Ageing Research Reviews 53 (2019) 100911

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

The operationalization of fatigue in frailty scales: a systematic review

V. Knoop[a,b], A. Costenoble[a,b], R. Vella Azzopardi[a,b,c], S. Vermeiren[a,b], A. Debain[a,b,c], B. Jansen[e,f], A. Scafoglieri[b,d], I. Bautmans[a,b,c], on behalf of the Gerontopole Brussels Study group (Ivan Bautmans[g,*], Dominque Verté[h], Ingo Beyer[i], Mirko Petrovic[j], Liesbeth De Donder[k], Tinie Kardol[l], Gina Rossi[m], Peter Clarys[n], Aldo Scafoglieri[o], Erik Cattrysse[p], Paul de Hert[q], Bart Jansen[r])

[a] Gerontology department, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090, Brussels, Belgium
[b] Frailty in Ageing (FRIA) Research department, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090, Brussels, Belgium
[c] Department of Geriatrics, Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, B-1090, Brussels, Belgium
[d] Supporting Clinical Science department and research department of Experimental Anatomy (EXAN), Vrije Universiteit Brussel (VUB), Brussels, Belgium
[e] Department of Electronics and Informatics ETRO, Vrije Universiteit Brussel (VUB), Elsene, Belgium
[f] imec, Leuven, Belgium
[g] FRIA, VUB, Belgium
[h] Belgian Ageing Studies BAST, VUB, Belgium
[i] Geriatric Medicine department, UZ Brussel, Belgium
[j] ReFrail, UGent, Belgium
[k] Belgian Ageing Studies BAST, VUB, Belgium
[l] Leerstoel Bevordering Active Ageing, VUB, Belgium
[m] Clinical and Lifespan Psychology KLEP, VUB, Belgium
[n] Physical Activity and Nutrition PANU, VUB, Belgium
[o] Experimental Anatomy EXAN, VUB, Belgium
[p] Experimental Anatomy EXAN, VUB, Belgium
[q] Fundamental Rights and Constitutionalism Research group FRC, VUB, Belgium
[r] Department of Electronics and Informatics ETRO, VUB, Belgium

A R T I C L E I N F O

Keywords:
Frailty assessment
Fatigue
Tiredness
Aged
Frail elderly

A B S T R A C T

Purpose: To identify the different fatigue items in existing frailty scales.
Methods: PubMed, Web of Knowledge and PsycINFO were systematically screened for frailty scales. 133 articles were included, describing 158 frailty scales. Fatigue items were extracted and categorized in 4 fatigue constructs: “mood state related tiredness”, “general feeling of tiredness”, “activity based feeling of tiredness” and “resistance to physical tiredness”.
Results: 120 fatigue items were identified, of which 100 belonged to the construct “general feeling of tiredness” and only 9 to the construct “resistance to physical tiredness”. 49,4% of the frailty scales included at least 1 fatigue item, representing 15 ± 9,3% of all items in these scales. Fatigue items have a significantly higher weight in single domain (dominantly physical frailty scales) versus multi domain frailty scales (21 ± 3.2 versus 10.6 ± 9.8%, p= < 0,05).
Conclusion: Fatigue is prominently represented in frailty scales, covering a great diversity in fatigue constructs and underlying pathophysiological mechanisms by which fatigue relates to frailty. Although fatigue items were more prevalent and had a higher weight in physical frailty scales, the operationalization of fatigue leaned more towards psychological constructs. This review can be used as a reference for choosing a suitable frailty scale depending on the type of fatigue of interest.

* Corresponding author at: Gerontology (GERO) and Frailty in Ageing Research (FRIA) Departments, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090, Brussels, Belgium.

https://doi.org/10.1016/j.arr.2019.100911
Received 12 December 2018; Received in revised form 16 May 2019; Accepted 20 May 2019
Available online 25 May 2019
1568-1637/

1. Introduction

Frailty is highly prevalent in older adults and represents an important risk for disability and other negative health outcomes at higher age (Vermeiren et al., 2016). Researchers generally agree that frailty is a dynamic, biopsychosocial, age-related condition characterized by a decline in homeostatic reserves in multiple physiological systems leading to a decreased resistance to stressors and an increased risk of adverse health outcomes (Fried et al., 2001; Gobbens et al., 2010a). Research on early stages of frailty is crucial as it is believed to be reversible at this stage. Fatigue is a central component in most frailty concepts. However, in contrast to other frailty characteristics such as sedentarity, muscle weakness and gait speed, fatigue seems to be non-responsive to treatments designed to combat frailty (Bendayan et al., 2014; Bibas et al., 2014; Cesari et al., 2015; Pahor et al., 2014; Puts et al., 2017). This might be due to the differences in how fatigue is operationalized in the large diversity of frailty scales.

Fatigue is defined by the Diagnostic and Statistical Manual of Mental Disorders-5th Edition as a state usually associated with a weakening or depletion of one's physical and/or mental resources, ranging from a general state of lethargy to a specific, work-induced burning sensation within one's muscles. Despite the existence of this definition, fatigue remains complex due to the multidimensional character and the co-existence of different underlying mechanisms (Hardy and A, 2010). Fatigue and the lack of energy are conceptually related to vitality, fatigue is thereby captured by low vitality status (O' Connor and Puetz, 2005). The different corresponding domains of fatigue may represent diverse symptoms and underlying causes. Broadly speaking, fatigue can be divided into self-perceived feeling of fatigue (including sleep problems, depressive feelings, tiredness and performance-based feeling of tiredness) and resistance to physical tiredness which include a fatigue assessment such as muscle fatigue. Theou et al. (2008) showed in an explorative study that muscle fatigue and frailty share the same biomedical determinants (ea. aging, disease, inflammation, physical inactivity, malnutrition, hormonal deficiencies, subjective fatigue and neuromuscular function and structure) leading to an enlarged risk for negative health outcomes. This is supported by a cross-sectional study in Italy showing that fatigued older adults aged 65 and over have an increased risk for reduced mobility, instrumental activities of daily living and physical mobility compared to their counterparts (Vestergaard et al., 2009). Furthermore, older adults who experience tiredness in daily activities measured by the Lower Limb-T fatigue Scale have a 1.7-fold greater risk for the onset of disability (Avlund et al., 2002; Avlund et al., 2003). These studies suggest that fatigue is an important early characteristic for the onset of frailty reflecting the depletion of physiological reserve capacity leading to fatigue and frailty. More insight in how fatigue is operationalized allows more understanding in the concept of frailty.

Because of the common biomedical determinants for muscle fatigue and frailty and because of the established relationship of fatigue with the core elements of frailty, fatigue could be an important clinical feature in the early stages of frailty. However, the complexity and the multidimensional character of fatigue makes the relationship with frailty unclear. Therefore, this study aims to give an overview of the different fatigue items that are used in the existing frailty scales. To the best of our knowledge, this is the first time that fatigue items of the existing frailty scales are identified and assigned into different fatigue constructs to have a better understanding of their relationship and the underlying mechanism.

2. Methodology

2.1. Literature search

The databases PubMed, Web of Knowledge and PsychINFO were screened (last search on September 30th, 2018) using the following combination of keywords: ("Aged" [Mesh] OR "Frail Elderly" [Mesh] OR "Aged, 80 and over" [Mesh]) AND Frailty AND ("Diagnosis" [Mesh] OR "Risk Assessment" [Mesh] OR "Classification" [Mesh]) for PubMed, (Topic = Aged OR Frail Elderly OR Ages, 80 and over) AND (Topic = Frailty) AND (Topic = Diagnosis OR Risk Assessment OR Classification) for Web of Knowledge and (Aged OR elderly OR (aged 80 and over)) AND (frailty)AND (diagnosis OR (Risk assessment) OR Classification) for PsychINFO.

Studies were included if they met the following criteria:

2.1.1. Inclusion criteria

- Studies involving subjects who were 65 year or older (This was operationalized by verifying whether subjects who were 65 year or older did participate in the study. When only the mean age of the participants was reported, articles were included when the upper limit of the 95% confidence interval for age (calculated as mean age + 1.96 × standard deviation) was 65 years or older).
- Articles describing the development of frailty scales or clinimetric properties of an original and modified instrument.
- Articles written in English, Dutch, French or German.

2.1.2. Exclusion criteria

- Articles describing the determinants of frailty, incidence of frailty, or outcomes of frailty
- Letters to editors, comments to other articles, reviews and systematic reviews

Inclusion and exclusion criteria were applied independently by two reviewers. Disagreement was resolved by discussion and consensus method. The systematic literature search ended in September 2018, a total number of 5838 articles were found. According to the in- and exclusion criteria and a first screening, 3209 potential articles were found in the electronic databases; i.e. 1640 in PubMed, 1526 in Web of Knowledge and 43 in Psych info were selected for further analysis. In total 577 articles were screened for full text. A total of 54 duplicates were removed. A detailed overview can be found in Fig. 1.

2.2. Identification of frailty scales

For data analysis, frailty scales were divided into 2 categories: multi domain and single domain frailty scales. The multi domain scales focus

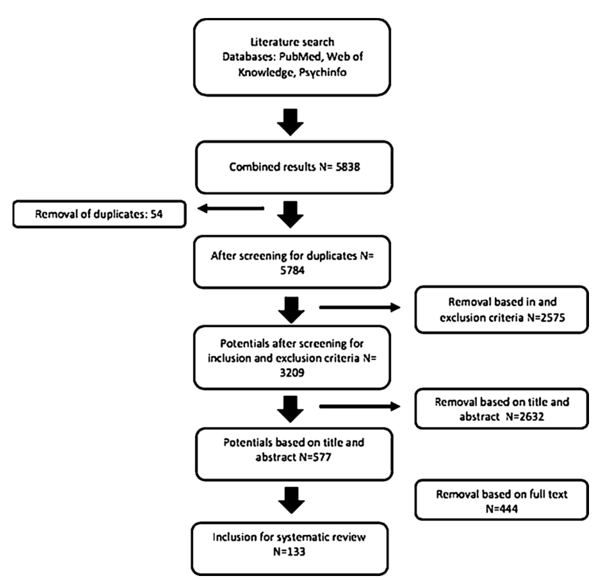

Fig. 1. Flow chart.

on a broad concept of frailty and include losses in the medical, psychological, cognitive, functional and social domains. In this concept, the multi domain deficit accumulation approach is a common used method based on a mathematical representation of accumulating deficits in an individual (Rockwood et al., 2005). On the other hand, the single domain scales solely focus on one frailty domain such as social frailty, cognitive frailty, biomarkers or physical frailty. The physical phenotype model proposed by Fried et al. (2001) is one of these single domain frailty scales. According to the physical phenotype model frailty is determined solely by a combination of 5 physical components: unintentional weight loss, exhaustion, weak grip strength, decreased gait speed and low physical activity. A detailed overview of the included frailty scales can be found in supplementary Table 1 + 2.

2.3. Identifying fatigue items in frailty scales

For the purpose of this review, all items regarding fatigue were extracted from the frailty scales. Items were extracted when (1) items referring to clinical expression/signs of fatigue or items that were assigned directly to fatigue by the authors of the frailty scale, and (2) items corresponding to reduced vitality (see Table 1 + 2). Clinical expressions of fatigue include self-reported tiredness or clinical signs of fatigue such as being out of breath after an activity. Vitality is defined as one's conscious experience of possessing energy and aliveness (Ryan and Frederick, 1997) and refers to variables that influence energy variations (and thus considered as an expression of fatigue). Items covering pathophysiological factors associated to fatigue were not included in this analysis.

Conceptually, fatigue items were divided into the construct of self-perceived fatigue and the construct of resistance to physical tiredness. Self-perceived fatigue was further subdivided into subcategories related to the domains "mood state related tiredness", "general feeling of tiredness" and "activity based feeling of tiredness". These constructs of fatigue capture initial dysregulation across multiple physiological and biological systems. The construct "mood state related tiredness" was included because of the coexistence and interrelation between physiological manifestations and fatigue (Avlund, 2010; Brown et al., 2017; Watt et al., 2000). Resistance to physical tiredness consists of physical tests to measure the level of fatigability. Muscle fatigability is the ability to produce sustained muscle force during an exercise and can help to discriminate robust older adults from those with a higher degree of frailty (De Dobbeleer et al., 2018; Kent-Braun et al., 2012). Because some authors related physical performance tests directly to fatigue (García-García et al., 2014), we included physical performance tests that measure the aerobic capacity by a repetitive muscle contraction in this analysis. Items that were labelled in the included articles as measures for fatigue, which did not correspond to the former domains, were categorized as "other fatigue items". If a frailty scale contained several fatigue items, they were separately assigned to the best fitting construct.

The weight of the fatigue items in relationship with the frailty scales (i.e. total score when relevant) was calculated, and when available the rationale to include the fatigue item(s) in the frailty scale was retrieved (Appendix). The weight calculation was expressed as a percentage of the total number of fatigue items divided by the total number of items For example, the 70-item Frailty Index (Rockwood et al., 2007a) contains 1 fatigue items, the weight was calculated as: 1/70 *100 = 1.5%. Next, frailty scales were checked if they contained a physical construct, a physical construct was defined as the presence of physical deficits such as; muscle weakness, physical activity, physical performance, endurance, balance or mobility (Studenski et al., 2004). At last, a distinction between fatigue instruments used in the frailty scales has been made. In case insufficient information was available in the article to assign fatigue items to the corresponding categories, the corresponding author was contacted to obtain detailed information.

2.4. Data analysis

The statistical package of SPSS (version 25.0) was used to analyze the relationship between the presence of fatigue items in multi domain and single domain frailty scales using the Chi Square test of independence. An independent T-test was used to determine whether there is a statistically significant difference between the number of fatigue items and the weight of the fatigue items between single and multi domain frailty scales.

3. Results

The literature search generated 133 articles that were included in this systematic review, reporting on 160 different frailty scales. Two frailty scales: 38-Burden model/ Health and retirement Study HRS (Cigolle et al., 2009) and the 43- item Frailty index (Lucicesare et al., 2010) were not specified in the articles and despite contact with the corresponding authors insufficient information was available to include them in this analysis. Out of the 158 remaining scales, there are 105 multi-domain frailty scales and 53 single domain scales (including 3 scales that are based on biomarkers, 1 social frailty scale and 49 physical frailty scales, see Appendix A).

In total 49,4% (n = 78 out of 158) of the frailty scales included at least 1 item related to fatigue, where single domain scales included significantly more often fatigue in the frailty operationalization compared to the multi domain frailty scales (n = 37, 69,8% versus n = 41, 39%, p= < 0.05, Chi square = 14,8). Noteworthy, in the 78 frailty scales that contain a component of fatigue, 120 fatigue items were identified (56 in the multi domain and 64 in the single domain frailty scales). No significant differences were found in the number of fatigue items between multi and single domain frailty scales (1.43 ± 0.5 versus 1.61 ± 0.7, p = 0.30).

Overall most fatigue items found in the frailty scales were clinical expressions of fatigue (n = 104, 86,7% of all extracted items) as can be seen in Table 1 followed by reduced vitality in Table 2(n = 16, 13,3% of all extracted items).

Within the clinical expressions of fatigue and reduced vitality items (Table 1 +2), the construct "general feeling of tiredness" was most prevalent (n = 100, 83,3% of all items) in both the multi domain (Clinical expressions of fatigue n = 40, vitality items N = 4) and single domain frailty scales (Clinical expressions of fatigue n = 45, vitality items n = 11).

While 7 (Chan et al., 2010; Clark et al., 2017; García-García et al., 2014; Rockwood et al., 2005; Rothman et al., 2008; Villareal et al., 2004; Woo et al., 2012) multi domain scales have items that cover more than one type of fatigue (e.g. clinical expressions of fatigue combined with reduced vitality items), this number is lower in the single domain scales where mainly clinical expressions of fatigue were included. Concerning, the single domain scales, there was only one frailty scale that included clinical signs of fatigue combined with reduced vitality (Woods et al., 2005).

As can be seen in Table 1, two multi domain scales (Hogan et al., 2012; Hubbard et al., 2010), and two single domain scales (Hogan et al., 2012; Kristjansson et al., 2012) contained other items that were reported by the authors as ''fatigue'' items, whereas it is questionable whether these are appropriate to evaluate fatigue. In fact, some of these scales consider fatigue based on either the answers of "feeling weak" on the European Organization for the Research and Treatment of Cancer quality of life questionnaire in the Modified Phenotype of frailty (Kristjansson et al., 2012) or the same question on top of the two items of the Center for Epidemiologic Studies Depression Scale (CES-D) (Hogan et al., 2012), while in the Chinese cohort the performance of "Daily walks for exercise" (Woo et al., 2012) is used to measure fatigue.

On average the fatigue components represent overall 15 ± 9.3% of all items in the frailty scales, which have a significantly higher weight in the single domain compared to the multi domain scales (21 ± 3.2

Table 1
Overview of clinical expressions of fatigue used in the frailty scales.

	Self-perceived fatigue items			Resistance to physical tiredness	Other fatigue items
	Mood state related fatigue	**General feeling of tiredness**	**Activity based feeling of tiredness**		
Multi domain frailty instruments N = 105	**N = 3** **-"Feeling exhausted for no reason" N = 1** (Fukutomi et al., 2013) **"Exhausted N = 2** (Di Bari et al., 2014; Goldstein et al., 2015)	**N = 40** **"Feeling tired" N = 10** (Blodgett et al., 2015; de Vries et al., 2013; Guler et al., 2017; Reid et al., 2018; Rockwood et al., 2015; Rockwood et al., 2006; Rockwood et al., 2005; Subra et al., 2012; Tocchi et al., 2014) **"I felt that everything I did was an effort"** ***(item extracted from the CES-D)*** **N = 11** (Abete et al., 2017; Afilalo et al., 2017; Castrejón-Pérez et al., 2018; de Vries et al., 2013; García-García et al., 2014; Jokar et al., 2016; Joseph et al., 2014; Rothman et al., 2008; Searle et al., 2008; Yeoh et al., 2017) **"Could not get going"** ***(item extracted from the CES-D)*** **N = 6** (Abete et al., 2017; Afilalo et al., 2017; de Vries et al., 2013; Rothman et al., 2008; Searle et al., 2008; Yeoh et al., 2017) **"Feeling fatigued" N = 3** (Hubbard et al., 2015; Kulminski et al., 2008; Lekan et al., 2017) **"No energy" N = 2** (Hubbard et al., 2010; Woo et al., 2012) **"Tired for no reason"** ***(item extracted from SF-36)*** **N = 2** (Dent et al., 2017; Swiecicka et al., 2017) **"Everything cost effort"** ***(item extracted from the K10)*** **N = 1** (Dent et al., 2017) **"Physical tiredness" N = 1** (Gobbens et al., 2010b) **"Tired"** ***(item extracted from PHQ-9)*** **N = 1** (Kaehr et al., 2015) **"Worn out" N = 1** (Reid et al., 2018) **-"Feeling slowed down" N = 2** (Chan et al., 2010; Rockwood et al., 2005)	**N = 2** **"Out of breath during normal activities" N = 2** (Geessink et al., 2017; van Kempen et al., 2015)	**N = 4** **Low energy and low endurance measured by 30 seconds chair stand test N = 1** (García-García et al., 2014) **Low energy and low endurance measured by 5 times sit to stand test N = 3** (Afilalo et al., 2017; Carrière et al., 2005; Villareal et al., 2004)	**N = 2** **"Fatigue: Can't complete day-to-day activities" N = 1** (Hogan et al., 2012) **"Exhaustion measured by performance of daily walks" N = 1** (Hubbard et al., 2010)
Single domain frailty instruments N = 53		**N = 45** **"Tired" N = 2** (Hogan et al., 2012; Rockwood et al., 2007b) **"I felt that everything I did was an effort"** ***(item extracted from the CES-D)*** **N = 16** (Ávila-Funes et al., 2009; Buchman et al., 2011; Cigolle et al., 2009; Fried et al., 2001; Furtado et al., 2017; Graham et al., 2009; Joseph et al., 2014; Kiely et al., 2009; Ma et al., 2018; Martín-Sánchez et al., 2017; Nadruz et al., 2016; Nunes et al., 2015; Op Het Veld et al., 2017; Pao et al., 2018; Purser et al., 2006; Savva et al., 2013) **"Could not get going"** ***(item extracted from the CES-D*** **N = 16** (Ávila-Funes et al., 2009; Buchman et al., 2011; Cigolle et al., 2009; Fried et al., 2001; Furtado et al., 2017; Graham et al., 2009; Joseph et al., 2014; Kiely et al., 2009; Ma et al., 2018; Martín-Sánchez et al., 2017; Nadruz et al., 2016; Nunes et al., 2015; Op Het Veld et al., 2017; Pao et al., 2018; Purser et al.,	**N = 2** **"No energy for normal activities" N = 1**(Romero-Ortuno et al., 2010) **"Too tired for normal activities"** ***(item extracted from the BDI)*** **N = 1** (O' Connell et al., 2013)	**N = 4** **Low energy and low endurance measured by 5 times sit to stand test N = 2** (Brown et al., 2000; Lai et al., 2017) **Upper extremity exhaustion N = 1** (Toosizadeh et al., 2016) **Low energy and low endurance measured by 30 seconds chair stand test N = 1** (Chang et al., 2014)	**N = 2** **"weak"** ***(item extracted from*** **EORTC QLQ-C30) N = 1** (Kristjansson et al., 2012) **"Weak" N = 1** (Hogan et al., 2012)

(*continued on next page*)

Table 1 (*continued*)

	Self-perceived fatigue items	Resistance to physical tiredness	Other fatigue items
	2006; Savva et al., 2013) **"Tired"** ***(item extracted from the*** **EORTC QLQ-C3) N = 1** (Kristjansson et al., 2012; Lee et al., 2017) **"Tired"** ***(item extracted from the SF-36)*** **N = 3** (Clark et al., 2017; Lee et al., 2017; Woods et al., 2005; Zaslavsky et al., 2017) **"Low energy" N = 3** (Hogan et al., 2012; Kamdem et al., 2017; Woo et al., 2012) **"Low energy"** ***(item extracted from the BDI)*** **N = 1** (O' Connell et al., 2013) **"Distressed by feeling low in energy or slowed down"** ***(item extracted from the Hopkins)*** **N = 1** (Gruenewald and Seeman, 2009) **"Feeling worn out"** ***(item extracted from the SF-36)*** **N = 2** (Clark et al., 2017; Woods et al., 2005)		

N:number; EORTC QLQ-C3: European Organization for the Research and Treatment of Cancer quality of life questionnaire; CES-D: Center for Epidemiologic Studies Depression Scale; GDS: Geriatric Depression Scale; BDI: Beck Depression Inventory; SF-36: 36-item Short Form Health; K10: Kessler Psychological Distress Scale; PHQ-9: Patient Health Questionnaire 9; CST: Chair Stand Test

Table 2
Overview of reduced vitality items used in the frailty scales.

	Self-perceived fatigue items			Resistance to physical tiredness	Other fatigue items
	Mood state related fatigue	**General feeling of tiredness**	**Activity based feeling of tiredness**		
Multi domain frailty instruments N = 105		**N = 4** **"Energetic" N = 1** (Rockwood et al., 2005) **"Feeling fit" N = 2** (Chan et al., 2010; Rockwood et al., 2005) **"Feel full energy"** ***(item extracted from GDS)*** **N = 1** (Solfrizzi et al., 2017)		**N = 1** **Peak Aerobic Power (VO2peak) N = 1** (Villareal et al., 2004)	
Single domain frailty instruments N = 53		**N = 11** **"feeling full of pep"** ***(item extracted from the SF-36)*** **N = 2** (Clark et al., 2017; Woods et al., 2005) "feeling full of pep" *(item extracted from the Vitality scale)* **N = 1** (Lee et al., 2017) "Feeling full of energy" *(items extracted from the Vitality scale)* N = 1 (Lee et al., 2017) **"Full of energy"** ***(item extracted from the GDS)*** **N = 3** (Ensrud et al., 2007; Ensrud et al., 2009; Forti et al., 2012) **"Feeling full of energy"** ***(item extracted from the SF-36)*** **N = 3** (Clark et al., 2017; Sirola et al., 2011; Woods et al., 2005) "Full of energy" *(item extracted from the 12-SF)* **N = 1** (Ribeiro et al., 2017)			

N:number; GDS: Geriatric Depression Scale; SF-36: 36-item Short Form Health; 12-item SF: 12 item Short-Form Health Survey

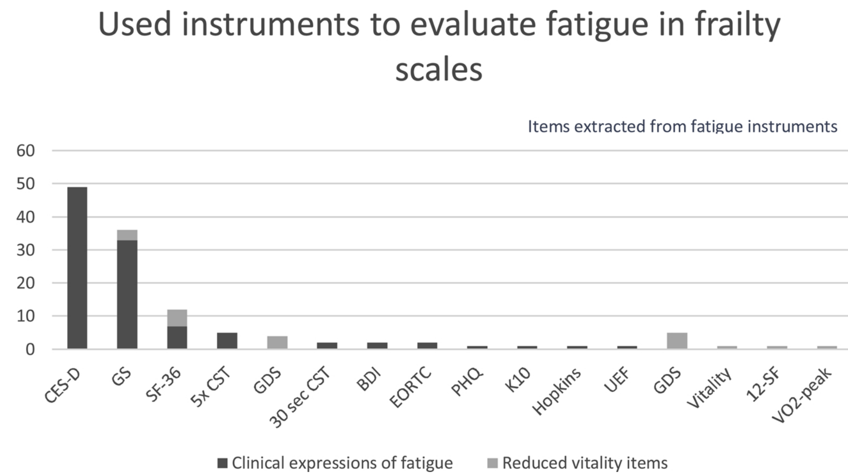

Fig. 2. Represents all fatigue items that have been extracted from different fatigue instruments in the frailty scales, a distinction has been made between clinical signs of fatigue (dark grey), and vitality items (light grey).

versus 10.6 ± 9.8%, p= < 0.05).

A great diversity of instruments has been used to evaluate fatigue in the frailty scales (Fig. 2). Most of the multi domain frailty scales did not include a validated instrument to measure fatigue but used a generic question (n = 29). The two questions extracted from the CES-D "I felt that everything I did was an effort" and "I could not get going" were used 32 times in the single domain and 17 times in the multi domain scales. These two items extracted from the CES-D were mostly (n = 49, 40,5% of all items) used to measure clinical expressions of fatigue and could not be found within the reduced vitality items. The item "Do you feel full of energy" extracted from the GDS was used once (Solfrizzi et al., 2017) in the multi domain frailty scales, while this item was used three times (Ensrud et al., 2007; Ensrud et al., 2009; Forti et al., 2012) to evaluate reduced vitality in the single domain frailty scales (Table 2).

Thirty-two single domain scales included the original and modified versions of the physical frailty phenotype based on the CHS as originally described by Fried et al. (2001). Exhaustion is one of the five components in this frailty phenotype (Fried et al., 2001) and is measured by using two questions of the CES-D. Interestingly, only 50% (n = 16) of these versions includes these specific CES-D questions while others (Clark et al., 2017; Lee et al., 2017; Sirola et al., 2011; Woods et al., 2005; Zaslavsky et al., 2017) use the questions "reporting low energy most or all of the time during the preceding 4 weeks", "did you feel full of pep?", "did you have a lot of energy?", "did you feel worn out?", and "did you feel tired?" which are derived from the 36-Item Short Form Survey Instrument (SF-36). The remaining instruments use the Beck Depression Inventory (Swiecicka et al., 2017) or the the 12-Item Short-Form Health Survey (Ribeiro et al., 2017) to evaluate fatigue.

Within all frailty scales, 9 performance based tests; e.g. 30 seconds chair stand test (n = 2) (Chang et al., 2014; García-García et al., 2014), 5 times sit to stand test (N = 5) (Afilalo et al., 2017; Brown et al., 2000; Carrière et al., 2005; Lai et al., 2017; Villareal et al., 2004), upper extremity exhaustion (N = 1) (Toosizadeh et al., 2016) and Peak Aerobic Power VO2Peak (n = 1) (Villareal et al., 2004) were used to measure "resistance to physical tiredness".

The rationale behind including fatigue as a predictor of frailty in the frailty scales remains unclear, since only a few authors have reported this information. The physical frailty phenotype contains five items based on the risk for negative outcomes in a 3 years prospective observational cohort (n = 5888) and the authors hypothesized that self-reported exhaustion is an indicator for energy expenditure (Fried et al., 2001). Energy expenditure is considered to play a key role in the cycle of frailty and is affected by physical performance and the resting metabolic rate. The Frailty Index approach selected deficits that are associated with health, generally increase with age and cover a range of systems (Searle et al., 2008). A number of instruments included fatigue as it is one of the items that has established predictive validity for disability, mortality (Di Bari et al., 2014; Villareal et al., 2004) and other negative health outcomes (van Kempen et al., 2015). The Frailty Index for Elders included tiredness based on evidence that shows that fatigue contributes to the development of frailty (Searle et al., 2008; Tocchi et al., 2014). Other authors stated that the inclusion of fatigue in the frailty scale was based on the experience and/or experts' opinions (de Vries et al., 2013; Lekan et al., 2017; Martín-Sánchez et al., 2017).

Within the 105 multi domain scales, 39 frailty instruments are based on a deficit accumulation model developed by Rockwood et al. (1999). In total, 15 (38,4%) of these frailty scales contained no fatigue items. In the others, clinical expression of fatigue items were most prevalent, and these items were divided in the constructs "general feeling of tiredness "(n = 16) and "mood state related tiredness" (n = 3).

As a final point, it has been noted that frailty scales which do not include any fatigue item also not contained a physical component (appendix A). This number is high in the multi domain frailty scales, of which 44 of the 64 (68,8%) multi domain scales did not contain a physical component and thereby did not include any fatigue item. In addition, out of the multi domain scales who did include fatigue items (n = 41) there were only 6 scales who did not contain a physical construct. In contrast, almost all single domain frailty scales (except of 6) included a physical construct.

4. Discussion

This systematic review shows that 49,4% of the 158 frailty scales retrieved in the literature include at least 1 element related to fatigue, representing 15 ± 9.3 of all items in these frailty scales. One hundred and twenty fatigue items were identified covering four different fatigue constructs. All fatigue items were divided into clinical signs of fatigue and items corresponding to reduced vitality. Clinical expressions of fatigue were most prevalent in the frailty scales (n = 104, 86,7% of all items), followed by reduced vitality items (n = 16, 13,3% of all items). This suggests that fatigue is an important clinical feature that is connected to the identification of frail older adults. There is a great diversity in fatigue constructs assessed in the currently available frailty scales, most items (n = 100) corresponded to the construct "general feeling of tiredness". The diversity and extent of the different fatigue items leads to ambiguity regarding fatigue operationalization. There is no uniformity in fatigue operationalization, and the 158 frailty scales comprise 37 unique fatigue items. Because of the heterogeneity, comparison of the scores on these fatigue items in function of their underlying construct is challenging.

Insight in underlying mechanisms of fatigue in frail elderly, and fatigue operationalization in the frailty scales according to these mechanisms hold the promise of better interventions to counter fatigue and eventually frailty. First, the lack of physical activity, the decline in mitochondrial function and sarcopenia contribute to muscle fatigue, which can be defined as the force that a person can maintain during an activity (Kent-Braun et al., 2002). Since daily activities require sustained intense muscle contractions these may be more challenging given the reduced muscle strength and could lead to tiredness. Second, fatigue may be influenced by several biological changes. A reduction in motor unit recruitment and changes in the contractile properties of the muscle results in a decline of physical and mental efficiency during exercises (Alexander et al., 2010; Allman and Rice, 2002; Eldadah, 2010). Also, cardiovascular impairment and the presence of peripheral arterial stiffness is associated with self-perceived fatigue and supports the explanation for feeling tired during physical activities in older adults (Gonzales et al., 2015). Additionally, changes in energy expenditure may cause fatigue, whereas older adults lower their physical activity to a range where the perceived fatigue is sustainable. In contrast, sedentary behaviour stimulates biopsychosocial processes that increase the feeling of fatigue (Avlund, 2010). Research also showed that protein intake has the potential to decrease muscle fatigue by creating more muscle mass, strength and functionality (Theou et al., 2008). Finally, an important process associated to the pathogenesis of fatigue and frailty is inflammation. Aging is accompanied with a chronic inflammatory profile, also known as inflammaging. Chronic inflammation is a key mechanism that contributes direct and indirect trough other pathophysiologic processes (Beyer et al., 2012). It has been shown that inflammation persuades sickness behaviour with fatigue as one of the symptoms (Dantzer and Kelley, 2007). This inflammatory profile, immune activation, decline in musculoskeletal and endocrine systems can lead to physical limitations and enhance fatigue and frailty (Bautmans et al., 2008; Cao Dinh et al., 2018; Goodpaster et al., 2006; Leng et al., 2002; Walston, 2002). There are numerous pathophysiological factors associated with fatigue, however for this article the authors focused only on clinical signs of fatigue and did not include pathophysiological underlying mechanism of fatigue. Fatigue is often present in chronic illness and has a multidimensional character with different causes and implications (Addington et al., 2001). Sleep problems could be seen as a clinical sign of fatigue as some of the features overlap (Shen et al., 2006). Research has shown that older adults who report sleep problems have a higher fold to feel fatigued than their counterparts (Avlund, 2010; Chervin, 2000; Goldman et al., 2008). In addition, a large Italian study shows that fatigued older adults who have sleep problems score higher on the CES-D (Vestergaard et al., 2009). Despite the coexistence and interrelation of these symptoms, sleep problems can be considered more as a pathophysiological pathway leading to fatigue and was thereby not considered as a clinical sign of fatigue in this review.

The sensation of fatigue may characterize frailty by reflecting depletion of physiological reserve capacities beyond a certain threshold leading to an enlarged risk for negative health outcomes. The operationalization of fatigue brings benefits to the understanding of frailty, among others since fatigue is a long-term risk for limitations in instrumental activities of daily living (ADL) and physical performance (Avlund et al., 2004; Avlund et al., 2003; Eldadah, 2010; Mueller-Schotte et al., 2016). Consequently, since it has been documented that fatigue is a risk factor for many negative health outcomes, the presence in frailty scales is not surprising.

Mood state related tiredness, is not a one-dimensional construct nor synonym for fatigue. Of note, it is one of the least present construct of fatigue in the analyzed frailty scales. However, it has been shown that robust older adults with altered mood have an increased risk to become frail compared to their robust counterparts (Buigues et al., 2015; Fried et al., 2001). In addition, frail older adults who are fatigued experience often mood related symptoms (Ní Mhaoláin et al., 2012; Watt et al., 2000), another cross-sectional study with 1803 older subjects shows that the presence of muscle fatigability was associated with altered mood states (Brown et al., 2017). There is an important but complex relationship between fatigue and mood related symptoms; they coexist and are bi-directionally associated. The appearance of symptoms of fatigue can affect mental and behavioural manifestations as feeling sad, feeling depressed, feeling blue and less joy in life (Avlund, 2010). Despite the existence of these psychological symptoms, self-perceived fatigue does not always correspond directly to psychological manifestations. Because of this complex relationship, it is uncertain whether physiological symptoms are either a cause, a symptom, or a contribution to fatigue (Katz, 2004; Stadje et al., 2016). To avoid ambiguity, we decided not to include psychological symptoms and altered mood as these were not directly intended to measure fatigue.

However, this approach might have led to an underestimation of the importance of fatigue in the analyzed frailty scales. Notwithstanding fatigue is one of the symptoms that is often assessed in depression scales (Haringsma et al., 2004; Olsen et al., 2003; Radloff, 1991; Yesavage et al., 1982), frailty scales containing the full GDS (Yesavage et al., 1982) and the CES-D (Kohout et al., 1993) were not included in our analysis. The GDS and CES-D are primarily used to screen for depressive symptoms, however they provide an overall score reflecting different domains among which fatigue. While isolated items of the GDS *"Do you feel full of energy"* and the CES-D *"I felt that everything I did was an effort"* and *"I could not get going"* were used frequently as separate fatigue items in the frailty scales, the total scores on these instruments were not included as fatigue items in our analysis since these might represent more the depressive symptoms rather than fatigue per se. On the other hand, not including the full depression scales in which the fatigue items are embedded might have induced an underestimation of the prevalence of fatigue items in the frailty instruments. If these depression scales were included in our analysis, the percentage of frailty scales that include at least one fatigue item would have been 53% instead of 49%.

The observation that "mood state related fatigue" items were only found in the multi domain frailty scales is explained by the fact that multi domain scales are mostly based on accumulation of health deficits. This is in line with the absence of items reflecting on mood state related fatigue in the single domain scales. Unfortunately, these authors did not provide a rationale for this choice.

General feeling of tiredness is the most used construct (100 identified items in the analyzed frailty scales) operationalized by 24 unique items such as "feeling tired", "feeling fatigued", "having no energy" or "could not get going". On the other hand, not many items concerning activity based feeling of tiredness have been retrieved in the frailty scales. Regarding to the 64 multi domain frailty scales that did not contain any fatigue item, 17 were deficit accumulation models. Lacking fatigue in these scales might be due to the fact that the presence of a physical component was relatively low. In fact, 44 of the 64 multi domain scales did not contain a physical component, of which 17 were based on a deficit model approach. In contrast, all single domain instruments contained a physical component and showed significant more fatigue items, with the exception for the social frailty index (Makizako et al., 2015), and the frailty scales that only focuses on biomarkers (Forcillo et al., 2017; Howlett et al., 2014; Klausen et al., 2017).

Although the presence of fatigue in frailty scales seems to be related to a physical construct, the way how fatigue is assessed leans more towards a psychological operationalization. Fatigue is often assessed trough psychological manifestations (e.g. feeling exhausted, effort to undertake anything, feeling worn out). These psychological manifestations are more related to a psychological construct rather than a physical construct. The contrast of operationalization between psychological clinical signs and physical clinical signs could explain the diversity and heterogeneity of the operationalization of fatigue. However, it has been shown previously that muscle fatigue and self-reported fatigue are interrelated and provide complementary information about fatigue in older adults (Bautmans et al., 2007; Bautmans et al., 2010; Hortobágyi et al., 2003). Remarkably, only 9 frailty instruments used performance-based tests to measure the level of fatigue. In the past few years there has been a shift towards more physical performance tests in the screening for frailty (Kleczynski et al., 2017): cut-off values have been proposed for the Short Physical Performance Battery (Chang et al., 2014), Timed up and Go (Savva et al., 2013), 5 meter walk test (Forcillo et al., 2017) and the hand grip strength test (Campo et al., 2017). However, none of the frailty tools reported in the literature include a direct assessment of muscle fatigue. This is surprising because it has been shown that muscle fatigue occurs before the onset of muscle weakness in a mouse model of premature aging (Yamada et al., 2012). This implies that muscle fatigue is an important early marker as it gives the possibility to sustain a certain level of performance in daily activities (Kent-Braun et al., 2002). Recently, it has been shown that muscle fatigue can help to discriminate robust older adults from those with a higher degree of frailty (De Dobbeleer et al., 2018).

In total there were four items covering items that were reported by the authors as “other fatigue items”, for which it is questionable whether these are appropriate to evaluate fatigue. For example Hogan et al. (2012) and Kristjansson et al. (2012) consider fatigue based on the answers of “feeling weak”, which corresponds more to the item “weakness” that is present in many frailty scales. On the other hand, these items reflect a physical manifestation of frailty which the authors link to fatigue.

This study has some strengths and limitations. First of all, the lack of a consensus and/or gold standard for fatigue operationalization implied that the authors used a framework based on literature and the extracted fatigue items. It cannot be excluded that items related to fatigue might have been missed. Secondly, some frailty scales might not be included in this review given the fact that we focused only on scales for adults aged 65 years and older. The strength of this study is the systematic inventarization of fatigue items in the existing frailty scales and their underlying constructs. This review can be used by clinicians or researchers as a reference for the choice of a suitable frailty scale depending on the type of fatigue of interest.

5. Conclusion

Our review shows that 49% of the frailty scales include fatigue as one of the characteristics of frailty, representing 15% of all items in these frailty scales. Therefore, we can conclude that fatigue is prominently represented in frailty scales. However, a heterogeneous array of 37 unique items covering a great diversity in fatigue constructs were found in the frailty scales, leading towards ambiguity regarding the operationalization of fatigue. Most fatigue items found in the frailty scales were clinical expressions of fatigue, while reduced vitality items were underrepresented. The presence of fatigue in frailty scales seems to be related to a physical construct, however the way how fatigue is assessed leans more towards a psychological operationalization. Because of the heterogeneity of the fatigue items, the link with the underlying pathophysiological mechanisms by which fatigue relates to frailty differs between frailty scales. Better understanding of how fatigue is operationalized in frailty scales can improve the identification of fatigue and can help to develop more effective interventions to combat fatigue in frail older persons. As a final point, this review can be used by clinicians or researchers as a reference for the choice of a suitable frailty scale depending on the type of fatigue of interest.

Declarations of interest

This study was partly funded by an “Interdisciplinary Research Program” grant (number IRP3) from the research council of the Vrije Universiteit Brussel (VUB).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100911.

References

Abete, P., Basile, C., Bulli, G., Curcio, F., Liguori, I., Della-Morte, D., Gargiulo, G., Langellotto, A., Testa, G., Galizia, G., Bonaduce, D., Cacciatore, F., 2017. The Italian version of the “frailty index” based on deficits in health: a validation study. Aging Clinical and Experimental Research 29, 913–926.

Addington, A.M., Gallo, J.J., Ford, D.E., Eaton, W.W., 2001. Epidemiology of unexplained fatigue and major depression in the community: the Baltimore ECA follow-up, 1981-1994. Psychol Med 31, 1037–1044.

Afilalo, J., Lauck, S., Kim, D.H., Lefèvre, T., Piazza, N., Lachapelle, K., Martucci, G., Lamy, A., Labinaz, M., Peterson, M.D., Arora, R.C., Noiseux, N., Rassi, A., Palacios, I.F., Généreux, P., Lindman, B.R., Asgar, A.W., Kim, C.A., Trnkus, A., Morais, J.A., Langlois, Y., Rudski, L.G., Morin, J.F., Popma, J.J., Webb, J.G., Perrault, L.P., 2017. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. Journal of the American College of Cardiology 70, 689–700.

Alexander, N.B., Taffet, Ã.G.E., Horne, M., Eldadah, B.A., Ferrucci, L., Nayfield, S., Studenski, S., Ãã, M.P.H., 2010. Bedside-to-Bench Conference : Research Agenda for Idiopathic. pp. 967–975.

Allman, B.L., Rice, C.L., 2002. Neuromuscular fatigue and aging: Central and peripheral factors. Muscle and Nerve 25, 785–796.

Ávila-Funes, J.A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., Carrière, I., Tavernier, B., Tzourio, C., Gutiérrez-Robledo, L.M., Dartigues, J.F., 2009. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The three-city study. Journal of the American Geriatrics Society 57, 453–461.

Avlund, K., 2010. Fatigue in older adults: an early indicator of the aging process? Aging Clin Exp Res 22, 100–115.

Avlund, K., Damsgaard, M.T., Sakari-Rantala, R., Laukkanen, P., Schroll, M., 2002. Tiredness in daily activities among nondisabled old people as determinant of onset of disability. Journal of Clinical Epidemiology 55, 965–973.

Avlund, K., Sakari-Rantala, R., Rantanen, T., Pedersen, A.N., Frändin, K., Schroll, M., 2004. Tiredness and onset of walking limitations in older adults. Journal of the American Geriatrics Society 52, 1963–1965.

Avlund, K., Vass, M., Hendriksen, C., 2003. Onset of mobility disability among community-dwelling old men and women. The role of tiredness in daily activities. Age and ageing 32, 579–584.

Bautmans, I., Gorus, E., Njemini, R., Mets, T., 2007. Handgrip performance in relation to self-perceived fatigue, physical functioning and circulating IL-6 in elderly persons without inflammation. BMC geriatrics 7 5-5.

Bautmans, I., Njemini, R., Backer, J.D., Waele, E.D., Mets, T., 2010. Surgery-Induced Inflammation in Relation to Age, Muscle Endurance. and Self-Perceived Fatigue. 65, 266–273.

Bautmans, I., Njemini, R., Predom, H., Lemper, J.-C., Mets, T., 2008. Muscle Endurance in Elderly Nursing Home Residents Is Related to Fatigue Perception, Mobility, and Circulating Tumor Necrosis Factor-Alpha, Interleukin-6, and Heat Shock Protein 70. Journal of the American Geriatrics Society 56, 389–396.

Bendayan, M., Bibas, L., Levi, M., Mullie, L., Forman, D.E., Afilalo, J., 2014. Therapeutic interventions for frail elderly patients: Part II: Ongoing and unpublished randomized trials. Progress in Cardiovascular Diseases 57, 144–151.

Beyer, I., Njemini, R., Bautmans, I., Demanet, C., Bergmann, P., Mets, T., 2012. Inflammation-related muscle weakness and fatigue in geriatric patients. EXG 47, 52–59.

Bibas, L., Levi, M., Bendayan, M., Mullie, L., Forman, D.E., Afilalo, J., 2014. Therapeutic interventions for frail elderly patients: Part I: Published randomized trials. Progress in Cardiovascular Diseases 57, 134–143.

Blodgett, J., Theou, O., Kirkland, S., Andreou, P., Rockwood, K., 2015. The association between sedentary behaviour, moderate-vigorousphysical activity and frailty in NHANES cohorts. Maturitas 80, 187–191.

Brown, M., Sinacore, D.R., Binder, E.F., Kohrt, W.M., 2000. Physical and Performance Measures for the Identification of Mild to Moderate Frailty. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 55, M350–M355.

Brown, P.J., Badreddine, D., Roose, S.P., Rutherford, B., Ayonayon, H.N., Yaffe, K., Simonsick, E.M., Goodpaster, B., 2017. Muscle fatigability and depressive symptoms in later life. International Journal of Geriatric Psychiatry 32, e166–e172.

Buchman, A.S., Leurgans, S.E., Boyle, P.A., Schneider, J.A., Arnold, S.E., Bennett, D.A., 2011. Combinations of motor measures more strongly predict adverse health outcomes in old age: The rush memory and aging project, a community-based cohort study. BMC Medicine 9 42-42.

Buigues, C., Padilla-Sánchez, C., Garrido, J.F., Navarro-Martínez, R., Ruiz-Ros, V., Cauli, O., 2015. The relationship between depression and frailty syndrome: a systematic review. Aging & Mental Health 19, 762–772.

Campo, G., Pavasini, R., Maietti, E., Tonet, E., Cimaglia, P., Scillitani, G., Bugani, G., Serenelli, M., Zaraket, F., Balla, C., Trevisan, F., Biscaglia, S., Sassone, B., Galvani, M., Ferrari, R., Volpato, S., 2017. The frailty in elderly patients receiving cardiac interventional procedures (FRASER) program: rational and design of a multicenter prospective study. Aging Clinical and Experimental Research 29, 895–903.

Cao Dinh, H., Bautmans, I., Beyer, I., Mets, T., Onyema, O.O., Forti, L.N., Renmans, W., Vander Meeren, S., Jochmans, K., Vermeiren, S., Azzopardi, R.V., Njemini, R., Gerontopole Brussels Study, g, 2018. Association between Immunosenescence

Phenotypes and pre-frailty in Older Subjects: Does Cytomegalovirus Play a Role? J Gerontol A Biol Sci Med Sci.
Carrière, I., Colvez, A., Favier, F., Jeandel, C., Blain, H., group, E.s, 2005. Hierarchical components of physical frailty predicted incidence of dependency in a cohort of elderly women. Journal of clinical epidemiology 58, 1180–1187.
Castrejón-Pérez, R.C., Aguilar-Salinas, C.A., Gutiérrez-Robledo, L.M., Cesari, M., Pérez-Zepeda, M.U., 2018. 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 30, 935–941.
Cesari, M., Vellas, B., Hsu, F.C., Newman, A.B., Doss, H., King, A.C., Manini, T.M., Church, T., Gill, T.M., Miller, M.E., Pahor, M., 2015. A physical activity intervention to treat the frailty syndrome in older persons - Results from the LIFE-P study. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 70, 216–222.
Chan, D.C., Tsou, H.H., Chen, C.Y., Chen, C.Y., 2010. Validation of the Chinese-Canadian study of health and aging clinical frailty scale (CSHA-CFS) telephone version. Archives of Gerontology and Geriatrics 50, e74–e80.
Chang, S.F., Yang, R.S., Lin, T.C., Chiu, S.C., Chen, M.L., Lee, H.C., 2014. The Discrimination of using the short physical performance battery to screen frailty for Community-Dwelling elderly people. Journal of Nursing Scholarship 46, 207–215.
Chervin, R.D., 2000. Sleepiness, fatigue, tired, and lack of energy in obstructive sleep apnea. Chest 118, 372–379.
Cigolle, C.T., Ofstedal, M.B., Tian, Z., Blaum, C.S., 2009. Comparing models of frailty: The health and retirement study. Journal of the American Geriatrics Society 57, 830–839.
Clark, D.A., Khan, U., Kiberd, B.A., Turner, C.C., Dixon, A., Landry, D., Moffatt, H.C., Moorhouse, P.A., Tennankore, K.K., 2017. Frailty in end-stage renal disease: comparing patient, caregiver, and clinician perspectives. BMC Nephrology 18, 1–8.
Dantzer, R., Kelley, K.W., 2007. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 21, 153–160.
De Dobbeleer, L., Theou, O., Beyer, I., Jones, G.R., Jakobi, J.M., Bautmans, I., 2018. Martin Vigorimeter assesses muscle fatigability in older adults better than the Jamar Dynamometer. Exp Gerontol 111, 65–70.
de Vries, N.M., Staal, J.B., Olde Rikkert, M.G.M., Nijhuis-van der Sanden, M.W.G., 2013. Evaluative Frailty Index for Physical Activity (EFIP): A Reliable and Valid Instrument to Measure Changes in Level of Frailty. Physical Therapy 93, 551–561.
Dent, E., Dal Grande, E., Price, K., Taylor, A.W., 2017. Frailty and usage of health care systems: Results from the South Australian Monitoring and Surveillance System (SAMSS). Maturitas 104, 36–43.
Di Bari, M., Profili, F., Bandinelli, S., Salvioni, A., Mossello, E., Corridori, C., Razzanelli, M., Di Fiandra, T., Francesconi, P., 2014. 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 62, 1933–1937.
Eldadah, B.A., 2010. Fatigue and Fatigability in Older Adults. PMRJ 2, 406–413.
Ensrud, K., Ewing, S., Taylor, B., Fink, H., Stone, K., Cauley, J., Tracy, J., Hochberg, M., Rodondi, N., Cawthon, P., 2007. Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 62, 744–751.
Ensrud, K.E., Ewing, S.K., Cawthon, P.M., Fink, H.A., Taylor, B.C., Cauley, J.A., Dam, T.-T., Marshall, L.M., Orwoll, E.S., Cummings, S.R., Osteoporotic Fractures in Men Research, G, 2009. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. Journal of the American Geriatrics Society 57, 492–498.
Forcillo, J., Condado, J.F., Ko, Y.A., Yuan, M., Binongo, J.N., Ndubisi, N.M., Kelly, J.J., Babaliaros, V., Guyton, R.A., Devireddy, C., Leshnower, B.G., Stewart, J.P., Perrault, L.P., Khairy, P., Thourani, V.H., 2017. Assessment of Commonly Used Frailty Markers for High- and Extreme-Risk Patients Undergoing Transcatheter Aortic Valve Replacement. Annals of Thoracic Surgery 104, 1939–1946.
Forti, P., Rietti, E., Pisacane, N., Olivelli, V., Maltoni, B., Ravaglia, G., 2012. A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. Archives of Gerontology and Geriatrics 54, 16–20.
Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., Cardiovascular Health Study Collaborative Research, G, 2001. Frailty in older adults: evidence for a phenotype. The journals of gerontology. Series A, Biological sciences and medical sciences 56, M146–M156.
Fukutomi, E., Okumiya, K., Wada, T., Sakamoto, R., Ishimoto, Y., Kimura, Y., Kasahara, Y., Chen, W.L., Imai, H., Fujisawa, M., Otuka, K., Matsubayashi, K., 2013. Importance of cognitive assessment as part of the "Kihon Checklist" developed by the Japanese ministry of health, labor and welfare for prediction of frailty at a 2-year follow up. Geriatrics and Gerontology International 13, 654–662.
Furtado, G., Patrício, M., Loureiro, M., Teixeira, A.M., Ferreira, J.P., 2017. Physical Fitness and Frailty Syndrome in Institutionalized Older Women. Perceptual and Motor Skills 124, 754–776.
García-García, F.J., Carcaillon, L., Fernandez-Tresguerres, J., Alfaro, A., Larrion, J.L., Castillo, C., Rodriguez-Mañas, L., 2014. A New Operational Definition of Frailty: The Frailty Trait Scale. Journal of the American Medical Directors Association 15 371.e377-e371.e313.
Geessink, N., Schoon, Y., Van Goor, H., Rikkert, M.O., Melis, R., 2017. Frailty and quality of life among older people with and without a cancer diagnosis: Findings from TOPICS-MDS. PLoS ONE 12, 1–14.
Gobbens, R.J.J., Luijkx, K.G., Wijnen-Sponselee, M.T., Schols, J.M.G.A., 2010a. In Search of an Integral Conceptual Definition of Frailty: Opinions of Experts. Journal of the American Medical Directors Association 11, 338–343.
Gobbens, R.J.J., van Assen, M.A.L.M., Luijkx, K.G., Wijnen-Sponselee, M.T., Schols, J.M.G.A., 2010b. The tilburg frailty indicator: Psychometric properties. Journal of the American Medical Directors Association 11, 344–355.
Goldman, S.E., Ancoli-Israel, S., Boudreau, R., Cauley, J.A., Hall, M., Stone, K.L., Rubin, S.M., Satterfield, S., Simonsick, E.M., Newman, A.B., Health, A., Body Composition, S., 2008. Sleep problems and associated daytime fatigue in community-dwelling older individuals. . J Gerontol A Biol Sci Med Sci 63, 1069–1075.
Goldstein, J., Hubbard, R.E., Moorhouse, P., Andrew, M.K., Mitnitski, A., Rockwood, K., 2015. The validation of a care partner-derived frailty index based upon comprehensive geriatric assessment (CP-FI-CGA) in emergency medical services and geriatric ambulatory care. Age and Ageing 44, 327–330.
Gonzales, J.U., Wiberg, M., Defferari, E., Proctor, D.N., 2015. Arterial stiffness is higher in older adults with increased perceived fatigue and fatigability during walking. Experimental Gerontology 61, 92–97.
Goodpaster, B.H., Park, S.W., Harris, T.B., Kritchevsky, S.B., Nevitt, M., Schwartz, A.V., Simonsick, E.M., Tylavsky, F.A., Visser, M., Newman, A.B., 2006. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. The journals of gerontology. Series A, Biological sciences and medical sciences 61, 1059–1064.
Graham, J.E., Snih, S.A., Berges, I.M., Ray, L.A., Markides, K.S., Ottenbacher, K.J., 2009. Frailty and 10-year mortality in community-living mexican american older adults. Gerontology 55, 644–651.
Gruenewald, A., Seeman, A., 2009. Allostatic Load and Frailty in Older Adults. J Am Geriatr Soc. 57, 1525–1531.
Guler, S.A., Kwan, J.M., Winstone, T.A., Milne, K.M., Dunne, J.V., Wilcox, P.G., Ryerson, C.J., 2017. Severity and features of frailty in systemic sclerosis-associated interstitial lung disease. Respiratory Medicine 129, 1–7.
Hardy, S.E.A.S.S., 2010. Qualities of Fatigue and Associated Chronic Conditions among older adults. Journal of Pain Symptom Management 39, 1033–1042.
Haringsma, R., Engels, G.I., Beekman, A.T., Spinhoven, P., 2004. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. Int J Geriatr Psychiatry 19, 558–563.
Hogan, D.B., Freiheit, E.A., Strain, L.A., Patten, S.B., Schmaltz, H.N., Rolfson, D., Maxwell, C.J., 2012. Comparing frailty measures in their ability to predict adverse outcome among older residents of assisted living. BMC Geriatrics 12 56-56.
Hortobágyi, T., Mizelle, C., Beam, S., DeVita, P., 2003. Old adults perform activities of daily living near their maximal capabilities. The journals of gerontology. Series A, Biological sciences and medical sciences 58, M453–M460.
Howlett, S.E., Rockwood, M.R.H., Mitnitski, A., Rockwood, K., 2014. Standard laboratory tests to identify older adults at increased risk of death. BMC Medicine 12, 1–8.
Hubbard, R.E., Andrew, M.K., Fallah, N., Rockwood, K., 2010. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. Diabetic Medicine 27, 603–606.
Hubbard, R.E., Peel, N.M., Samanta, M., Gray, L.C., Fries, B.E., Mitnitski, A., Rockwood, K., 2015. Derivation of a frailty index from the interRAI acute care instrument. BMC Geriatrics 15, 1–8.
Jokar, T.O., Ibraheem, K., Rhee, P., Kulavatunyou, N., Haider, A., Phelan, H.A., Fain, M., Mohler, M.J., Joseph, B., 2016. Emergency general surgery specific frailty index: A validation study. Journal of Trauma and Acute Care Surgery 81, 254–260.
Joseph, B., Pandit, V., Rhee, P., Aziz, H., Sadoun, M., Wynne, J., Tang, A., Kulvatunyou, N., O'Keeffe, T., Fain, M.J., Friese, R.S., 2014. Predicting hospital discharge disposition in geriatric trauma patients. Journal of Trauma and Acute Care Surgery 76, 196–200.
Kaehr, E., Visvanathan, R., Malmstrom, T.K., Morley, J.E., 2015. Frailty in nursing homes: The FRAIL-NH scale. Journal of the American Medical Directors Association 16, 87–89.
Kamdem, B., Seematter-Bagnoud, L., Botrugno, F., Santos-Eggimann, B., 2017. Relationship between oral health and Fried's frailty criteria in community-dwelling older persons. BMC Geriatrics 17, 1–8.
Katz, I.R., 2004. Depression and frailty: the need for multidisciplinary research. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 12, 1–6.
Kent-Braun, J.A., Fitts, R.H., Christie, A., 2012. Skeletal muscle fatigue. Comprehensive Physiology 2, 997–1044.
Kent-Braun, J.A., Ng, A.V., Doyle, J.W., Towse, T.F., 2002. Human skeletal muscle responses vary with age and gender during fatigue due to incremental isometric exercise. Journal of Applied Physiology 93, 1813–1823.
Kiely, D.K., Cupples, L.A., Lipsitz, L.A., 2009. Validation and comparison of two frailty indexes: The MOBILIZE Boston study. Journal of the American Geriatrics Society 57, 1532–1539.
Klausen, H.H., Petersen, J., Bandholm, T., Juul-Larsen, H.G., Tavenier, J., Eugen-Olsen, J., Andersen, O., 2017. Association between routine laboratory tests and long-term mortality among acutely admitted older medical patients: A cohort study. BMC Geriatrics 17, 1–14.
Kleczynski, P., Dziewierz, A., Bagienski, M., Rzeszutko, L., Sorysz, D., Trebacz, J., Sobczynski, R., Tomala, M., Stapor, M., Dudek, D., 2017. Impact of frailty on mortality after transcatheter aortic valve implantation. American Heart Journal 185, 52–58.
Kohout, F.J., Berkman, L.F., Evans, D.A., Cornoni-Huntley, J., 1993. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. Journal of aging and health 5, 179–193.
Kristjansson, S.R., Rønning, B., Hurria, A., Skovlund, E., Jordhøy, M.S., Nesbakken, A., Wyller, T.B., 2012. A comparison of two pre-operative frailty measures in older surgical cancer patients. Journal of Geriatric Oncology 3, 1–7.
Kulminski, A.M., Ukraintseva, S.V., Kulminskaya, I.V., Arbeev, K.G., Land, K., Yashin, A.I., 2008. Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: lessons from the Cardiovascular Health Study. Journal of the American Geriatrics Society 56, 898–903.

Lai, J.C., Covinsky, K.E., Dodge, J.L., Boscardin, W.J., Segev, D.L., Roberts, J.P., Feng, S., 2017. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology (Baltimore, Md.) 66, 564–574.
Lee, S.Y., Yang, D.H., Hwang, E., Kang, S.H., Park, S.H., Kim, T.W., Lee, D.H., Park, K., Kim, J.C., 2017. The Prevalence, Association, and Clinical Outcomes of Frailty in Maintenance Dialysis Patients. Journal of Renal Nutrition 27, 106–112.
Lekan, D.A., Wallace, D.C., McCoy, T.P., Hu, J., Silva, S.G., Whitson, H.E., 2017. Frailty Assessment in Hospitalized Older Adults Using the Electronic Health Record. Biological research for nursing 19, 213–228.
Leng, S., Chaves, P., Koenig, K., Walston, J., 2002. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: A pilot study. Journal of the American Geriatrics Society 50, 1268–1271.
Lucicesare, A., Hubbard, R.E., Fallah, N., Forti, P., Searle, S.D., Mitnitski, A., Ravaglia, G., Rockwood, K., 2010. Comparison of two frailty measures in the conselice study of brain ageing. Journal of Nutrition, Health and Aging 14, 278–281.
Ma, L., Wang, J., Tang, Z., Chan, P., 2018. Simple Physical Activity Index Predicts Prognosis in Older Adults: Beijing Longitudinal Study of Aging. The journal of nutrition, health & aging 22, 854–860.
Makizako, H., Shimada, H., Tsutsumimoto, K., Lee, S., Doi, T., Nakakubo, S., Hotta, R., Suzuki, T., 2015. Social Frailty in Community-Dwelling Older Adults as a Risk Factor for Disability. Journal of the American Medical Directors Association 16 1003.e1007-1003.e1011.
Martín-Sánchez, F.J., Rodríguez-Adrada, E., Vidan, M.T., García, Llopis, G, González del Castillo, J, Rizzi, et al., 2017. Impact of Frailty and Disability on 30-Day Mortality in Older Patients With Acute Heart Failure. American Journal of Cardiology 120, 1151–1157.
Mueller-Schotte, S., Bleijenberg, N., van der Schouw, Y.T., Schuurmans, M.J., 2016. Fatigue as a long-term risk factor for limitations in instrumental activities of daily living and/or mobility performance in older adults after 10 years. Clinical Interventions in Aging 11, 1579–1587.
Nadruz, W., Kitzman, D., Windham, B.G., Kucharska-Newton, A., Butler, K., Palta, P., Griswold, M.E., Wagenknecht, L.E., Heiss, G., Solomon, S.D., Skali, H., Shah, A.M., 2016. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 00, glw199-glw199.
Ní Mhaoláin, A.M., Fan, C.W., Romero-Ortuno, R., Cogan, L., Cunningham, C., Kenny, R.A., Lawlor, B., 2012. Frailty, depression, and anxiety in later life. International Psychogeriatrics 24, 1265–1274.
Nunes, D.P., Duarte, Y.A.d.O., Santos, J.L.F., Lebrão, M.L., 2015. Screening for frailty in older adults using a self-reported instrument. Revista de Saude Publica 49.
O'Connell, M.D.L., Tajar, A., O'Neill, T.W., Roberts, S.A., Lee, D.M., Pye, S.R., Silman, A.J., Finn, J.D., Bartfai, G., Boonen, S., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Huhtaniemi, I.T., Kula, K., Lean, M.E.J., Pendleton, N., Punab, M., Vanderschueren, D., Wu, F.C.W., 2013. Frailty Is Associated with Impaired Quality of Life and Falls in Middle-Aged and Older European Men. The Journal of frailty & aging 2, 77–83.
O'Connor, P.J., Puetz, T.W., 2005. Chronic physical activity and feelings of energy and fatigue. Med Sci Sports Exerc 37, 299–305.
Olsen, L.R., Jensen, D.V., Noerholm, V., Martiny, K., Bech, P., 2003. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol Med 33, 351–356.
Op Het Veld, L.P.M., Ament, B.H.L., Van Rossum, E., Kempen, G.I.J.M., De Vet, H.C.W., Hajema, K., Beurskens, A.J.H.M., 2017. Can resources moderate the impact of levels of frailty on adverse outcomes among (pre-) frail older people? A longitudinal study. BMC Geriatrics 17, 1–8.
Pahor, M., Guralnik, J.M., Ambrosius, W.T., Blair, S., Bonds, D.E., Church, T.S., Espeland, M.A., Fielding, R.A., Gill, T.M., Groessl, E.J., King, A.C., Kritchevsky, S.B., Manini, T.M., McDermott, M.M., Miller, M.E., Newman, A.B., Rejeski, W.J., Sink, K.M., Williamson, J.D., investigators, L.s., for the, L.S.i, 2014. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE Study randomized clinical trial. J Am Med Dir Assoc 311, 2387–2396.
Pao, Y.C., Chen, C.Y., Chang, C.I., Chen, C.Y., Tsai, J.S., 2018. Self-reported exhaustion, physical activity, and grip strength predict frailty transitions in older outpatients with chronic diseases. Medicine (United States) 97.
Purser, J.L., Kuchibhatla, M.N., Fillenbaum, G.G., Harding, T., Peterson, E.D., Alexander, K.P., 2006. Identifying frailty in hospitalized older adults with significant coronary artery disease. Journal of the American Geriatrics Society 54, 1674–1681.
Puts, M.T.E., Toubasi, S., Andrew, M.K., Ashe, M.C., Ploeg, J., Atkinson, E., Ayala, A.P., Roy, A., Monforte, M.R., Bergman, H., McGilton, K., 2017. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: A scoping review of the literature and international policies. Age and Ageing 46, 383–392.
Radloff, L.S., 1991. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. J Youth Adolesc 20, 149–166.
Reid, D.B.C., Daniels, A.H., Ailon, T., Miller, E., Sciubba, D.M., Smith, J.S., Shaffrey, C.I., Schwab, F., Burton, D., Hart, R.A., Hostin, R., Line, B., Bess, S., Ames, C.P., 2018. Frailty and Health-Related Quality of Life Improvement Following Adult Spinal Deformity Surgery. World Neurosurgery 112, e548–e554.
Ribeiro, R.V., Hirani, V., Senior, A.M., Gosby, A.K., Cumming, R.G., Blyth, F.M., Naganathan, V., Waite, L.M., Handelsman, D.J., Kendig, H., Seibel, M.J., Simpson, S.J., Stanaway, F., Allman-Farinelli, M., Le Couteur, D.G., 2017. Diet quality and its implications on the cardio-metabolic, physical and general health of older men: The Concord Health and Ageing in Men Project (CHAMP). British Journal of Nutrition 118, 130–143.
Rockwood, K., Abeysundera, M.J., Mitnitski, A., 2007a. How should we grade frailty in nursing home patients? Journal of the American Medical Directors Association 8, 595–603.
Rockwood, K., Andrew, M., Mitnitski, A., 2007b. A comparison of two approaches to measuring frailty in elderly people. The journals of gerontology. Series A, Biological sciences and medical sciences 62, 738–743.
Rockwood, K., McMillan, M., Mitnitski, A., Howlett, S.E., 2015. A Frailty Index Based on Common Laboratory Tests in Comparison With a Clinical Frailty Index for Older Adults in Long-Term Care Facilities. Journal of the American Medical Directors Association 16, 842–847.
Rockwood, K., Mitnitski, A., Song, X., Steen, B., Skoog, I., 2006. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. Journal of the American Geriatrics Society 54, 975–979.
Rockwood, K., Song, X., Macknight, C., Bergman, H., Hogan, D.B., McDowell, I., Mitnitski, A., 2005. A global clinical measure of fitness and frailty in elderly people. CMAJ 173, 9–13.
Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hébert, R., Hogan, D.B., 1999. A brief clinical instrument to classify frailty in elderly people. Lancet (London, England) 353, 205–206.
Romero-Ortuno, R., Walsh, C.D., Lawlor, B.A., Kenny, R.A., 2010. A Frailty Instrument for primary care: Findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC Geriatrics 10.
Rothman, M.D., Leo-Summers, L., Gill, T.M., 2008. Prognostic significance of potential frailty criteria. Journal of the American Geriatrics Society 56, 2211–2216.
Ryan, R.M., Frederick, C., 1997. On energy, personality, and health: subjective vitality as a dynamic reflection of well-being. J Pers 65, 529–565.
Savva, G.M., Donoghue, O.A., Horgan, F., O'Regan, C., Cronin, H., Kenny, R.A., 2013. Using timed up-and-go to identify frail members of the older population. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 68, 441–446.
Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatrics 8, 1–10.
Shen, J., Barbera, J., Shapiro, C.M., 2006. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev 10, 63–76.
Sirola, J., Pitkala, K.H., Tilvis, R.S., Miettinen, T.A., Strandberg, T.E., 2011. Definition of frailty in older men according to questionnaire data (RAND-36/SF-36): The Helsinki Businessmen study. Journal of Nutrition, Health and Aging 15, 783–787.
Solfrizzi, V., Scafato, E., Lozupone, M., Seripa, D., Giannini, M., Sardone, R., Bonfiglio, C., Abbrescia, D.I., Galluzzo, L., Gandin, C., Baldereschi, M., Di Carlo, A., Inzitari, D., Daniele, A., Sabbà, C., Logroscino, G., Panza, F., Farchi, G., Lepore, V., Livrea, P., Motta, L., Carnazzo, G., Motta, M., Bentivegna, P., Bonaiuto, S., Cruciani, G., Postacchini, D., Amaducci, L., Gandolfo, C., Conti, M., Canal, N., Franceschi, M., Scarlato, G., Candelise, L., Scapini, E., Rengo, F., Abete, P., Cacciatore, F., Enzi, G., Battistin, L., Sergi, G., Crepaldi, G., Maggi, S., Minicucci, N., Noale, M., Grigoletto, F., Perissinotto, E., Carbonin, P., 2017. Additive Role of a Potentially Reversible Cognitive Frailty Model and Inflammatory State on the Risk of Disability: The Italian Longitudinal Study on Aging. American Journal of Geriatric Psychiatry 25, 1236–1248.
Stadje, R., Dornieden, K., Baum, E., Becker, A., Biroga, T., Bösner, S., Haasenritter, J., Keunecke, C., Viniol, A., Donner-Banzhoff, N., 2016. The differential diagnosis of tiredness: A systematic review. BMC Family Practice 17.
Studenski, S., Hayes, R.P., Leibowitz, R.Q., Bode, R., Lavery, L., Walston, J., Duncan, P., Perera, S., 2004. Clinical global impression of change in physical frailty: Development of a measure based on clinical judgment. Journal of the American Geriatrics Society 52, 1560–1566.
Subra, J., Gillette-Guyonnet, S., Cesari, M., Oustric, S., VellaS, B., 2012. The integration of frailty into clinical practice: Preliminary results from the gérontopôle. Journal of Nutrition, Health and Aging 16, 714–720.
Swiecicka, A., Lunt, M., Ahern, T., O'Neill, T.W., Bartfai, G., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Lean, M.E.J., Pendleton, N., Punab, M., Slowikowska-Hilczer, J., Vanderschueren, D., Huhtaniemi, I.T., Wu, F.C.W., Rutter, M.K., 2017. Nonandrogenic anabolic hormones predict risk of frailty: European male ageing study prospective data. Journal of Clinical Endocrinology and Metabolism 102, 2798–2806.
Theou, O., Jones, G.R., Overend, T.J., Kloseck, M., Vandervoort, A.A., 2008. An exploration of the association between frailty and muscle fatigue. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 33, 651–665.
Tocchi, C., Dixon, J., Naylor, M., Jeon, S., McCorkle, R., 2014. Development of a Frailty Measure for Older Adults: The Frailty Index for Elders. Journal of Nursing Measurement 22, 223–240.
Toosizadeh, N., Joseph, B., Heusser, M.R., Orouji Jokar, T., Mohler, J., Phelan, H.A., Najafi, B., 2016. Assessing Upper-Extremity Motion: An Innovative, Objective Method to Identify Frailty in Older Bed-Bound Trauma Patients. Journal of the American College of Surgeons 223, 240–248.
van Kempen, J.A.L., Schers, H.J., Philp, I., Olde Rikkert, M.G.M., Melis, R.J.F., 2015. Predictive validity of a two-step tool to map frailty in primary care. BMC medicine 13 287-287.
Vermeiren, S., Vella-Azzopardi, R., Beckwée, D., Habbig, A.K., Scafoglieri, A., Jansen, B., Bautmans, I., Bautmans, I., Verté, D., Beyer, I., Petrovic, M., De Donder, L., Kardol, T., Rossi, G., Clarys, P., Scafoglieri, A., Cattrysse, E., de Hert, P., Jansen, B., 2016. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. Journal of the American Medical Directors Association 17 1163.e1161–1163.e1117.
Vestergaard, S., Nayfield, S.G., Patel, K.V., Eldadah, B., Cesari, M., Ferrucci, L., Ceresini, G., Guralnik, J.M., 2009. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 64, 76–82.
Villareal, D.T., Banks, M., Siener, C., Sinacore, D.R., Klein, S., 2004. Physical frailty and body composition in obese elderly men and women. Obes Res 12, 913–920.
Walston, J., 2002. Frailty and Activation of the Inflammation and Coagulation Systems

With and Without Clinical Comorbidities&subtitle&Results From the Cardiovascular Health Study&/subtitle&gt. Archives of Internal Medicine 162 2333-2333.

Watt, T., Groenvold, M., Bjorner, J.B., Noerholm, V., Rasmussen, N.A., Bech, P., 2000. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. J Epidemiol Community Health 54, 827–833.

Woo, J., Leung, J., Morley, J.E., 2012. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. Journal of the American Geriatrics Society 60, 1478–1486.

Woods, N.F., LaCroix, A.Z., Gray, S.L., Aragaki, A., Cochrane, B.B., Brunner, R.L., Masaki, K., Murray, A., Newman, A.B., 2005. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative observational study. Journal of the American Geriatrics Society 53, 1321–1330.

Yamada, T., Ivarsson, N., Hernández, A., Fahlström, A., Cheng, A.J., Zhang, S.J., Bruton, J.D., Ulfhake, B., Westerblad, H., 2012. Impaired mitochondrial respiration and decreased fatigue resistance followed by severe muscle weakness in skeletal muscle of mitochondrial DNA mutator mice. Journal of Physiology 590, 6187–6197.

Yeoh, H.L., Cheng, A.C., Cherry, C.L., Weir, J.M., Meikle, P.J., Hoy, J.F., Crowe, S.M., Palmer, C.S., 2017. Immunometabolic and Lipidomic Markers Associated With the Frailty Index and Quality of Life in Aging HIV+ Men on Antiretroviral Therapy. EBioMedicine 22, 112–121.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research 17, 37–49.

Zaslavsky, O., Zelber-Sagi, S., Lacroix, A.Z., Brunner, R.L., Wallace, R.B., Cochrane, B.B., Woods, N.F., 2017. Comparison of the Simplified sWHI and the Standard CHS Frailty Phenotypes for Prediction of Mortality, Incident Falls, and Hip Fractures in Older Women. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 72, 1394–1400.