

Validation of the FNIH sarcopenia criteria and SOF frailty index as predictors of long-term mortality in ambulatory older men

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Abstract

Objective: we aimed to evaluate the Foundation for the National Institutes of Health (FNIH) criteria for weakness and low muscle mass and the Study of Osteoporotic Fractures (SOF) frailty index for prediction of long-term, all-cause mortality.

Design: community-based cohort study.

Setting: semi-rural community of Merelbeke (Belgium).

Subjects: ambulatory men aged 74 and more ($n = 191$).

Methods: weakness was defined on previously established criteria as low grip strength (<26 kg) or low grip strength-to-body mass index (BMI) ratio (<1.00). Low muscle mass (dual-energy x-ray absorptiometry) was categorised as low appendicular lean mass (ALM; predefined <19.75 kg) or low ALM-to-BMI ratio (predefined <0.789). Frailty status was assessed using the components of weight loss, inability to rise from a chair and poor energy (SOF index). Survival time was calculated as the number of months from assessment in 2000 until death or up to 15 years of follow-up.

Results: mean age of the participants was 78.4 ± 3.5 years. Combined weakness and low muscle mass was present in 3–8% of men, depending on the criteria applied. Pre-frailty and frailty were present in 30 and 7% of men, respectively. After 15 years of follow-up, 165 men (86%) died. Both the presence of combined weakness and low ALM-to-BMI ratio (age-adjusted HR = 2.50, 95% CI = 1.30–4.79) and the presence of SOF frailty (age-adjusted HR = 2.64, 95% CI = 1.44–4.86) were associated with mortality.

Conclusions: our findings confirm the predictive value for mortality of the non-distribution-based FNIH criteria and SOF index in older community-dwelling Belgian men.

Keywords: ambulatory older men, mortality, FNIH sarcopenia, SOF frailty

Introduction

Sarcopenia and frailty are geriatric syndromes that have received particular attention in the last decade, especially because of their association with negative health-related outcomes [1]. However, no consensus exists so far on operational definitions for both syndromes. Definitions using criteria that do not rely on distribution-based cut-off points seem appealing for clinical practice, since the establishment of a reference population is not required.

Sarcopenia is characterised by the age-related loss of muscle mass and muscle function [2, 3]. Several expert groups have proposed an operational definition for

sarcopenia, using the medical literature and founding their criterion for low muscle mass on its distribution in healthy young [3, 4] or well-functioning older [2] reference populations. Recently, the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium developed new criteria for the diagnosis of weakness and low muscle mass in older adults [5], using a data-driven approach and founding their criteria on discriminative and predictive ability. They used classification and regression tree analyses in pooled cross-sectional data from several cohort studies which first retained cut-off points for grip strength and grip strength adjusted to body mass index (BMI) associated with mobility

impairment [6], and then cut-off points for appendicular lean mass (ALM) and ALM adjusted to BMI (ALM_{BMI}) discriminating the presence or absence of weakness [7]. Finally, they determined the association of these criteria for weakness and low muscle mass with increased likelihood for incident mobility impairment and mortality [8]. The recommended combination of grip strength and ALM_{BMI} was the only one for which there was no heterogeneity. Nevertheless, mortality risk patterns were inconsistent, and further validation of their cut-off points for weakness and low muscle mass in other populations is needed [8].

Frailty is characterised by a physiologic decrease of reserve capacity and resistance to stressors [9]. Several operational definitions have been proposed; the most extensively studied one is the physical frailty phenotype developed by Fried *et al.* [9] in the Cardiovascular Health Study (CHS), including weight loss, weakness, exhaustion, slowness and low activity. In 2008, the Study of Osteoporotic Fractures (SOF) Research Group developed a more straightforward index to identify frailty that includes only three components (weight loss, inability to rise from a chair five times without using the arms and self-reported poor energy) and is more practical to assess in the clinical setting [10]. No difference between the parsimonious SOF index and the more complicated CHS index was found in predictive accuracy for discriminating falls, disability and death in both the female SOF and male MrOs Sleep studies [10, 11]. Nevertheless, inconsistent associations of the SOF index with mortality have been found depending on ethnicity and setting of the population examined [12–15].

We aimed to evaluate the FNIH cut-off points for weakness and low muscle mass and the SOF frailty index for prediction of all-cause mortality in a well-described sample of apparently healthy community-dwelling older men in Belgium with long-term follow-up.

Methods

Study population

Men aged 70–85 were recruited from the population register of a community of $\pm 20,000$ inhabitants (Merelbeke, Belgium). The recruitment has been described previously [16] and is briefly summarised in the Supplementary data, Figure S1, available in *Age and Ageing* online. This cohort study started in 1996 with follow-up visits annually until 2000, one visit in 2003 and thereafter annual follow-up by postal questionnaires and telephone contacts. Sarcopenia and frailty could be identified retrospectively based on data acquired at the fifth visit in 2000. All participants gave written informed consent. This study was conducted according to the Declaration of Helsinki and approved by the ethics committee of Ghent University Hospital.

Measurements

Weight and height were measured in indoor clothing without shoes. BMI was calculated as weight in kilograms divided by

the square of height in metres. The Short Form-36 was completed to evaluate self-reported health (range 0–100) [17]. Subjects were asked about their educational degree, residence, recreational physical activity, any falls in the previous year, medication use (range 0–8+) and smoking status. The Geriatric Depression Scale (range 0–30) was used to evaluate depressive symptoms [18]. The first part of the Rapid Disability Rating Scale-2 was used to rate the amount of assistance required in eight activities of daily living (range 8–32) [19]. Physical performance was assessed using the Timed Up and Go test [20] (fastest time of two consecutive measurements). Furthermore, participants had to complete five full stands from seated position as quickly as possible [21]. Grip strength of the dominant hand was measured twice consecutively using JAMAR dynamometry (maximum value achieved). ALM was calculated as the sum of lean mass from both arms and legs, acquired from total body scans using dual-energy x-ray absorptiometry (Hologic QDR-4500A; Hologic Inc., Bedford, MA, USA; software V8.26a).

FNIH sarcopenia criteria

Weakness and low muscle mass at the fifth visit were defined according to the FNIH criteria [5].

Weakness as identified by maximum grip strength < 26 kg or grip strength-to-BMI ratio < 1.00 .

Low muscle mass as identified by $ALM < 19.75$ kg or ALM_{BMI} ratio < 0.789 .

SOF frailty index

Frailty status at the fifth visit was defined according to the SOF index [10, 11]. Subjects are considered to be ‘frail’ if two or all of the following components are present, ‘pre-frail’ if only one component is present and ‘robust’ if none of the components is present:

Weight loss (irrespective of intent to lose weight) of 5% or more between the second and fifth visit (mean time between visits 3.0 ± 0.05 years). For subjects with missing data on weight at the second visit ($n = 15$), weight at the first visit was used.

Inability to rise from a chair five consecutive times without using the arms.

Poor energy as identified by a negative answer to the question “do you feel full of energy?” on the 30-item Geriatric Depression Scale [18].

Mortality

Data on all-cause mortality were obtained through yearly postal questionnaires and by contacting proxies and the treating general practitioners via telephone. Survival time was calculated as the number of months from assessment in 2000 until death or up to 15 years of follow-up (until 1 January 2015 if there was a response to the postal questionnaire ($n = 16$), until 8 July 2015 if the proxy or treating general practitioner was contacted

by telephone ($n = 9$), until last date of contact if the subject was lost to follow-up in 2015 ($n = 1$).

Statistical analysis

Descriptive data are presented as mean \pm standard deviation (SD), median and inter-quartile range (IQR), or total number and percentage. Differences between subjects were compared using the Independent Samples t -test, Mann–Whitney U or χ^2 test, depending on the type and distribution of the characteristic.

Age-adjusted Cox proportional hazards models were used to analyse the associations of sarcopenia and frailty with all-cause mortality. The hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using as a reference men who are not weak and have normal lean mass or robust men, respectively. No violations of the proportional hazards assumption were detected. Moreover, multivariate analyses with forward selection of BMI category*, low education, living alone, smoking status, number of medications and total score on the Geriatric Depression Scale were performed. *Analyses regarding the FNIH criteria were not adjusted for BMI category. All analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was indicated by a P value < 0.05 ; all P values were two-tailed.

Results

In total, 208 men attended the fifth visit (Supplementary data, Figure S1, available in *Age and Ageing* online); assessment of both sarcopenia and frailty was complete for 191 of them. Supplementary data, Table S1, available in *Age and Ageing* online shows their characteristics. Mean age was 78.4 (± 3.5) years. Combined weakness and low muscle mass was present in 3–8% of men, depending on the criteria applied (Figure 1A). Pre-frailty and frailty were present in 30 and 7%, respectively (Figure 1B). Weakness was more likely in men with frailty compared with robust ($P < 0.001$) or pre-frail men ($P = 0.001$). Similarly, inability to rise from a chair was more likely in men with weakness compared with men without weakness ($P = 0.005$).

After 15 years of follow-up, 165 men (86%) died (Supplementary data, Figure S1 and Table S1, available in *Age and Ageing* online). Median survival time was 8.3 (IQR 4.3–12.4) years.

Of 191 men, 61.3% had normal grip strength and normal ALM_{BMI} (41.9% was robust, 17.3% was pre-frail and 2.1% was frail) and 63.4% was robust (4.7% had weakness alone, 14.7% had low ALM_{BMI} alone and 2.1% had both). The combination of frailty, weakness and low ALM_{BMI} was present in 1.6% of men.

FNIH sarcopenia criteria

Low ALM_{BMI} (age-adjusted HR = 1.47, 95% CI = 1.05–2.07) was associated with all-cause mortality, but low grip strength (age-adjusted HR = 1.31, 95% CI = 0.85–2.02), low grip strength-to-BMI ratio (age-adjusted HR = 1.45, 95% CI = 0.90–2.34) and low ALM (age-adjusted HR = 1.08,

95% CI = 0.75–1.55) were not. Figure 1A shows age-adjusted Cox proportional hazard models each time including one of the four different combinations of weakness and low lean mass criteria. The presence of both weakness and low lean mass defined by ALM_{BMI} was associated with a twofold higher hazard of mortality (age-adjusted HR = 2.50, 95% CI = 1.30–4.79). Multivariate forward regression, retaining number of medications in the analysis, did not alter significance of this finding (age and medication number-adjusted HR = 2.30, 95% CI = 1.20–4.43).

After 3 years, the proportion of deceased men who had presented with weakness and low ALM_{BMI} was 41.7% (positive predictive value), while the proportion of survivors who were not weak and had normal ALM_{BMI} was 89.7% (negative predictive value). The age-adjusted AUC was 0.700. After 9 years, positive predictive value increased to 83.3%, but negative predictive value decreased to 53.8%. The age-adjusted AUC was 0.671.

Analyses in men without weakness ($n = 164$) did not reveal a significant association of low ALM_{BMI} with mortality ($P = 0.121$). Compared with men without weakness, only men with combined weakness and low muscle mass had an increased mortality hazard ($P = 0.015$).

SOF frailty index

Weight loss (age-adjusted HR = 1.99, 95% CI = 1.27–3.11) and poor energy (age-adjusted HR = 1.78, 95% CI = 1.26–2.51) were associated with all-cause mortality, but not inability to rise from a chair (age-adjusted HR = 1.23, 95% CI = 0.67–2.27). Both pre-frail and frail status were associated with higher mortality rates, independently from age (Figure 1B). Multivariate forward regression, which retained the number of medications in the analysis, did not alter significance of the association between frailty and mortality (age and medication number-adjusted HR = 1.95, 95% CI = 1.01–3.77).

After 3 years, the proportion of deceased men who had presented with frailty was 38.5% while the proportion of survivors who were robust was 86.8% (age-adjusted AUC was 0.675). After 9 years, positive predictive value increased to 92.3%, but negative predictive value decreased to 52.9% (age-adjusted AUC was 0.674).

The age-adjusted survival curves show the association of the FNIH sarcopenia criteria and SOF frailty index with mortality rates (Figure 2).

Both indices were independently associated with mortality when they were entered into the same Cox regression model (adjusted HR for combined weakness and low ALM_{BMI} = 2.02, 95% CI = 1.04–3.90, adjusted HR for pre-frail state = 1.65, 95% CI = 1.17–2.33, adjusted HR for frail state = 2.41, 95% CI = 1.29–4.51).

Discussion

We evaluated the FNIH cut-off points for weakness and low muscle mass and the SOF frailty index for prediction of all-

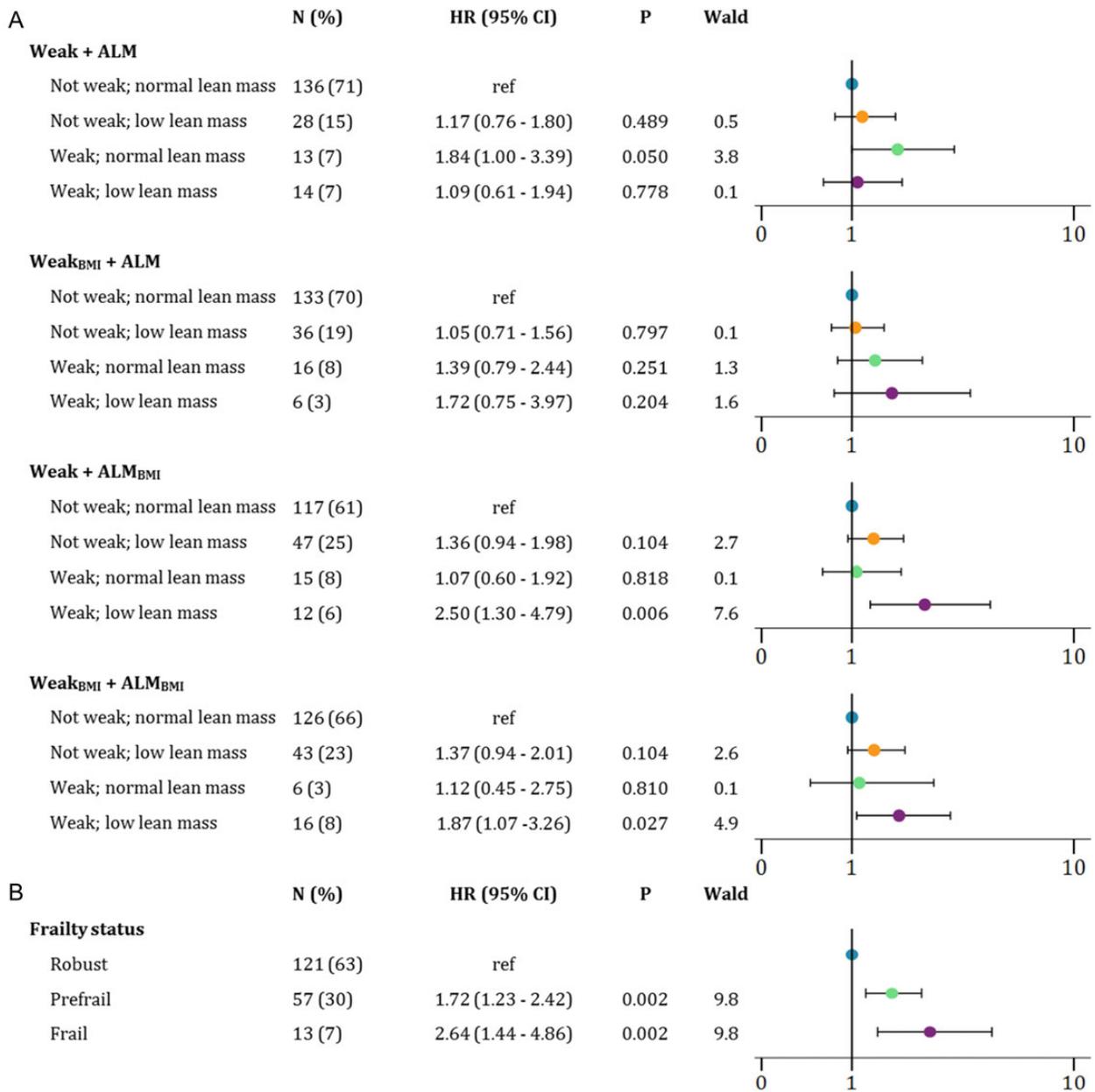


Figure 1. Association of sarcopenia and frailty states with all-cause mortality after 15-year follow-up of community-dwelling older Belgian men ($n = 191$). Age-adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression models. When the CI encompasses the value 1, the association is not significant at the 95% significance level ($P < 0.05$). HR, hazard ratio; CI, confidence interval; ALM, appendicular lean mass; BMI, body mass index; Ref, reference.

cause mortality in a sample of community-dwelling older Belgian men. The presence of combined weakness and low ALM_{BMI}, as well as the presence of SOF frailty, was associated with twofold higher hazards of mortality, independently from age and medication number. Low ALM (without adjustment for BMI) was not associated with mortality hazard, both in age-adjusted and in age- and weakness-adjusted models.

Currently, very few studies have evaluated the FNIH criteria for prediction of all-cause mortality [8, 22, 23]. The FNIH Research Group [8] found no consistent association with mortality; however, weakness appeared to be the predominant predictor over lean mass. We however found subjects with low

ALM_{BMI} having the highest mortality hazards regardless of their weakness status (grip strength or grip strength-to-BMI). But, when ALM was not adjusted for BMI, lean mass did not have any predictive value. Similarly, Woo *et al.* [22] found men with low grip strength and low ALM_{BMI} to have higher odds for mortality after 10 years compared with men without sarcopenia in a Chinese community-dwelling sample. Lastly, Hirani *et al.* [23] found low ALM and low grip strength to be associated with mortality in Australian community-dwelling men, but their criteria were not adjusted for BMI. Their age-adjusted AUC for predicting 9-year mortality was 0.68, which corresponds with our value of 0.67.

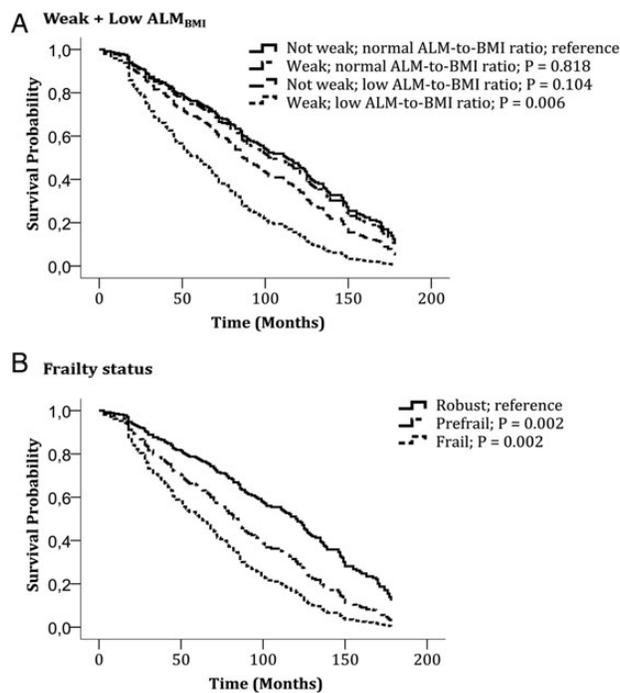


Figure 2. Survival curves for sarcopenia and frailty states in community-dwelling older Belgian men ($n = 191$), predicted from age-adjusted Cox regression models. ALM, appendicular lean mass; BMI, body mass index.

In addition to being data-driven, the FNIH Biomarkers Consortium approach distinguishes itself from other expert group strategies, by consistently discriminating the contributions of muscle mass and function. This is in contrast with, for example, the IWGS approach [2], which combines its parameters into a single classification of sarcopenia. Regarding these independent contributions of muscle mass and function, our findings support the clinical paradigm in which first low grip strength is established, before the presence or absence of low lean mass is assessed. In this final selection of older persons, low lean mass might be a possible cause of their weakness [5].

The SOF index has been evaluated in different settings and populations for prediction of all-cause mortality. The index was associated with mortality in community-dwelling older Caucasians in the USA [10, 11] and Italy [24]. Our findings confirm this association in Caucasian community-dwellers. Albeit our age-adjusted AUC for predicting 3-year mortality (0.68) was slightly lower than the 0.71 found in the MrOS Sleep study [11]. The index has been inconsistent in hospitalised patients [12, 15] and non-significant in community-dwelling older persons of Asian or African American ethnicity [13, 14].

Our findings have some implications both for research and for clinical practice. In research, reporting the sarcopenic and/or frailty status of older study participants can help characterising their overall health, which might facilitate comparison across studies.

For clinical practice, this interpretation is more complex, because both the FNIH criteria and the SOF index have

demonstrated low PPV (<54%) and high NPV (>80%) for short-term mortality (3 years), and contrariwise for long-term mortality (9 years). This suggests that men without weakness and low muscle mass as well as robust men are likely to be in good health and function within the next 3 years, while men with weakness and low muscle mass and frail men are likely to be in poor health and function within the next 9 years.

Moreover, the FNIH criteria and the SOF index may help identifying older people in need of an intervention, both in research and in clinical practice. Although the FNIH criteria and SOF index did not identify the same men (there was only 1.6% overlap between weakness, low ALM_{BMI} and frailty), both might be used to target subjects for similar interventions such as exercise interventions, optimising protein intake and correcting vitamin D insufficiency.

Several factors additionally promote the implementation of the FNIH criteria and SOF index in clinical practice. All measurements can be performed quickly and easily, with minimal professional training needed and with relatively low costs. The criteria do not rely on distribution-based cut-off points, and thus, no knowledge of the underlying distribution in a given population is required.

However, several proposals for further research can be formulated. A first proposal is to examine the generalisability of these criteria to other ethnicities and settings, because the clinical relevance of both criteria might be limited to the population and setting in which they were developed. The FNIH criteria were derived from nine studies performed mostly in the USA and some in Europe. Around 90% of all subjects were Caucasian. Similarly, the SOF index was developed using data from Caucasian women in the USA. Applicability of both criteria to other ethnic groups is hence uncertain and might explain some of the divergent findings mentioned earlier. Moreover, both criteria were developed in ambulatory older persons and previous studies pointed out the inconsistent validity of the SOF index in hospital setting.

A second proposal relates to the range of existing operational definitions for both sarcopenia and frailty. Studies comparing the predictive accuracy of the FNIH criteria and SOF index with other instruments of sarcopenia and frailty, respectively, might help researchers and clinicians with the challenge of deciding which consensus definition to use.

A third proposal might focus on the meaning of change/transitions in these syndromes. Both sarcopenia and frailty are used as outcome measures for interventions [25, 26], since they are driving the disability cascade but are (unlike disability) still potentially reversible. Therefore, it is important to understand the effect on mortality risk of transitions from and to non-sarcopenic and robust states over time. Moreover, evidence is needed for a link between improvement in sarcopenia or frailty state and clinical outcomes to justify the use of these syndromes as outcome measurements in interventions [27].

Our study has some limitations. First, our cohort study had a baseline participation rate of 47%, which is in accordance with other population-based studies [28]. Unfortunately, no clinical data are available for the men who declined to participate, and it is likely that these non-participating men had

higher mortality rates than our participants [29]. Second, analyses were restricted to all-cause mortality, because cause of death could not be validated based on death certificates, but relied on communication with the treating general practitioner.

A major strength of this study is its long follow-up period of 15 years, which is the longest follow-up for any mortality study implementing the FNIH criteria (previously max 10 years [8, 22]) or SOF index (previously max 9 years [10, 14]). This long follow-up contributes to the exceptionally high mortality rate of 86.4% in our study. Mortality rates in previous studies evaluating the FNIH or SOF criteria in men range from 7.7 to 31.9% and from 6.5 to 27.4%, respectively. The small survival rate in our study entails that few observations are censored in the analyses; this reduces the risk of bias in estimates and standard errors.

Furthermore, our study population seems to be a representative sample. This is indicated by the correspondence of our prevalences with those reported in other population-based studies implementing the FNIH criteria (prevalence varied between 1 and 7.7% [8, 22, 23]) or SOF index (prevalence of pre-frailty and frailty ranged from 19 to 50% and from 4 to 17%, respectively [10, 11, 13, 14, 30]).

Key points

- This community-based, cohort study in ambulatory older Belgian men applied the FNIH criteria and the SOF index.
 - Combined weakness and low muscle mass was found in 3–8%. Pre-frailty and frailty were present in 30 and 7%, respectively.
 - The FNIH criteria for weakness and low muscle mass and the SOF index for frailty predicted 15-year all-cause mortality.
 - The non-distributional characteristics of these criteria facilitate their application in clinical setting.
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Authors' contributions

S.L.D.B. created the concept, performed the statistical analyses and wrote the manuscript. M.P. and Y.E.T. contributed to conception of the manuscript and revised the article. B.L. provided statistical support and critical revisions of the manuscript. K.R.C.T. contributed substantially to acquisition of data and revised the article. J.-M.K. and S.G. designed the study, supported data collection and provided critical revisions of the manuscript.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Conflicts of interest

None declared.

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