 (0.6; 2.2)	1.0 (0.2; 2.1)	0.9 (0.4; 2.0)
NLTCS	1.4 (0.4; 4.4)	1.5 (0.5; 4.9)	1.3 (0.4; 4.1)	0.7 (0.2; 2.7)	CGA pre-frail	1.1 (0.7; 1.8)	1.2 (0.8; 1.9)	1.1 (0.2; 1.8)	1.1 (0.7; 1.8)
FI40	1.2 (0.5; 2.8)	1.5 (0.6; 3.6)	1.2 (0.5; 3.0)	0.7 (0.3; 2.0)	FI70 frail	1.1 (0.6; 1.8)	1.1 (0.7; 1.9)	1.1 (0.2; 1.9)	1.0 (0.5; 1.2)
EFIP	1.2 (0.5; 2.8)	1.4 (0.6; 3.3)	1.2 (0.5; 2.8)	0.7 (0.2; 2.1)	FI40 frail	1.1 (0.6; 1.7)	1.1 (0.7; 1.9)	1.1 (0.2; 1.8)	0.9 (0.5; 1.6)
FIBLSA	1.2 (0.4; 3.1)	1.4 (0.5; 3.7)	1.3 (0.4; 3.0)	0.6 (0.2; 1.9)					
CGA	1.0 (0.4; 2.9)	1.4 (0.5; 3.9)	1.1 (0.4; 3.2)	0.6 (0.2; 2.0)					
Disability approach									
WHRH	1.3 (0.7; 2.4)	1.5 (0.8; 2.7)	1.3 (0.7; 2.5)	1.4 (0.6; 2.9)	WHRH frail	1.1 (0.6; 2.0)	1.2 (0.6; 2.2)	1.1 (0.6; 2.1)	1.0 (0.5; 2.1)
VES13	1.2 (0.6; 2.3)	1.4 (0.7; 2.8)	1.3 (0.6; 2.5)	1.3 (0.6; 2.8)	VES13 frail	1.1 (0.6; 1.8)	1.1 (0.7; 1.9)	1.1 (0.1; 1.9)	1.1 (0.6; 1.0)
HRCA	1.2 (0.6; 2.4)	1.4 (0.7; 2.9)	1.2 (0.6; 2.5)	1.1 (0.4; 2.7)	SHCFS frail	1.1 (0.5; 2.2)	1.1 (0.5; 2.3)	1.0 (0.5; 2.2)	1.0 (0.4; 2.1)
SHCFS	1.2 (0.7; 2.0)	1.2 (0.7; 2.1)	1.1 (0.7; 1.9)	0.9 (0.5; 1.8)	HRCA frail	1.0 (0.6; 1.7)	1.1 (0.6; 1.8)	1.0 (0.2; 1.8)	1.0 (0.5; 1.9)

[1]Model 0= Crude models. [2]Model 1= HR adjusted by sex. [3]Model 2= Model 1 + smoking status and alcohol consumption. [4]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. Models were fitted using age as time scale, with time 0 = age at entry of study and time 1 =age at event or censoring date.

S8 Table. Cancer hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and continuous analysis

Table S8. Cancer hazard ratios of frailty scores assessed in intervals from1 to 7 years[1]: age-adjusted model and continuous analysis

Scores	HR 1 (LCI; UCI)	HR 2 (LCI; UCI)	HR 2.5 (LCI; UCI)	HR 3 (LCI; UCI)	HR 4 (LCI; UCI)	HR 5 (LCI; UCI)	HR 6 (LCI; UCI)	HR 7 (LCI; UCI)
BDE	0.6 (0.3; 1.0)	0.7 (0.4; 1.2)	0.7 (0.4; 1.2)	0.7 (0.4; 1.3)	0.7 (0.4; 1.1)	0.8 (0.5; 1.4)	0.9 (0.5; 1.5)	0.9 (0.5; 1.5)
BFI	0.5 (0.3; 0.9)	0.7 (0.4; 1.2)	0.8 (0.5; 1.4)	0.8 (0.5; 1.5)	0.7 (0.4; 1.2)	1.1 (0.6; 1.8)	1.1 (0.7; 2.0)	1.2 (0.7; 2.1)
CGA	0.4 (0.2; 1.3)	0.8 (0.3; 2.3)	1.0 (0.4; 2.9)	1.2 (0.4; 3.4)	1.0 (0.4; 3.0)	1.9 (0.7; 5.3)	2.2 (0.8; 6.2)	2.5 (0.9; 7.1)
CGAST	0.9 (0.4; 1.8)	1.3 (0.7; 2.8)	1.5 (0.7; 3.2)	1.7 (0.8; 3.6)	1.5 (0.7; 3.0)	2.4 (1.2; 4.9)	2.7 (0.3; 5.5)	2.9 (1.4; 6.1)
CSBA	1.5 (0.7; 3.3)	2.1 (1.0; 4.6)	2.4 (1.1; 5.2)	2.6 (1.2; 5.7)	2.2 (1.0; 4.8)	3.3 (1.5; 7.3)	3.7 (1.7; 8.0)	3.9 (1.8; 8.6)
EFIP	0.6 (0.3; 1.4)	1.0 (0.4; 2.3)	1.2 (0.5; 2.8)	1.4 (0.6; 3.2)	1.2 (0.5; 2.7)	2.0 (0.9; 4.7)	2.3 (0.0; 5.4)	2.6 (1.1; 6.1)
EFS	0.8 (0.3; 2.0)	1.6 (0.7; 3.9)	2.0 (0.8; 4.8)	2.4 (1.0; 5.7)	2.1 (0.9; 5.1)	3.8 (1.6; 9.3)	4.5 (0.9; 11.1)	5.3 (2.2; 12.8)
FI40	0.6 (0.2; 1.3)	1.0 (0.4; 2.4)	1.2 (0.5; 2.8)	1.4 (0.6; 3.3)	1.2 (0.5; 2.9)	2.1 (0.9; 5.0)	2.4 (0.0; 5.9)	2.8 (1.1; 6.7)
FI70	0.6 (0.2; 1.3)	1.0 (0.4; 2.3)	1.2 (0.5; 2.7)	1.3 (0.6; 3.1)	1.2 (0.5; 2.7)	2.0 (0.9; 4.6)	2.3 (0.0; 5.3)	2.6 (1.1; 6.0)
FIBLSA	0.5 (0.2; 1.3)	1.0 (0.4; 2.5)	1.2 (0.4; 3.1)	1.4 (0.5; 3.7)	1.3 (0.5; 3.3)	2.3 (0.9; 6.0)	2.7 (0.0; 7.1)	3.1 (1.2; 8.2)
FiND	0.9 (0.5; 1.5)	1.2 (0.7; 2.0)	1.3 (0.8; 2.2)	1.4 (0.8; 2.4)	1.2 (0.7; 2.0)	1.7 (1.0; 3.0)	1.9 (0.1; 3.2)	2.0 (1.2; 3.4)
FS	0.8 (0.5; 1.6)	1.1 (0.6; 2.1)	1.3 (0.7; 2.3)	1.4 (0.7; 2.5)	1.2 (0.6; 2.1)	1.7 (0.9; 3.1)	1.8 (0.0; 3.4)	2.0 (1.1; 3.6)
FSS	0.8 (0.5; 1.4)	1.1 (0.7; 2.0)	1.3 (0.7; 2.2)	1.4 (0.8; 2.3)	1.2 (0.7; 2.0)	1.7 (1.0; 2.9)	1.8 (0.1; 3.1)	2.0 (1.2; 3.4)
G8	1.3 (0.6; 3.1)	1.7 (0.7; 4.0)	1.9 (0.8; 4.3)	2.0 (0.9; 4.6)	1.7 (0.7; 3.9)	2.4 (1.0; 5.5)	2.5 (1.1; 5.8)	2.7 (1.2; 6.2)
GFI	0.9 (0.4; 1.9)	1.3 (0.6; 2.8)	1.5 (0.7; 3.2)	1.7 (0.8; 3.5)	1.4 (0.7; 3.0)	2.3 (1.1; 4.8)	2.6 (0.2; 5.3)	2.8 (1.3; 5.8)
HRCA	0.6 (0.3; 1.3)	1.0 (0.5; 2.1)	1.2 (0.6; 2.4)	1.3 (0.6; 2.8)	1.1 (0.5; 2.4)	1.9 (0.9; 3.9)	2.2 (0.0; 4.5)	2.4 (1.2; 5.0)
HSF	0.6 (0.3; 1.3)	0.9 (0.5; 1.9)	1.1 (0.5; 2.1)	1.2 (0.6; 2.4)	1.0 (0.5; 2.0)	1.6 (0.8; 3.1)	1.7 (0.9; 3.5)	1.9 (0.9; 3.8)
IFQ	0.7 (0.3; 1.5)	1.1 (0.5; 2.4)	1.3 (0.6; 2.8)	1.5 (0.7; 3.1)	1.3 (0.6; 2.7)	2.1 (1.0; 4.4)	2.4 (0.1; 5.0)	2.6 (1.3; 5.5)
MFS	0.9 (0.5; 1.8)	1.1 (0.6; 2.0)	1.1 (0.6; 2.1)	1.2 (0.6; 2.1)	1.1 (0.6; 1.9)	1.3 (0.7; 2.4)	1.3 (0.7; 2.4)	1.3 (0.7; 2.5)
MPHF	0.9 (0.5; 1.5)	1.2 (0.7; 2.0)	1.3 (0.8; 2.2)	1.4 (0.9; 2.4)	1.2 (0.7; 2.0)	1.8 (1.1; 3.0)	1.9 (0.2; 3.2)	2.1 (1.2; 3.5)
NLTCS	0.5 (0.1; 1.5)	1.0 (0.3; 3.4)	1.4 (0.4; 4.4)	1.7 (0.5; 5.4)	1.6 (0.5; 5.1)	3.0 (0.9; 9.7)	3.7 (0.1; 12.0)	4.4 (1.4; 14.3)
PFI	0.7 (0.4; 1.3)	1.1 (0.6; 1.8)	1.2 (0.7; 2.0)	1.3 (0.8; 2.2)	1.1 (0.7; 1.9)	1.7 (1.0; 2.9)	1.9 (0.1; 3.2)	2.1 (1.2; 3.5)
PHF	1.3 (0.7; 2.2)	1.6 (0.9; 2.7)	1.7 (1.0; 2.9)	1.8 (1.0; 3.0)	1.5 (0.9; 2.6)	2.1 (1.2; 3.5)	2.2 (1.3; 3.7)	2.3 (1.3; 3.9)
SDFI	0.6 (0.3; 1.2)	0.8 (0.4; 1.6)	0.9 (0.5; 1.8)	1.0 (0.5; 2.0)	0.9 (0.4; 1.7)	1.3 (0.7; 2.6)	1.4 (0.7; 2.9)	1.5 (0.8; 3.1)
SHCFS	0.8 (0.5; 1.4)	1.1 (0.6; 1.8)	1.2 (0.7; 2.0)	1.2 (0.7; 2.1)	1.1 (0.6; 1.8)	1.5 (0.9; 2.6)	1.6 (0.0; 2.8)	1.7 (1.0; 2.9)
SI	0.4 (0.2; 1.0)	0.8 (0.4; 1.8)	1.0 (0.5; 2.1)	1.2 (0.5; 2.5)	1.0 (0.5; 2.2)	1.8 (0.8; 3.9)	2.1 (0.0; 4.6)	2.4 (1.1; 5.2)
SOF	0.9 (0.5; 1.7)	1.4 (0.8; 2.4)	1.5 (0.9; 2.7)	1.7 (0.9; 3.0)	1.4 (0.8; 2.5)	2.2 (1.2; 3.9)	2.4 (0.4; 4.3)	2.6 (1.5; 4.7)
SPPB	1.3 (0.6; 2.8)	1.6 (0.7; 3.6)	1.8 (0.8; 3.9)	1.9 (0.8; 4.1)	1.6 (0.7; 3.6)	2.2 (1.0; 5.0)	2.4 (1.1; 5.3)	2.5 (1.1; 5.6)
SPQ	0.7 (0.3; 1.4)	1.0 (0.5; 2.1)	1.2 (0.6; 2.4)	1.3 (0.7; 2.7)	1.1 (0.6; 2.3)	1.8 (0.9; 3.8)	2.1 (0.0; 4.2)	2.3 (1.1; 4.7)
TFI	0.8 (0.4; 1.5)	1.1 (0.6; 2.1)	1.2 (0.6; 2.4)	1.4 (0.7; 2.6)	1.1 (0.6; 2.2)	1.7 (0.9; 3.3)	1.9 (0.0; 3.7)	2.1 (1.1; 4.0)
VES13	0.7 (0.4; 1.3)	1.1 (0.5; 2.0)	1.2 (0.6; 2.3)	1.3 (0.7; 2.6)	1.1 (0.6; 2.2)	1.8 (0.9; 3.6)	2.0 (0.1; 4.0)	2.2 (1.2; 4.4)
WHRH	0.8 (0.4; 1.5)	1.1 (0.6; 2.1)	1.3 (0.7; 2.4)	1.4 (0.7; 2.6)	1.2 (0.6; 2.2)	1.8 (1.0; 3.5)	2.0 (0.1; 3.8)	2.2 (1.2; 4.1)
ZED1	0.7 (0.4; 1.1)	1.0 (0.6; 1.5)	1.1 (0.7; 1.7)	1.2 (0.8; 1.9)	1.0 (0.6; 1.6)	1.6 (1.0; 2.5)	1.7 (0.1; 2.8)	1.9 (1.2; 3.0)
ZED2	1.1 (0.7; 1.7)	1.4 (0.9; 2.1)	1.5 (0.9; 2.3)	1.5 (1.0; 2.5)	1.3 (0.8; 2.1)	1.8 (1.1; 2.9)	1.9 (1.2; 3.1)	2.0 (1.3; 3.2)
ZED3	0.6 (0.4; 1.1)	0.9 (0.5; 1.6)	1.0 (0.6; 1.7)	1.1 (0.6; 1.9)	0.9 (0.5; 1.6)	1.4 (0.8; 2.4)	1.5 (0.8; 2.7)	1.6 (0.9; 2.9)

[1]Hazard ratios calculated from age at baseline to age at the end of the interval.

S9 Table. Cancer hazard ratios of frailty scores assessed in intervals from 1 to 7 years: Age-adjusted model and categorical analysis

Table S9. Cancer hazard ratios of frailty scores assessed in intervals from1 to 7 years: age-adjusted model and categorical analysis

Scores	HR1 (LCI; UCI)	HR2 (LCI; UCI)	HR2.5 (LCI; UCI)	HR3 (LCI; UCI)	HR4 (LCI; UCI)	HR5 (LCI; UCI)	HR6 (LCI; UCI)	HR7 (LCI; UCI)
BFI frail	0.5 (0.3; 0.9)	0.7 (0.3; 1.7)	0.8 (0.3; 2.1)	0.9 (0.3; 2.6)	1.0 (0.3; 3.4)	1.1 (0.3; 4.2)	1.2 (0.3; 5.0)	1.3 (0.3; 5.8)
CGA frail	0.9 (0.6; 1.2)	1.1 (0.6; 1.9)	1.1 (0.6; 2.2)	1.2 (0.6; 2.5)	1.3 (0.6; 3.0)	1.4 (0.6; 3.5)	1.4 (0.6; 3.9)	1.5 (0.5; 4.3)
CGA pre-frail	0.9 (0.7; 1.2)	1.1 (0.7; 1.7)	1.2 (0.7; 1.9)	1.2 (0.7; 1.1)	1.4 (0.7; 2.4)	1.5 (0.7; 2.7)	1.5 (0.7; 3.0)	1.6 (0.8; 3.3)
CGAST frail	1.0 (0.7; 1.4)	1.2 (0.7; 2.1)	1.2 (0.7; 2.3)	1.4 (0.7; 2.6)	1.4 (0.7; 3.0)	1.4 (0.7; 3.4)	1.5 (0.7; 3.8)	1.6 (1.6; 4.1)
CGAST pre frail	0.9 (0.7; 1.3)	1.1 (0.7; 1.8)	1.1 (0.7; 2.0)	1.3 (0.7; 2.2)	1.3 (0.7; 2.6)	1.3 (0.7; 2.9)	1.4 (0.7; 3.2)	1.4 (0.6; 3.5)
CSBA frail	1.0 (0.8; 1.3)	1.1 (0.8; 1.6)	1.1 (0.8; 1.8)	1.3 (0.8; 1.9)	1.2 (0.8; 2.2)	1.2 (0.8; 2.3)	1.2 (0.8; 2.5)	1.3 (1.6; 2.7)
EFS frail	1.1 (0.6; 2.1)	1.3 (0.6; 3.8)	1.4 (0.6; 4.7)	2.1 (0.6; 4.5)	1.5 (0.6; 7.1)	1.6 (0.6; 8.6)	1.7 (0.6; 10.2)	1.8 (1.3; 11.7)
FI40 frail	0.9 (0.7; 1.2)	1.1 (0.7; 1.7)	1.1 (0.7; 1.9)	1.2 (0.7; 1.0)	1.2 (0.7; 2.3)	1.3 (0.7; 2.6)	1.4 (0.7; 2.8)	1.4 (0.6; 3.0)
FI70 frail	0.9 (0.7; 1.2)	1.1 (0.7; 1.7)	1.1 (0.7; 1.9)	1.2 (0.7; 1.1)	1.3 (0.7; 2.5)	1.3 (0.7; 2.8)	1.4 (0.7; 3.1)	1.4 (0.6; 3.3)
FiND frail	1.1 (0.8; 1.5)	1.2 (0.8; 2.2)	1.3 (0.8; 2.5)	1.5 (0.8; 2.8)	1.4 (0.8; 3.2)	1.5 (0.8; 3.6)	1.5 (0.8; 4.0)	1.6 (1.6; 4.3)
FS frail	0.9 (0.6; 1.4)	1.1 (0.6; 2.4)	1.2 (0.6; 2.8)	1.4 (0.6; 2.3)	1.4 (0.6; 4.1)	1.6 (0.6; 4.8)	1.7 (0.6; 5.6)	1.7 (0.5; 6.3)
FS pre- frail	1.0 (0.8; 1.2)	1.2 (0.8; 1.8)	1.3 (0.8; 2.1)	1.2 (0.8; 2.3)	1.6 (0.8; 2.8)	1.7 (0.8; 3.1)	1.8 (0.8; 3.5)	1.9 (1.9; 3.8)
FSS frail	1.0 (0.7; 1.4)	1.2 (0.7; 2.1)	1.2 (0.7; 2.4)	1.4 (0.7; 2.7)	1.4 (0.7; 3.2)	1.5 (0.7; 3.6)	1.5 (0.7; 4.0)	1.6 (1.6; 4.4)
FSS pre frail	1.1 (0.8; 1.3)	1.3 (0.8; 1.9)	1.3 (0.8; 2.1)	1.3 (0.8; 2.3)	1.5 (0.8; 2.7)	1.6 (0.8; 3.0)	1.7 (0.8; 3.3)	1.7 (1.9; 3.5)
G8 frail	1.0 (0.8; 1.2)	1.1 (0.8; 1.7)	1.1 (0.8; 1.8)	1.2 (0.8; 1.0)	1.2 (0.8; 2.3)	1.3 (0.8; 2.5)	1.3 (0.8; 2.7)	1.4 (1.7; 2.9)
GFI frail	1.0 (0.8; 1.3)	1.1 (0.8; 1.7)	1.1 (0.8; 1.9)	1.3 (0.8; 1.0)	1.2 (0.8; 2.3)	1.3 (0.8; 2.5)	1.3 (0.8; 2.7)	1.4 (1.7; 2.9)
HRCA frail	0.9 (0.7; 1.1)	1.0 (0.7; 1.6)	1.1 (0.7; 1.8)	1.1 (0.7; 1.0)	1.2 (0.7; 2.3)	1.3 (0.7; 2.6)	1.3 (0.7; 2.9)	1.4 (0.6; 3.1)
IFQ frail	1.5 (0.8; 2.9)	1.4 (0.8; 4.3)	1.4 (0.8; 4.9)	2.9 (0.8; 4.4)	1.3 (0.8; 6.4)	1.3 (0.8; 7.3)	1.3 (0.8; 8.1)	1.3 (1.2; 8.8)
MFS frail	0.9 (0.6; 1.3)	1.0 (0.6; 2.1)	1.1 (0.6; 2.4)	1.3 (0.6; 2.8)	1.2 (0.6; 3.3)	1.2 (0.6; 3.9)	1.3 (0.6; 4.4)	1.3 (0.4; 4.8)
MFS pre-frail	0.9 (0.6; 1.3)	1.1 (0.6; 2.0)	1.1 (0.6; 2.3)	1.3 (0.6; 2.6)	1.2 (0.6; 3.1)	1.3 (0.6; 3.5)	1.3 (0.6; 3.9)	1.4 (0.4; 4.3)
PFI frail	0.8 (0.4; 1.6)	1.2 (0.4; 3.5)	1.3 (0.4; 4.5)	1.6 (0.4; 4.6)	1.7 (0.4; 7.8)	1.9 (0.4; 10.1)	2.1 (0.4; 12.4)	2.3 (0.4; 14.9)
PFI pre frail	0.9 (0.6; 1.2)	1.3 (0.6; 2.1)	1.4 (0.6; 2.6)	1.2 (0.6; 2.0)	1.8 (0.6; 3.8)	2.0 (0.6; 4.6)	2.2 (0.6; 5.4)	2.4 (0.9; 6.2)
PHF frail	0.9 (0.6; 1.5)	1.2 (0.6; 2.5)	1.3 (0.6; 3.0)	1.5 (0.6; 3.5)	1.5 (0.6; 4.4)	1.6 (0.6; 5.3)	1.7 (0.6; 6.1)	1.8 (0.5; 6.9)
PHF pre-frail	0.9 (0.6; 1.3)	1.1 (0.6; 2.1)	1.2 (0.6; 2.4)	1.3 (0.6; 2.8)	1.4 (0.6; 3.4)	1.6 (0.6; 3.9)	1.7 (0.6; 4.5)	1.7 (0.6; 5.0)
SDFI frail	0.7 (0.5; 0.9)	0.9 (0.5; 1.4)	1.0 (0.5; 1.6)	0.9 (0.5; 1.8)	1.1 (0.5; 2.1)	1.2 (0.5; 2.5)	1.3 (0.5; 2.7)	1.3 (0.6; 3.0)
SHCFS frail	0.9 (0.6; 1.3)	1.1 (0.6; 2.0)	1.1 (0.6; 2.3)	1.3 (0.6; 2.6)	1.3 (0.6; 3.1)	1.3 (0.6; 3.6)	1.4 (0.6; 4.1)	1.5 (0.5; 4.5)
SI frail	0.5 (0.2; 1.2)	0.8 (0.2; 4.1)	1.0 (0.2; 6.0)	1.2 (0.2; 6.2)	1.4 (0.2; 13.7)	1.7 (0.2; 20.2)	2.0 (0.2; 27.8)	2.2 (0.1; 36.4)
SOF frail	1.0 (0.7; 1.6)	1.3 (0.7; 2.8)	1.5 (0.7; 3.4)	1.6 (0.7; 3.9)	1.7 (0.7; 5.0)	1.9 (0.7; 5.9)	2.0 (0.7; 6.9)	2.1 (1.6; 7.8)
SOF pre-frail	1.0 (0.8; 1.3)	1.3 (0.8; 2.0)	1.4 (0.8; 2.3)	1.3 (0.8; 2.5)	1.7 (0.8; 3.0)	1.8 (0.8; 3.5)	1.9 (0.8; 3.9)	2.0 (1.0; 4.3)
SPPB frail	1.0 (0.8; 1.3)	1.1 (0.8; 1.7)	1.2 (0.8; 1.9)	1.3 (0.8; 1.0)	1.2 (0.8; 2.3)	1.3 (0.8; 2.5)	1.3 (0.8; 2.7)	1.4 (1.6; 2.9)
SPQ frail	1.0 (0.8; 1.2)	1.3 (0.8; 1.8)	1.4 (0.8; 2.1)	1.2 (0.8; 2.3)	1.7 (0.8; 2.8)	1.9 (0.8; 3.2)	2.1 (0.8; 3.6)	2.2 (1.2; 3.9)
TFI frail	0.9 (0.7; 1.2)	1.0 (0.7; 1.6)	1.1 (0.7; 1.7)	1.2 (0.7; 1.9)	1.2 (0.7; 2.1)	1.2 (0.7; 2.3)	1.2 (0.7; 2.5)	1.3 (0.6; 2.6)
VES13 frail	0.9 (0.7; 1.2)	1.1 (0.7; 1.7)	1.1 (0.7; 1.9)	1.2 (0.7; 1.1)	1.3 (0.7; 2.5)	1.3 (0.7; 2.8)	1.4 (0.7; 3.1)	1.5 (0.6; 3.4)
WHRH frail	0.9 (0.7; 1.3)	1.1 (0.7; 1.9)	1.2 (0.7; 2.2)	1.3 (0.7; 2.4)	1.3 (0.7; 2.8)	1.4 (0.7; 3.2)	1.4 (0.7; 3.5)	1.5 (0.6; 3.8)
ZED1 frail	0.4 (0.2; 1.3)	0.9 (0.2; 5.3)	1.1 (0.2; 8.4)	1.3 (0.2; 8.2)	1.8 (0.2; 22.1)	2.2 (0.2; 34.8)	2.7 (0.2; 50.6)	3.1 (0.1; 69.4)
ZED2 frail	0.1 (0.0; 1.5)	0.3 (0.0; 18.9)	0.4 (0.0; 42.6)	1.5 (0.0; 42.7)	0.7 (0.0; 235.6)	0.9 (0.0; 530.8)	1.2 (0.0; 1030.8)	1.4 (0.0; 1806.6)
ZED3 frail	0.0 (0.0; 37.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)	0.0 (0.0;>99.9)

[1]Hazard ratios calculated from age at baseline to age at the end of the interval.

S10 Table. Discriminative assessment of cardiovascular models using Harrell's C statistic (n= 4,554).

Table S10. Discriminative assessment of cardiovascular models using Harrell's C statistic (n=4554)

Continuous analysis				Cut-off analysis			
Frailty Score	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Frailty Score	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]
	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
Basic models	70.1 (65.7; 74.4)[2]	69.5 (63.9; 75.0)[2]	70.6 (65.4; 75.8)[2]	Basic models	70.1 (65.7; 74.4)[2]	69.5 (63.9; 75.0)[2]	70.6 (65.4; 75.8)[2]
				Phenotype of frailty approach			
ZED3	0.6 (-3.6; 2.1)	0.6 (-0.8; 2.1)	0.3 (-0.5; 1.2)	PFI frail	0.6 (-0.8; 2.0)	0.4 (-0.7; 1.5)	0.2 (-0.4; 0.7)
FS	0.0 (-F.0; 1.7)	0.0 (-1.7; 1.7)	0.1 (-0.5; 0.7)	PFI pre frail	-0.7 (-1.7; 0.2)	-0.4 (-1.4; 0.5)	-0.2 (-0.8; 0.3)
SOF	0.0 (-O.0; 1.7)	0.0 (-1.6; 1.5)	0.0 (-0.8; 0.7)	FS frail	-0.3 (-0.9; 0.4)	0.0 (-0.7; 0.7)	0.0 (-0.3; 0.2)
FiND	-0.1 (-D.1; 1.8)	-0.1 (-2.1; 2.0)	0.2 (-0.6; 0.9)	FS pre- frail	0.6 (-1.0; 2.2)	0.4 (-0.8; 1.6)	0.3 (-0.4; 0.9)
ZED2	-0.1 (-2.1; 1.1)	-0.1 (-1.3; 1.0)	-0.1 (-0.7; 0.6)	SOF frail	0.4 (-1.0; 1.8)	0.3 (-0.9; 1.4)	0.1 (-0.5; 0.8)
PFI	-0.3 (-I.3; 1.6)	-0.3 (-2.3; 1.8)	-0.1 (-0.9; 0.8)	SOF pre-frail	-0.3 (-1.3; 0.6)	-0.1 (-0.7; 0.4)	0.0 (-0.3; 0.3)
BDE	-0.5 (-D.5; 1.7)	-0.5 (-3.0; 2.1)	0.2 (-0.6; 1.0)	FiND frail	0.3 (-0.6; 1.2)	0.2 (-0.5; 1.0)	0.1 (-0.4; 0.7)
PHF	-0.8 (-H.8; 1.6)	-0.8 (-3.2; 1.7)	-0.2 (-1.0; 0.7)	ZED1 frail	-0.1 (-0.3; 0.2)	0.0 (-0.2; 0.2)	0.0 (-0.3; 0.3)
ZED1	-0.8 (-1.8; 1.0)	-0.8 (-2.5; 0.9)	-0.1 (-0.7; 0.4)	ZED3 frail	-0.1 (-0.3; 0.1)	-0.1 (-0.4; 0.3)	0.0 (-0.2; 0.2)
MPHF	-1.0 (-R.0; 1.4)	-1.0 (-3.6; 1.6)	-0.5 (-1.7; 0.7)	ZED2 frail	-0.2 (-0.6; 0.3)	0.0 (-0.4; 0.3)	0.0 (-0.2; 0.2)
SPPB	-1.6 (-B.6; 1.2)	-1.6 (-3.7; 0.6)	-0.3 (-1.2; 0.7)	PHF frail	-0.4 (-1.9; 1.2)	-0.3 (-1.7; 1.1)	0.0 (-0.6; 0.7)
				PHF pre-frail	-0.7 (-1.8; 0.4)	-0.5 (-1.4; 0.5)	0.0 (-0.5; 0.4)
				SPPB frail	-1.4 (-3.1; 0.4)	-1.1 (-2.5; 0.4)	-0.4 (-1.4; 0.5)
				Multidimensional approach			
HSF	0.5 (-S.5; 2.5)	0.5 (-1.7; 2.7)	0.7 (-0.7; 2.2)	G8 frail	1.8 (0.4; 2.8)	1.3 (0.2; 2.4)	0.9 (-0.4; 2.2)
EFS	0.1 (-F.1; 2.2)	0.1 (-2.0; 2.1)	1.4 (0.1; 2.8)	SDFI frail	0.1 (-2.4; 2.7)	0.3 (-1.5; 2.1)	0.4 (-0.2; 1.1)
SDFI	0.0 (-I.0; 2.0)	0.0 (-1.7; 1.6)	0.3 (-0.2; 0.8)	SI frail	0.1 (-0.3; 0.6)	0.2 (-0.4; 0.7)	0.0 (-0.4; 0.4)
G8	-0.1 (-.1; 1.6)	-0.1 (-2.1; 1.9)	0.0 (-0.9; 0.8)	MFS frail	0.1 (-2.1; 2.3)	0.4 (-1.1; 1.9)	0.0 (-1.5; 1.4)
GFI	-0.1 (-F.1; 1.8)	-0.1 (-1.7; 1.5)	0.2 (-0.4; 0.8)	MFS pre-frail	-0.1 (-1.4; 1.2)	0.3 (-0.8; 1.3)	0.0 (-1.0; 1.0)
SI	-0.1 (-S.1; 1.2)	-0.1 (-1.7; 1.4)	0.0 (-0.3; 0.4)	FSS frail	-0.3 (-1.5; 1.0)	-0.1 (-0.9; 0.8)	-0.1 (-0.4; 0.3)
FSS	-0.2 (-S.2; 2.3)	-0.2 (-2.7; 2.4)	0.1 (-0.6; 0.8)	FSS pre frail	0.0 (-0.5; 0.5)	0.0 (-0.4; 0.3)	0.0 (-0.3; 0.3)
MFS	-0.3 (-S.3; 2.3)	-0.3 (-2.5; 1.8)	0.2 (-1.5; 1.9)	SPQ frail	0.0 (-1.3; 1.3)	0.2 (-0.8; 1.1)	0.1 (-0.2; 0.4)
IFQ	-0.6 (-2.6; 0.8)	-0.6 (-2.1; 0.8)	0.0 (-0.3; 0.4)	IFQ frail	-0.1 (-0.5; 0.4)	0.0 (-0.3; 0.4)	0.0 (-0.3; 0.3)
CGAST	-0.4 (-C.4; 1.4)	-0.4 (-2.5; 1.7)	0.2 (-0.3; 0.7)	EFS frail	-0.1 (-0.5; 0.3)	0.1 (-0.3; 0.4)	0.0 (-0.4; 0.3)
SPQ	-0.4 (-P.4; 1.1)	-0.4 (-1.9; 1.1)	-0.1 (-0.5; 0.4)	GFI frail	-0.4 (-2.2; 1.5)	-0.1 (-1.3; 1.0)	-0.1 (-0.9; 0.7)
CSBA	-0.9 (-A.9; 1.1)	-0.9 (-3.2; 1.4)	-0.2 (-0.7; 0.4)	BFI frail	-0.5 (-1.3; 0.3)	-0.3 (-1.0; 0.3)	0.0 (-0.3; 0.4)
TFI	-1.4 (-F.4; 0.4)	-1.4 (-3.4; 0.6)	-0.2 (-0.9; 0.5)	CSBA frail	-0.6 (-2.6; 1.5)	-0.2 (-1.8; 1.4)	-0.2 (-0.7; 0.3)
BFI	-1.6 (-F.6; 0.3)	-1.6 (-4.0; 0.8)	-0.1 (-0.7; 0.4)	CGAST frail	-0.7 (-2.4; 1.0)	-0.2 (-1.4; 1.1)	0.0 (-0.5; 0.5)
				CGAST pre frail	-0.7 (-1.8; 0.5)	-0.4 (-1.2; 0.4)	0.1 (-0.4; 0.6)
				TFI frail	-1.7 (-3.7; 0.3)	-1.1 (-2.6; 0.3)	-0.7 (-1.8; 0.5)
				Accumulation of deficits approach			
EFIP	0.0 (-P.0; 2.5)	0.0 (-2.9; 2.9)	0.8 (-0.9; 2.4)	CGA frail	0.5 (-0.9; 1.9)	0.5 (-0.5; 1.6)	0.8 (-0.3; 1.9)
NLTCS	-0.1 (-F.1; 2.4)	-0.1 (-2.2; 2.0)	0.5 (-0.7; 1.6)	CGA pre-frail	-0.4 (-1.3; 0.5)	-0.2 (-0.7; 0.4)	-0.2 (-1.0; 0.5)
FI70	-0.2 (-70.2; 2.5)	-0.2 (-3.2; 2.8)	1.1 (-0.4; 2.6)	FI70 frail	-0.8 (-3.0; 1.5)	-0.4 (-2.2; 1.4)	0.3 (-1.2; 1.8)
FIBLSA	-0.2 (-L.2; 2.0)	-0.2 (-2.5; 2.1)	0.0 (-1.2; 1.2)	FI40 frail	-1.0 (-3.5; 1.5)	-0.6 (-2.6; 1.3)	0.2 (-1.4; 1.7)
FI40	-0.3 (-40.3; 3.0)	-0.3 (-3.0; 2.3)	0.6 (-1.0; 2.3)				
CGA	-0.4 (-G.4; 2.0)	-0.4 (-3.1; 2.2)	0.6 (-0.6; 1.7)				
				Disability approach			
VES13	0.7 (-1.7; 3.1)	0.7 (-1.9; 3.3)	1.1 (-0.2; 2.3)	VES13 frail	0.8 (-1.3; 2.8)	0.8 (-1.1; 2.7)	1.1 (-0.4; 2.7)
HRCA	0.5 (-A.5; 2.5)	0.5 (-2.0; 3.1)	0.1 (-0.7; 1.0)	WHRH frail	0.2 (-1.5; 2.0)	0.3 (-0.8; 1.3)	0.3 (-0.5; 1.1)
WHRH	0.4 (-F.4; 2.5)	0.4 (-2.2; 3.0)	0.7 (-0.2; 1.6)	SHCFS frail	-0.2 (-1.1; 0.7)	0.0 (-0.9; 1.0)	0.0 (-0.6; 0.6)
SHCFS	0.3 (-F.3; 2.0)	0.3 (-1.5; 2.0)	0.3 (-0.6; 1.2)	HRCA frail	-0.3 (-2.4; 1.8)	0.0 (-1.9; 1.9)	-0.1 (-0.9; 0.8)

Model 1 = age and sex. Model 2 = model 1 + smoking status and maximum alcohol consumption. Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life 1Delta = percent of improvement adding the frailty score to model. 2Harrel's C statistic of each model (lower confidence interval; upper confidence interval)*100.

S11 Table. Discriminative assessment of cancer models using Harrell's C statistic (n = 4,792).

Table S11. Discriminative assessment of cancer models using Harrell's C statistic (n=4792)

Continuous analysis				Cut-off analysis			
Frailty Score	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Frailty Score	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]	Delta (*100) LCI; UCI with 95% CI[1]
	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
models	55.7 (51.7; 59.6)[2]	57.1 (52.8; 61.3)[2]	59.4 (55.3; 63.4)[2]	Basic models	55.7 (51.7; 59.6)[2]	57.1 (52.8; 61.3)[2]	59.4 (55.3; 63.4)[2]
Phenotype of frailty approach							
FS	0.1 (-0.5; 0.7)	-0.1 (-0.7; 0.5)	0.0 (-0.3; 0.4)	ZED2 frail	0.6 (-0.4; 1.6)	0.5 (-0.5; 1.0)	0.4 (-0.5; 1.3)
FiND	0.1 (-0.5; 0.7)	0.2 (-0.6; 1.0)	0.0 (-0.2; 0.2)	PFI frail	0.0 (-0.3; 0.4)	0.1 (-0.3; 1.0)	0.1 (-0.4; 0.5)
SOF	0.1 (-0.7; 0.8)	-0.1 (-0.6; 0.3)	0.0 (-0.6; 0.5)	PFI pre frail	0.2 (-0.4; 0.9)	0.1 (-0.4; 1.0)	0.0 (-0.3; 0.4)
ZED3	0.1 (-0.4; 0.5)	0.0 (-0.3; 0.3)	0.0 (-0.2; 0.3)	SOF frail	0.0 (-0.5; 0.5)	-0.1 (-0.5; 1.0)	0.0 (-0.3; 0.2)
PFI	0.0 (-0.3; 0.4)	0.1 (-0.6; 0.7)	0.0 (-0.2; 0.2)	SOF pre-frail	0.1 (-0.7; 1.0)	0.1 (-0.5; 1.0)	0.0 (-0.3; 0.2)
PHF	0.0 (-0.9; 1.0)	-0.1 (-0.6; 0.5)	0.0 (-0.6; 0.7)	ZED1 frail	0.1 (-0.5; 0.7)	0.0 (-0.4; 1.0)	0.0 (-0.2; 0.2)
MPHF	0.0 (-0.6; 0.6)	0.0 (-0.4; 0.4)	0.0 (-0.3; 0.3)	FS frail	0.0 (-0.4; 0.5)	0.0 (-0.3; 1.0)	0.0 (-0.3; 0.3)
ZED1	-0.1 (-0.6; 0.5)	-0.1 (-0.4; 0.3)	0.0 (-0.3; 0.3)	FS pre- frail	0.1 (-0.4; 0.5)	0.0 (-0.4; 1.0)	0.0 (-0.4; 0.4)
BDE	-0.1 (-0.6; 0.4)	-0.1 (-0.9; 0.8)	0.1 (-0.5; 0.6)	PHF frail	0.0 (-0.4; 0.4)	-0.1 (-0.4; 1.0)	0.0 (-0.3; 0.2)
SPPB	-0.2 (-0.9; 0.5)	-0.1 (-0.4; 0.3)	0.0 (-0.5; 0.4)	PHF pre-frail	0.0 (-0.4; 0.3)	0.0 (-0.4; 1.0)	0.0 (-0.3; 0.2)
ZED2	-0.3 (-1.1; 0.6)	0.0 (-0.4; 0.3)	-0.3 (-0.1; 0.5)	ZED3 frail	0.0 (-0.5; 0.5)	-0.1 (-0.9; 1.0)	-0.1 (-0.4; 0.2)
				FiND frail	-0.1 (-1.1; 0.9)	-0.2 (-0.9; 1.0)	-0.1 (-0.8; 0.7)
				SPPB frail	-0.5 (-1.4; 0.3)	-0.5 (-1.3; 1.0)	-0.3 (-0.8; 0.3)
Multidimensional approach							
FSS	0.2 (-0.5; 1.0)	0.0 (-0.3; 0.3)	0.0 (-0.3; 0.3)	BFI frail	0.5 (-1.1; 2.0)	0.7 (-0.7; 2.0)	0.5 (-0.8; 1.8)
CGAST	0.1 (-0.7; 1.0)	-0.1 (-0.3; 0.2)	0.1 (-0.4; 0.5)	CGAST frail	0.3 (-0.9; 1.5)	0.1 (-0.8; 2.0)	0.1 (-0.4; 0.6)
SDFI	0.1 (-0.5; 0.8)	-0.1 (-0.5; 0.4)	-0.1 (-0.5; 0.3)	CGAST pre frail	0.2 (-0.5; 0.9)	0.0 (-0.5; 2.0)	0.0 (-0.3; 0.2)
BFI	0.1 (-0.3; 0.6)	-0.1 (-0.5; 0.4)	0.1 (-0.8; 0.9)	G8 frail	0.2 (-0.8; 1.2)	0.1 (-0.4; 2.0)	-0.1 (-1.3; 1.1)
EFS	0.1 (-0.9; 1.1)	0.0 (-0.5; 0.6)	0.0 (-0.3; 0.2)	FSS frail	0.2 (-0.5; 1.0)	0.0 (-0.4; 2.0)	0.0 (-0.2; 0.2)
SPQ	0.1 (-0.7; 0.8)	-0.2 (-0.7; 0.3)	0.0 (-0.4; 0.4)	FSS pre frail	0.2 (-0.6; 1.0)	0.2 (-0.5; 2.0)	0.1 (-0.6; 0.7)
IFQ	0.1 (-0.6; 0.7)	-0.1 (-0.7; 0.5)	0.0 (-0.2; 0.2)	SPQ frail	0.2 (-0.6; 1.0)	0.0 (-0.6; 2.0)	0.1 (-0.4; 0.6)
HSF	0.0 (-0.3; 0.3)	-0.1 (-0.5; 0.3)	0.2 (-0.4; 0.7)	EFS frail	0.1 (-0.5; 0.7)	0.0 (-0.3; 2.0)	0.0 (-0.1; 0.2)
GFI	0.0 (-0.7; 0.7)	0.0 (-0.3; 0.3)	0.0 (-0.2; 0.2)	GFI frail	0.1 (-0.6; 0.8)	0.0 (-0.7; 2.0)	0.0 (-0.2; 0.3)
TFI	0.0 (-0.5; 0.5)	0.0 (-0.4; 0.4)	0.1 (-0.3; 0.5)	SDFI frail	0.0 (-0.4; 0.5)	0.1 (-0.5; 2.0)	-0.1 (-0.8; 0.5)
SI	0.0 (-0.5; 0.4)	-0.1 (-0.7; 0.5)	0.0 (-0.3; 0.3)	TFI frail	0.0 (-0.4; 0.4)	0.0 (-0.3; 2.0)	0.1 (-0.6; 0.8)
CSBA	-0.1 (-0.7; 0.5)	-0.1 (-0.6; 0.3)	0.2 (-0.5; 0.9)	SI frail	0.0 (-0.3; 0.3)	0.0 (-0.3; 2.0)	-0.1 (-0.3; 0.2)
G8	-0.1 (-0.7; 0.4)	0.0 (-0.3; 0.3)	-0.5 (-0.7; 0.7)	MFS frail	-0.1 (-0.6; 0.4)	0.0 (-0.4; 2.0)	0.0 (-0.4; 0.4)
MFS	-0.2 (-0.7; 0.3)	-0.2 (-0.6; 0.3)	0.0 (-0.4; 0.5)	MFS pre-frail	0.0 (-0.4; 0.4)	0.0 (-0.4; 2.0)	0.0 (-0.3; 0.3)
				IFQ frail	0.0 (-0.4; 0.3)	-0.1 (-0.4; 2.0)	0.0 (-0.2; 0.2)
				CSBA frail	-0.3 (-1.0; 0.3)	-0.2 (-0.8; 2.0)	0.1 (-0.4; 0.6)
Accumulation of deficits approach							
FI40	0.1 (-0.5; 0.6)	0.0 (-0.4; 0.4)	0.2 (-0.4; 0.8)	FI40 frail	0.3 (-0.7; 1.3)	0.1 (-0.5; 3.0)	0.0 (-0.3; 0.3)
FI70	0.1 (-0.6; 0.7)	-0.1 (-0.8; 0.6)	0.1 (-0.4; 0.7)	CGA frail	0.1 (-0.5; 0.8)	0.0 (-0.4; 3.0)	0.0 (-0.4; 0.4)
NLTCS	0.1 (-0.4; 0.6)	-0.3 (-0.9; 0.2)	0.0 (-0.3; 0.2)	CGA pre-frail	0.0 (-0.3; 0.3)	0.0 (-0.4; 3.0)	0.0 (-0.3; 0.4)
CGA	0.1 (-0.5; 0.7)	0.0 (-0.5; 0.5)	-0.1 (-0.7; 0.6)	FI70 frail	0.0 (-0.4; 0.4)	-0.1 (-0.6; 3.0)	0.3 (-0.6; 1.1)
FIBLSA	0.1 (-0.5; 0.6)	0.0 (-0.5; 0.5)	-0.1 (-0.8; 0.6)				
EFIP	0.0 (-0.5; 0.4)	-0.1 (-0.5; 0.3)	0.0 (-0.5; 0.6)				
Disability approach							
WHRH	0.2 (-0.6; 0.9)	-0.1 (-0.5; 0.4)	-0.1 (-0.2; 1.0)	WHRH frail	0.2 (-0.4; 0.8)	0.0 (-0.4; 4.0)	-0.1 (-1.2; 0.9)
HRCA	0.0 (-0.5; 0.5)	-0.1 (-0.5; 0.3)	0.0 (-0.3; 0.4)	VES13 frail	0.1 (-0.5; 0.7)	0.0 (-0.5; 4.0)	0.0 (-0.2; 0.3)
VES13	-0.1 (-0.7; 0.6)	-0.4 (-0.1; 0.4)	0.0 (-0.2; 0.2)	HRCA frail	0.0 (-0.5; 0.6)	-0.1 (-0.5; 4.0)	0.0 (-0.2; 0.3)
SHCFS	-0.2 (-0.6; 0.3)	0.0 (-0.3; 0.2)	0.0 (-0.4; 0.3)	SHCFS frail	-0.1 (-0.5; 0.3)	-0.1 (-0.4; 4.0)	0.0 (-0.3; 0.3)

Model 1 = age and sex. Model 2 = model 1 + smoking status and maximum alcohol consumption. Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. 1Delta = percent of improvement adding the frailty score to model. 2Harrel's C statistic of each model (lower confidence interval; upper confidence interval).

S12 Table. Sensitivity analysis: Mortality hazard ratios of frailty scores (n = 5,253)

Table S12. Sensitivity analysis[1]: mortality hazard ratios of frailty scores (n=5253)

Continuous analysis					Cut-off analysis				
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[2]	Model 1[3]	Model 2[4]	Model 3[5]	Frailty Score	Model 0[2]	Model 1[3]	Model 2[4]	Model 3[5]
Phenotype of frailty approach									
MPHF	4.5 (1.0; 6.7)	5.1 (3.4; 7.6)	4.4 (2.9; 6.5)	2.5 (1.6; 4.0)	PFI frail	1.8 (0.6; 4.9)	2.0 (0.7; 5.3)	1.9 (0.7; 5.1)	1.3 (0.4; 3.6)
SPPB	4.1 (1.0; 6.4)	4.9 (3.1; 7.8)	4.5 (2.8; 7.1)	2.2 (1.3; 3.7)	PFI pre frail	2.8 (1.7; 4.7)	3.0 (1.8; 5.0)	2.8 (1.8; 4.7)	2.3 (1.3; 3.9)
PHF	4.1 (1.0; 6.2)	4.6 (3.1; 6.9)	4.1 (2.7; 6.1)	2.4 (1.5; 3.8)	FS frail	2.2 (1.0; 4.8)	2.4 (1.1; 5.2)	2.2 (1.1; 4.8)	1.4 (0.6; 3.2)
FS	3.5 (1.0; 5.8)	4.0 (2.4; 6.7)	3.6 (2.1; 5.9)	1.7 (1.0; 3.0)	FS pre- frail	2.7 (1.8; 4.2)	2.9 (1.9; 4.5)	2.7 (1.9; 4.2)	2.2 (1.4; 3.5)
FiND	3.3 (1.0; 5.0)	3.8 (2.5; 5.8)	3.4 (2.2; 5.1)	1.9 (1.2; 3.1)	SOF frail	2.1 (1.0; 4.6)	2.3 (1.1; 4.9)	2.2 (1.1; 4.6)	1.6 (0.7; 3.7)
SOF	3.0 (1.0; 4.8)	3.3 (2.1; 5.3)	3.1 (1.9; 4.9)	2.1 (1.3; 3.5)	SOF pre-frail	2.7 (1.8; 4.2)	2.9 (1.9; 4.5)	2.7 (1.8; 4.2)	2.4 (1.5; 3.9)
ZED2	2.8 (1.0; 4.0)	3.1 (2.1; 4.4)	2.9 (2.0; 4.1)	2.0 (1.3; 2.9)	PHF frail	2.6 (1.0; 6.6)	2.9 (1.1; 7.3)	2.5 (1.1; 6.5)	1.5 (0.6; 4.1)
ZED3	2.1 (1.0; 3.3)	2.5 (1.5; 4.0)	2.2 (1.4; 3.6)	1.5 (0.9; 2.6)	PHF pre-frail	2.6 (1.2; 5.7)	2.8 (1.3; 6.2)	2.6 (1.3; 5.7)	2.2 (1.0; 4.9)
ZED1	2.2 (1.0; 3.1)	2.5 (1.7; 3.6)	2.2 (1.5; 3.2)	1.3 (0.9; 2.0)	ZED3 frail	2.1 (0.2; 20.5)	2.2 (0.2; 21.2)	2.1 (1.4; 3.0)	1.6 (0.2; 14.8)
PFI	1.9 (1.0; 2.9)	2.1 (1.4; 3.2)	2.0 (1.3; 3.0)	1.3 (0.8; 2.0)	ZED2 frail	1.9 (0.6; 6.2)	2.0 (0.6; 6.5)	2.0 (0.6; 6.4)	1.4 (0.4; 4.7)
BDE	1.4 (1.0; 2.0)	1.5 (1.1; 2.1)	1.3 (0.9; 1.9)	1.8 (1.2; 2.8)	ZED1 frail	1.7 (0.6; 5.0)	1.8 (0.6; 5.3)	1.8 (0.6; 5.3)	1.2 (0.4; 3.6)
					SPPB frail	1.6 (0.9; 2.9)	1.7 (0.9; 3.0)	1.6 (0.9; 2.9)	1.2 (0.7; 2.3)
					FiND frail	1.5 (0.7; 2.9)	1.6 (0.8; 3.1)	1.5 (0.8; 2.9)	1.1 (0.5; 2.3)
Multidimensional approach									
CSBA	23.0 (2.0; 40.5)	18.1 (10.1; 32.4)	14.0 (7.7; 25.2)	2.6 (1.2; 5.2)	FSS frail	1.8 (0.9; 3.5)	1.9 (0.9; 3.8)	1.7 (0.9; 3.5)	1.1 (0.5; 2.4)
G8	9.9 (2.0; 18.0)	13.2 (7.3; 24.1)	10.7 (5.8; 19.5)	3.5 (1.8; 7.0)	FSS pre frail	3.1 (2.0; 4.8)	3.2 (2.1; 4.9)	3.0 (2.1; 4.7)	2.5 (1.6; 4.0)
EFS	9.8 (2.0; 19.4)	12.5 (6.3; 24.8)	10.1 (5.1; 20.2)	6.0 (2.7; 13.2)	CGAST frail	2.8 (1.3; 6.0)	3.0 (1.4; 6.6)	2.8 (1.4; 6.0)	1.8 (0.8; 4.1)
CGAST	6.4 (2.0; 11.7)	8.1 (4.5; 14.9)	6.9 (3.8; 12.6)	2.5 (1.2; 4.9)	CGAST pre frail	3.1 (1.6; 6.1)	3.2 (1.6; 6.3)	3.1 (1.6; 6.0)	2.8 (1.4; 5.6)
TFI	5.2 (2.0; 8.5)	7.3 (4.5; 12.0)	5.9 (3.6; 9.7)	3.2 (1.7; 5.8)	MFS frail	1.3 (0.4; 3.7)	2.6 (0.9; 7.9)	2.3 (0.9; 6.9)	1.7 (0.6; 5.1)
GFI	5.1 (2.0; 9.0)	6.4 (3.6; 11.4)	5.3 (3.0; 9.5)	1.6 (0.8; 3.2)	MFS pre-frail	1.3 (0.5; 3.5)	2.8 (1.0; 7.6)	2.5 (1.0; 7.0)	2.3 (0.8; 6.4)
SDFI	3.7 (2.0; 6.2)	6.4 (3.8; 10.8)	5.0 (3.0; 8.5)	1.5 (0.8; 2.7)	G8 frail	2.1 (1.2; 3.7)	2.2 (1.2; 3.9)	2.0 (1.2; 3.6)	1.4 (0.7; 2.6)
IFQ	4.4 (2.0; 7.9)	5.8 (3.3; 10.4)	4.8 (2.7; 8.7)	1.9 (1.0; 3.5)	CSBA frail	2.1 (1.2; 3.6)	1.9 (1.1; 3.3)	1.7 (1.1; 3.0)	1.2 (0.7; 2.1)
MFS	5.2 (2.0; 8.0)	5.8 (3.8; 8.9)	5.0 (3.2; 7.7)	3.1 (2.0; 4.8)	IFQ frail	1.8 (0.5; 6.7)	1.9 (0.5; 7.3)	1.8 (0.5; 6.9)	1.3 (0.4; 5.1)
HSF	3.9 (2.0; 6.5)	4.2 (2.5; 7.1)	3.7 (2.2; 6.2)	1.3 (0.7; 2.3)	EFS frail	1.8 (0.6; 5.2)	1.9 (0.6; 5.6)	1.8 (0.6; 5.3)	1.3 (0.4; 4.0)
BFI	2.2 (2.0; 3.5)	3.0 (1.9; 4.8)	2.5 (1.6; 4.0)	1.3 (0.8; 2.1)	TFI frail	1.7 (1.0; 2.9)	1.9 (1.1; 3.2)	1.7 (1.1; 3.0)	1.4 (0.8; 2.5)
FSS	2.5 (2.0; 3.9)	2.8 (1.8; 4.3)	2.5 (1.6; 3.8)	1.1 (0.7; 1.8)	SDFI frail	1.5 (0.9; 2.7)	1.8 (1.0; 3.1)	1.6 (1.0; 2.8)	1.2 (0.7; 2.2)
SI	2.1 (2.0; 4.1)	2.7 (1.4; 5.2)	2.4 (1.2; 4.6)	0.8 (0.4; 1.6)	GFI frail	1.5 (0.9; 2.6)	1.6 (0.9; 2.7)	1.5 (0.9; 2.6)	1.0 (0.6; 1.9)
SPQ	1.8 (2.0; 3.2)	2.3 (1.3; 4.1)	2.0 (1.1; 3.6)	0.9 (0.5; 1.7)	BFI frail	1.2 (0.5; 2.8)	1.4 (0.6; 3.1)	1.3 (0.6; 2.9)	1.0 (0.4; 2.3)
					SI frail	1.2 (0.4; 4.0)	1.3 (0.4; 4.3)	1.3 (1.1; 1.6)	0.9 (0.3; 2.8)
					SPQ frail	1.1 (0.6; 2.0)	1.2 (0.7; 2.2)	1.2 (1.0; 1.4)	0.9 (0.5; 1.7)
Accumulation of deficits approach									
FI40	7.9 (3.0; 15.3)	11.0 (5.7; 21.2)	9.1 (4.6; 17.7)	8.2 (4.7; 14.1)	CGA frail	1.9 (1.0; 3.9)	2.2 (1.1; 4.5)	2.1 (1.1; 4.1)	1.6 (0.7; 3.4)
CGA	6.9 (3.0; 15.3)	10.8 (4.9; 24.2)	8.8 (3.9; 19.8)	3.8 (1.5; 9.6)	CGA pre-frail	2.8 (1.8; 4.4)	3.1 (2.0; 4.8)	2.9 (2.0; 4.5)	2.7 (1.7; 4.3)
FI70	6.5 (3.0; 12.3)	9.6 (5.1; 18.4)	7.9 (4.1; 15.2)	5.4 (2.5; 11.6)	FI70 frail	1.7 (1.0; 3.0)	1.9 (1.1; 3.3)	1.8 (1.1; 3.1)	1.6 (0.9; 2.8)
EFIP	5.7 (3.0; 10.9)	7.4 (3.9; 14.2)	6.1 (3.1; 11.7)	3.3 (1.5; 7.3)	FI40 frail	1.7 (1.0; 2.9)	1.8 (1.1; 3.1)	1.7 (1.1; 3.0)	1.7 (1.1; 2.4)
NLTCS	6.1 (3.0; 15.3)	7.1 (2.8; 17.8)	5.9 (2.4; 14.9)	1.0 (0.4; 2.9)					
FIBLSA	4.6 (3.0; 9.6)	5.8 (2.8; 12.1)	4.9 (2.4; 10.3)	1.2 (0.5; 2.7)					
Disability approach									
VES13	3.6 (4.0; 6.0)	4.6 (2.8; 7.6)	4.0 (2.4; 6.6)	2.1 (1.2; 3.7)	HRCA frail	1.6 (0.9; 2.7)	1.8 (1.1; 3.1)	1.7 (1.1; 2.9)	1.2 (0.7; 2.2)
HRCA	3.1 (4.0; 5.7)	4.0 (2.2; 7.2)	3.5 (1.9; 6.3)	1.3 (0.7; 2.6)	VES13 frail	1.5 (0.9; 2.7)	1.7 (1.0; 2.9)	1.6 (0.9; 2.8)	1.3 (0.7; 2.3)
WHRH	2.9 (4.0; 4.9)	3.4 (2.0; 5.8)	3.1 (1.8; 5.2)	1.9 (1.0; 3.5)	SHCFS frail	1.6 (0.8; 3.1)	1.7 (0.8; 3.3)	1.6 (0.8; 3.1)	1.1 (0.5; 2.2)
SHCFS	2.6 (4.0; 3.9)	2.9 (1.9; 4.4)	2.6 (1.7; 4.0)	1.1 (0.7; 1.8)	WHRH frail	1.5 (0.8; 2.8)	1.6 (0.9; 3.1)	1.6 (0.9; 2.9)	1.0 (0.5; 1.9)

[1]Sensitivity analysis: excluding participants with events the first year of follow-up; [2]Model 0= Crude models. [3]Model 1= HR adjusted by sex. [4]Model 2= Model 1 + smoking status and alcohol consumption.[5]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. Abbreviations frailty scores:

S13 Table. Mortality hazard ratios of frailty scores in men (n = 2,377) calculated at median time follow-up (3.5 years)

Table S13. Mortality hazard ratios of frailty scores in men (n=2377) calculated at median time follow-up (3.5 years)

	Continuous analysis				Cut-off analysis		
	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)
Score	Model 0[1]	Model 2[2]	Model 3[3]	Frailty Score	Model 0[1]	Model 2[2]	Model 3[3]
Phenotype of frailty approach							
MPHF	7.7 (5.0; 12.0)	6.6 (4.2; 10.3)	3.6 (2.3; 6.1)	SOF frail	3.2 (1.5; 7.2)	3.0 (1.4; 6.7)	2.1 (0.9; 5.3)
FS	7.0 (4.2; 11.7)	6.2 (3.7; 10.3)	2.8 (1.2; 5.0)	SOF pre-frail	2.7 (1.6; 4.4)	2.6 (1.6; 4.2)	2.2 (1.2; 3.8)
SPPB	6.7 (3.9; 11.5)	6.1 (3.5; 10.6)	2.3 (1.2; 4.4)	PHF frail	3.4 (1.2; 9.2)	3.0 (1.1; 8.3)	1.6 (0.5; 4.8)
PHF	6.5 (4.2; 10.0)	5.5 (3.6; 8.6)	2.7 (1.2; 4.7)	ZED3 frail	3.3 (1.9; 5.7)	2.6 (1.5; 4.5)	1.7 (0.2; 13.4)
FiND	6.0 (3.9; 9.2)	5.3 (3.4; 8.1)	2.6 (1.2; 4.5)	ZED1 frail	2.6 (2.0; 3.5)	2.6 (1.9; 3.4)	1.7 (0.6; 4.4)
SOF	5.4 (3.4; 8.7)	4.9 (3.1; 8.0)	2.9 (1.2; 5.2)	PFI frail	2.3 (0.7; 7.2)	2.3 (0.7; 7.2)	1.3 (0.4; 4.5)
ZED2	4.4 (2.9; 6.5)	3.9 (2.6; 5.8)	2.5 (1.2; 3.9)	PFI pre frail	2.3 (1.3; 4.2)	2.2 (1.2; 4.0)	1.7 (0.9; 3.4)
ZED3	4.4 (2.7; 7.4)	3.7 (2.2; 6.1)	2.2 (1.2; 3.8)	ZED2 frail	2.3 (1.6; 3.3)	2.1 (1.5; 3.1)	1.5 (0.4; 4.9)
ZED1	4.0 (2.7; 5.7)	3.6 (2.5; 5.2)	1.8 (1.1; 2.9)	FS frail	2.1 (1.0; 4.4)	1.9 (0.9; 4.1)	1.9 (0.8; 4.5)
PFI	2.5 (1.6; 3.9)	2.4 (1.5; 3.8)	1.4 (0.1; 2.2)	FS pre- frail	2.3 (1.4; 3.8)	2.2 (1.3; 3.7)	1.7 (1.0; 2.9)
BDE	2.3 (1.5; 3.7)	2.0 (1.3; 3.3)	2.0 (1.2; 3.2)	PHF pre-frail	2.0 (0.8; 4.7)	1.9 (0.8; 4.4)	1.5 (0.6; 3.7)
				SPPB frail	1.7 (0.9; 3.1)	1.6 (0.8; 3.0)	1.2 (0.6; 2.3)
				FiND frail	1.5 (0.7; 3.1)	1.4 (0.6; 2.9)	1.0 (0.5; 2.2)
Multidimensional approach							
EFS	30.5 (14.6; 63.8)	26.1 (12.3; 55.5)	13.8 (5.13; 33.9)	FSS frail	3.4 (1.6; 7.4)	3.2 (1.5; 6.9)	1.0 (0.4; 2.4)
G8	30.1 (15.0; 60.6)	22.7 (11.1; 46.1)	5.3 (2.5; 12.5)	FSS pre frail	2.3 (1.4; 3.8)	2.2 (1.3; 3.6)	1.7 (1.0; 2.9)
CSBA	28.2 (13.9; 57.2)	20.5 (10.0; 42.1)	2.4 (1.2; 6.0)	EFS frail	2.7 (2.0; 3.6)	2.5 (1.9; 3.4)	1.8 (0.6; 5.3)
CGAST	15.5 (7.9; 30.4)	12.9 (6.5; 25.5)	4.3 (1.4; 9.8)	MFS frail	1.8 (0.5; 6.3)	2.6 (0.8; 9.0)	1.8 (0.5; 6.4)
TFI	16.1 (9.0; 28.7)	12.8 (7.0; 23.1)	7.5 (3.7; 15.7)	MFS pre-frail	1.3 (0.4; 4.3)	2.0 (0.6; 6.3)	1.8 (0.6; 5.8)
GFI	13.4 (7.0; 25.7)	11.1 (5.7; 21.6)	3.0 (1.3; 6.8)	CGAST frail	2.8 (1.3; 5.7)	2.6 (1.2; 5.4)	1.8 (0.7; 4.7)
SDFI	13.3 (7.2; 24.5)	10.4 (5.5; 19.4)	2.4 (1.2; 5.1)	CGAST pre frail	2.3 (1.4; 3.8)	2.2 (1.3; 3.6)	2.0 (0.9; 4.6)
IFQ	11.1 (5.8; 21.1)	8.8 (4.6; 17.0)	3.2 (1.3; 6.6)	G8 frail	2.4 (1.2; 4.5)	2.2 (1.1; 4.1)	1.3 (0.6; 2.8)
MFS	7.8 (4.7; 12.8)	6.5 (3.9; 10.9)	3.7 (2.3; 6.3)	SPQ frail	1.2 (1.0; 1.4)	1.1 (0.9; 2.4)	0.9 (0.5; 1.8)
HSF	6.3 (3.6; 11.0)	5.7 (3.2; 10.1)	1.4 (0.1; 2.9)	TFI frail	2.2 (1.2; 3.8)	2.0 (1.2; 3.5)	1.6 (0.9; 3.0)
SI	5.8 (2.9; 11.6)	5.2 (2.6; 10.4)	1.5 (0.1; 3.4)	CSBA frail	2.0 (1.1; 3.7)	1.9 (1.0; 3.4)	1.1 (0.6; 2.3)
BFI	5.2 (3.1; 8.9)	4.4 (2.5; 7.5)	2.2 (1.2; 3.9)	SDFI frail	2.0 (1.1; 3.6)	1.8 (1.0; 3.3)	1.3 (0.7; 2.4)
FSS	3.8 (2.3; 6.3)	3.4 (2.0; 5.5)	1.1 (0.1; 1.9)	SI frail	1.9 (0.5; 7.6)	1.8 (0.4; 7.2)	1.0 (0.2; 4.3)
SPQ	2.8 (1.4; 5.5)	2.3 (1.2; 4.6)	0.9 (0.0; 1.8)	BFI frail	1.9 (0.8; 4.7)	1.8 (0.7; 4.4)	1.3 (0.5; 3.3)
				GFI frail	1.9 (1.0; 3.3)	1.8 (1.0; 3.1)	1.2 (0.6; 2.2)
				IFQ frail	1.3 (0.7; 2.4)	1.2 (0.6; 2.3)	1.7 (0.4; 7.2)
Accumulation of deficits approach							
CGA	27.2 (11.0; 67.1)	22.4 (8.9; 56.3)	8.0 (2.8; 23.5)	CGA frail	3.3 (1.4; 7.8)	3.0 (1.3; 7.3)	1.9 (0.8; 4.2)
FI40	23.2 (11.1; 48.3)	19.7 (9.3; 41.7)	11.2 (5.11; 23.3)	CGA pre-frail	2.4 (1.1; 5.4)	2.3 (1.0; 5.2)	2.0 (1.1; 3.4)
FI70	21.0 (10.2; 42.9)	17.8 (8.5; 37.1)	13.2 (5.13; 32.2)	FI40 frail	2.0 (1.2; 3.5)	1.9 (1.1; 3.4)	1.6 (1.0; 2.5)
EFIP	15.8 (7.7; 32.1)	13.1 (6.4; 27.1)	6.7 (2.6; 16.2)	FI70 frail	2.0 (1.2; 3.5)	1.9 (1.1; 3.3)	1.6 (0.8; 3.0)
NLTCS	12.1 (4.5; 32.9)	10.2 (3.7; 28.1)	1.0 (0.1; 3.3)				
FIBLSA	10.1 (4.5; 22.7)	8.7 (3.8; 19.8)	1.2 (0.1; 3.2)				
Disability approach							
VES13	7.5 (4.3; 13.1)	6.5 (3.7; 11.4)	2.6 (1.2; 5.2)	HRCA frail	2.1 (1.2; 3.7)	2.0 (1.1; 3.4)	1.2 (0.6; 2.4)
HRCA	6.7 (3.6; 12.6)	6.0 (3.2; 11.4)	1.6 (0.1; 3.5)	WHRH frail	2.0 (1.1; 3.7)	1.9 (1.0; 3.6)	1.0 (0.5; 2.2)
WHRH	5.1 (3.0; 8.7)	4.7 (2.7; 8.0)	2.5 (1.2; 4.8)	SHCFS frail	2.0 (1.1; 3.8)	1.8 (1.5; 2.2)	1.2 (0.6; 2.4)
SHCFS	4.4 (2.9; 6.8)	4.0 (2.6; 6.2)	1.5 (0.1; 2.6)	VES13 frail	2.0 (1.1; 3.5)	1.9 (1.0; 3.3)	1.4 (0.7; 2.6)

[1]Model 0= Crude models. [2]Model 2= Model 1 + smoking status and alcohol consumption. [3]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life.

S14 Table. Mortality hazard ratios of frailty scores in women (n = 2,917) calculated at median time follow-up (3.5 years)

Continuous analysis				Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[1]	Model 2[2]	Model 3[3]	Frailty Score	Model 0[1]	Model 2[2]	Model 3[3]
Phenotype of frailty approach							
MPHF	4.7 (2.7; 8.0)	6.6 (4.2; 10.3)	2.3 (1.2; 4.3)	PHF frail	4.3 (0.7; 25.9)	3.8 (0.6; 23.2)	2.5 (0.4; 15.9)
FS	3.3 (1.7; 6.3)	6.2 (3.7; 10.3)	1.3 (0.6; 2.7)	PHF pre-frail	4.2 (0.8; 22.1)	3.8 (0.7; 20.0)	3.1 (0.6; 17.0)
SPPB	5.6 (3.1; 10.1)	6.1 (3.5; 10.6)	2.8 (1.4; 5.4)	PFI frail	2.2 (0.7; 7.0)	2.0 (0.6; 6.6)	1.5 (0.4; 5.2)
PHF	4.9 (2.9; 8.2)	5.5 (3.6; 8.6)	3.1 (1.7; 5.8)	PFI pre frail	2.8 (1.5; 5.2)	2.6 (1.4; 4.8)	2.2 (1.1; 4.2)
FiND	3.3 (1.9; 5.8)	5.3 (3.4; 8.1)	1.8 (0.9; 3.4)	FiND frail	2.7 (0.7; 10.7)	2.5 (0.6; 10.0)	1.8 (0.4; 7.4)
SOF	2.8 (1.6; 5.0)	4.9 (3.1; 8.0)	2.0 (1.0; 3.7)	FS frail	2.1 (0.8; 5.8)	2.0 (0.7; 5.4)	1.1 (0.4; 3.4)
ZED2	3.2 (2.0; 5.0)	3.9 (2.6; 5.8)	2.2 (1.3; 3.5)	FS pre- frail	2.6 (1.5; 4.8)	2.4 (1.3; 4.4)	2.0 (1.1; 3.7)
ZED3	2.2 (1.2; 4.1)	3.7 (2.2; 6.1)	1.7 (0.9; 3.2)	ZED2 frail	2.1 (0.6; 7.2)	2.2 (0.6; 7.3)	1.7 (0.5; 5.9)
ZED1	2.0 (1.2; 3.2)	3.6 (2.5; 5.2)	1.2 (0.7; 2.2)	SPPB frail	2.2 (0.9; 5.5)	2.1 (0.9; 5.2)	1.6 (0.6; 4.2)
PFI	2.3 (1.4; 3.7)	2.4 (1.5; 3.8)	1.5 (0.9; 2.6)	SOF frail	2.0 (0.8; 5.2)	1.9 (0.7; 4.9)	1.5 (0.5; 4.2)
BDE	1.8 (1.1; 2.9)	2.0 (1.3; 3.3)	2.4 (1.4; 4.2)	SOF pre-frail	2.2 (1.2; 4.0)	2.1 (1.2; 3.7)	2.0 (1.1; 3.7)
				ZED3 frail	1.8 (0.0; 68.3)	1.9 (0.1; 69.9)	1.6 (0.0; 51.5)
				ZED1 frail	1.5 (0.4; 5.7)	1.6 (0.4; 5.9)	1.1 (0.3; 4.4)
Multidimensional approach							
EFS	9.9 (4.2; 23.6)	26.1 (12.3; 55.5)	4.6 (1.7; 12.8)	MFS frail	1.9 (0.2; 17.6)	3.2 (0.4; 29.8)	2.4 (0.3; 22.4)
G8	11.3 (5.2; 24.7)	22.7 (11.1; 46.1)	4.1 (1.7; 9.9)	MFS pre-frail	1.8 (0.2; 16.2)	3.2 (0.4; 28.0)	2.9 (0.3; 25.0)
CSBA	23.1 (10.0; 53.1)	20.5 (10.0; 42.1)	4.2 (1.5; 11.7)	CGAST frail	3.5 (1.0; 12.1)	3.2 (0.9; 10.9)	2.0 (0.5; 7.3)
CGAST	6.7 (3.1; 14.8)	12.9 (6.5; 25.5)	1.7 (0.7; 4.2)	CGAST pre frail	3.4 (1.1; 10.9)	3.2 (1.0; 10.3)	2.9 (0.9; 9.3)
TFI	5.5 (2.9; 10.5)	12.8 (7.0; 23.1)	2.2 (1.0; 5.0)	FSS frail	2.1 (0.8; 5.2)	1.9 (0.8; 4.8)	1.3 (0.5; 3.5)
GFI	5.1 (2.4; 10.9)	11.1 (5.7; 21.6)	1.1 (0.4; 2.8)	FSS pre frail	3.4 (1.8; 6.3)	3.2 (1.7; 5.9)	2.7 (1.4; 5.2)
SDFI	4.7 (2.3; 9.5)	10.4 (5.5; 19.4)	1.1 (0.5; 2.5)	G8 frail	2.6 (1.0; 6.5)	2.4 (1.0; 6.0)	1.7 (0.6; 4.5)
IFQ	4.9 (2.3; 10.5)	8.8 (4.6; 17.0)	1.5 (0.6; 3.5)	CSBA frail	2.1 (1.0; 4.6)	1.9 (0.9; 4.2)	1.4 (0.6; 3.1)
MFS	6.8 (3.8; 12.2)	6.5 (3.9; 10.9)	3.9 (2.1; 7.3)	IFQ frail	1.9 (0.5; 7.8)	1.8 (0.4; 7.5)	1.3 (0.3; 5.6)
HSF	4.9 (2.5; 9.4)	5.7 (3.2; 10.1)	1.7 (0.8; 3.7)	TFI frail	1.9 (0.9; 4.0)	1.8 (0.9; 3.7)	1.4 (0.7; 3.1)
SI	1.9 (0.8; 4.4)	5.2 (2.6; 10.4)	0.5 (0.2; 1.3)	SDFI frail	1.9 (0.9; 4.0)	1.7 (0.8; 3.7)	1.3 (0.6; 2.9)
BFI	2.4 (1.3; 4.3)	4.4 (2.5; 7.5)	0.9 (0.5; 1.8)	EFS frail	1.7 (0.6; 5.3)	1.6 (0.5; 5.0)	1.2 (0.4; 4.0)
FSS	2.8 (1.6; 5.0)	3.4 (2.0; 5.5)	1.2 (0.6; 2.3)	GFI frail	1.6 (0.8; 3.2)	1.5 (0.7; 3.0)	1.0 (0.5; 2.2)
SPQ	2.7 (1.3; 5.7)	2.3 (1.2; 4.6)	1.2 (0.5; 2.7)	SPQ frail	1.3 (0.6; 2.8)	1.2 (0.6; 2.7)	1.0 (0.5; 2.2)
				BFI frail	1.2 (0.4; 3.3)	1.1 (0.4; 3.1)	0.9 (0.3; 2.5)
				SI frail	1.2 (0.3; 4.6)	1.1 (0.3; 4.5)	0.8 (0.2; 3.3)
Accumulation of deficits approach							
CGA	8.9 (3.2; 24.6)	22.4 (8.9; 56.3)	3.1 (0.9; 10.4)	CGAtot	2.3 (0.9; 5.9)	2.1 (0.9; 5.4)	1.6 (0.6; 4.5)
FI40	9.6 (4.1; 22.3)	19.7 (9.3; 41.7)	6.4 (3.0; 13.8)	CGAtotpre	3.1 (1.6; 6.0)	2.9 (1.5; 5.6)	2.7 (1.4; 5.2)
FI70	7.9 (3.4; 18.1)	17.8 (8.5; 37.1)	3.9 (1.4; 10.9)	FI70tot	2.1 (1.0; 4.3)	2.0 (1.0; 4.0)	1.7 (0.8; 3.7)
EFIP	6.3 (2.7; 14.6)	13.1 (6.4; 27.1)	2.9 (1.0; 8.0)	FI40tot	2.0 (1.0; 3.9)	1.8 (0.9; 3.7)	1.7 (1.0; 3.0)
NLTCS	8.8 (2.7; 27.9)	10.2 (3.7; 28.1)	2.0 (0.5; 7.6)				
FIBLSA	6.0 (2.4; 15.1)	8.7 (3.8; 19.8)	1.6 (0.6; 4.9)				
Disability approach							
VES13	4.4 (2.3; 8.3)	6.5 (3.7; 11.4)	2.6 (1.2; 5.4)	HRCAtot	1.8 (0.9; 3.6)	1.7 (0.8; 3.4)	1.3 (0.6; 2.7)
HRCA	3.7 (1.8; 7.9)	6.0 (3.2; 11.4)	1.4 (0.6; 3.3)	VES13tot	1.7 (0.8; 3.5)	1.6 (0.8; 3.3)	1.4 (0.6; 2.9)
WHRH	3.4 (1.8; 6.6)	4.7 (2.7; 8.0)	2.1 (1.0; 4.5)	SHCFStot	1.6 (0.7; 3.7)	1.5 (0.7; 3.6)	1.1 (0.4; 2.6)
SHCFS	2.8 (1.6; 4.8)	4.0 (2.6; 6.2)	1.1 (0.6; 2.2)	DFStot	1.6 (0.7; 3.4)	1.5 (0.7; 3.2)	1.2 (0.5; 2.8)

[1]Model 0= Crude models. [2]Model 2= Model 1 + smoking status and alcohol consumption. [3]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life.

S15 Table. Mortality hazard ratios of frailty scores in participants older than 70 years (n = 2,536) calculated at median time follow-up (3.5 years)

	Continuous analysis					Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]	Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]
Phenotype of frailty approach									
SPPB	4.1 (2.6; 6.3)	5.1 (3.2; 8.0)	4.8 (3.1; 7.6)	2.7 (1.6; 4.5)	FS frail	2.2 (1.1; 4.5)	2.4 (1.2; 4.9)	2.3 (0.1; 4.7)	1.5 (0.7; 3.3)
MPHF	4.3 (2.9; 6.3)	4.9 (3.3; 7.2)	4.3 (2.9; 6.4)	2.6 (1.7; 4.1)	FS pre- frail	2.4 (1.6; 3.6)	2.5 (1.7; 3.9)	2.4 (0.6; 3.7)	2.0 (1.3; 3.2)
PHF	4.1 (2.8; 5.9)	4.5 (3.1; 6.6)	4.1 (2.8; 6.0)	2.6 (1.6; 4.0)	SOF frail	2.2 (1.1; 4.3)	2.4 (1.2; 4.6)	2.2 (0.1; 4.4)	1.8 (0.8; 3.7)
FS	3.4 (2.1; 5.4)	4.0 (2.5; 6.4)	3.6 (2.3; 5.8)	1.9 (1.1; 3.3)	SOF pre-frail	2.3 (1.5; 3.6)	2.5 (1.6; 3.8)	2.4 (0.6; 3.7)	2.2 (1.4; 3.4)
FiND	3.2 (2.1; 4.7)	3.7 (2.5; 5.5)	3.4 (2.3; 5.0)	2.1 (1.3; 3.3)	PFI frail	1.9 (0.8; 4.4)	2.1 (0.9; 4.8)	2.0 (0.8; 4.7)	1.4 (0.6; 3.5)
SOF	3.0 (2.0; 4.5)	3.4 (2.3; 5.1)	3.2 (2.1; 4.8)	2.3 (1.5; 3.7)	PFI pre frail	2.2 (1.4; 3.5)	2.4 (1.5; 3.8)	2.3 (0.4; 3.7)	1.9 (1.1; 3.1)
ZED2	2.8 (2.0; 4.0)	3.1 (2.2; 4.4)	3.0 (2.1; 4.2)	2.1 (1.5; 3.1)	PHF frail	2.1 (0.8; 5.9)	2.4 (0.9; 6.6)	2.2 (0.8; 6.0)	1.4 (0.5; 4.1)
ZED3	2.2 (1.4; 3.4)	2.7 (1.7; 4.1)	2.4 (1.5; 3.8)	1.8 (1.1; 2.9)	PHF pre-frail	1.8 (0.7; 4.6)	2.0 (0.8; 4.9)	1.8 (0.7; 4.6)	1.6 (0.6; 4.0)
ZED1	2.1 (1.5; 2.9)	2.4 (1.7; 3.4)	2.2 (1.6; 3.2)	1.4 (0.9; 2.1)	ZED3 frail	1.9 (0.2; 15.7)	2.1 (0.3; 16.3)	1.8 (1.2; 2.7)	1.7 (0.2; 12.8)
PFI	1.9 (1.3; 2.7)	2.1 (1.5; 3.0)	2.0 (1.4; 2.9)	1.4 (1.0; 2.1)	ZED2 frail	1.9 (0.8; 4.9)	2.0 (0.8; 5.1)	2.0 (0.8; 5.1)	1.5 (0.6; 4.0)
BDE	1.6 (1.1; 2.3)	1.7 (1.2; 2.5)	1.6 (1.1; 2.3)	2.1 (1.4; 3.2)	ZED1 frail	1.7 (0.7; 4.0)	1.8 (0.7; 4.3)	1.8 (0.8; 4.3)	1.3 (0.5; 3.2)
					SPPB frail	1.7 (0.9; 3.2)	1.8 (0.9; 3.4)	1.7 (0.9; 3.3)	1.3 (0.7; 2.6)
					FiND frail	1.3 (0.6; 2.9)	1.5 (0.7; 3.2)	1.4 (0.6; 3.0)	1.1 (0.5; 2.4)
Multidimensional approach									
CSBA	20.2 (11.2; 36.5)	15.4 (8.4; 28.2)	12.6 (6.8; 23.3)	2.5 (1.2; 5.4)	MFS frail	1.9 (0.2; 20.6)	3.9 (0.4; 41.6)	3.5 (0.3; 37.8)	2.5 (0.2; 27.5)
G8	9.2 (5.1; 16.3)	12.6 (7.1; 22.5)	10.6 (5.9; 19.1)	4.0 (2.0; 7.8)	MFS pre-frail	1.8 (0.2; 19.4)	3.5 (0.3; 36.9)	3.3 (0.3; 34.8)	2.9 (0.3; 30.8)
EFS	8.4 (4.4; 16.0)	11.2 (5.8; 21.4)	9.5 (4.9; 18.4)	5.6 (2.6; 12.3)	CGAST frail	3.2 (1.3; 8.0)	3.5 (1.4; 8.8)	3.2 (0.3; 8.1)	2.2 (0.8; 5.9)
CGAST	5.7 (3.2; 10.3)	7.5 (4.2; 13.6)	6.6 (3.6; 11.9)	2.6 (1.3; 5.2)	CGAST pre frail	3.4 (1.4; 8.0)	3.5 (1.4; 8.2)	3.3 (0.4; 7.9)	3.1 (1.3; 7.5)
TFI	4.7 (2.9; 7.7)	7.1 (4.3; 11.5)	5.9 (3.6; 9.7)	3.3 (1.8; 6.0)	FSS frail	1.8 (0.9; 3.4)	1.9 (1.0; 3.6)	1.8 (0.9; 3.4)	1.2 (0.6; 2.5)
MFS	5.8 (3.8; 8.9)	6.6 (4.3; 10.1)	5.8 (3.8; 9.0)	3.7 (2.4; 5.8)	FSS pre frail	2.5 (1.6; 4.0)	2.6 (1.7; 4.1)	2.5 (0.6; 3.9)	2.2 (1.4; 3.5)
GFI	4.4 (2.5; 7.7)	5.8 (3.3; 10.2)	5.1 (2.9; 9.0)	1.6 (0.8; 3.3)	G8 frail	1.9 (1.0; 3.7)	2.1 (1.1; 4.0)	1.9 (0.0; 3.7)	1.3 (0.7; 2.7)
IFQ	4.1 (2.3; 7.1)	5.6 (3.2; 9.8)	4.8 (2.8; 8.5)	2.0 (1.1; 3.8)	IFQ frail	1.8 (0.7; 5.1)	2.0 (0.7; 5.6)	1.9 (0.7; 5.4)	1.5 (0.5; 4.1)
SDFI	3.2 (1.9; 5.3)	5.6 (3.3; 9.4)	4.6 (2.7; 7.8)	1.5 (0.8; 2.8)	TFI frail	1.7 (1.0; 2.9)	1.9 (1.1; 3.1)	1.8 (0.1; 3.0)	1.5 (0.8; 2.5)
HSF	3.8 (2.4; 6.0)	4.2 (2.6; 6.7)	3.8 (2.4; 6.1)	1.5 (0.9; 2.6)	CSBA frail	2.1 (1.2; 3.5)	1.9 (1.1; 3.3)	1.8 (0.0; 3.0)	1.3 (0.7; 2.3)
BFI	1.9 (1.2; 3.1)	2.8 (1.8; 4.5)	2.4 (1.5; 3.9)	1.3 (0.8; 2.2)	EFS frail	1.6 (1.3; 2.0)	1.7 (1.4; 2.1)	1.6 (1.3; 2.1)	1.3 (0.5; 3.1)
FSS	2.4 (1.6; 3.7)	2.7 (1.8; 4.2)	2.5 (1.6; 3.8)	1.2 (0.7; 2.0)	SDFI frail	1.5 (0.9; 2.5)	1.7 (1.0; 2.9)	1.6 (0.9; 2.7)	1.2 (0.7; 2.1)
SI	2.1 (1.1; 3.8)	2.7 (1.4; 4.9)	2.4 (1.3; 4.5)	0.9 (0.5; 1.8)	GFI frail	1.4 (0.9; 2.4)	1.5 (0.9; 2.6)	1.5 (0.9; 2.5)	1.1 (0.6; 1.9)
SPQ	1.8 (1.1; 3.2)	2.4 (1.4; 4.2)	2.2 (1.3; 3.9)	1.1 (0.6; 2.0)	BFI frail	1.3 (0.6; 2.6)	1.4 (0.7; 2.9)	1.3 (0.7; 2.8)	1.1 (0.5; 2.2)
					SI frail	1.3 (0.5; 3.4)	1.3 (0.5; 3.7)	1.3 (0.5; 3.7)	0.9 (0.3; 2.7)
					SPQ frail	1.1 (0.7; 2.0)	1.1 (0.6; 1.8)	1.2 (0.7; 2.0)	1.0 (0.6; 1.8)
Accumulation of deficits approach									
FI40	7.2 (3.8; 13.7)	10.6 (5.6; 20.0)	9.2 (4.8; 17.6)	6.9 (3.8; 12.7)	CGA frail	1.8 (0.9; 3.6)	2.1 (1.1; 4.2)	2.0 (0.0; 3.9)	1.5 (0.7; 3.3)
CGA	5.6 (2.6; 12.2)	9.4 (4.3; 20.6)	8.2 (3.7; 18.0)	3.4 (1.3; 8.6)	CGA pre-frail	2.3 (1.5; 3.7)	2.6 (1.6; 4.0)	2.4 (0.5; 3.9)	2.2 (1.4; 3.6)
FI70	5.7 (3.0; 10.6)	8.9 (4.8; 16.8)	7.8 (4.1; 14.8)	5.5 (2.5; 12.0)	FI40 frail	1.7 (1.0; 2.8)	1.9 (1.1; 3.1)	1.8 (0.1; 2.9)	1.6 (1.1; 2.4)
EFIP	5.4 (2.9; 10.1)	7.5 (4.0; 14.1)	6.5 (3.5; 12.3)	3.8 (1.8; 8.4)	FI70 frail	1.7 (1.0; 2.8)	1.9 (1.1; 3.1)	1.8 (0.1; 2.9)	1.5 (0.9; 2.7)
NLTCS	5.7 (2.4; 13.6)	6.8 (2.8; 16.1)	6.1 (2.5; 14.6)	1.4 (0.5; 3.8)					
FIBLSA	4.4 (2.2; 8.7)	5.6 (2.8; 11.2)	5.1 (2.6; 10.2)	1.4 (0.6; 3.3)					
Disability approach									
HRCA	3.3 (1.9; 5.6)	4.3 (2.5; 7.5)	3.9 (2.3; 6.8)	1.9 (1.0; 3.6)	HRCA frail	1.5 (0.9; 2.6)	1.8 (1.1; 3.0)	1.7 (0.0; 2.9)	1.3 (0.7; 2.3)
VES13	3.3 (2.1; 5.3)	4.3 (2.7; 6.9)	3.9 (2.4; 6.3)	2.2 (1.3; 3.9)	VES13 frail	1.5 (0.9; 2.5)	1.7 (1.0; 2.8)	1.6 (0.0; 2.7)	1.4 (0.8; 2.4)
WHRH	2.9 (1.8; 4.7)	3.5 (2.2; 5.7)	3.3 (2.0; 5.4)	2.3 (1.3; 4.0)	WHRH frail	1.5 (0.9; 2.6)	1.6 (0.9; 2.9)	1.6 (0.9; 2.8)	1.1 (0.6; 2.0)
SHCFS	2.5 (1.7; 3.7)	2.8 (1.9; 4.2)	2.7 (1.8; 4.0)	1.3 (0.8; 2.0)	SHCFS frail	1.5 (0.8; 2.8)	1.6 (0.9; 3.0)	1.6 (0.9; 2.9)	1.1 (0.6; 2.2)

[1]Model 0= Crude models. [2]Model 1= HR adjusted by sex. [3]Model 2= Model 1 + smoking status and alcohol consumption. [4]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. Models were fitted using age as time scale, with time 0 = age at entry of study and time 1 =age at event or censoring date.

S16 Table. Mortality hazard ratios of frailty scores in participants of 70 years and younger (n = 2,758) calculated at median time follow-up (3.5 years)

	Continuous analysis					Cut-off analysis			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]	Frailty Score	Model 0[1]	Model 1[2]	Model 2[3]	Model 3[4]
Phenotype of frailty approach									
MPHF	12.8 (7.4; 22.2)	13.8 (8.0; 23.8)	10.6 (6.0; 18.9)	3.9 (1.0; 10.1)	PHF frail	6.6 (3.5; 12.5)	7.1 (3.8; 13.5)	5.6 (2.9; 10.7)	2.2 (0.3; 14.7)
PHF	10.8 (5.8; 20.4)	12.7 (6.7; 23.8)	9.8 (5.1; 19.0)	4.8 (1.0; 12.1)	PHF pre-frail	2.3 (1.3; 4.0)	2.4 (1.4; 4.3)	2.2 (1.2; 3.9)	2.0 (0.5; 8.2)
SPPB	8.9 (3.0; 26.9)	12.6 (4.8; 32.7)	6.6 (3.7; 11.7)	2.3 (1.0; 7.2)	ZED3 frail	7.4 (3.3; 16.7)	6.5 (2.9; 14.7)	4.3 (1.9; 9.8)	1.7 (0.0; 104.1)
FS	10.5 (6.1; 18.2)	10.8 (6.3; 18.6)	8.3 (4.7; 14.6)	1.9 (1.0; 5.2)	FS frail	4.5 (3.1; 6.6)	4.5 (3.1; 6.6)	1.7 (1.3; 2.3)	1.5 (0.3; 6.6)
FiND	9.2 (5.5; 15.1)	9.5 (5.7; 15.6)	7.2 (4.3; 12.2)	3.0 (1.0; 7.5)	FS pre- frail	1.8 (1.4; 2.4)	1.9 (1.4; 2.5)	3.6 (2.3; 5.6)	1.3 (0.6; 3.2)
SOF	7.5 (4.3; 13.1)	8.0 (4.6; 14.0)	6.4 (3.2; 12.9)	2.7 (1.0; 6.7)	ZED1 frail	5.0 (3.2; 7.9)	4.8 (3.0; 7.6)	4.0 (2.5; 6.3)	1.6 (0.4; 6.9)
ZED2	6.9 (4.3; 11.2)	7.3 (4.5; 11.8)	6.3 (3.9; 10.3)	3.3 (1.0; 6.6)	ZED2 frail	5.1 (2.5; 10.3)	5.0 (2.5; 10.2)	3.9 (1.9; 8.0)	1.5 (0.2; 9.7)
ZED3	5.5 (3.2; 9.5)	6.4 (3.7; 11.2)	4.9 (2.8; 8.7)	2.7 (1.0; 6.7)	SOF frail	4.0 (2.6; 6.2)	4.1 (2.7; 6.4)	1.9 (1.4; 2.5)	1.9 (0.4; 8.8)
ZED1	5.6 (3.7; 8.5)	5.9 (3.9; 9.0)	4.7 (3.0; 7.3)	2.2 (1.0; 4.9)	SOF pre-frail	2.0 (1.5; 2.6)	2.0 (1.5; 2.7)	2.3 (1.8; 3.0)	1.5 (0.6; 3.6)
PFI	4.7 (2.9; 7.4)	4.9 (3.1; 7.8)	4.1 (2.5; 6.6)	1.7 (1.0; 4.2)	PFI frail	3.2 (1.5; 6.8)	3.4 (1.6; 7.1)	3.0 (1.4; 6.5)	1.4 (0.1; 16.1)
BDE	3.9 (1.7; 9.1)	3.8 (1.6; 8.7)	3.1 (1.3; 7.2)	2.3 (1.0; 5.2)	PFI pre frail	2.8 (2.0; 3.9)	2.8 (2.0; 4.0)	2.4 (1.7; 3.4)	1.7 (0.5; 5.5)
					FiND frail	2.3 (0.7; 7.5)	2.4 (0.7; 8.0)	2.1 (0.6; 7.2)	1.4 (0.4; 5.1)
					SPPB frail	1.9 (0.8; 4.6)	1.9 (0.8; 4.7)	1.8 (0.7; 4.4)	1.3 (0.5; 3.4)
Multidimensional approach									
CSBA	154.8 (51.9; 461.2)	145.0 (46.1; 456.4)	89.9 (27.8; 290.7)	7.2 (2.0; 34.7)	EFS frail	5.2 (3.3; 8.1)	5.0 (3.2; 7.8)	4.1 (2.6; 6.4)	2.3 (0.5; 11.7)
EFS	81.9 (36.3; 184.4)	83.8 (37.5; 187.4)	57.3 (24.5; 134.1)	30.5 (2.0; 120.0)	IFQ frail	3.5 (1.3; 9.5)	3.4 (1.3; 9.2)	2.4 (0.9; 6.5)	1.6 (0.0; 229.5)
G8	57.5 (21.4; 154.7)	68.2 (25.3; 183.6)	40.5 (14.6; 112.2)	8.1 (2.0; 37.0)	CGAST frail	3.1 (2.0; 4.8)	3.3 (2.2; 5.1)	3.0 (2.0; 4.7)	1.4 (0.4; 5.2)
GFI	35.1 (16.0; 76.9)	35.7 (16.4; 77.8)	23.7 (10.5; 53.6)	4.5 (2.0; 18.3)	CGAST pre frail	1.3 (0.9; 2.1)	1.4 (0.9; 2.2)	1.4 (0.9; 2.2)	1.3 (0.4; 3.7)
SDFI	20.0 (8.9; 44.9)	35.5 (12.5; 101.2)	21.9 (7.5; 63.8)	2.7 (2.0; 9.6)	MFS frail	2.9 (1.7; 4.9)	3.3 (0.8; 13.1)	2.6 (1.5; 4.4)	1.7 (0.4; 7.1)
CGAST	30.6 (14.0; 67.2)	31.6 (14.6; 68.5)	23.2 (10.5; 51.2)	3.1 (2.0; 11.6)	MFS pre-frail	1.3 (0.8; 2.2)	1.8 (0.5; 5.7)	1.3 (0.8; 2.1)	1.4 (0.4; 4.6)
TFI	24.1 (11.6; 50.3)	28.3 (11.0; 73.2)	18.2 (8.4; 39.3)	8.6 (2.0; 31.0)	G8 frail	2.9 (1.2; 7.2)	3.1 (1.2; 7.7)	2.2 (1.5; 3.3)	1.7 (0.6; 5.0)
IFQ	24.7 (11.3; 54.0)	25.5 (11.7; 55.4)	16.8 (7.5; 37.8)	3.8 (2.0; 14.0)	FSS frail	2.6 (1.8; 3.9)	2.6 (1.8; 3.8)	2.3 (1.7; 3.0)	1.1 (0.3; 4.7)
HSF	22.0 (11.4; 42.5)	21.2 (11.0; 40.6)	15.6 (7.8; 31.0)	2.3 (2.0; 9.2)	FSS pre frail	2.3 (1.7; 3.0)	2.4 (1.8; 3.2)	3.9 (2.6; 5.7)	1.8 (0.7; 4.2)
MFS	6.4 (2.8; 14.9)	10.4 (4.2; 25.3)	5.2 (2.2; 12.1)	3.2 (2.0; 8.2)	SDFI frail	2.4 (1.8; 3.1)	2.8 (1.0; 7.4)	2.4 (0.9; 6.5)	1.5 (0.5; 4.3)
SI	7.3 (3.6; 14.7)	9.3 (4.6; 18.5)	6.8 (4.1; 11.3)	0.8 (2.0; 3.1)	SPQ frail	1.6 (1.2; 2.2)	1.7 (1.3; 2.3)	1.5 (1.1; 2.0)	0.9 (0.3; 3.2)
BFI	7.5 (3.2; 17.8)	8.4 (3.6; 20.0)	6.1 (2.5; 14.8)	1.6 (2.0; 4.2)	TFI frail	2.5 (1.9; 3.3)	2.6 (2.0; 3.4)	2.3 (1.8; 3.0)	1.7 (0.6; 4.6)
FSS	6.9 (3.8; 12.4)	7.0 (3.9; 12.5)	5.2 (2.9; 9.5)	1.3 (2.0; 3.6)	CSBA frail	2.8 (2.2; 3.7)	2.6 (2.0; 3.4)	2.3 (1.7; 3.1)	1.1 (0.4; 3.2)
SPQ	5.1 (2.2; 11.8)	5.8 (1.7; 20.2)	3.7 (1.6; 8.7)	0.8 (2.0; 3.2)	GFI frail	2.5 (1.9; 3.2)	2.5 (1.9; 3.3)	2.3 (1.7; 3.0)	1.3 (0.5; 3.5)
					SI frail	1.8 (1.1; 3.0)	2.0 (1.2; 3.3)	1.6 (1.0; 2.6)	0.6 (0.0; 10.3)
					BFI frail	1.9 (1.3; 2.7)	2.0 (1.3; 2.9)	1.6 (1.1; 2.4)	0.8 (0.1; 5.6)
Accumulation of deficits approach									
CGA	76.2 (29.2; 199.3)	87.2 (33.8; 224.9)	54.6 (20.1; 148.5)	24.2 (3.0; 124.0)	CGA frail	4.1 (2.9; 5.8)	4.4 (3.1; 6.2)	3.7 (2.6; 5.3)	2.8 (0.8; 10.2)
NLTCS	53.8 (19.6; 147.5)	54.9 (20.0; 150.6)	33.1 (11.5; 95.0)	1.4 (3.0; 10.3)	CGA pre-frail	2.1 (1.5; 2.8)	2.3 (1.7; 3.1)	2.1 (1.6; 2.9)	2.1 (0.9; 4.8)
FI70	40.4 (18.4; 88.9)	46.1 (21.2; 100.6)	30.3 (13.3; 69.1)	19.3 (3.0; 76.3)	FI70 frail	2.9 (2.2; 3.8)	3.1 (2.4; 4.0)	2.7 (2.1; 3.5)	2.2 (0.8; 5.8)
FI40	39.5 (18.5; 84.3)	44.6 (21.0; 94.7)	31.0 (13.8; 69.4)	17.5 (3.0; 52.6)	FI40 frail	2.5 (1.9; 3.2)	2.6 (2.0; 3.4)	1.8 (1.3; 2.3)	1.8 (0.8; 3.9)
FIBLSA	26.6 (11.7; 60.3)	30.4 (8.2; 112.9)	18.6 (7.9; 43.9)	1.4 (3.0; 7.4)					
EFIP	26.8 (12.5; 57.5)	27.1 (12.7; 57.7)	17.4 (7.8; 38.9)	8.5 (3.0; 33.6)					
Disability approach									
VES13	16.7 (9.0; 31.2)	17.9 (9.7; 33.1)	13.1 (6.9; 25.1)	5.4 (4.0; 17.5)	SHCFS frail	3.0 (2.2; 4.1)	3.0 (2.2; 4.1)	2.5 (1.8; 3.5)	1.2 (0.4; 3.8)
HRCA	9.0 (4.8; 16.7)	9.5 (5.1; 17.5)	6.5 (3.4; 12.6)	0.8 (4.0; 3.0)	VES13 frail	2.7 (2.0; 3.5)	2.8 (2.1; 3.6)	2.4 (1.8; 3.2)	1.6 (0.5; 4.6)
SHCFS	8.8 (5.4; 14.4)	8.9 (5.5; 14.4)	19.4 (8.4; 45.0)	2.0 (4.0; 4.7)	HRCA frail	2.5 (1.9; 3.2)	2.7 (2.1; 3.5)	2.4 (1.8; 3.1)	1.3 (0.4; 3.6)
WHRH	7.3 (4.5; 11.9)	7.8 (4.8; 12.6)	6.1 (3.6; 10.1)	2.7 (4.0; 6.8)	WHRH frail	2.5 (1.9; 3.4)	2.6 (1.9; 3.4)	2.2 (1.6; 3.0)	0.8 (0.2; 2.5)

[1]Model 0= Crude models. [2]Model 1= HR adjusted by sex. [3]Model 2= Model 1 + smoking status and alcohol consumption. [4]Model 3= Model 2 + physical activity, BMI, diabetes, hypertension, cardiovascular, cancer, anaemia, COPD, arthritis, neuropsychiatric, depression, cognition, self-rated health & quality of life. Models were fitted using age as time scale, with time 0 = age at entry of study and time 1 =age at event or censoring date.

Chapter 4. Study III

Prospective association of baseline diabetes related variables and frailty trajectories in an elderly population

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4.1. Abstract

OBJECTIVE

Frailty is a dynamic state of vulnerability in the elderly, which increases the risk of mortality. We aimed to examine whether individuals with diabetes, different levels of baseline glycaemia/HbA1c experience different frailty trajectories with ageing.

RESEARCH DESIGN AND METHODS

Diabetes, HbA_{1c}, fasting plasma glucose (FPG) and other determinants were measured at baseline (2004-2005) and frailty status was assessed every two years from 2004-2005 to 2014-2015 in participants 60 years and older from the English Longitudinal Study of Ageing. We fitted quadratic frailty age-trajectories by diabetes/HBA1c/glycaemic status using mixed effects models.

RESULTS

We analysed 5333 participants (mean age 71.2 years (SD 8.0), 44.4 % men). The Frailty Index increased from (median (IQR)) 0.15 (0.08; 0.25), 35.6% frail at baseline to 0.19 (0.12; 0.31), 46.1% frail 10 years later. In a model adjusted for age and sex, during a 10-year follow-up and compared to non-diabetes at baseline, diabetes significantly increases the progression of frailty. Similarly, higher levels of HbA1c were associated with the progression of frailty. FPG was not significantly associated with progression of frailty. In a further adjusted model, only diabetes was significantly associated with increased frailty trajectories. However, at the end of life frailty trajectories of diabetic and non-diabetic individuals tended to converge.

CONCLUSIONS

People with diabetes or higher HbA_{1c} at baseline had a higher level of frailty throughout later life and experienced a steeper deterioration of frailty with ageing. The observation that baseline diabetes was associated with frailty trajectories could also reflect the role of diabetes complications on frailty trajectories. The observation that HbA_{1c} but not FPG was related to differences in frailty trajectories suggests that mean glucose levels during the day in real life situations have a stronger connection to frailty than fasting glycaemia or that HbA_{1c} may function as an indicator of pathophysiological processes beyond glycaemia.

4.2. Introduction

Most countries in the world are experiencing an increase in the longevity of the population. However, the ageing process is heterogeneous with a large individual variability in health status and disability as years progress [48]. This phenomenon also affects the diabetic population, which is living much longer than before, but at the same time, experiencing a significant increase in chronic complications [137].

Another consequence of the population ageing is that there is also an increase in the number of frail elderly people, who are easily affected by stressors. Frailty is a state of vulnerability in the elderly, which increases the risk of poor health outcomes such as falls, fractures, hospitalisation, institutionalisation, disability and mortality[38]. Frailty is highly prevalent in elderly populations. Collard et al performed a systematic review and they obtained very wide ranges from 4 to 59% and (weighted prevalence: 11%) depending on which instrument was used to assess frailty [138]. There are many different operational definitions of frailty, which are based on a few different underlying concepts of frailty: are the 'phenotype of frailty' [31], the 'accumulation of deficit' [35] and the 'multidimensional model' [38]. The plethora of available frailty scores makes it difficult to compare the prevalence, determinants and consequences of across studies [114 139]. However, despite these differences, most experts agree that frailty is a dynamic process that increases over time [38]. There is evidence that frailty can be reverted by treatment [140] highlighting the need to detect it early.

Diabetes and frailty share some pathophysiological mechanisms such as low grade inflammation, insulin resistance and sarcopenia [137]. Also, there is some epidemiological evidence of the association between diabetes and frailty.

However, the effect of diabetes on the evolution of frailty measured at different times during the follow-up has not yet been studied. Also, the impact of diabetes and hyperglycaemia on frailty scores that include variables beyond physical functioning, such as disability, cognition or comorbidity, has not been evaluated.

The purpose of this study was to evaluate the association of diabetes, fasting plasma glucose (FPG) and HbA_{1c} on long-term frailty trajectories. We hypothesized that diabetes, FPG and $HbA1_c$ would be associated with a higher level of frailty and a more marked change in frailty with ageing.

4.3. Research design and methods

Study population

This was an observational longitudinal study trajectory analysis. We estimated trajectories of frailty scores by diabetes-related variables as determinants over a 10-year follow-up period from 2004-2005 to 2014-2015. Data from participants in the English Longitudinal Study on Aging (ELSA) were used. ELSA is an ongoing cohort study based on a representative sample of the elderly English population. ELSA has data on mental and physical health, determinants of health, social and economic data. Data are collected at two-year intervals from 2002. Even waves also included a clinical examination and blood samples [49].

Inclusion criteria

Participants aged 60 years or older and assessed at Wave 2 (2004-2005) of ELSA in the interview and clinical examination were included because the variables needed to calculate the frailty scores began to be measured in this wave and some were not measured in younger participants.

Frailty scores

The outcome was frailty status measured in each wave from waves 2 to 7 with three different frailty scores: A 36-item Frailty Index[46], the Edmonton Frail Scale[92] and the Phenotype of Frailty score [31].

Frailty index

A 36-item frailty index (FI) was calculated based on the 40-item frailty index of Searle [46], from the accumulation of deficits approach, which included 36 variables of disability, comorbidity (excluding diabetes), physical functioning, and mental health. The FI was chosen because of its high reliability, predictive and discriminative ability of mortality [114 139]. The score dichotomises most variables as 0 (deficit not present) or 1 (deficit present). The FI is calculated by adding the current deficits and is subsequently rescaled to go from 0 (robust) to 1 (maximum frailty) and considered as a continuous variable in our analyses.

Edmonton Frail Scale

The Edmonton Frail Scale (EFS) [92], is a multidimensional frailty score which includes 11 subjective and objective variables of different dimensions such as cognition, social support, self-reported health,

continence, nutrition, disability and mood. The EFS was chosen because it performs better than other scores in discriminative ability for mortality outcomes [114 139].The scale goes from 0 (robust) to 17 (maximal frailty). The EFS was rescaled to a continuous scale from 0 (robust) to 1 (maximum frailty).

Phenotype of frailty score

The Phenotype of frailty score (PHF) [31], from the phenotype of frailty approach, is a frailty score developed by Fried, based on a physiological model and centred on physical frailty. The PHF includes 5 subjective and objective variables such as unintentional weight loss, weakness, exhaustion, slow gait and low physical activity. This score was chosen because it is the most used and cited frailty score [41].The cut-off for defining frailty is a score >3 and pre-frail a score >=1. The PHF was rescaled to a continuous scale from 0 (robust) to 1 (maximal frailty).

Exposures

Main exposures were baseline diagnosis of diabetes (not differentiated into type 1 and type 2 diabetes) and glycaemic measures: FPG and HbA_{1c}.

Diabetes was defined as self-reported medical diagnosis of diabetes, or FPG>7mmol/L or HbA_{1c}>=6 % (>=42 mmol/mol) and analysed as a binary variable. FPG and HbA_{1c} were analysed as continuous variables.

Covariates

Relevant demographic and lifestyle variables at baseline were included such as: age, sex, family income, social class, smoking status, maximum alcohol per day. Family income was categorised into 3 levels: high, moderate and low. Also, social class was categorised in 3 levels: high, intermediate and low. Smoking status was categorised as never, former and current smoker. Maximum alcohol consumption per day last week was categorised in 0, 1, 2 and 2 or more units of alcohol per day. Haemoglobin was also included as a covariate because it may influence the HbA_{1c} levels, and was analysed as continuous variable. Abdominal obesity was defined as a waist circumference >=101 cm in men and >= 88 cm in women. Cardiovascular disease was defined as myocardial infarction, heart failure, or stroke.

Missing data and calculation frailty scores

We applied multiple imputation was applied to deal with missing data. To have the best plausible values, the imputation was performed before calculating frailty scores on the underlying variables necessary to

calculate the scores. The percentage of missing data in variables from wave 2 to 7 ranged from 0.02% to 83.48%. A missing at random mechanism was assumed and the chained equations approach was applied [141]. One hundred datasets were generated and all models were adjusted in each of the generated datasets. Then, the final estimates and the corresponding standard errors were calculated were calculated according to Rubin's rules.[75]. Finally, imputation in wave 3 to 7, where participants did not participate, were removed.

In order to enhance readability the methods and results from this point onward are described in the language applicable to a single analysis. However, all results presented in this paper are have been calculated according to the100-fold multiple imputation procedure as described above.

The three frailty scores (FI, EFS and PHF) were calculated in the baseline and follow-up waves. The FI was calculated in each wave from 2 to 7, the EFS and the PHF were calculated in clinical examination waves 2, 4 and 6, because they need objective variables (measured only in at nurse visits) for their calculation.

If the variables necessary to calculate the frailty scores were measured only in clinical examination waves, for example weight, the last weight value obtained for this variable was used and then, the frailty score was calculated. For diagnoses of diseases and risk factors such as hypertension, as there were objective values in clinical examination waves 2, 4, and 6, we used self-reported of new events plus previous diagnoses in questionnaire only waves and objectives values self-reported of new events plus previous diagnoses in clinical examination waves. We define hypertension as a systolic or diastolic blood pressure ≥ 40 or ≥ 90 mm Hg, respectively, or self-reported high blood pressure medications.

Statistical analysis

Frailty age trajectories were fitted using mixed effects models with age and age squared as fixed effects, and subject and age as random effects. Age was centred to 60 years for better interpretability of the coefficient estimates. These models take into account the intra-individual correlation.

Separate models were fitted with diabetes, FPG and HbA_{1c} as exposures and different levels of adjustment: model 1 was adjusted for sex, while model 2 was further adjusted for family income, smoking status, physical activity, BMI, and haemoglobin. For diabetes model 2 was also further adjusted by HbA_1 in order, to isolate the effect of the diabetes diagnosis itself, including its treatments, over and above its function as a dichotomous classification of hyperglycaemia, To avoid collinearity problems, variables that were part of

the frailty scores were not included in the models, such as physical activity, comorbidities, disability, and all BMI-related variables (underweight/obesity/BMI, weight loss).

Quadratic terms and interactions with age terms were tested in the models. The final models were determined through likelihood ratio tests.

We performed sensitivity analyses stratifying models by diabetes diagnosis (for models with HbA1c as determinant), central obesity, cardiovascular disease and physical activity.

We used the Mice (multiple imputation), lme4 (mixed models), mitml (pool results according to Rubin's rules) packages in R version 3.3.0 for statistical analysis and generation of plots.

4.4. Results

From 9,432 participants who participated in wave two, 5,333 participants (44.4 % men) fulfilled the inclusion criteria (being 60 years and having participated in the clinical examination) were included in this study. Ten years later in wave seven, 2,666 (50% of the baseline participants) were assessed with 1,075 participants who died during the follow-up (20% of the baseline participants) and 1,592 (30% of the baseline participants) who were lost to follow-up (Supplemental figure 1).

At base-line (wave 2), mean age was 71.3 (95% CI: 71.0; 71.5), 11.3% had diabetes and 13.7% had cardiovascular disease. Table 1 shows characteristics of the study population at baseline stratified by baseline diagnosis of diabetes. Participants with baseline diagnosis of diabetes were slightly older, more frequently men, lower family income and social class, former smokers, no drinkers, with low-sedentary physical activity, higher BMI, more frequent abdominal obesity, more frequent CVD and more frequent frail than participants without baseline diagnosis of diabetes.

Figure 1 shows frailty trajectories (measured with: FI, EFS and PHF) for men and women with and without baseline diagnosis of diabetes. In model 1 adjusted by sex, frailty trajectories levels were higher among participants with baseline diabetes diagnosis throughout the follow-up period (Figure 1 and table 2). There was a constant increase of frailty levels in both groups: diabetes and non-diabetes. However, the differences in frailty trajectories among these two groups kept constant without a steeper deterioration for diabetes. With model 2, the differences between diabetes and non-diabetes are still significant. However, at the end of life the frailty trajectory curves tended to overlap.

Figure 2 shows frailty trajectories (measured with: FI, EFS and PHF) for participants at three different levels of HbA1c (5%, 6% and 7%) at baseline. Table 2 shows coefficients estimates with 95% confidence intervals from the mixed models.

Diabetes was significantly associated with frailty trajectories with the three frailty scores in age-sex adjusted model 1. With model 1 at age 60, having diabetes at baseline was associated with a 0.08 (0.07; 0.09) higher values of frailty index, with a 0.08 (0.072; 0.091) higher values of EFS, and 0.10 (0.09; 0.12) higher values PH. With the further adjusted model 2, at age 60 having diabetes at baseline was associated with a 0.08 (0.06; 0.09) higher values of FI, 0.08 (0.07; 0.09) higher values of EFS and 0.11 (0.09; 0.13) higher values of PHF.

In model 1, adjusted by sex, higher levels of HbA_{1c} at baseline were significantly associated with increased frailty trajectories only in the age-adjusted model 1 and only with the FI. The interaction of the quadratic term of HbA_{1c}-age was highly significant. The association lost its significance with further adjusted model 2.and neither with the further adjusted model 2. This association was not observed when frailty was measured with the EFS and PHF, although the tendency at least with model 1 is that individuals with a baseline HbA_{1c} =7% have increased and separated trajectories of frailty compared with individuals with baseline HbA_{1c} = 5% (figure 2).

In contrast with baseline diabetes, FPG was not associated with frailty trajectories (table 2).

Sensitivity analyses

In a sensitivity analysis stratifying by central obesity, the strength of the association's attenuated, but remained statistically significant (Supplemental table 1). Analysing the effect of HbA_{1c} on frailty trajectories, for individuals with baseline diagnosis of diabetes, comparing HbA1c=7% with 6 and 5%, participants with higher levels of HbA1c showed frailty trajectories similar to those between ages from 60 to 80 and with HbA1c=5 or 6%, (no increased) but at ages 80 and more the trajectories of frailty increase (Supplemental figure 2 and Supplemental table 2). In individuals without diabetes at baseline 5, frailty trajectories looks increased in comparison with HbA1c of 6% compared to 5% throughout all the follow-up. However, the differences in frailty trajectories were not significant. (Supplemental figures 2 and 3).

Participants with central obesity at baseline show increased frailty trajectories compared with participants without central obesity in participants with or without diabetes (Supplemental figures 4 and 5). The effect

higher levels HbA1c on frailty trajectories is observed in the frailty trajectories for central obesity, but the effect is lost in participants without this condition (Supplemental figures 6 and 7).

No changes in frailty trajectories depending on diabetes at baseline or different levels of HbA1c, when participants had cardiovascular disease (Supplemental figures 8 to 11).

The effects of increased frailty trajectories throughout life in participants with diabetes is attenuated in participants with sedentary/low level physical activity (Supplemental figures 12 to 15).

Table 1. Baseline characteristics of study participants by diabetes diagnosis[£]

Variable	No diabetes	Diabetes
n	4733	600
Age, years	71.1 (70.9; 71.4)	72.1 (71.4; 72.7)
Male, %	42.6	54.4
Low family income, %	32.5	35.3
Low social class, %	21.2	26.8
Smoking status, %		
current	12.3	12.4
former	51.0	56.5
never	36.7	31.2
Maximum alcohol, %		
>2 units /day	18.8	13.8
2 units/day	17.5	10.8
1 unit/day	13.2	10.0
not at all	50.5	65.3
Physical activity, %		
moderate-high	67.2	51.2
low-sedentary	32.8	48.9
BMI (kg/m2)	27.5 (27.4; 27.7)	30.0 (29.7; 30.4)
Abdominal obesity, %	50.5	71.1
Haemoglobin (mg/dl)	14.2 (14.2; 14.3)	14.2 (14.0; 14.3)
Cardiovascular disease[*], %	12.2	25.5
Glycaemia, mm/L[ǂ]	5.1 (4.9; 6.2)	5.1 (4.7; 5.8)
HBA1c, %[ǂ]	5.4 (5.2; 5.6)	6.5 (5.5; 7.1)
HBA1c, mmol/mol[ǂ]	35.5 (33.3; 37.7)	47.5 (36.6; 54.1)
Frailty index, units[ǂ]	0.14 (0.08; 0.24)	0.22 (0.14; 0.35)
Frailty index frail, %	33.2	54.0
Edmonton Frail Scale, units[ǂ]	0.12 (0.06; 0.22)	0.22 80.12; 0.33)
Edmonton Frail Scale, frail, %	12.8	29.7
Phenotype of frailty, units[ǂ]	0.27 (0.07; 0.47)	0.40 (0.27; 0.53)
Phenotype of frailty frail, %	12.7	22.5

Phenotype of frailty pre-frail, %	78.8	73.8

[£] Defined as self-reported medical diagnosis or fasting glucose >=7 mml/L or HbA_{1c} >=6.5%;

[*] Defined as medical diagnosis of infarction or heart failure or stroke; [ł] Median (IQR)

Table 2. Mixed effects models of frailty trajectories by diabetes, HbA_{1c} or fasting plasma glucose

	Frailty index	Edmonton Frail Scale	Phenotype of frailty
		Diabetes	
Model 1			
Intercept	0.14 (0.13; 0.15)***	0.11 (0.10; 0.12)***	0.22 (0.21; 0.23)***
Diabetes	0.079 (0.069; 0.090)***	0.082 (0.072; 0.091)***	0.102 (0.086; 0.118)***
age	0.0019 (0.0011; 0.0026)***	0.0029 (0.0021; 0.0038)***	0.0064 (0.0047; 0.0080)***
age^2	0.00020 (0.00017; 0.00022)***	0.00009 (0.00006; 0.00011)***	0.00014 (0.00009; 0.00019)***
Model 2			
Intercept	0.69 (0.46; 0.93)***	0.48 (0.27; 0.69)***	0.84 (0.49; 1.20)***
Diabetes	0.076 (0.063; 0.088)***	0.081 (0.070; 0.093)***	0.107 (0.087; 0.126)***
age	-0.0028 (-0.0060; 0.0004)	0.0045 (0.0011; 0.0080)**	0.0066 (0.0004; 0.0127)**
age^2	0.00020 (0.00015; 0.00026)***	0.00006 (-0.00002; 0.00013)	0.00014 (0.00001; 0.00028)**
		HbA_{1c}	
Model 1			
Intercept	0.01 (-0.10; 0.12)	-0.02 (-0.12; 0.08)	0.03 (-0.13; 0.19)
HbA1c	0.034 (0.001; 0.066)*	0.027 (-0.002; 0.056)	0.040 (-0.007; 0.087)
$HbA1c^2$	-0.0017 (-0.0040; 0.0007)	-0.0003 (-0.0024; 0.0019)	-0.0012 (-0.0047; 0.0022)
age	0.0004 (-0.0009; 0.0017)	0.0084 (0.0059; 0.0108)***	0.0037 (0.0023; 0.0051)***
age^2	0.00019 (0.00017; 0.00022)***	0.00008 (0.00006; 0.00011)***	0.00013 (0.00008; 0.00018)***
age*HbA_{1c}^2	0.000059 (0.000025; 0.000094)***	-0.000019 (-0.000079; 0.000041)	-0.000021 (-0.000056; 0.000015)
Model 2			
Intercept	0.57 (0.34; 0.81)***	0.35 (0.13; 0.56)**	0.68 (0.33; 1.04)***
HbA_{1c}	0.012 (-0.020; 0.044)	0.021 (-0.008; 0.050)	0.026 (-0.021; 0.073)
HbA_{1c}^2	-0.0003 (-0.0026; 0.0019)	-0.0001 (-0.0021; 0.0019)	-0.0005 (-0.0038; 0.0027)
age	-0.0038 (-0.0068; -0.0008)	0.0029 (-0.0004; 0.0061)	0.0063 (0.0006; 0.0120)*
age^2	0.00021 (0.00017; 0.00025)***	0.00010 (0.00005; 0.00014)***	0.00014 (0.00005; 0.00022)**
age*HbA_{1c}	0.0008 (0.0004; 0.0013)***	-0.0002 (-0.0007; 0.0003)	-0.0002 (-0.0011; 0.0006)
		Fasting plasma glucose	
Model 1			
Intercept	0.11 (0.06; 0.16)***	0.08 (0.03; 0.12)**	0.16 (0.08; 0.23)***
FPG	0.005 (-0.009; 0.019)	0.009 (-0.004; 0.022)	0.011 (-0.010; 0.032)
FPG^2	0.00012 (-0.00079; 0.00103)	-0.00013 (-0.00098; 0.00073)	-0.00002 (-0.00140; 0.00136)
age	0.0023 (0.0016; 0.0029)***	0.0031 (0.0023; 0.0039)***	0.0078 (0.0063; 0.0093)***
age^2	0.00019 (0.00017; 0.00022)***	0.00008 (0.00006; 0.00011)***	0.00013 (0.00008; 0.00018)***
Model 2			
Intercept	0.58 (0.37; 0.80)***	0.40 (0.20; 0.59)***	0.73 (0.40; 1.05)***
FPG	0.008 (-0.006; 0.021)	0.011 (-0.001; 0.024)	0.015 (-0.006; 0.035)
FPG^2	-0.00009 (-0.00098; 0.00079)	-0.00031 (-0.00114; 0.00052)	-0.00028 (-0.00162; 0.00105)
age	0.0009 (-0.0004; 0.0023)	0.0017 (0.0001; 0.0032)*	0.0050 (0.0021; 0.0079)**
age^2	0.00021 (0.00018; 0.00025)***	0.00010 (0.00005; 0.00014)***	0.00014 (0.00005; 0.00022)**

Table 2. Mixed effects models of frailty trajectories by diabetes, HbA_{1c} or fasting plasma glucose
Values are coefficients (95% confidence intervals). Model 1: age (60 years), sex (male), diabetes (yes). Model 2: age (60 years), sex (male), diabetes (yes), income (low), social class (middle), smoking status (former smoker), Maximum alcohol per day (>2 units/day), haemoglobin, $haemoglobin^2$; HbA_{1c} (only for diabetes) and HbA_{1c}^2 (only for diabetes) *p value<0.05, **p value<0.01, *** p value <0.001.

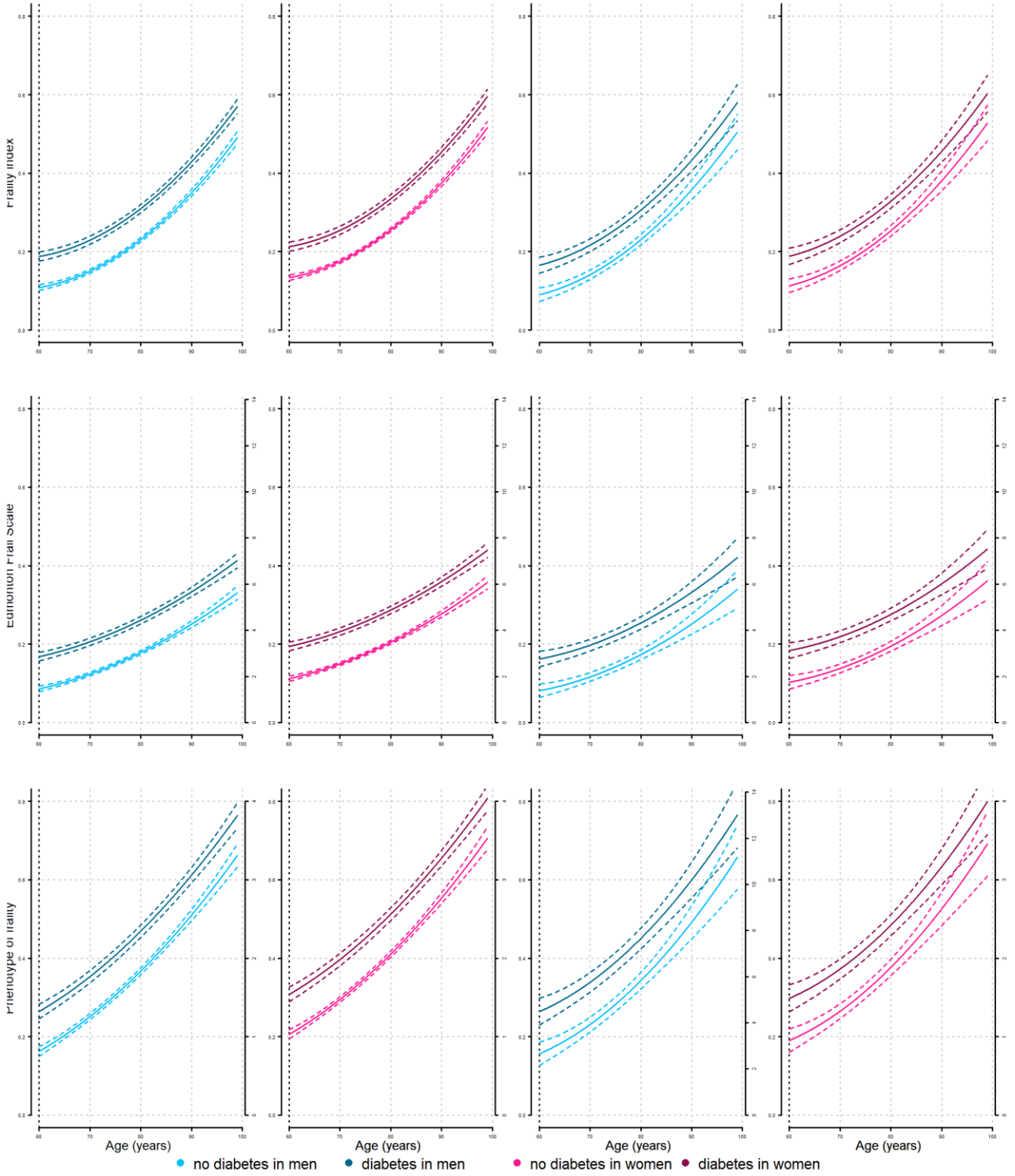


Figure 1. Frailty trajectories by baseline diabetes diagnosis. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of frailty score.

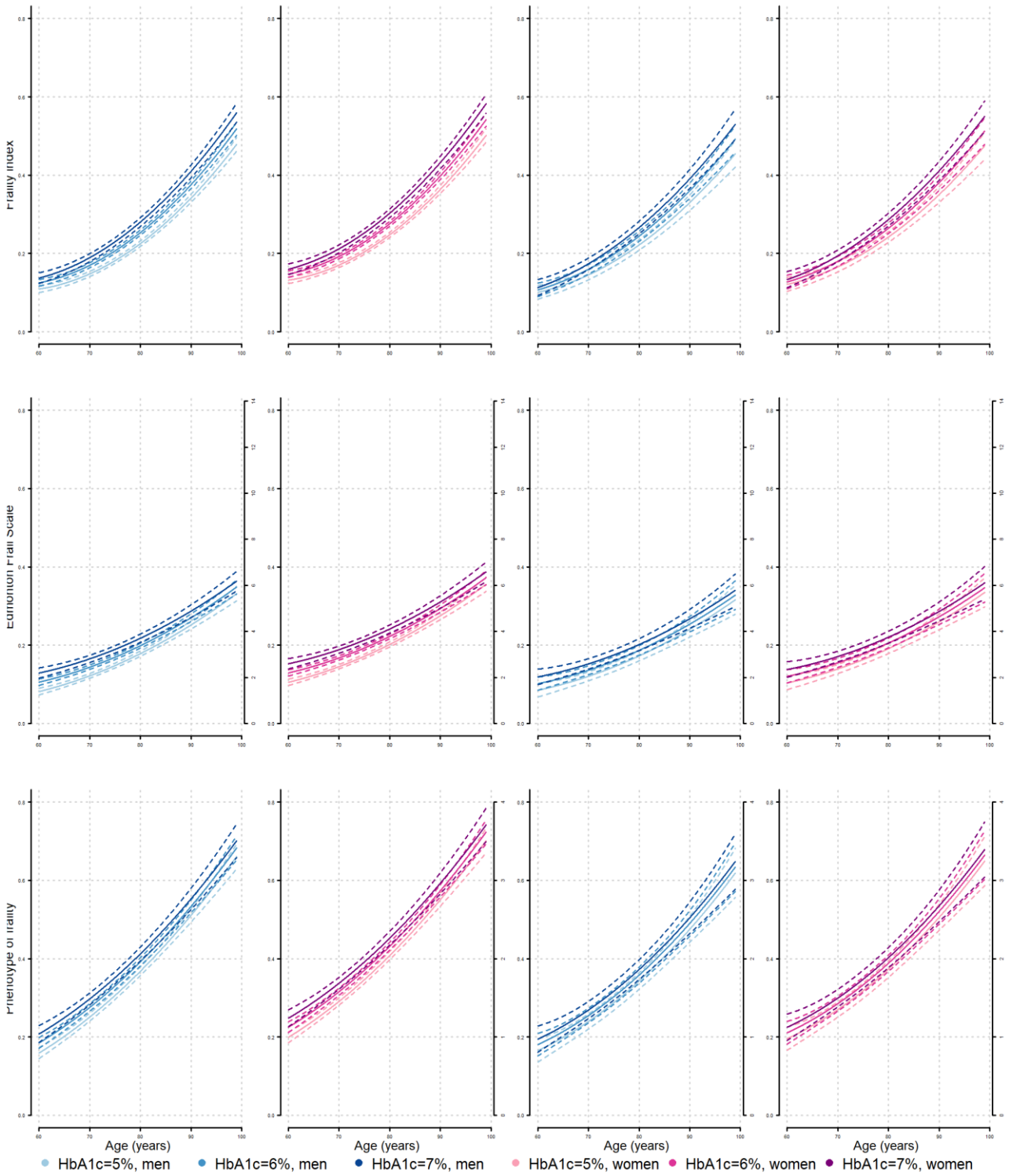


Figure 2. Frailty trajectories at different values of HbA_{1c}. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of Frailty score.

4.5 . Discussion

We investigated the association of baseline values of diabetes, HbA_{1c}, and FPG with frailty trajectories over a 10-year period and found that diabetes and HbA_{1c} were significantly associated to a higher level of frailty throughout the follow up period, but FPG was not. Increased frailty trajectories over time in participants with diabetes tend to deaccelerate after the age of 80. Also, we found that frailty trajectories progress over time in participants with and without diabetes.

To our knowledge this is the first study to explore diabetes related variables in relation to long term frailty trajectories. We used three different frailty scores, which represent the three main frailty concepts. The results are consistent regardless of the frailty score used, supporting our hypothesis that diabetes is associated to frailty.

We found that effects of diabetes on frailty trajectories were attenuated when stratifying by central, physical activity and were lost in cardiovascular disease. The most likely explanation of the observed effect of baseline diabetes on frailty progression is that diabetes and frailty have some deeper causes in common, such as low physical functioning/activity, low socio-economic status.

Slightly higher levels of HbA_{1c} were associated with higher frailty trajectories over time. However these effects were lost when adjusting for potential confounders. This suggests that the effects are not direct, and in all likelihood explained by preceding confounding factors.

We found that FPG was not associated with frailty levels or trajectories. In fact $HbA_{1c,}$ despite its limitations linked to red blood cell survival and anaemias, is a reflection of mean glycaemia over a longer time period, has less intra-individual variation and is more strongly associated with diabetes comorbidities than FPG [142]. It may thus capture the relevant exposure with more precision than FPG.

For all determinants, the estimates were higher with the phenotype of frailty score than with the frailty index or the Edmonton Frail Scale (table 2). This confirms our hypothesis, concerning the type of variables that make part of this frailty scores, which are strongly associated to the phenomenon of sarcopenia [143], which is a pathophysiological mechanism in common with frailty and pathological ageing.

The FI or the EFS have many other different variables that are not linked to this pathophysiological mechanism, which is shared with diabetes. There are three main operationalisation definitions of frailty. First, the phenotype of frailty approach defines frailty as "a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation, of multiple physiologic systems" [9] [31].

Disability or comorbidity are considered as outcomes of frailty and not part of the syndrome. The phenotype of frailty approach is focused mainly on physical frailty. Second, the accumulation of deficits approach, which defines frailty based on the number of deficits acquired during ageing, regardless the type of deficit and requires the assessment of at least 30 variables [43] [46]. And finally, the multidimensional approach, which defines frailty as a dynamic process affecting one or more areas of functioning, such as physical functioning, disability, social support, cognition and comorbidity. Differently from the accumulation of deficit approach, these scores can have less than 30 variables [38].

Our findings are consistent with previous studies that suggest the association on diabetes and frailty. Castrejón-Pérez et al in a cross-sectional study found a significant association between diabetes and frailty with an OR of 2.32 (95% CI 1.93–2.73) [144]. Hubbard et al studied the elderly general population and found that diabetes was associated to frailty, suggesting that diabetes increases biological age by two years[145]. In addition, diabetes risks factors have also been associated with incident frailty. In the Whitehall II study with a 10-year follow-up, Bouillon et al found that the Cambridge and Finnish diabetes risk scores were associated to incidence of a frail/pre-frail state [146]. In a longitudinal study Ottenbacher et al studied elderly Mexican-Americans, evaluating a series of determinants of frailty and found that diabetes at baseline was associated with frailty status 10 years later [147].

There are two longitudinal studies that associate diabetes with incident frailty: Garcia-Esquinas et al et Zaslavsky et al [148] [149]. The two studies used the phenotype of frailty score developed by Fried as an instrument for measuring frailty status.

Our results on diabetes are consistent with the results of Garcia-Esquinas et al[148], who found a prospective association of baseline diabetes with incident frailty up to 3 years of follow-up (odds ratio 2.18, 95% 95% CI 1.42-3.37). They also observed that the strength of association was lower after adjustment, suggesting that

the diabetes-frailty association is at least in part confounded by determinants shared between diabetes and frailty. Indeed, the possibility exists that the remaining association between diabetes and frailty in our study is still residually confounded. However, or aim was not no isolate the aetiological role of glycaemia for the development of frailty, but to show to which degree patients with diabetes and even people with non-diabetic intermediate glycaemic levels experience frailty in later life. In addition, to try to study the effect of relevant risk factors or comorbidity, we performed sensitivity analyses, which attenuated the strength of the association.

In a survival analysis, Zaslavsky et al found that diabetes was associated to a higher risk of frailty in 4.5 years later. They analysed diabetes markers as time varying variables. They found that for example a glycaemia=110 mg/dl was associated with higher risk of frailty in non-diabetic participants compared to a value of 100 mg/dl. In diabetic participants values below 160 and over 180 mg/dl were associated to higher risk for incident frailty [149]. These results are consistent with ours, because we also found a prospective association of HbA_{1c} and frailty trajectories. However, we did not find a significant association with FPG. This could be explained by the long-term assessment nature of HbA_{1c} that reflects much better the actual glucose metabolism state. In addition to this, Zaslavsky combined the results of HbA_{1c} and glycaemia with Bayesian methods and we analysed the 2 values separately. Concerning diabetic participants, they found a U-shape relationship. We observed different results when we stratified HbA_{1c} models by diabetes diagnosis with just lost of effect of HbA1c on frailty progression in participants with diabetes.

Our finding of an association between baseline diabetes and frailty trajectories, even after adjustment and with three different frailty scores, suggests that diabetes or conditions associated with diabetes influence the ageing process. The inverse phenomenon, frailty influencing diabetes progression, is also possible. Most likely, these processes occur simultaneously. Diabetes and frailty share pathophysiological mechanisms that could be involved in accelerating the aging process. These associations are probably bidirectional. The underlying mechanisms are mediated by adipose tissue dysfunction, where accelerated aging is driven by an increase in pro-inflammatory cytokines, macrophage dysfunction, and increased oxidative stress [27]. These processes contribute to metabolic dysregulation and insulin resistance with redistribution of adipose tissue and muscular dysfunction [27].

Diabetes and frailty are associated probably because they share pathophysiology mechanism such as low grade of inflammation [150]. With advanced age, increase the prevalence of sarcopenia, insulin resistance and

obesity. Insulin resistance may cause sarcopenia and sarcopenia can lead to insulin resistance. Sarcopenia development is accentuated with higher levels of HbA_{1c} and attenuated with the use of insulin [151]. In addition to this evidence, metabolic syndrome and insulin resistance measured with HOMA has been prospectively associated to frailty in general elderly population and evaluated with the phenotype of frailty score [152].

This study has several strengths. It has a prospective design with repeated measures on frailty. Also, a very efficient technique of multiple imputation was applied for dealing with missing data for longitudinal design. Moreover, it uses mixed models that take in account the intra-individual correlation.

A limitation is that some variables were tailored to calculate the frailty scores in the ELSA dataset. We could not differentiate between type 1 and type 2 diabetes with the ELSA data that could lead to misclassification. This could lead to some bias results. However, we think that due to that the data indicate that all participants were diagnosed at 50 years and over, it is likely that the proportion of type 1 diabetes be low. Another limitation is that we could not include relevant variables in the adjusted models, because they were also part of the frailty scores, such as disability, physical activity, comorbidity and obesity. We tried to improve the results with the sensitivity analysis, stratifying by some of these variables.

Conclusions

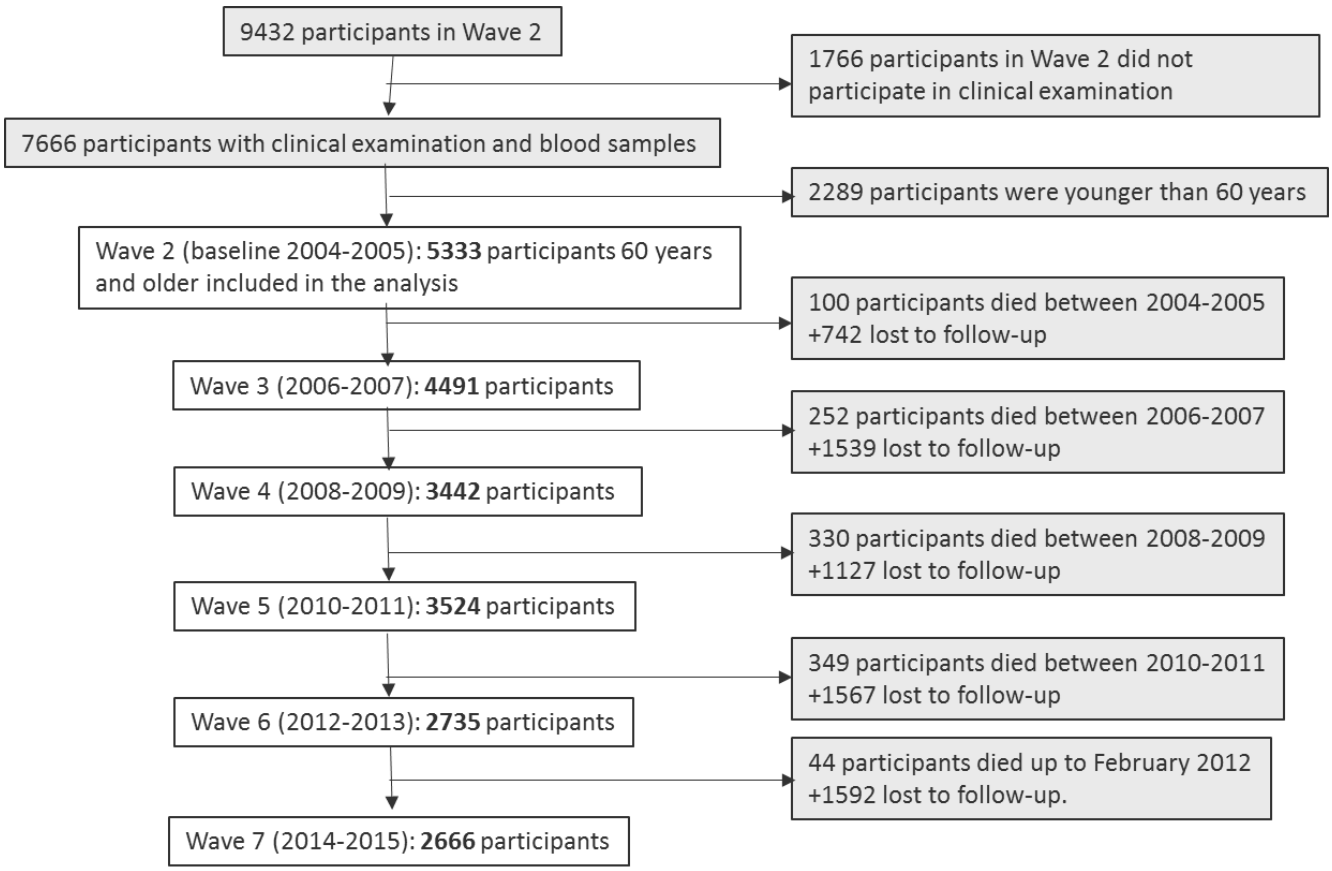
Diabetes is associated with frailty progression. After age 80, diabetic individuals are likely to deaccelerate frailty progression. Older diabetics are a heterogeneous group. Those who are also frail, they have much higher risks. Therefore, this group should be detected, should receive a tailored treatment and be re-evaluated regularly. Therefore, we agree with Morley that there is enough evidence to support the recommendation for diabetic population to be screened for frailty already from middle age [153]. Also, diabetes management should be personalised depending on the presence of frailty syndrome, avoiding medicaments with a higher risk of hypoglycaemia in frail individuals [154].

Although our results are consistent in the fact that diabetes is a determining factor in the evolution of frailty, we cannot exclude that the evolution of frailty may be determinant for diabetes in the future. As a result, future research should examine the causality and mechanisms of this association.

4.6 . Acknowledgments

We gratefully acknowledge the UK Data Archive for supplying the ELSA data. ELSA was developed by a team of researchers based at University College London, the Institute of Fiscal Studies, and the National Centre for Social Research (data sharing project number 82538).

The data creators or the funders of the data collections and the UK Data Archive do not bear any responsibility for the analyses or interpretations presented here.



Supplemental figure 1. Flowchart of study participation and follow-up over 10 years.

Supplemental table 1.

Mixed effects models of change for frailty state by baseline diabetes stratified by central obesity (model 2)

	Frailty index	Edmonton Frail Scale	Phenotype of frailty
Non central obesity participants			
Intercept	0.65 (0.32; 0.98)***	0.48 (0.17; 0.78)**	1.03 (0.50; 1.56)***
Diabetes	0.071 (0.048; 0.094)***	0.079 (0.058; 0.100)***	0.116 (0.079; 0.152)***
age	-0.0021 (-0.0072; 0.0030)	0.0042 (-0.0012; 0.0096)	0.0077 (-0.0023; 0.0177)
age^2	0.00022 (0.00013; 0.00031)***	0.00006 (-0.00005; 0.00016)	-0.00004 (-0.00023; 0.00015)
Central obesity participants			
Intercept	0.78 (0.44; 1.12)***	0.50 (0.21; 0.80)***	0.74 (0.27; 1.21)**
Diabetes	0.067 (0.051; 0.084)***	0.077 (0.063; 0.092)***	0.095 (0.073; 0.118)***
age	-0.0035 (-0.0078; 0.0009)	0.0038 (-0.0010; 0.0085)	0.0011 (-0.0072; 0.0095)
age^2	0.00020 (0.00011; 0.00029)***	0.00007 (-0.00003; 0.00018)	0.00035 (0.00016; 0.00054)***

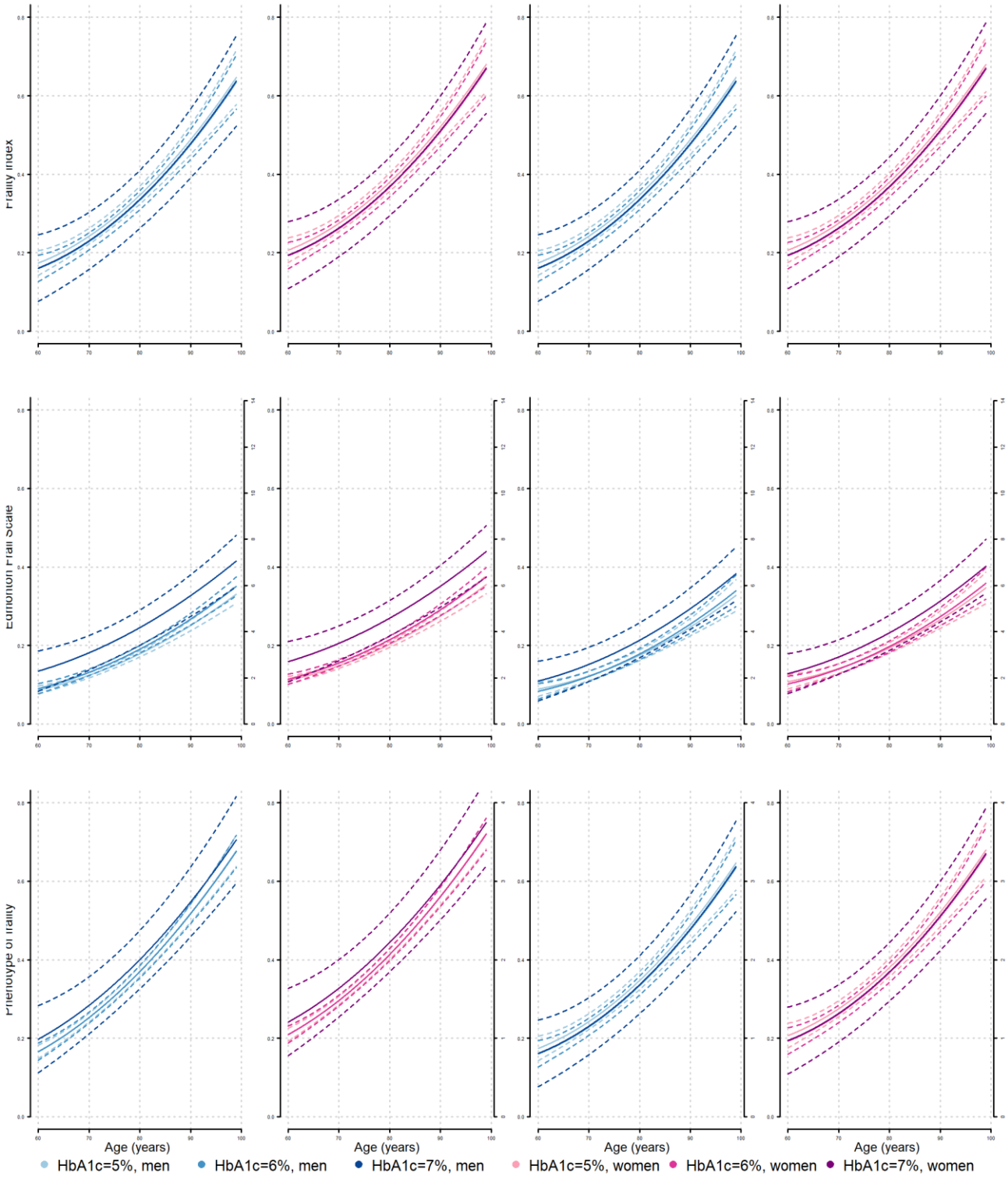
Values are coefficients (95% confidence intervals). Model 2: age (centred 60 years), sex (male), diabetes (yes), income (low), social class (middle), smoking status (former smoker), maximum alcohol (>2 units/day), haemoglobin, $haemoglobin^2$; HbA_{1c} and HbA_{1c}^2 . *p value<0.05, **p value<0.01,*** p value <0.001.

Supplemental table 2.

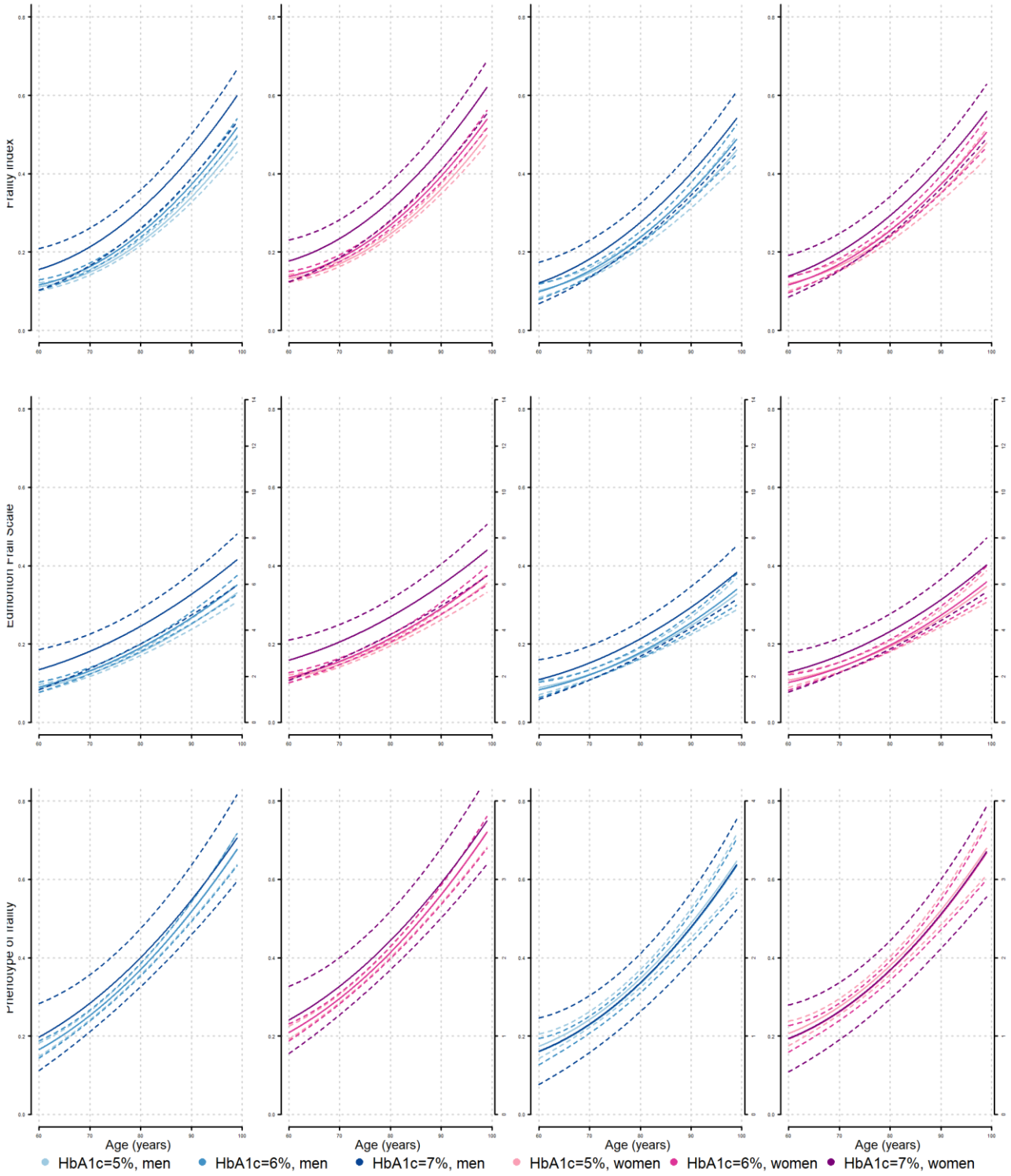
Mixed effects models of change for frailty state by HbA1c stratified by diabetes diagnose (model 2)

	Frailty index	Edmonton Frail Scale	Phenotype of frailty
		No diabetes diagnosis	
Intercept	0.60 (0.03; 1.17)*	0.78 (0.25; 1.30)**	0.68 (-0.19; 1.55)
HbA_{1c}	-0.183 (-0.392; 0.027)	-0.252 (-0.446; -0.058)	-0.178 (-0.498; 0.142)
HbA_{1c}^2	0.0177 (-0.0015; 0.0370)	0.0237 (0.0059; 0.0416)**	0.0168 (-0.0126; 0.0462)
age	0.0021 (0.0014; 0.0028)***	0.0030 (0.0022; 0.0038)***	0.0069 (0.0054; 0.0085)***
age^2	0.00012 (0.00003; 0.00022)*	0.00010 (-0.00001; 0.00020)	0.00021 (0.00003; 0.00040)*
		Diabetes diagnosis	
Intercept	0.62 (0.41; 0.83)***	0.52 (0.35; 0.70)***	0.70 (0.42; 0.99)***
HbA_{1c}	-0.094 (-0.151; -0.037)**	-0.078 (-0.124; -0.032)***	-0.088 (-0.165; -0.012)*
HbA_{1c}^2	0.0052 (0.0014; 0.0089)**	0.0047 (0.0016; 0.0078)**	0.0048 (-0.0003; 0.0099)
age	0.0024 (-0.0003; 0.0051)	0.0016 (-0.0014; 0.0046)	0.0083 (0.0026; 0.0140)**
age^2	0.00008 (-0.00003; 0.00018)	0.00012 (0.00001; 0.00022)*	-0.00001 (-0.00019; 0.00017)

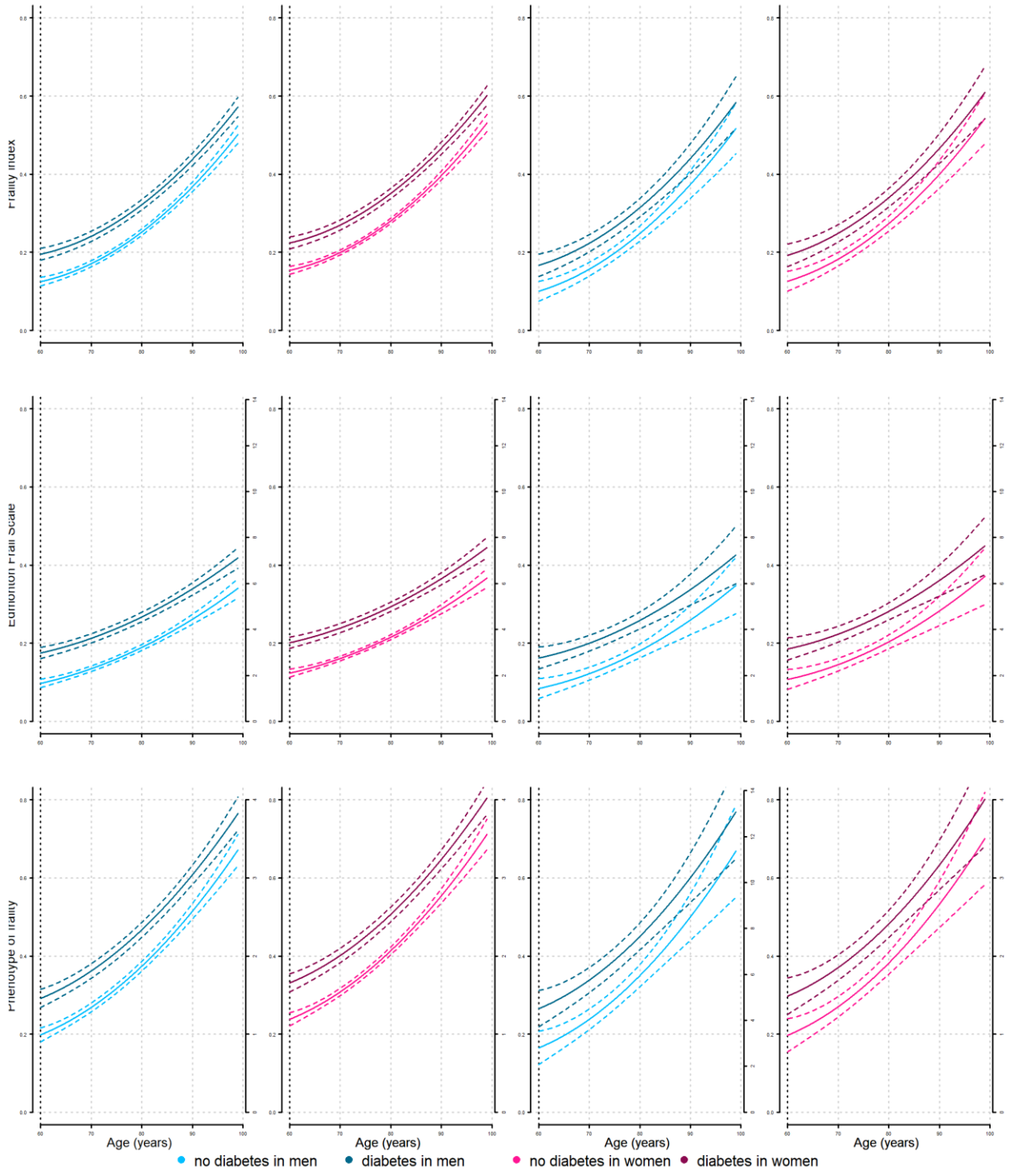
Values are coefficients (95% confidence intervals). Model 2: age (centred 60 years), sex (male), diabetes (yes), income (low), social class (middle), smoking status (former smoker), maximum alcohol (>2 units/day), haemoglobin, $haemoglobin^2$; HbA_{1c} and HbA_{1c}^2 . *p value<0.05, **p value<0.01,*** p value <0.001.



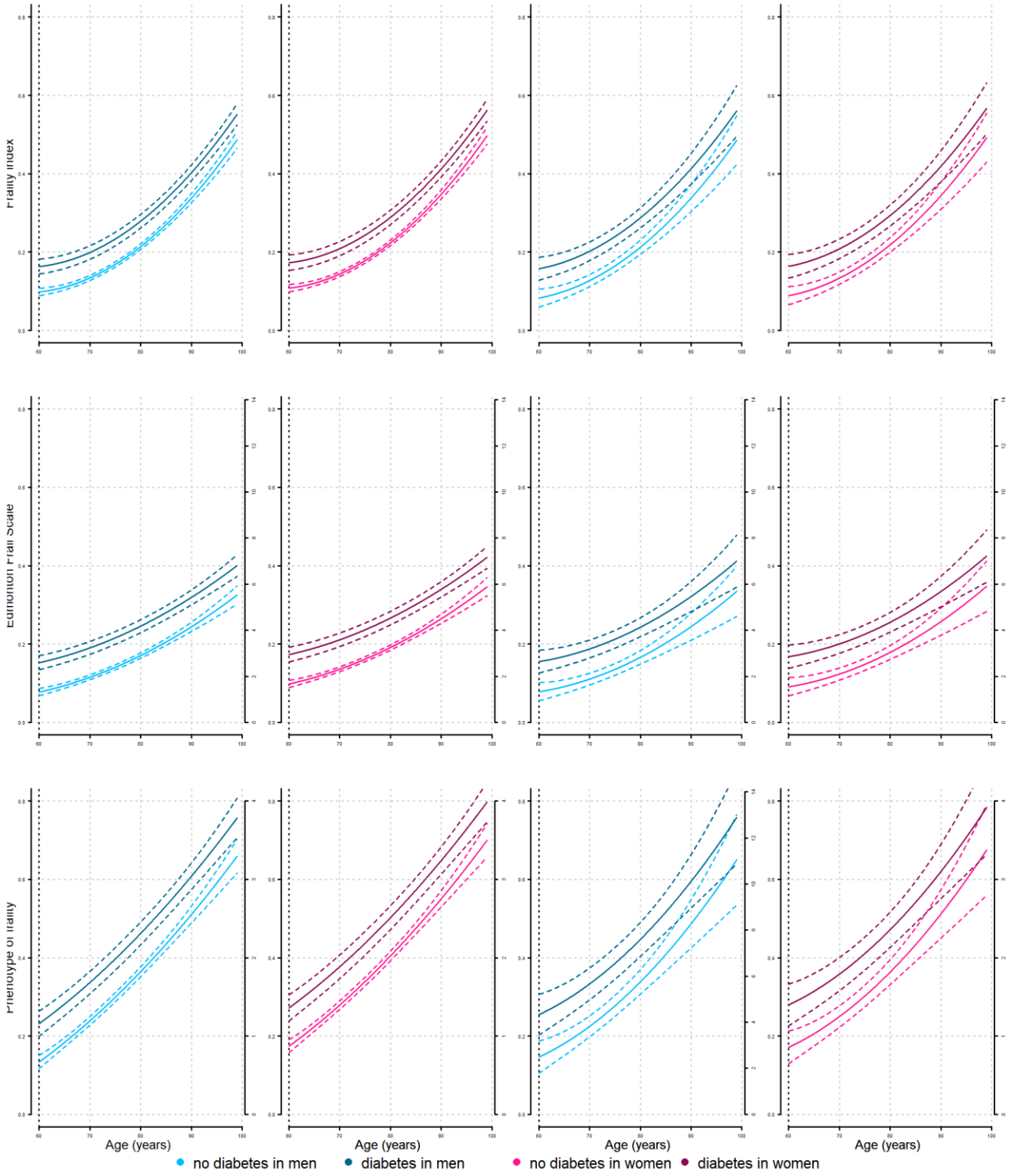
Supplementary figure 2. Frailty trajectories at different values of HbA_{1c} in participants with diabetes diagnosis at baseline. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of Frailty score.



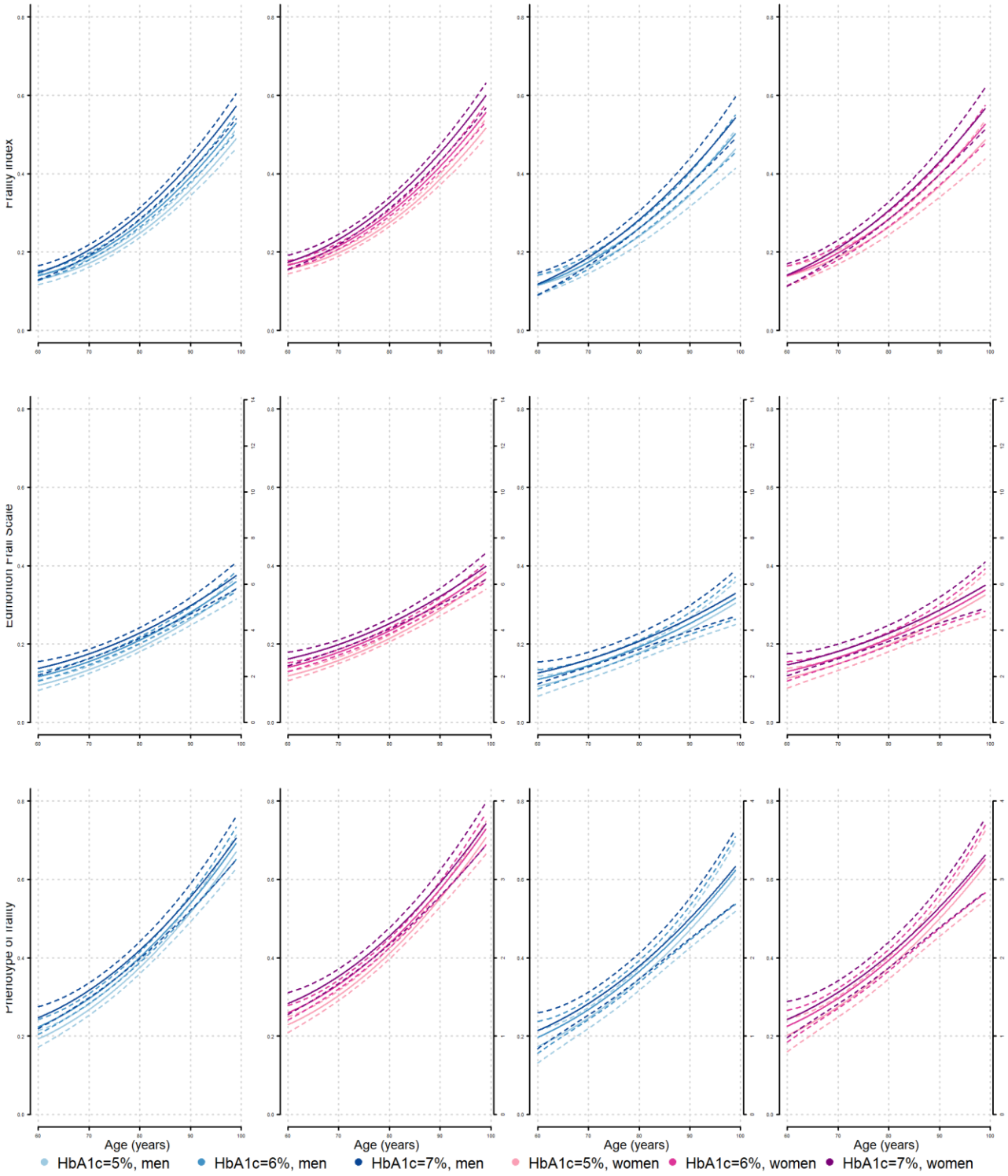
Supplementary figure 3. Frailty trajectories at different values of HbA1c in participants without diabetes diagnosis at baseline. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of Frailty score.



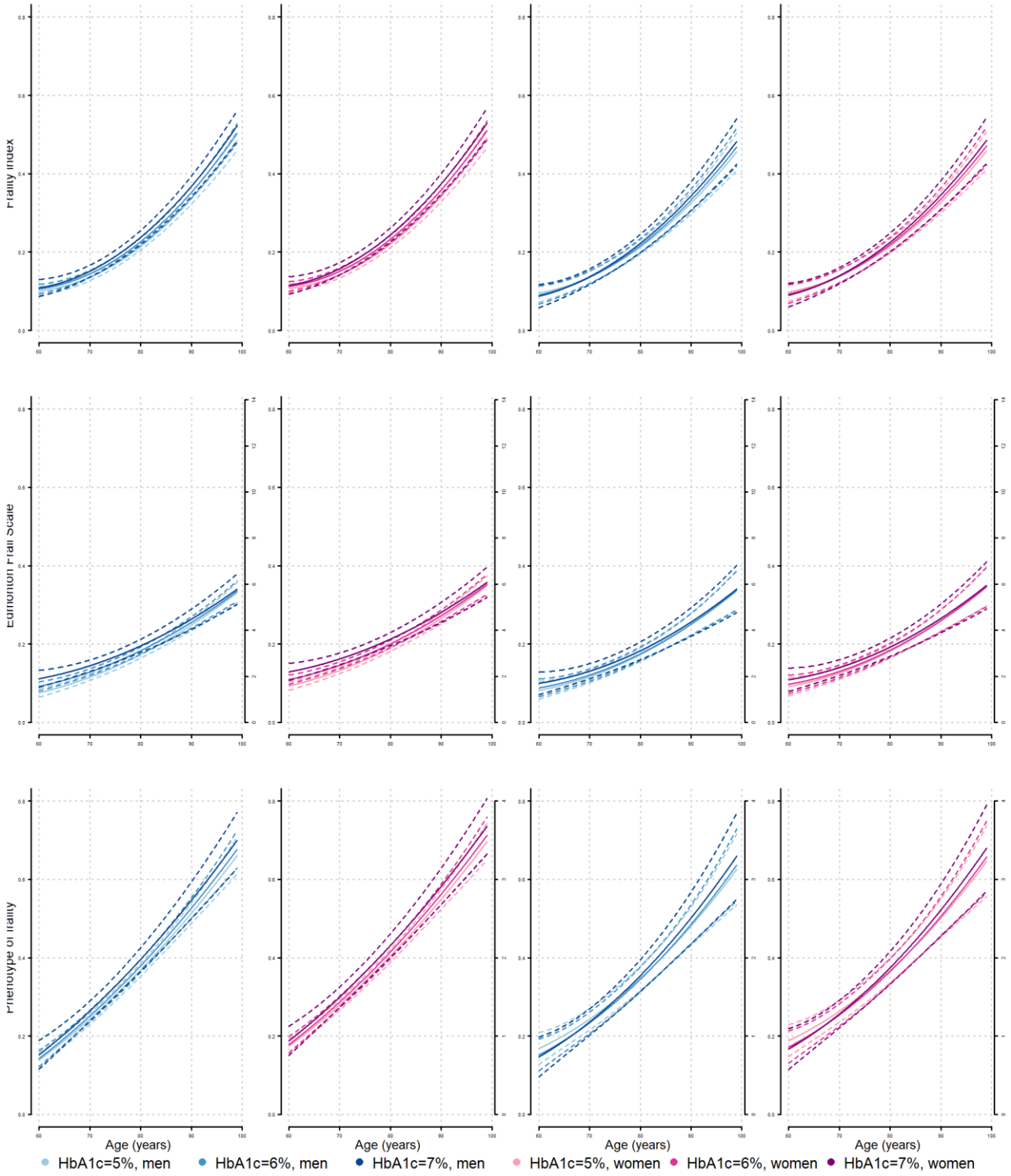
Supplementary figure 4. Frailty trajectories by baseline diabetes diagnosis in participants with diagnosis of central obesity. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of frailty score.



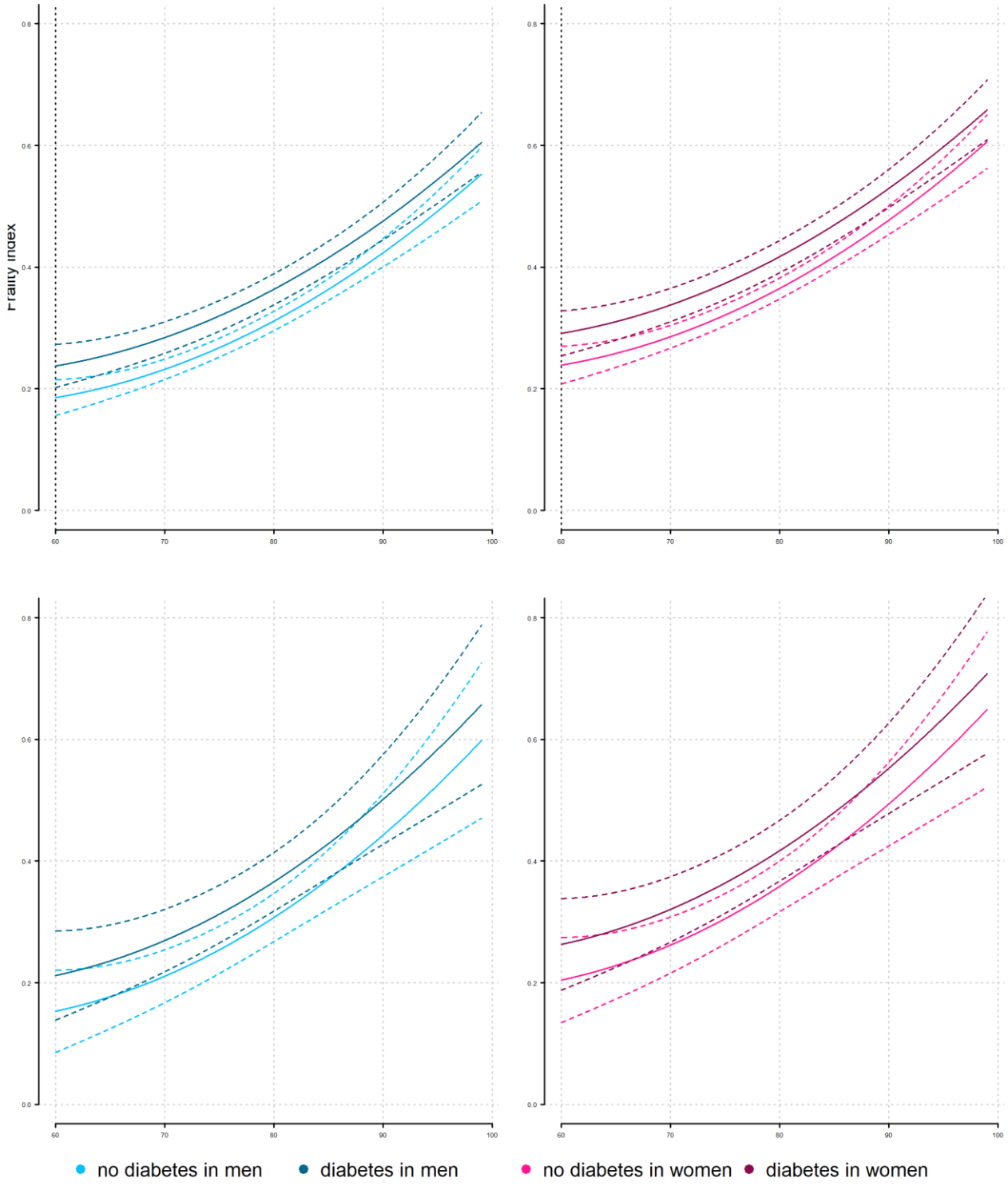
Supplementary figure 5. Frailty trajectories by baseline diabetes diagnosis in participants without diagnosis of central obesity. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}... First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of frailty score.



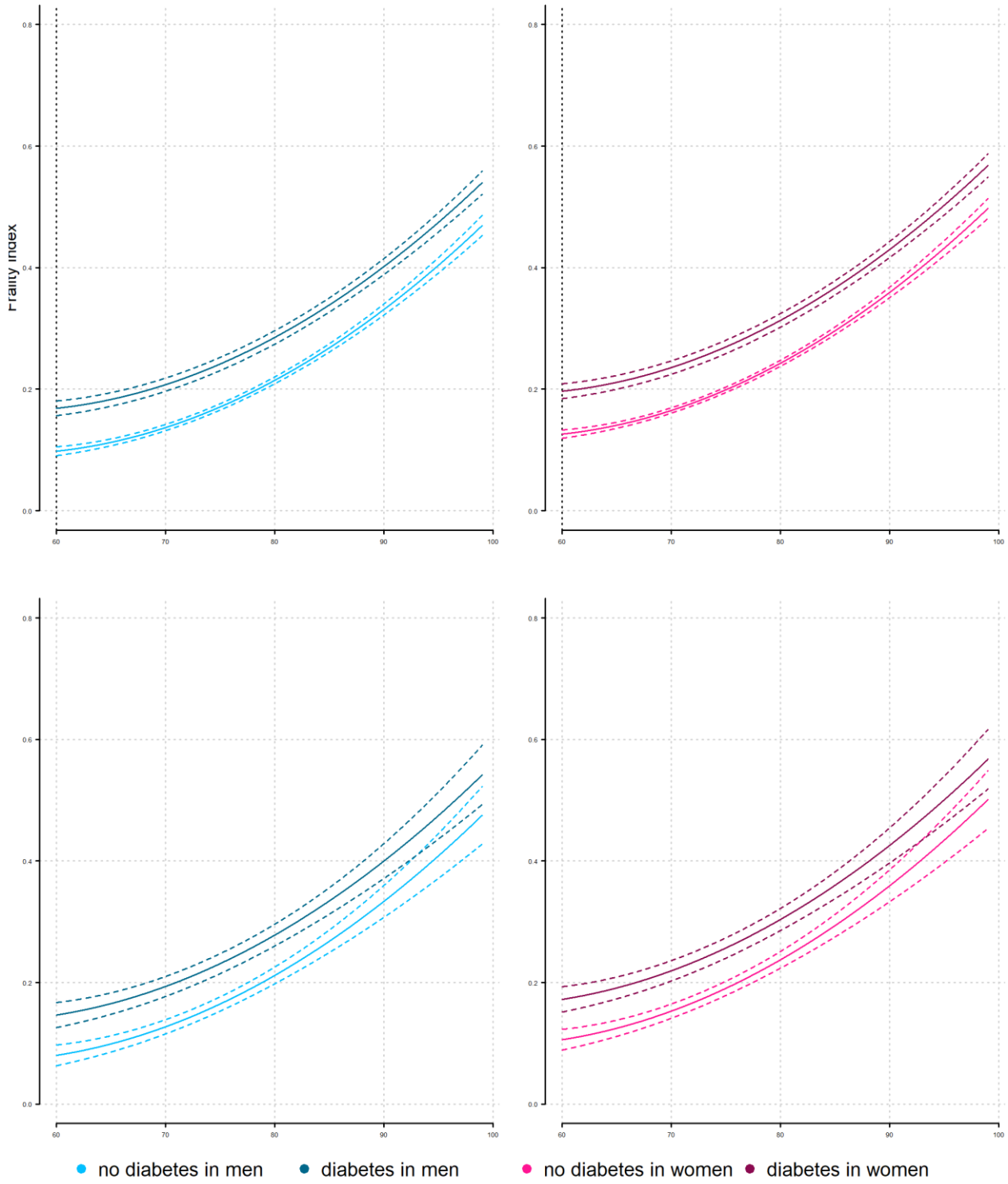
Supplementary figure 6. Frailty trajectories at different values of HbA1c in participants with diagnosis of central obesity at baseline. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin. First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of Frailty score.



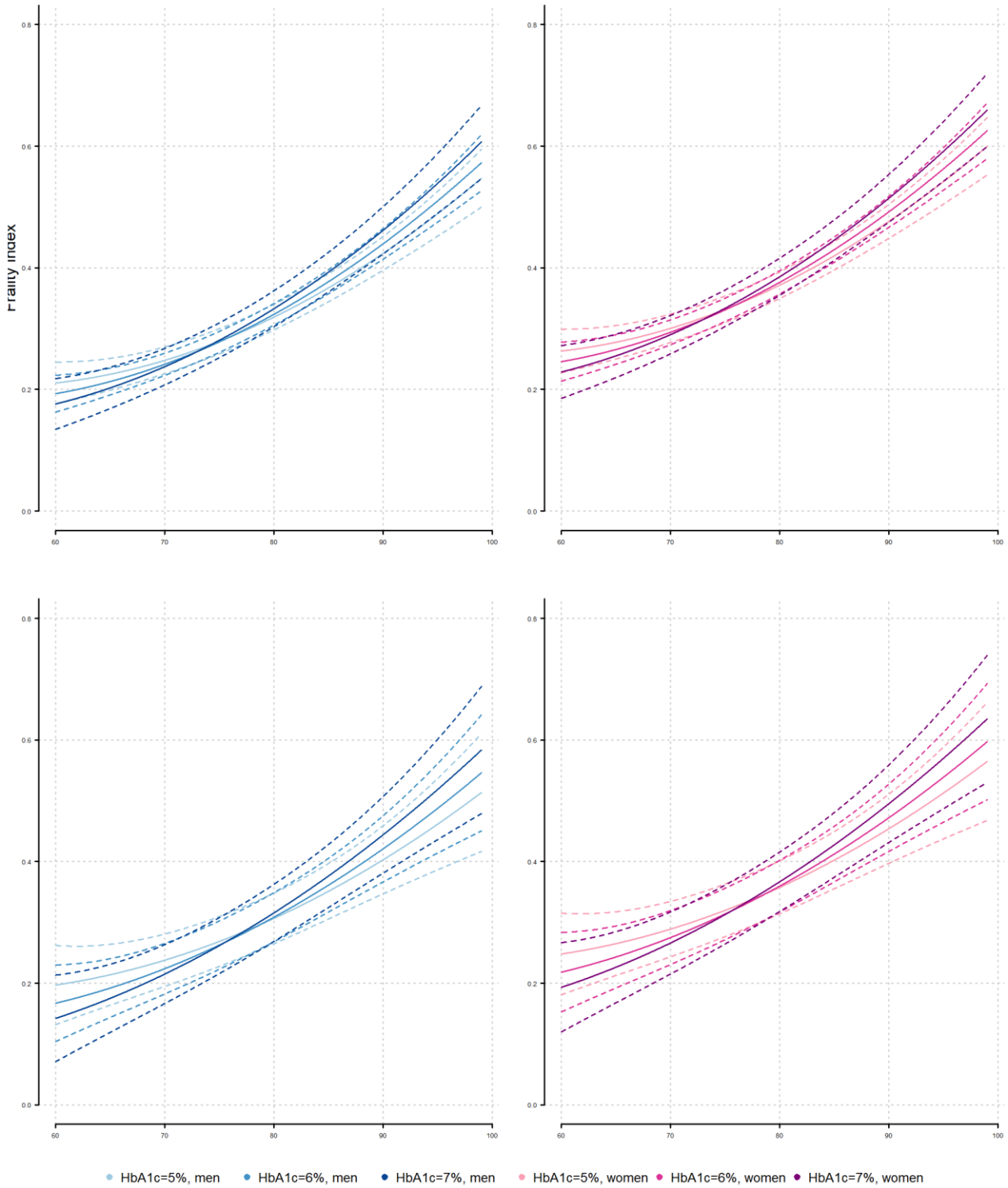
Supplementary figure 7. Frailty trajectories at different values of HbA1c in participants without diagnosis of central obesity at baseline. First and second columns: model 1 (adjusted by age and sex); third and fourth columns: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin First row, Frailty index, second row: Edmonton Frail Scale, third row: Phenotype of Frailty score.



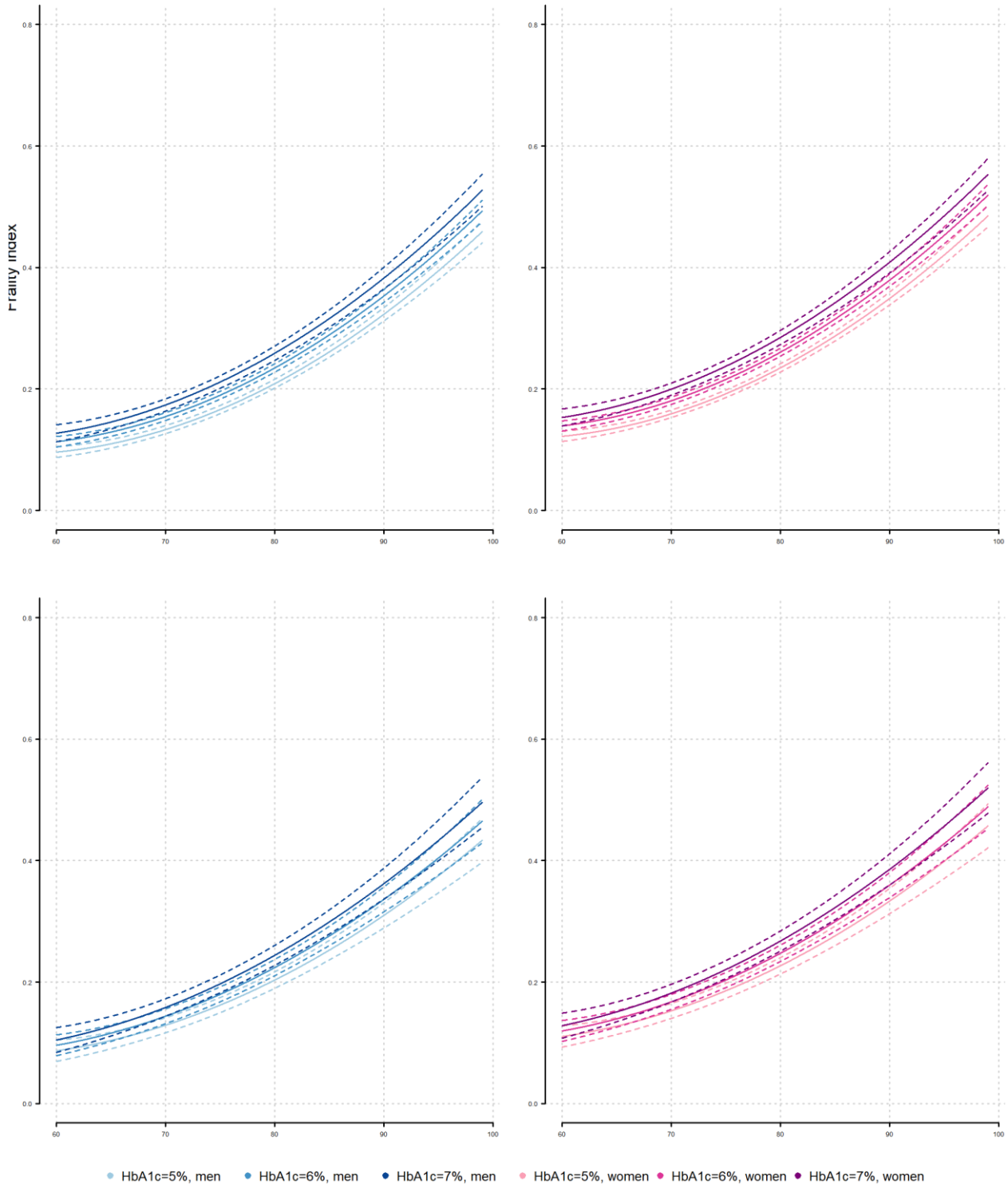
Supplementary figure 8. Frailty trajectories (with Frailty Index) by baseline diabetes diagnosis in participants with diagnosis of cardiovascular disease. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}.



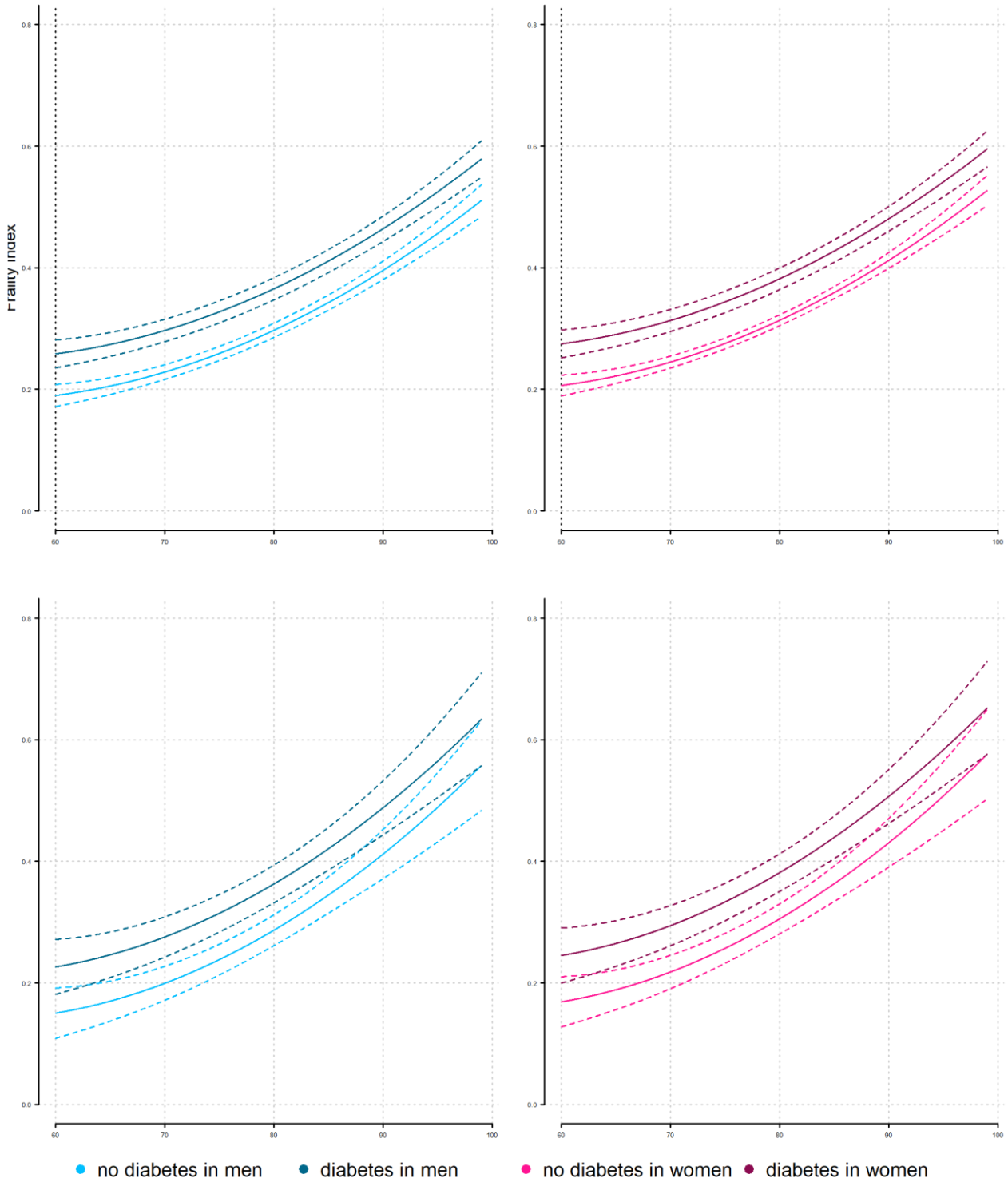
Supplementary figure 9. Frailty trajectories (with Frailty Index) by baseline diabetes diagnosis in participants without diagnosis of cardiovascular disease. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}.



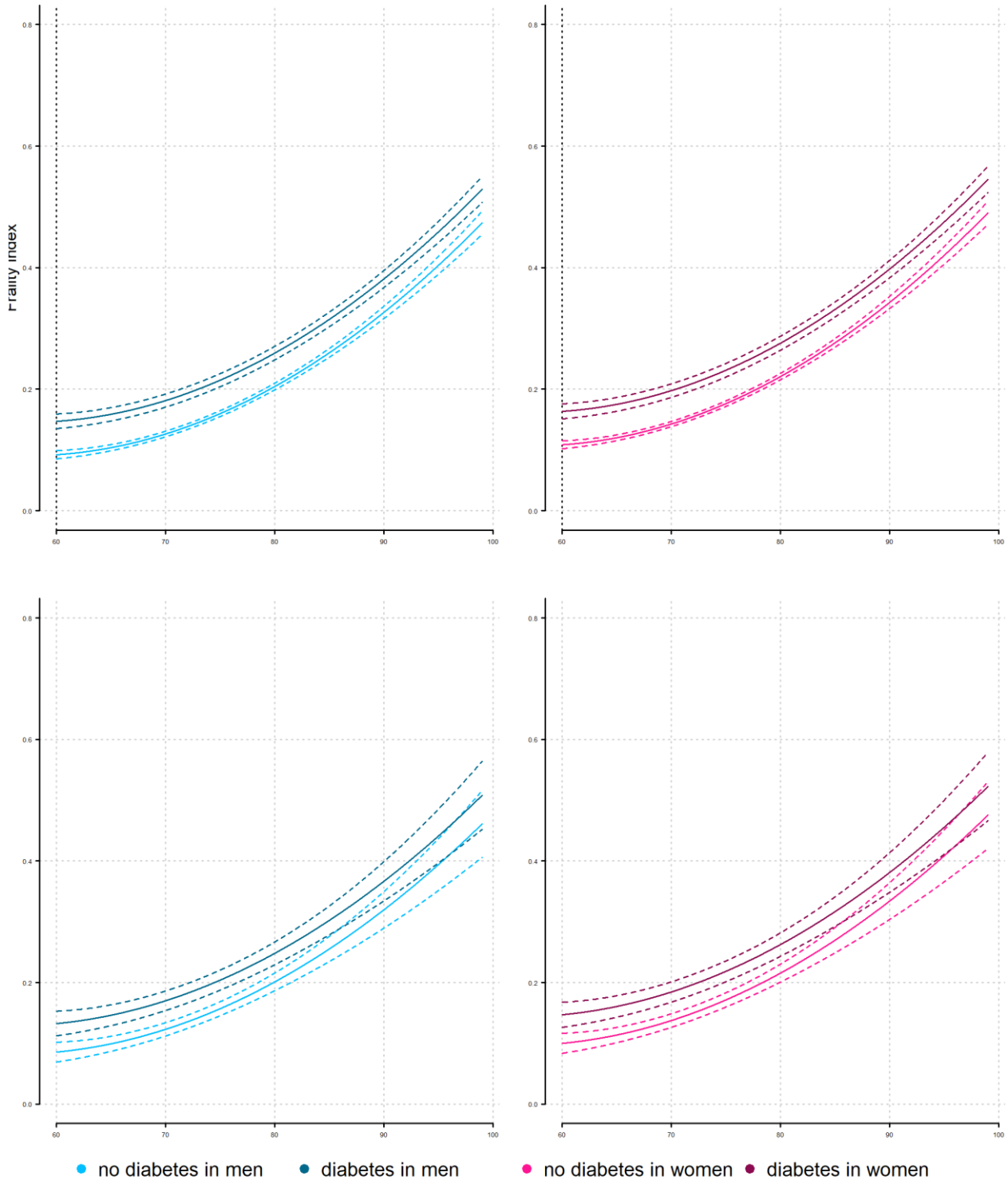
Supplementary figure 10. Frailty trajectories at different values of HbA_{1c} (with Frailty Index) in participants with diagnosis of cardiovascular disease at baseline. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin.



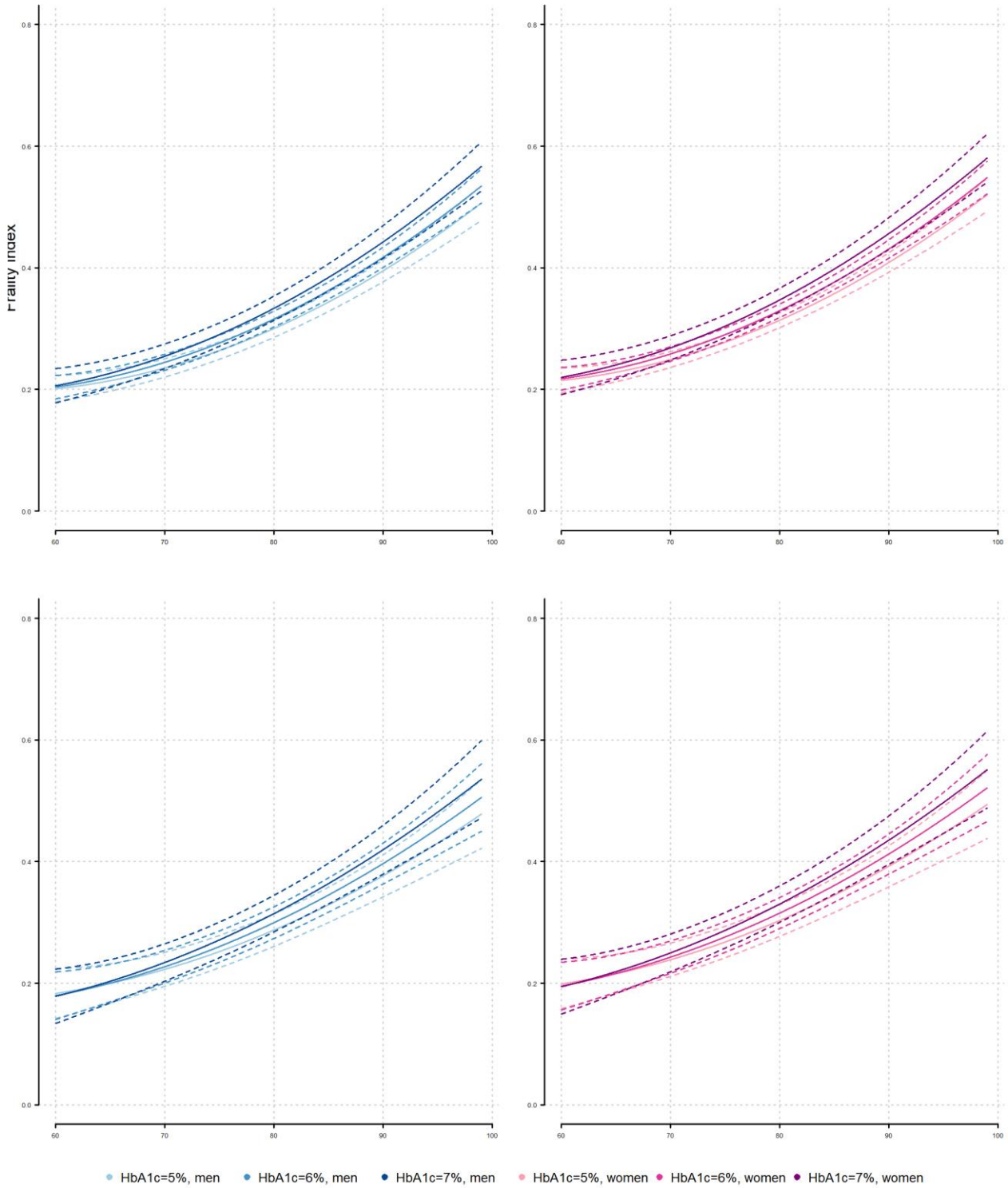
Supplementary figure 11. Frailty trajectories at different values of HbA_{1c} (with Frailty Index) in participants without diagnosis of cardiovascular disease at baseline. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin.



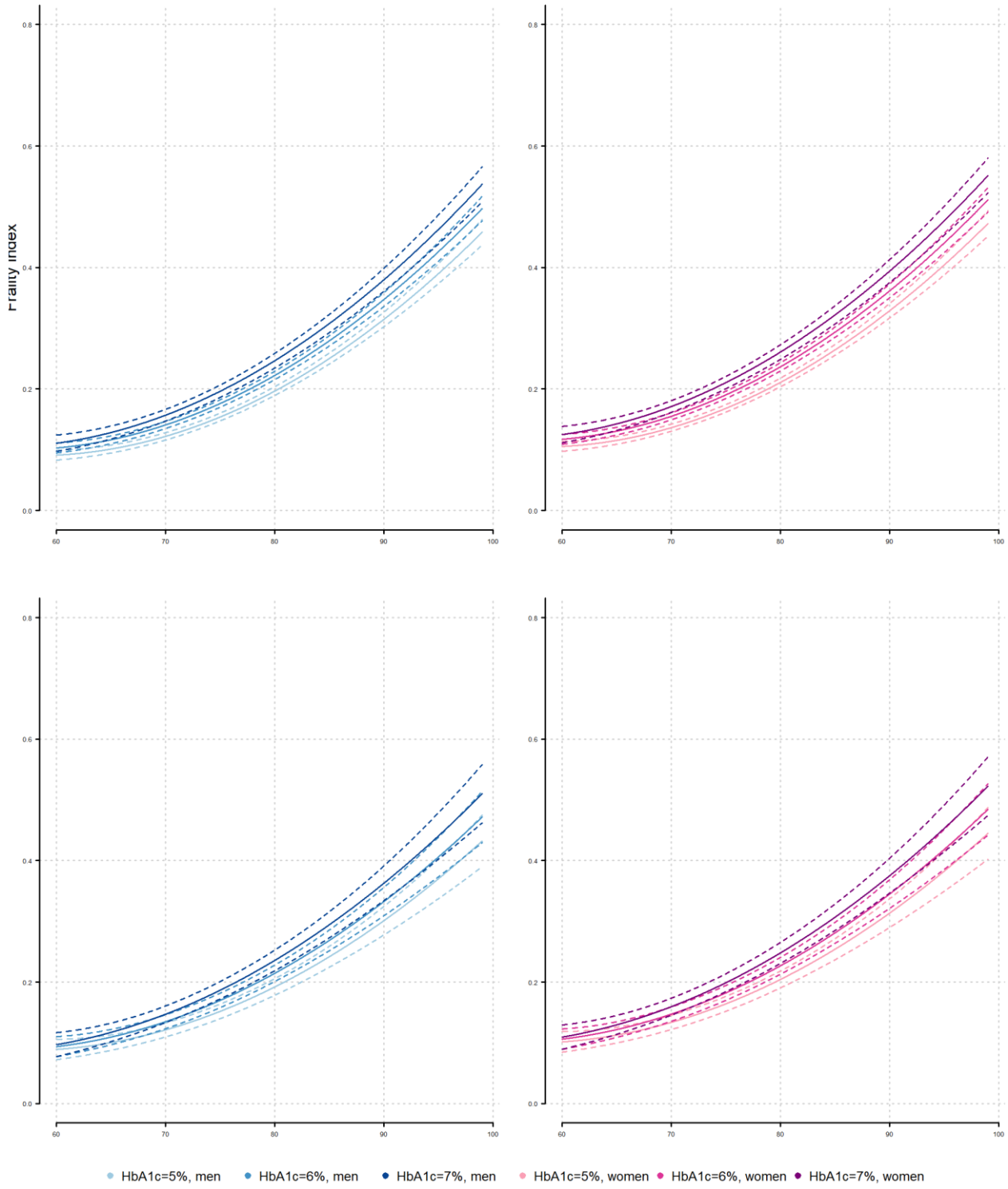
Supplementary figure 12. Frailty trajectories (with Frailty Index) by baseline diabetes diagnosis in participants with sedentary / low levels of baseline physical activity. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and HbA_{1c}.



Supplementary figure 13. Frailty trajectories (with Frailty Index) by baseline diabetes diagnosis in participants with high / moderate levels of baseline physical activity. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, haemoglobin and $HbA_{1c.}$



Supplementary figure 14. Frailty trajectories at different values of HbA_{1c} (with Frailty Index) in participants with sedentary or low levels of baseline physical activity. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin.



Supplementary figure 15. Frailty trajectories at different values of HbA_{1c} (with Frailty Index) in participants with high or moderate levels of baseline physical activity. First row: model 1 (adjusted by age and sex); third and fourth columns: Second row: model 2 further adjusted by income, social class, smoking status, alcohol consumption, and haemoglobin.

Chapter 5. Discussion

5.1. General Introduction

People do not age at the same pace. Therefore, studying the causes of this heterogeneity in the general population is a highly relevant research question from both a clinical and public health perspective. Frailty represents the abnormal accelerated aging process as well as the ensuing state of vulnerability.

People use the frailty concept in different contexts and in with different objectives, such as to study pathophysiological process of ageing as a determinant of poor health outcomes, as an outcome of risk factors earlier in life, as a prognostic marker, as a therapeutic target/tracker or as a clinical decision tool. However, there is no conclusive evidence that the concept of frailty is useful in all these contexts.

A better understanding of the concept of frailty could help to clarify its use in some of the described contexts. This thesis has been devoted to improving current knowledge on frailty.

In a research context, frailty has aroused the interest of researchers since it began to be described in the seventies until today with an exponential increase the number of articles published in the last ten years.

In a clinical context, frailty instruments are more and more used to identify patients at risk as shown by Walston[155].

Likewise, frailty is increasingly becoming a key concept in clinical and public health settings to guide decisions aimed at maintaining a good quality of life, and to promote independence in the older population[156]. Therefore, all efforts to disentangling the concept of frailty are also relevant, to improve the detection of this condition, to fine-tune the treatments and finally to avoid the increased health costs of a vulnerable older population.

5.2. Objectives and main findings

The main objective of this thesis was to understand and quantify the impact of the large variety of current operational definitions of frailty on the application of the frailty concept in clinical practice and public health research. This main objective was achieved, in practice with a thorough

and comprehensive comparative analysis of frailty scores with different operational definitions. The results of thesis have helped to clarify at least in part the concept of frailty and its operational definitions.

The main findings of this thesis were that the agreement between existing frailty scores was low and that all scores were associated with mortality events but to a different degree. Also, multidimensional scores were the least biased scores and had the best predictive validity and discriminant ability. Similarly, scores with many variables from the accumulation of deficits approach showed the best agreement with other scores and were also associated with incident cardiovascular disease. Nevertheless, the use of cut-offs lead to a loss of strength for the predictive ability and the discriminant capacity. Finally, frailty tended to increase over time in all subjects and diabetes was associated with trajectories of more pronounced frailty.

The results of this thesis provide new insights to the field of frailty. First, the results of Study I provide a direct and comprehensive quantification of the agreement between frailty scores. Study II was the most comprehensive external validity study of frailty scores regarding all-cause mortality, cardiovascular and cancer events to date. This study was the first to analyse the prospective association of baseline frailty and cancer and demonstrated for the first time the association of frailty with cardiovascular events. Finally, Study III was the first study to analyse the variables related to diabetes and the trajectories of frailty assessed as repeated measures.

Until now, the concept of frailty and mostly its operational definition is differently defined by the main experts in the field. [65 68 157] Consequently, the many existing frailty scores also differ in their constitution, the number and type of variables that make up the score, the use of cut-offs, and the underlying frailty concept on which the score is based. This thesis may guide efforts to achieve a consensus operational definition.

On the other hand, the results of this thesis suggest that the operational definition of frailty should not be limited to physical frailty. These results also suggests that a multidimensional approach may have a stronger association with mortality in elderly general population.

Also this thesis provides arguments to suggest that disability and comorbidity could be in the operational definitions of frailty, being at the same time frailty outcomes included.

In summary, the results of this thesis provide a clearer understanding of frailty instruments and their quality as health assessment instruments in the context that they are applied.

5.3. A closer look at the study results

In Study I, after identifying the published frailty scores with a systematic review of the literature, the frailty scores that could be calculated with the ELSA data were selected. With a cross-sectional study design, the agreement and the accuracy of 35 frailty scores was explored. The scores were designed with different operational definitions and for different types of populations (patients versus general population). With two methods of agreement evaluation (Cohen's kappa statistics and Bland-Altman models), it was observed that some scores over/underestimate frailty and fail to agree in the identification of the same individuals as frail. Moreover, agreement was low for most of the comparison between scores. The scores that had the best agreement compared to frailty scores included in the study were those of the deficit accumulation approach, characterised by more than 30 variables. The least biased scores were those from the multidimensional approach, which assess more than one area of functioning.

Study II, with a longitudinal study design, examined the potential association of frailty scores with three relevant clinical outcomes in the elderly population, i.e. all-cause mortality, cardiovascular and cancer events. In a 7-year follow-up and using Cox proportional hazard models, all frailty scores were associated with mortality outcomes. However, the strength of the association was very heterogeneous. Multidimensional and deficit accumulation scores were the best performing scores for predicting mortality. In addition, the deficit accumulation scores were also prospectively associated with cardiovascular events. None of the scores were associated with cancer events. Using Harrell's C statistic to assess the added predictive ability over basic age-based models, the best performing scores were the multidimensional scores.

Study III examined the association of baseline diabetes and its related variables (HbA1c and fasting plasma glucose) as determinants of frailty trajectories. The frailty scores were calculated every two years over a 10-year follow-up period. Baseline diabetes and baseline HbA_{1c} were significantly associated with the progression of frailty. In contrast, no association between baseline fasting glucose plasma and progression of frailty was found.

5.4. Existent instruments to measure frailty status

Studies I and II were designed to help clarify which instruments are best suited to different objectives. Similarly, having so many different instruments of frailty that can measure different subsets of the population as frail is reflected in at least six reviews about frailty instruments written to date[41 69 73 158-160].

De Vries et al 2011 carried out a systematic review on frailty scores targeting the assessment of outcomes[69]. They identified 20 frailty scores evaluating the content validity taking a multidimensional concept[38] as gold standard. They assessed whether or not frailty scores described eight factors and three dimensions (physical, psychological and social). The authors found that only one frailty score, the frailty index of Mitnitski[35] included all factors and dimensions. In contrast, there were many scores evaluating only the physical dimension. To illustrate this, the physical domain was included in all scores, the psychological domain was present in 55% of the scores and only 30% of the scores included the social domain.

Study I confirmed that some scores only report physical frailty. These are frailty scores, which are based on the Phenotype of Frailty approach developed by Fried, which is the most cited score [114]. However, other group of scores include other variables. These scores, which are not as used and cited as the Phenotype of frailty are numerous and mostly multidimensional.

Sternberg et al published in 2011 a systematic review on frailty scores, which focused on clinical definitions, and identified 22 articles with original frailty scores. Most of the frailty scores included physical function, walking speed, and cognition as variables. The most common outcomes were mortality, disability, and institutionalisation[73] .

Based on the results of this thesis, the phenotype of frailty scores are arguably more interesting for research than for clinical evaluation given that these scores are based on a pathophysiological concept of accelerated aging and link with underlying frailty mechanisms. In clinical settings, the main limitation is that measurements (strength, walking speed) are not routine measurements in patients and it is not a score useful to evaluate changes. However, this score includes only five variables, with a cut-off for identifying frail and pre-frail condition. This straightforward structure make easy the diagnosis of frailty in clinical settings. Concerning the accumulation deficit approach, these scores show better agreement with other scores (Study I). In addition, they have a continuous

scale (Studies 1 to III). As a result, they are sensitive to changes in frailty. Nevertheless, they are not easily applicable in a clinical setting.

In 2013, Bouillon et al conducted a review of the literature and identified 27 frailty scores with a large number of variables and many different items. Reliability and validity were rated for 26% of these scores only. The risk / odds ratios for mortality were also very heterogeneous from 1.21 (0.78, 1.87) to 6.03 (3.00; 12.08) for the frailty phenotype and 1.57 (1, 41, 1.74) to 10.53 (7.06, 15.70) for the frailty index[146]. In Study II[139] the external validity of 35 frailty scores was assessed. The results of Study II were consistent with those obtained by Bouillon, observing also heterogeneity in the hazard ratio values of the associations of scores with mortality. The frailty index showed on of the strongest prospective associations with mortality. Similarly, in the Study I[114], the frailty index was the instrument with the best agreement compared to the other evaluated frailty scores. The phenotype of frailty score, did not show the same qualities as the frailty index.

This evidence supports the idea that the phenotype of the frailty approach may be somewhat incomplete as operational definition. Furthermore, Bouillon pointed out that the most cited score was the phenotype of frailty score developed by Fried [31] (69% of publications), with the second most cited being the Frailty Index developed by Mitnitski [35] (12%). The Edmonton Frail Scale developed by Rolfson (4%) [92] was third most cited. However, half of the frailty scores were not cited at all. This more frequent use of Fried's phenotype of frailty score could be because researchers try to use instruments that can be compared with other studies, and this implies using the same scale. In addition, the Phenotype of frailty scores has only 5 variables and it is very easy to calculate and interpret.

After the completion of the literature review for this thesis, three new reviews were published. The first, Sutton et al in 2016 in the search of a "gold standard" highlighted the relevance of measuring properties of frailty instruments, such as reliability and validity. They found very few instruments that were tested for and had good properties. Also, they reported that some frailty scores, mostly the earlier ones, measure disability rather than frailty. This construction could lead to erroneous associations because they do not represent frailty as a different concept from disability[159]. Sutton considers that a frailty score should have at least 2 variables, due to the complex structure of frailty syndrome[159].

The second review was by Buta et al in 2016, which identified 67 frailty scores[158]. Importantly, it was the same number I found in our literature review. Most of the scores were analysed for use, evaluation of risks and for etiological studies. The authors concluded that in selecting a frailty score, one must consider the purpose, the domains captured, the way the instrument was used in the past, and the feasibility. They stressed that other studies on reliability were needed[41 146 158]. Study I[114] filled this gap by being the most comprehensive study on the reliability of frailty scores. In addition, Buta recommended future studies on discriminant ability, which I analysed in Study II[139] with Harrell's C-statistic analyses[115 161] using the same complete list of frailty scores in the ELSA study.

The third review was by Gilardi et al in 2018. They summarised the results of 10 review articles on frailty screening. The criteria to evaluate the quality of the scores as screening instruments for detecting frailty were multidimensionality, quick and easy administration, accurate risk prediction of negative outcomes and high sensitivity and specificity. They concluded that from the proposed frailty scores, only one, the Tilburg Frailty Indicator[47] fulfilled the criteria [160].

This thesis does not give a specific recommendation for a "best" frailty score, although the results of the thesis are in agreement with the criteria applied by Gilardi concerning the relevance of scores to be multidimensional and easily applicable in different population settings. The results of Study I and II suggest that a reliable and performant frailty score should be multidimensional due to the complexity of the frailty syndrome, which is not limited to just physical components.

Another relevant aspect to consider in the selection of a frailty score highlighted by Gilardi[160] is the feasibility. However, the quick and easy administration depends on which population the score is target. In clinical settings, a score should be easy to apply as well as to interpret. In practice, the scores with many variables are difficult to apply in these clinical situations.

In a research setting, some tests, which are not measured in a clinical context, are more easily performed such as grip strength or balance, given that these measures are often included in population studies. In this case, is even possible to apply frailty scores with numerous variables that provide further precision, because many population studies are very rich on data.

Finally, a simple and easy screening instrument could be the most appropriate instrument for public health providers. Despite these specificities, the main experts on frailty recommend to assess frailty.

From the public health point of view, a screening instrument for frailty may be applied to try to diminish hospitalisations and institutionalisations due to this condition. From clinical practice perspective, the frailty instrument should be applicable in clinical settings due to the association of frailty with negative outcomes[162].

5.5. Different approaches of operational definitions of frailty assessment

Although most of the literature describes two main approaches for making an operational definition of frailty, this thesis defines four frailty approaches rather than two. Beside the phenotype of frailty developed by Fried[31] and the accumulation of deficit approach developed by Mitnitski [35], this thesis reported a multidimensional approach described by Gobbens[38] which is implemented in numerous frailty scores. The accumulation of deficit approach has many variables from different domains. To be considered in this category, the frailty score should have at least 30 variables. These scores include variables from different dimensions. However, there are scores that include dimensions and cannot classified as being part of the accumulation of deficit approach, given that these scores have less than 30 variables. Also, contrasting with the accumulation of deficit approach that give the same weight to each variable, some multidimensional frailty scores provide different weight to the underlying variables.

Finally, even if most of the literature makes a difference between frailty and disability, some scores have in fact, mainly disability variables and I classified them within a group named “disability approach”.

The findings of this thesis support an operational definition of multidimensional frailty because multidimensional instruments are more sensitive and accurate to detect individuals at risk and they are easily applicable in clinical and community dwelling contexts.

5.6. Filling a gap in the literature: Agreement of frailty scores

Study I provides evidence for the impact of the heterogeneity in operational definitions of frailty scores, which yielded a wide range of frailty prevalence estimates, from 0.8–65.0 %. This wide range on prevalence is consistent with other studies[111 163]. Collard et al performed a systematic review on prevalence of frailty using different instruments and study populations. They found a mean

prevalence of frail diagnosis of 10.7% with a wide range going from 4.0% to 59.1% in 21 cohort studies, using frailty scores based on the phenotype of frailty approach. Widagdo et al. assessed frailty using four different instruments in the same population and they obtained ranges going from 2% to 49.4%, with only 0.5% of participants evaluated as frail by all instruments[163].

Frailty instruments provide scores with different ranges or categories (i.e. outcomes can be binary, categorical or continuous). Thus, the comparison of these instruments is complex and in the thesis, required a first step which consisted in rescaling the score to a common 0 (non-frail)-1 (maximum frail) scale.

This thesis used classical methods for evaluating agreement such as Cohen's kappa for analysing scores with a cut-off, but also in parallel, agreement was analysed with modified and classical Bland-Altman models, for analysing scores as continuous variables. The novelty of this analysis was not only the comparison of the most comprehensive list of frailty scores analysed so far but also the application of this two complementary approaches evaluating agreement on the same dataset. The two approaches led to a consistent result: frailty scores with numerous variables showed better agreement and those with dimensions had the least bias.

5.7. External validity of frailty scores

5.7.1. Association with mortality

Study II compared all frailty scores regarding their association with mortality. Other relevant outcomes were analysed such as cardiovascular and cancer events, although in the literature, there is very little evidence regarding the association of frailty with cardiovascular disease and no prior evidences for cancer events[117]. Study II provides evidence of the prospective association of all measured frailty scores with mortality. However, the strength of the association varied among the scores and their approaches. This heterogeneity in association strength is one of the main findings of this thesis.

5.7.2. Prediction of frailty scores analysis with cut-offs compared with continuous analysis

In Study II, frailty scores analysed with cut-off do not have the same predictive ability that the same frailty scores analysed on a continuous scale. When using cut-offs in the survival analysis, the

strength of the association was weakened, due to the loss of information caused by categorisation of a continuous variables. One relevant issue is that in clinical practice, frailty scores are used with cut-offs, because it is easier for interpretation and in consequence, for decision making. Study I also highlight an additional problem: the cut-offs are not often well calibrated when they are used in a different population than that in which the score was developed and validated.

5.7.3. Frailty scores and cardiovascular/cancer prediction

Klein et al in 2005 found that frailty could predict risk of cardiovascular events and suggests also cancer prediction[117]. However, apart from this little evidence there is limited epidemiological data of this prospective association of frailty with cardiovascular or cancer events. Indeed, frailty scores have been designed for predicting mortality, disability, hospitalisations, but not cardiovascular or cancer events. Surprisingly, Study II was found that some frailty scores from the accumulation of deficit approach were associated with future cardiovascular events. However, the discriminative ability over a basic model including age and sex did not improve. Schaller et al in a study published this year, obtained similar results to Study II and found a hazard ratio of 9.2 (2.6-32.4) for predicting major cardiovascular events also with a frailty score from the accumulation of deficit approach[164]. They interpret their results speculating on the shared pathophysiology of frailty and cardiovascular disease, suggesting multisystem dysregulation, increased atherogenesis, low grade of inflammation, and insulin resistance[165]. With cancer, no significant association of frailty scores was found.

5.8. Trajectories of frailty in ELSA

Study III, as expected found a non-linearly increased in the trajectory of frailty over time, accelerating after age 80. Hsu and Chang in 2014[166] studied the trajectories of frailty in 2,306 participants in the general population. The authors identified three trajectories: the maintenance of non-frailty, the progression towards frailty and the high risk of frailty. Being a woman, older and with a low level of education were associated with a high risk of frailty. The limit of our analysis in this paper is the loss of follow-up and that the study included only the survivors. In Study II, data from all participants was included because I used mixed models and three frailty scores representing three different frailty approaches. Therefore, our results may better reflect the actual trajectories of frailty of the participants. I think that because Hsu et al [166] , the frailty score was defined with Phenotype of frailty approach of Fried, which is categorical, they could have missed the dynamical structure of frailty.

5.9. Frailty in younger populations

In Study II, I performed a sensitivity analysis stratifying the population by age groups (>=70 years vs. < 70 years). Hazard ratios of frailty scores for mortality were much higher for people in the younger age than in the older age groups. These results are in agreement with the results of two recent studies. Chamberlain et al in 2016 found that behavioural factors such as education and excessive alcohol consumption were associated with the progression of frailty, but with a stronger association in the younger group (60-69 years) [167].

Smart et al in 2017 found that frailty was also prevalent in the adults younger than 65 years in the emergency surgical units (16% vs 38% for older than 65 years). Frailty in younger patients was associated with multi-morbidity, polypharmacy, and cognitive impairment. In the elderly, frailty was only associated with age[168]. These observations and the results of Study II suggest that frailty diagnosis in a younger person becomes more relevant because of the increased risk of having an event or the likelihood of having other problems associated compared with older individuals with the same frailty level.

The male-female health survival paradox

Most studies show higher prevalence of frailty in women compared to men. However, women live longer[111 169-172]. Consistent with the literature, Study I found that women were more frail than men. However, at the same level of frailty, women had lower mortality risk than men (Study II). Examining scores from different operational definitions confirmed this observation. Puts (2005)[169] found that frailty was associated with mortality in a dynamic and static context in women independently of disability and comorbidity. Only static frailty was associated with mortality in men. Fernández-Bolaños et al in 2008[171] analysed frailty at the end of a 13-years of follow-up and found much higher prevalence of frailty in women (30.9%) than in men (9.3%). These large differences could be explained in part by a health survival effect, with men still alive and included in the cohort being the healthiest.

Gordon et al in 2016[172] performed a systematic review, analysing gender differences with the frailty index. They found that women were more frail at all ages but that the difference increased over time until the age of 90, when the difference started to diminish. A plausible explanation for these

results could be that the frailest men died. The causal mechanisms behind this gender differences are not totally elucidated. They could be attributed to gender differences in health care utilisation and self-reported behaviour as well as biological differences in inflammatory cytokines, sarcopenia, increased abdominal obesity and cognition decline in women. Hubbard and Rockwood in 2011 postulated that women tolerated better health deficits due to the higher physiological reserves compared to men. Higher mortality rates in men could be attributed to lower access to preventive medicine and higher prevalence of lethal comorbidities in men[173].

5.10. Statistical techniques used in this thesis

In this thesis, some statistical techniques were applied, which were necessary to obtain the most reliable data, such as the multiple imputation technique for dealing with missing data, Cox models, and analysis of discriminative ability for survival studies.

5.10.1. Multiple imputation in longitudinal studies

There are two recognized techniques for applying multiple imputation in longitudinal studies: multivariate normal imputation and chained equation approach[174]. In Study III, the chained equation approach was selected for imputation, because the use of multivariate normal imputation requires an imputation model without missing data and this was not the case in the Study III.

Due to the difficulty of retaining participants, missing data are common in observational cohort studies[175]. Also, a missing value can be an answer such as: “refusal”, “don’t know”, “not possible to perform the test”[78]. Data analysis excluding missing data may be biased depending on the missing data mechanims[176]. Therefore, it is crucial to consider these mechanisms before deciding how to handle the missing information[78]. According to Rubin[75], there are three possible mechanisms for missing data: missing completely at random, missing at random, and missing not at random. In the mechanism missing completely at random, the missing data are independent of the outcomes and other variables. In the missing at random mechanism, the data are missing regardless of the unmeasured variables but depend on the measured variables. Finally, in the missing not at random mechanism, the missing data depend on unknown, unmeasured variables, often associated with the outcome[75].

There are many ways to handle missing data and these options depend on missing data mechanisms. When the mechanism is completely random, the completed case analysis is acceptable and the results are unbiased, but a loss of power is possible, especially when calculating the scores. When the missing data mechanism is missing at random, a complete data analysis is likely to be biased and a maximum likelihood method could be applied to obtain reliable estimates. However, this method has limitations because it requires a large sample size. Another alternative is the multiple imputation technique which replaces each missing value with a list of n values generating m data sets. Each of the data sets is analysed in the same way as the complete analysis, but the standard errors are calculated taking into account the within and between variance[75].

Another issue is how to apply multiple imputation in cohort studies. Multiple imputation in a context of all waves seems to be an acceptable approach. It is not advisable to impute data in non-measured waves but impute within waves values[177]. A second issue is what technique to use. Many techniques are described for missing values in cohort studies, such as joint modelling, multivariate normal imputation, Bayesian approach, and chained equations approach[174 178]. This latest technique was proven to be sensitive to the correlation between repeated measurements[76 77 141]. It consists of a set of imputation models by specification of each imputed value in a variable-by-variable basis. The model starts with a first imputation and follows by iterating based on these specified conditional densities[141].

For Study I, an issue was the missing data in the underlying variables necessary to calculate the scores. Without multiple imputation to deal with missing underlying variables, many frailty scores could not have been calculated and thus the analysis would have suffered from loss of precision and power.

In addition, depending on the missing data mechanism, complete data analysis can lead to biased results[176]. Tan et al compared four techniques for treating missing data in a cross-sectional observational study and found that with sufficient available information, multiple imputation was the technique with less biased results[179]. For these reasons, multiple imputation was applied.

The imputation model was constructed with the strongest predictors of the missing data. A chained equation approach was chosen because this technique can handle different types of variables: continuous, categorical ordered/unordered and binary using and appropriate and tailored imputation model for each type of variable[141].

Study II was a time-to event longitudinal analysis. A very similar approach for missing data was applied, since it was necessary to impute only the baseline underlying variables to calculate frailty scores. The difference with Study I was that the prediction model was improved, by including in the model the outcomes and the time –to event variable, but without imputing these variables. If the outcome and the time to event variables are not included in the prediction model, this falsely weaken the association[176]. In our case it would falsely weak the association between the determinant (baseline frailty score value) and the outcome (total-mortality / cardiovascular / cancer events).

Study III was a longitudinal trajectory analysis of frailty scores, in which the frailty scores were the outcome and calculated in each wave of ELSA from wave two to seven. The particularity of such analysis is the correlation in outcome data (repeated values) that should be taken into account in the imputation procedure. The missing underlying variables across all waves and baseline determinants were imputed at the same time using the same approach used in Study II.

5.10.2. Survival analysis with Cox proportional hazard models: alternative analyses when the proportional hazard assumption is violated

In Study II, Cox proportional hazard models were used to assess the potential association of frailty scores for three outcomes: total mortality, cardiovascular events, and cancer. One of the assumptions of Cox's proportional risk models is a constant risk ratio over time. To test this condition, the most common choices are: log-negative-log trace of Kaplan Meier curves (just for categorical covariates), Schoenfeld residuals[180] and the inclusion of an interaction of the covariate with time in the model[128]. The first option was not possible, because frailty scores were defined as continuous variables, the second option was performed, and the last option was selected finally for the analysis since this method allows to manage continuous and categorical covariates and if the proportional risk assumption is not satisfied, the next step is using the same model to calculate multiple intermediate hazard ratios[128]. This was the next step in Study II.

5.10.3. Alternatives for evaluating discriminative ability in survival analysis

The most common method to evaluate discriminative ability is to calculate area under de curve in the Receiver Operating Characteristic (ROC) curves. Harrell's C statistic is the equivalent to ROC curves but assessing survival models, with a continuous outcome (time to event).

Uno developed a modified Harrell's C-statistic that is independent of study-specific censoring distribution[115]. Other alternatives to evaluate discriminative ability are cumulative case/dynamic control ROC/AUC[181]. Newer methods include the net reclassification improvement, based on reclassification tables with and without events and the integrated discrimination improvement, focused on differences in models with and without the event[55]. In Study II, the modified version of Harrell's C-statistic was applied because the study-specific censoring distribution could be an issue in the analysis.

5.11. Strength and limitations of this thesis

This thesis provide evidence based on data analysis in the field of frailty.

A strength is that the three studies of this thesis were based on data drawn from a well-characterized cohort of the general elderly population, which is a source of high quality information with numerous subjective and objective variables about physical and mental health as well as health determinants in a large sample of elderly general population.

In addition, to deal with the missing data and avoid biased results, multiple imputation with the chained equation approach was applied.

Moreover, a systematic approach to analysis and classification of frailty scores in conceptual families was applied. This approach facilitates the comparison among studies and the link of each scores with its underlying operational definition.

Study filled a gap in the lack of agreement studies in frailty scores. Also, Study II provided novel evidence based on data analysis concerning frailty as determinant of other important outcomes apart mortality such as cardiovascular disease and cancer, filling a gap in the literature in the field. Study III used a prospective design with repeated measures on frailty to investigate diabetes as a determinant of frailty progression over a period of 10-year follow-up period, using robust standard procedures.

This thesis also has some limitations, which warrant consideration. First of all, in the literature review on available frailty scores, it is possible that some instruments were not included. Also, a common limitation to all three studies is that some underlying variables necessaries to calculate the scores should be tailored to the ELSA data, which could be a source of distortion of some frailty scores.

Also, the participants of the ELSA study are mostly of European origin, and only participants older than 60 years were included, which limits the generalisability of the result of this thesis to similar populations in age and ethnic origin.

In addition, for the first article, the main limitation comes from the fact that there was no consensus on the definition of frailty. Therefore, the methods had to be adapted to this fact, making a “gold standard” as the mean value of all included and rescaled frailty scores

In study II, a limitation was the proportion of participants lost to follow-up during the study. However, the data analysis techniques used in these studies take into account this uncertainty, although it is not possible to exclude a certain degree of bias.

5.12. Implications of this thesis

The results of this thesis will be informative and useful for different purposes, such as research, clinical practice and public health

5.12.1. Implications for research

This thesis provides novel information on the understanding of the mechanisms of frailty and its determinants.

This thesis also provides evidence to help researchers to choose the most suitable frailty score for their purposes, including which are the scores with better agreement, which are the most sensitive to identify higher risk to relevant outcomes, and which scores could be used for identifying elderly persons with risks of cardiovascular events. Studies that use scores within the same family (approach) become comparable.

Finally, the results of thesis suggest that a frailty index of the deficit accumulation approach is the most appropriate instrument for research purposes because of their high agreement and multidimensionality (Study I), their high predictive association with relevant outcomes in elderly population with stability after adjustment (Study II). In addition, their continuous scale, which is consistent with the dynamic nature of frailty make it suitable for the study of progression over time (Study III).

5.12.2. Implications for clinical practice

This thesis provides to health professionals who work with elderly patients with high quality information to guide the choice of frailty scores to evaluate in and out-patients risk.

5.12.3. Implications for public health

In public health, the results of this thesis can be used to choose the most suitable frailty scores as a screening tool to identify high-risk individuals in the elderly general population. Also, the information about frailty scores will be useful for future planning and prevention measures of frailty and other common outcomes in elderly population.

5.13. Future research in the field

Several open questions still remain in the field of frailty. For example, the possible determinants of gender differences in frailty and longevity such as pregnancy, menopause, and use of hormones as well as the role of other determinants of frailty such as depression and/or alcohol. Further avenues of research may be the study of markers of frailty and longevity using the most performant scores. Also, the study of the role of socioeconomic determinants of frailty is still a field a further investigate.

Finally, more research is needed for discovering and evaluating new treatments. For example, the setup of a multi-centre randomized trial for the treatment of frailty.

5.14. Conclusions

This thesis has filled important gaps in the area of frailty, such as the evaluation of the precision, predictive validity and discriminative ability of the frailty instruments. However, despite the scientific contribution of this thesis, there is still no common operational definition and many questions are still without an answer. Still, with the scientific evidence that this thesis provides, I believe I have offered one more step in the direction of finding a common operational definition for frailty.

References

1. Kontis V, Bennett JE, Mathers CD, et al. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet* 2017 doi: 10.1016/s0140-6736(16)32381-9
2. Melorose J, Perroy R, Careas S. World Population Prospects: The 2015 Revision, Key Findings and Advance Tables. Working Paper No ESA/P/WP 2412015:1-59.
3. Rechel B, Grundy E, Robine J-M, et al. Ageing in the European union. *The Lancet* 2013;381(9874):1312-22.
4. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet* 2012;380(9836):37-43.
5. Heikkinen E. What are the main risk factors for disability in old age and how can disability be prevented. *Copenhagen: WHO Regional Office for Europe* 2003
6. Bloom DE, Chatterji S, Kowal P, et al. Macroeconomic implications of population ageing and selected policy responses. *The Lancet* 2015;385(9968):649-57.
7. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *Journal of the American Geriatrics Society* 2006;54(6):991-1001. doi: 10.1111/j.1532-5415.2006.00745.x [published Online First: 2006/06/17]
8. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *The Lancet* 2013;381(9868):752-62. doi: 10.1016/s0140-6736(12)62167-9
9. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The journals of gerontology Series A, Biological sciences and medical sciences* 2004;59(3):255-63. [published Online First: 2004/03/20]
10. Lai JC, Covinsky KE, McCulloch CE, et al. The Liver Frailty Index Improves Mortality Prediction of the Subjective Clinician Assessment in Patients With Cirrhosis. *The American journal of gastroenterology* 2018;113(2):235-42. doi: 10.1038/ajg.2017.443 [published Online First: 2017/12/13]
11. Wagner D, Buttner S, Kim Y, et al. Clinical and morphometric parameters of frailty for prediction of mortality following hepatopancreaticobiliary surgery in the elderly. *The*

British journal of surgery 2016;103(2):e83-92. doi: 10.1002/bjs.10037 [published Online First: 2015/11/26]

12. Hippisley-Cox J, Coupland C. Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study. *BMJ (Clinical research ed)* 2017;358:j4208. doi: 10.1136/bmj.j4208 [published Online First: 2017/09/22]
13. Vermeiren S, Vella-Azzopardi R, Beckwee D, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *Journal of the American Medical Directors Association* 2016;17(12):1163.e1-63.e17. doi: 10.1016/j.jamda.2016.09.010 [published Online First: 2016/11/26]
14. Lang PO, Michel JP, Zekry D. Frailty Syndrome: A Transitional State in a Dynamic Process. *Gerontology* 2009;55(5):539-49.
15. Walters K, Frost R, Kharicha K, et al. Home-based health promotion for older people with mild frailty: the HomeHealth intervention development and feasibility RCT. *Health technology assessment (Winchester, England)* 2017;21(73):1-128. doi: 10.3310/hta21730 [published Online First: 2017/12/08]
16. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proceedings of the National Academy of Sciences* 2015 doi: 10.1073/pnas.1506264112
17. Kaplan GA, Baltrus PT, Raghunathan TE. The shape of health to come: prospective study of the determinants of 30-year health trajectories in the Alameda County Study. *International Journal of Epidemiology* 2007;36(3):542-48.
18. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews* 2011;10(4):430-39.
19. Beard JR, Officer A, de Carvalho IA, et al. The World report on ageing and health: a policy framework for healthy ageing. *The Lancet* 2016;387(10033):2145-54. doi: 10.1016/s0140-6736(15)00516-4
20. Peel N, Bartlett H, McClure R. Healthy ageing: How is it defined and measured? *Australasian journal on ageing* 2004;23(3):115-19.
21. Sieber CC. Frailty - From concept to clinical practice. *Experimental gerontology* 2017;87(Pt B):160-67. doi: 10.1016/j.exger.2016.05.004 [published Online First: 2016/05/26]
22. Kaiser MJ, Bauer JM, Uter W, et al. Prospective validation of the modified mini nutritional assessment short-forms in the community, nursing home, and rehabilitation setting. *Journal of the American Geriatrics Society* 2011;59(11):2124-8. doi: 10.1111/j.1532-5415.2011.03659.x [published Online First: 2011/11/19]

23. Swiecicka A, Lunt M, Ahern T, et al. Nonandrogenic Anabolic Hormones Predict Risk of Frailty: European Male Ageing Study Prospective Data. *The Journal of clinical endocrinology and metabolism* 2017;102(8):2798-806. doi: 10.1210/jc.2017-00090 [published Online First: 2017/06/14]
24. Calvani R, Marini F, Cesari M, et al. Biomarkers for physical frailty and sarcopenia: state of the science and future developments. *Journal of cachexia, sarcopenia and muscle* 2015;6(4):278-86.
25. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *BMJ (Clinical research ed)* 2017;358:j2856. doi: 10.1136/bmj.j2856 [published Online First: 2017/07/07]
26. Kuo CK, Lin LY, Yu YH, et al. Inverse association between insulin resistance and gait speed in nondiabetic older men: results from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999-2002. *BMC Geriatr* 2009;9:49. doi: 10.1186/1471-2318-9-49 [published Online First: 2009/11/20]
27. Stout MB, Justice JN, Nicklas BJ, et al. Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. *Physiology (Bethesda, Md)* 2017;32(1):9-19. doi: 10.1152/physiol.00012.2016 [published Online First: 2016/12/09]
28. Goulet ED, Hassaine A, Dionne IJ, et al. Frailty in the elderly is associated with insulin resistance of glucose metabolism in the postabsorptive state only in the presence of increased abdominal fat. *Experimental gerontology* 2009;44(11):740-4. doi: 10.1016/j.exger.2009.08.008 [published Online First: 2009/09/03]
29. Woodhouse KW, Wynne H, Baillie S, et al. Who are the frail elderly? *The Quarterly journal of medicine* 1988;68(255):505-6. [published Online First: 1988/07/01]
30. Pawlson LG. Hospital length of stay of frail elderly patients. Primary care by general internists versus geriatricians. *Journal of the American Geriatrics Society* 1988;36(3):202-8. [published Online First: 1988/03/01]
31. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2001;56(3):M146-M57. [published Online First: 2001/03/17]
32. Winograd CH, Gerety MB, Chung M, et al. Screening for frailty: criteria and predictors of outcomes. *Journal of the American Geriatrics Society* 1991;39(8):778-84. [published Online First: 1991/08/11]
33. Buchner DM, Wagner EH. Preventing frail health. *Clinics in geriatric medicine* 1992;8(1):1-17.

34. Rockwood K, Fox RA, Stolee P, et al. Frailty in elderly people: an evolving concept. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 1994;150(4):489-95. [published Online First: 1994/02/15]

35. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *The Scientific World Journal* 2001;1:323-36.

36. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age and ageing* 1997;26(4):315-18.

37. Rockwood K. Frailty and its definition: a worthy challenge. *Journal of the American Geriatrics Society* 2005;53(6):1069-70.

38. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. Toward a conceptual definition of frail community dwelling older people. *Nursing outlook* 2010;58(2):76-86. doi: 10.1016/j.outlook.2009.09.005 [published Online First: 2010/04/07]

39. Van Kan GA, Rolland Y, Bergman H, et al. The IANA Task Force on frailty assessment of older people in clinical practice. *The Journal of Nutrition Health and Aging* 2008;12(1):29-37.

40. Theou O, Rockwood MR, Mitnitski A, et al. Disability and co-morbidity in relation to frailty: how much do they overlap? *Archives of gerontology and geriatrics* 2012;55(2):e1-8. doi: 10.1016/j.archger.2012.03.001 [published Online First: 2012/03/31]

41. Bouillon K, Kivimaki M, Hamer M, et al. Measures of frailty in population-based studies: an overview. *BMC Geriatr* 2013;13:64. doi: 10.1186/1471-2318-13-64 [published Online First: 2013/06/22]

42. Villacampa-Fernandez P, Navarro-Pardo E, Tarin JJ, et al. Frailty and multimorbidity: Two related yet different concepts. *Maturitas* 2017;95:31-35. doi: 10.1016/j.maturitas.2016.10.008 [published Online First: 2016/11/28]

43. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clinics in geriatric medicine* 2011;27(1):17-26.

44. Mitnitski AB, Graham JE, Mogilner AJ, et al. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC geriatrics* 2002;2(1):1.

45. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *The journals of gerontology Series A, Biological sciences and medical sciences* 2007;62(7):738-43. [published Online First: 2007/07/20]

46. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatr* 2008;8:24. doi: 10.1186/1471-2318-8-24 [published Online First: 2008/10/02]

47. Gobbens RJ, van Assen MA, Luijkx KG, et al. The Tilburg frailty indicator: psychometric properties. *Journal of the American Medical Directors Association* 2010;11(5):344-55.

48. Kivimaki M, Ferrie JE. Epidemiology of healthy ageing and the idea of more refined outcome measures. *Int J Epidemiol* 2011;40(4):845-7. doi: 10.1093/ije/dyr114 [published Online First: 2011/07/19]
49. Steptoe A, Breeze E, Banks J, et al. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol* 2013;42(6):1640-8. doi: 10.1093/ije/dys168
50. Banks J, Batty GD, Begum N, et al. The dynamics of ageing: evidence from the English Longitudinal Study of Ageing 2002–15: The Institute for Fiscal Studies 2012.
51. Ioannidis JP. Why most published research findings are false. *PLoS medicine* 2005;2(8):e124.
52. Marshall M, Lockwood A, Bradley C, et al. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *The British journal of psychiatry : the journal of mental science* 2000;176:249-52. [published Online First: 2001/02/07]
53. Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use: Oxford University Press, USA 2015.
54. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;21(1):128-38. doi: 10.1097/EDE.0b013e3181c30fb2 [published Online First: 2009/12/17]
55. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27(2):157-72; discussion 207-12. doi: 10.1002/sim.2929
56. Yourman LC, Lee SJ, Schonberg MA, et al. Prognostic indices for older adults: a systematic review. *Jama* 2012;307(2):182-92.
57. Kottner J, Streiner DL. The difference between reliability and agreement. *Journal of clinical epidemiology* 2011;64(6):701-02.
58. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Physical therapy* 2005;85(3):257-68.
59. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;37(5):360-63.
60. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Statistical methods in medical research* 1999;8(2):135-60.
61. Giavarina D. Understanding bland altman analysis. *Biochemia medica: Biochemia medica* 2015;25(2):141-51.
62. Cook DA, Beckman TJ. Current concepts in validity and reliability for psychometric instruments: theory and application. *The American journal of medicine* 2006;119(2):166. e7-66. e16.

63. Brown JD. Statistics Corner. What is construct validity? *Shiken: JALT Testing & Evaluation, SIG Newsletter* 2000;4(2):8-12.

64. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014;9:433-41. doi: 10.2147/CIA.S45300 [published Online First: 2014/03/29]

65. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. In search of an integral conceptual definition of frailty: opinions of experts. *Journal of the American Medical Directors Association* 2010;11(5):338-43.

66. Fairhall N, Langron C, Sherrington C, et al. Treating frailty-a practical guide. *BMC medicine* 2011;9(1):83.

67. Cawthon PM, Marshall LM, Michael Y, et al. Frailty in older men: prevalence, progression, and relationship with mortality. *Journal of the American Geriatrics Society* 2007;55(8):1216-23. doi: 10.1111/j.1532-5415.2007.01259.x [published Online First: 2007/07/31]

68. Morley JE, Vellas B, Van Kan GA, et al. Frailty consensus: a call to action. *Journal of the American Medical Directors Association* 2013;14(6):392-97.

69. de Vries NM, Staal JB, van Ravensberg CD, et al. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011;10(1):104-14. doi: 10.1016/j.arr.2010.09.001

70. Theou O, Brothers TD, Mitnitski A, et al. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *Journal of the American Geriatrics Society* 2013;61(9):1537-51. doi: 10.1111/jgs.12420 [published Online First: 2013/09/14]

71. Marmot M, Oldfield Z, Clemens S, et al. English Longitudinal Study of Ageing: Waves 0-6, 1998-2013 [data collection] Colchester, Essex, UK: UK Data Service; 2015 [updated Updated May, 17 2016. 23rd Edition:[SN: 5050]. Available from: http://dx.doi.org/10.5255/UKDA-SN-5050-10 accessed January, 11 2016.

72. Pel-Littel R, Schuurmans M, Emmelot-Vonk M, et al. Frailty: defining and measuring of a concept. *JNHA-The Journal of Nutrition, Health and Aging* 2009;13(4):390-94.

73. Sternberg SA, Schwartz AW, Karunananthan S, et al. The identification of frailty: a systematic literature review. *Journal of the American Geriatrics Society* 2011;59(11):2129-38.

74. Peters LL, Boter H, Buskens E, et al. Measurement properties of the Groningen Frailty Indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical Directors Association* 2012;13(6):546-51. doi: 10.1016/j.jamda.2012.04.007 [published Online First: 2012/05/15]

75. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons 2004.

76. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30(4):377-99. doi: 10.1002/sim.4067
77. Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. *Journal of statistical software* 2011;45(3)
78. Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychological Methods* 2002;7(2):147-77. doi: 10.1037/1082-989x.7.2.147
79. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *The lancet* 1986;327(8476):307-10.
80. Klein BE, Klein R, Knudtson MD, et al. Relationship of measures of frailty to visual function: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2003;101:191-6; discussion 96-9. [published Online First: 2004/02/20]
81. Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in physically frail, elderly persons who live at home. *New England Journal of Medicine* 2002;347(14):1068-74.
82. Cesari M, Demougeot L, Boccalon H, et al. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. *PloS one* 2014;9(7):e101745.
83. van Kan GA, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. *Journal of the American Medical Directors Association* 2008;9(2):71-72.
84. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. *Journal of the American Geriatrics Society* 2008;56(12):2211-116. doi: 10.1111/j.1532-5415.2008.02008.x [published Online First: 2008/12/20]
85. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *The journals of gerontology Series A, Biological sciences and medical sciences* 2007;62(7):744-51. [published Online First: 2007/07/20]
86. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *Journals of Gerontology* 1994;49:M85-M85.
87. Chin APMJ, Dekker JM, Feskens EJ, et al. How to select a frail elderly population? A comparison of three working definitions. *Journal of clinical epidemiology* 1999;52(11):1015-21. [published Online First: 1999/10/20]

88. Freiheit EA, Hogan DB, Eliasziw M, et al. Development of a frailty index for patients with coronary artery disease. *Journal of the American Geriatrics Society* 2010;58(8):1526-31. doi: 10.1111/j.1532-5415.2010.02961.x [published Online First: 2010/07/17]

89. Hubbard RE, O'Mahony MS, Woodhouse KW. Characterising frailty in the clinical setting—a comparison of different approaches. *Age and ageing* 2009;38(1):115-19. doi: 10.1093/ageing/afn252

90. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *The oncologist* 2000;5(3):224-37.

91. Ravaglia G, Forti P, Lucicesare A, et al. Development of an easy prognostic score for frailty outcomes in the aged. *Age and ageing* 2008;37(2):161-6. doi: 10.1093/ageing/afm195

92. Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the Edmonton Frail Scale. *Age and ageing* 2006;35(5):526-29.

93. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *European journal of clinical investigation* 2005;35(12):723-30.

94. Bellera C, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Annals of Oncology* 2012:mdr587.

95. Steverink N, Slaets J, Schuurmans H, et al. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). *Order* 2001;501:17134.

96. Brody KK, Johnson RE, Ried LD. Evaluation of a self-report screening instrument to predict frailty outcomes in aging populations. *The Gerontologist* 1997;37(2):182-91.

97. Puts M, Lips P, Deeg D. Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning. *Journal of clinical epidemiology* 2005;58(11):1188-98.

98. Maly RC, Hirsch SH, Reuben DB. The performance of simple instruments in detecting geriatric conditions and selecting community-dwelling older people for geriatric assessment. *Age and ageing* 1997;26(3):223-31.

99. Hébert R, Bravo G, Korner-Bitensky N, et al. Predictive validity of a postal questionnaire for screening community-dwelling elderly individuals at risk of functional decline. *Age and ageing* 1996;25(2):159-67.

100. Di Bari M, Profili F, Bandinelli S, et al. Screening for Frailty in Older Adults Using a Postal Questionnaire: Rationale, Methods, and Instruments Validation of the INTER-FRAIL Study. *Journal of the American Geriatrics Society* 2014;62(10):1933-7. doi: 10.1111/jgs.13029 [published Online First: 2014/10/07]

101. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *Journal of the American Geriatrics Society* 2004;52(11):1929-33. doi: 10.1111/j.1532-5415.2004.52521.x [published Online First: 2004/10/28]

102. de Vries NM, Staal JB, Olde Rikkert MG, et al. Evaluative frailty index for physical activity (EFIP): a reliable and valid instrument to measure changes in level of frailty. *Phys Ther* 2013;93(4):551-61. doi: 10.2522/ptj.20120127 [published Online First: 2012/12/12]

103. Theou O, Brothers TD, Rockwood MR, et al. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age and ageing* 2013;42(5):614-9. doi: 10.1093/ageing/aft010 [published Online First: 2013/02/28]

104. Fang X, Shi J, Song X, et al. Frailty in relation to the risk of falls, fractures, and mortality in older Chinese adults: results from the Beijing Longitudinal Study of Aging. *The journal of nutrition, health & aging* 2012;16(10):903-7. doi: 10.1007/s12603-012-0368-6 [published Online First: 2012/12/05]

105. Kulminski A, Yashin A, Arbeev K, et al. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: results from analyses of the National Long Term Care Survey. *Mechanisms of ageing and development* 2007;128(3):250-58.

106. Dayhoff NE, Suhrheinrich J, Wigglesworth J, et al. Balance and muscle strength as predictors of frailty among older adults. *J Gerontol Nurs* 1998;24(7):18-27; quiz 54-5. [published Online First: 1998/11/05]

107. Morris JN, Sherwood S, Mor V. An Assessment Tool for Use in IdentifyingFunctionally Vulnerable Persons in the Community. *The Gerontologist* 1984;24(4):373-79.

108. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2005;173(5):489-95. doi: 10.1503/cmaj.050051 [published Online First: 2005/09/01]

109. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *Journal of the American Geriatrics Society* 2001;49(12):1691-99.

110. Van Iersel MB, Rikkert M. Frailty criteria give heterogeneous results when applied in clinical practice. *J Am Geriatr Soc* 2006;54(4):728-9.

111. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society* 2012;60(8):1487-92.

112. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing* 2015;44(1):162-5. doi: 10.1093/ageing/afu148 [published Online First: 2014/10/15]

113. Schuurmans H, Steverink N, Lindenberg S, et al. Old or frail: what tells us more? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2004;59(9):M962-M65.

114. Aguayo GA, Donneau AF, Vaillant MT, et al. Agreement Between 35 Published Frailty Scores in the General Population. *American journal of epidemiology* 2017;186(4):420-34. doi: 10.1093/aje/kwx061

115. Uno H, Cai T, Pencina MJ, et al. On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data. *Statistics in medicine* 2011;30(10):1105-17. doi: 10.1002/sim.4154

116. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Lippincott Williams & Wilkins 2008.

117. Klein BE, Klein R, Knudtson MD, et al. Frailty, morbidity and survival. *Archives of gerontology and geriatrics* 2005;41(2):141-9. doi: 10.1016/j.archger.2005.01.002 [published Online First: 2005/08/09]

118. Hippisley-Cox J, Coupland C. Symptoms and risk factors to identify men with suspected cancer in primary care: derivation and validation of an algorithm. *The British Journal of General Practice* 2013;63(606):e1-e10. doi: 10.3399/bjgp13X660724

119. Marmot M. English Longitudinal Study of Ageing: Waves 0-6, 1998-2013 [computer file]. : UK Data Service; 2014 [Available from: http://discover.ukdataservice.ac.uk/catalogue?sn=5050.

120. Taylor R, Conway L, Calderwood L, et al. Health, wealth and lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing Technical Report. *London: Institute of Fiscal Studies* 2007

121. Cacciatore F, Testa G, Galizia G, et al. Clinical frailty and long-term mortality in elderly subjects with diabetes. *Acta diabetologica* 2013;50(2):251-60. doi: 10.1007/s00592-012-0413-2 [published Online First: 2012/06/27]

122. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26(suppl 1):s5-s20. doi: 10.2337/diacare.26.2007.S5

123. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth

Joint National Committee (JNC 8). *JAMA* 2014;311(5):507-20. doi: 10.1001/jama.2013.284427

124. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood* 2006;107(5):1747-50.
125. Steel N, Huppert F, McWilliams B, et al. Physical and cognitive function. In: Marmot M, Banks J, Blundell R, et al., eds. Health, wealth and lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing2004.
126. Howel D. Interpreting and evaluating the CASP-19 quality of life measure in older people. *Age and ageing* 2012;41(5):612-7. doi: 10.1093/ageing/afs023
127. Radloff LS. The CES-D scale a self-report depression scale for research in the general population. *Applied psychological measurement* 1977;1(3):385-401.
128. Thomas L, Reyes EM. Tutorial: survival estimation for Cox regression models with time-varying coefficients using SAS and R. *Journal of Statistical Software* 2014;61(1):1-23.
129. Afilalo J. Frailty in patients with cardiovascular disease: why, when, and how to measure. *Current cardiovascular risk reports* 2011;5(5):467.
130. Chen MA. Frailty and cardiovascular disease: potential role of gait speed in surgical risk stratification in older adults. *Journal of geriatric cardiology : JGC* 2015;12(1):44-56. doi: 10.11909/j.issn.1671-5411.2015.01.006 [published Online First: 2015/02/14]
131. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001;56(3):M158-66. [published Online First: 2001/03/17]
132. White HD, Westerhout CM, Alexander KP, et al. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: Insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *European heart journal Acute cardiovascular care* 2016;5(3):231-42. doi: 10.1177/2048872615581502 [published Online First: 2015/04/22]
133. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes* 2012;5(2):222-8. doi: 10.1161/CIRCOUTCOMES.111.963157
134. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Archives of internal medicine* 2008;168(4):382-9. doi: 10.1001/archinternmed.2007.113 [published Online First: 2008/02/27]

135. Sourial N, Bergman H, Karunananthan S, et al. Implementing frailty into clinical practice: a cautionary tale. *The journals of gerontology Series A, Biological sciences and medical sciences* 2013;68(12):1505-11. doi: 10.1093/gerona/glt053 [published Online First: 2013/05/04]

136. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls2009.

137. Kalyani RR, Golden SH, Cefalu WT. Diabetes and Aging: Unique Considerations and Goals of Care. *Diabetes Care* 2017;40(4):440-43. doi: 10.2337/dci17-0005 [published Online First: 2017/03/23]

138. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society* 2012;60(8):1487-92. doi: 10.1111/j.1532-5415.2012.04054.x [published Online First: 2012/08/14]

139. Aguayo GA, Vaillant MT, Donneau AF, et al. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer and total mortality in an elderly general population in England: an observational study. *PLoS medicine* 2018

140. Rolland Y, Dupuy C, Abellan van Kan G, et al. Treatment strategies for sarcopenia and frailty. *The Medical clinics of North America* 2011;95(3):427-38, ix. doi: 10.1016/j.mcna.2011.02.008 [published Online First: 2011/05/10]

141. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, et al. Fully conditional specification in multivariate imputation. *Journal of Statistical Computation and Simulation* 2006;76(12):1049-64. doi: 10.1080/10629360600810434

142. Selvin E, Crainiceanu CM, Brancati FL, et al. Short-term variability in measures of glycemia and implications for the classification of diabetes. *Archives of internal medicine* 2007;167(14):1545-51.

143. Jang HC. Sarcopenia, Frailty, and Diabetes in Older Adults. *Diabetes & metabolism journal* 2016;40(3):182-9. doi: 10.4093/dmj.2016.40.3.182 [published Online First: 2016/04/22]

144. Castrejon-Perez RC, Aguilar-Salinas CA, Gutierrez-Robledo LM, et al. Frailty, diabetes, and the convergence of chronic disease in an age-related condition: a population-based nationwide cross-sectional analysis of the Mexican nutrition and health survey. *Aging clinical and experimental research* 2017 doi: 10.1007/s40520-017-0852-2 [published Online First: 2017/11/29]

145. Hubbard R, Andrew M, Fallah N, et al. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. *Diabetic Medicine* 2010;27(5):603-06.

146. Bouillon K, Batty GD, Hamer M, et al. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study. *Heart* 2013;99(10):737-42. doi: 10.1136/heartjnl-2012-302922 [published Online First: 2013/03/19]

147. Ottenbacher KJ, Graham JE, Al Snih S, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. *Am J Public Health* 2009;99(4):673-9. doi: 10.2105/ajph.2008.143958 [published Online First: 2009/02/07]

148. Garcia-Esquinas E, Graciani A, Guallar-Castillon P, et al. Diabetes and risk of frailty and its potential mechanisms: a prospective cohort study of older adults. *Journal of the American Medical Directors Association* 2015;16(9):748-54. doi: 10.1016/j.jamda.2015.04.008 [published Online First: 2015/05/20]

149. Zaslavsky O, Walker RL, Crane PK, et al. Glucose Levels and Risk of Frailty. *The journals of gerontology Series A, Biological sciences and medical sciences* 2016;71(9):1223-9. doi: 10.1093/gerona/glw024 [published Online First: 2016/03/05]

150. Perkisas S, Vandewoude M. Where frailty meets diabetes. *Diabetes/metabolism research and reviews* 2016;32 Suppl 1:261-7. doi: 10.1002/dmrr.2743 [published Online First: 2015/10/11]

151. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *The lancet Diabetes & endocrinology* 2014;2(10):819-29.

152. Perez-Tasigchana RF, Leon-Munoz LM, Lopez-Garcia E, et al. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age and ageing* 2017;46(5):807-12. doi: 10.1093/ageing/afx023 [published Online First: 2017/03/25]

153. Morley JE, Malmstrom TK, Rodriguez-Manas L, et al. Frailty, sarcopenia and diabetes. *Journal of the American Medical Directors Association* 2014;15(12):853-9. doi: 10.1016/j.jamda.2014.10.001 [published Online First: 2014/12/03]

154. Sinclair AJ, Abdelhafiz A, Dunning T, et al. An International Position Statement on the Management of Frailty in Diabetes Mellitus: Summary of Recommendations 2017. *The Journal of frailty & aging* 2018;7(1):10-20. doi: 10.14283/jfa.2017.39 [published Online First: 2018/02/08]

155. Walston J, Buta B, Xue QL. Frailty Screening and Interventions: Considerations for Clinical Practice. *Clinics in geriatric medicine* 2018;34(1):25-38. doi: 10.1016/j.cger.2017.09.004 [published Online First: 2017/11/14]

156. Debra S. Disentangling frailty. *Geriatric Nursing* 2017;38(6):606. doi: https://doi.org/10.1016/j.gerinurse.2017.10.012

157. Rodriguez-Manas L, Feart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *The journals of gerontology Series A, Biological sciences and medical sciences* 2013;68(1):62-7. doi: 10.1093/gerona/gls119 [published Online First: 2012/04/19]

158. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev* 2016;26:53-61. doi: 10.1016/j.arr.2015.12.003 [published Online First: 2015/12/18]

159. Sutton JL, Gould RL, Daley S, et al. Psychometric properties of multicomponent tools designed to assess frailty in older adults: A systematic review. *BMC Geriatr* 2016;16:55. doi: 10.1186/s12877-016-0225-2 [published Online First: 2016/03/02]

160. Gilardi F, Capanna A, Ferraro M, et al. Frailty screening and assessment tools: a review of characteristics and use in Public Health. *Annali di igiene : medicina preventiva e di comunita* 2018;30(2):128-39. doi: 10.7416/ai.2018.2204 [published Online First: 2018/02/22]

161. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15(4):361-87. doi: 10.1002/(sici)1097-0258(19960229)15:4<361::Aid-sim168>3.0.Co;2-4 [published Online First: 1996/02/28]

162. Buckinx F, Rolland Y, Reginster J-Y, et al. Burden of frailty in the elderly population: perspectives for a public health challenge. *Archives of Public Health* 2015;73(1):19.

163. Widagdo I, Pratt N, Russell M, et al. How common is frailty in older Australians? *Australasian journal on ageing* 2015;34(4):247-51. doi: 10.1111/ajag.12184 [published Online First: 2015/06/04]

164. Schaller MS, Ramirez JL, Gasper WJ, et al. Frailty Is Associated with an Increased Risk of Major Adverse Cardiac Events in Patients with Stable Claudication. *Annals of vascular surgery* 2018 doi: 10.1016/j.avsg.2017.12.002 [published Online First: 2018/02/27]

165. Barzilay JI, Blaum C, Moore T, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Archives of internal medicine* 2007;167(7):635-41. doi: 10.1001/archinte.167.7.635 [published Online First: 2007/04/11]

166. Hsu HC, Chang WC. Trajectories of frailty and related factors of the older people in Taiwan. *Experimental aging research* 2015;41(1):104-14. doi: 10.1080/0361073x.2015.978219 [published Online First: 2014/12/17]

167. Chamberlain AM, St Sauver JL, Jacobson DJ, et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. *BMJ open* 2016;6(5):e011410. doi: 10.1136/bmjopen-2016-011410 [published Online First: 2016/05/29]

168. Smart R, Carter B, McGovern J, et al. Frailty Exists in Younger Adults Admitted as Surgical Emergency Leading to Adverse Outcomes. *The Journal of frailty & aging* 2017;6(4):219-23. doi: 10.14283/jfa.2017.28 [published Online First: 2017/11/23]

169. Puts MT, Lips P, Deeg DJ. Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. *Journal of the American Geriatrics Society* 2005;53(1):40-47.

170. Mitnitski AB, Song X, Rockwood K. The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *The journals of gerontology Series A, Biological sciences and medical sciences* 2004;59(6):M627-32. [published Online First: 2004/06/25]

171. Fernandez-Bolaños M, Otero Á, Zunzunegui MV, et al. Sex differences in the prevalence of frailty in a population aged 75 and older in Spain. *Journal of the American Geriatrics Society* 2008;56(12):2370-71.

172. Gordon EH, Peel NM, Samanta M, et al. Sex differences in frailty: A systematic review and meta-analysis. *Experimental gerontology* 2016 doi: 10.1016/j.exger.2016.12.021 [published Online First: 2017/01/04]

173. Hubbard RE, Rockwood K. Frailty in older women. *Maturitas* 2011;69(3):203-7. doi: 10.1016/j.maturitas.2011.04.006 [published Online First: 2011/05/17]

174. Kalaycioglu O, Copas A, King M, et al. A comparison of multiple-imputation methods for handling missing data in repeated measurements observational studies. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2016;179(3):683-706.

175. Karahalios A, Baglietto L, Carlin JB, et al. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. *BMC medical research methodology* 2012;12(1):96.

176. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ (Clinical research ed)* 2009;338 doi: 10.1136/bmj.b2393

177. Adams P, Ghanem T, Stachler R, et al. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery. *JAMA Otolaryngol Head Neck Surg* 2013;139(8):783-9. doi: 10.1001/jamaoto.2013.3969 [published Online First: 2013/08/21]

178. Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: a review. *Test (Madrid, Spain)* 2009;18(1):1-43. doi: 10.1007/s11749-009-0138-x

179. Tan J-p, Li N, Lan X-y, et al. The impact of methods to handle missing data on the estimated prevalence of dementia and mild cognitive impairment in a cross-sectional study including non-responders. *Archives of gerontology and geriatrics* 2017;73:43-49. doi: https://doi.org/10.1016/j.archger.2017.07.009

180. Abeysekera W, Sooriyarachchi R. Use of Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazards model: an application to a clinical study. 2009

181. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000;56(2):337-44. [published Online First: 2000/07/06]

Scientific contribution

Peer-reviewed publications

Aguayo GA, Donneau AF, Vaillant MT, et al. Agreement Between 35 Published Frailty Scores in the General Population. American journal of epidemiology 2017;186(4):420-34. doi: 10.1093/aje/kwx061

Aguayo G, Vaillant MT, Donneau AF, et al. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer and total mortality in an elderly general population in England: an observational study. PLoS medicine 2018

Published abstracts

Aguayo G, Donneau AF, Vaillant MT, et al. Mortality prediction of 35 frailty scores in a 7-years follow-up study in elderly general population. European Journal of Public Health 2016;26(suppl_1):ckw174.044-ckw174.044. doi: 10.1093/eurpub/ckw174.044

Aguayo GA, Schritz A, Donneau A-F, et al. Predictive Ability of 35 Frailty Scores for Cardiovascular Events in the General Population. Circulation. 2017;135(Suppl 1):AP011-AP.

Aguayo GA, Schritz A, Donneau A-F, et al. Predictive Ability of 35 Frailty Scores for Cardiovascular Events in the General Population. Circulation 2017;135(Suppl 1):AP011-AP11.

Aguayo GA, Vaillant MT, Donneau AF, et al. Association between 35 frailty scores and 7-years mortality, cardiovascular and cancer events in an elderly general population. Submited_under_review 2017

Scientific presentations

Frailty trajectories in an elderly general population at different levesl of glycated heamoglobin GA Aguayo, A Hulman, MT Vaillant, A-F Donneau, A Schritz, S Stranges, L

Malisoux, L Huiart, M Guillaume, M Muller, S Sabia, DR Witte. Presented in the 52th meeting of the European Diabetes Epidemiology Group (Elsinore, Denmark on April 21-24 2018).

Análisis comparativo de la asociación entre 35 scores de fragilidad y la incidencia de eventos cardiovasculares, cáncer y mortalidad total. Aguayo G.Conference presented in Spanish for the Department of Public Health Pontifical Catholic University of Chile. Santiago, Chile, January 3, 2018.

Assessment of 35 Frailty Scores for predicting cardiovascular events, cancer and total mortality in an Elderly General Population. Aguayo G. Presented in the PhD day of Belgian Universities. Brussels, November, 2017.

Cross sectional concordance of frailty scores in the English Longitudinal Study of Ageing. G.A. Aguayo, D. R. Witte, M.T. Vaillant, O. H. Franco, S. Stranges, A. Schritz, A.F. Donneau and M. Guillaume. Presented in the 50th meeting of the European Diabetes Epidemiology Group (Chantilly, France 2015)

Cross sectional concordance of frailty scores in the English Longitudinal Study of Ageing. G.A. Aguayo, D. R. Witte, M.T. Vaillant, O. H. Franco, S. Stranges, A. Schritz, A.F. Donneau and M. Guillaume presented in the Symposium “Methods in Epidemiology” organized by the Epidemiology Research Group – KU Leuven - University of Leuven, Belgium), Leuven, Belgium 2015).

Publications for general public

Aguayo G. «Mieux vieillir c’est possible ! ». Semper Luxembourg. 2017. N°95, pages 12-14.

Aguayo G. « Aider les seniors à vieillir en bonne santé » Ons Stad. Luxembourg 2016. Nro.113, pages 28-29.