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# The operationalization of fatigue in frailty scales: a systematic review

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Keywords: Frailty assessment, Fatigue, Tiredness, Aged, Frail elderly

**Abstract**

***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.

## 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:

*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.

*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 figure 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 on a broad concept of frailty and includes 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 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 1,2,3.

*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 1,2,3). 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 the 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 instruments, there was only one frailty scale that included clinical signs of fatigue 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 versus 10.6±9.8%, p=<0.05).

A great diversity of instruments has been used to evaluate fatigue in the frailty scales (figure 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, 8 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 under-estimation 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 (identified  times 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 8 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.

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

2

| | 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**<br>**-"Feeling exhausted for no reason" N=1** (Fukutomi et al., 2013)<br>- **"Exhausted N=2 (Di Bari et al., 2014; Goldstein et al., 2015)** | **N= 40**<br>- **"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)<br>- **"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)<br>- **"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)<br>- **"Feeling fatigued" N=3** (Hubbard et al., 2015; Kulminski et al., 2008; Lekan et al., 2017)<br>- **"No energy" N=2** (Hubbard et al., 2010; Woo et al., 2012)<br>- **"Tired for no reason" *(item extracted from SF-36)* N=2** (Dent et al., 2017; Swiecicka et al., 2017)<br>- **"Everything cost effort" *(item extracted from the K10)* N=1** (Dent et al., 2017)<br>- **"Physical tiredness" N=1** (Gobbens et al., 2010b)<br>- **"Tired" *(item extracted from PHQ-9)* N=1** (Kaehr et al., 2015)<br>- **"Worn out" N=1** (Reid et al., 2018)<br>**-"Feeling slowed down" N=2** (Chan et al., 2010; Rockwood et al., 2005) | **N= 2**<br>- **"Out of breath during normal activities" N=2** (Geessink et al., 2017; van Kempen et al., 2015) | **N= 4**<br>- **Low energy and low endurance measured by 30 seconds chair stand test N= 1** (García-García et al., 2014)<br>- **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**<br>- **"Fatigue: Can't complete day-to-day activities" N=1** (Hogan et al., 2012)<br>- **"Exhaustion measured by performance of daily walks" N=1** (Hubbard et al., 2010) |
| Single domain frailty instruments N=53 | | **N=45**<br>- **"Tired" N=2** (Hogan et al., 2012; Rockwood et al., 2007b)<br>- **"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)<br>- **"Could not get going" *(item extracted from the CES-D* N=16**<br>(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) | **N=2**<br>- **"No energy for normal activities" N=1**(Romero-Ortuno et al., 2010)<br>- **"Too tired for normal activities" *(item extracted from the BDI)* N=1** (O'Connell et al., 2013) | **N=4**<br>- **Low energy and low endurance measured by 5 times sit to stand test N= 2** (Brown et al., 2000; Lai et al., 2017)<br>- **Upper extremity exhaustion N=1** (Toosizadeh et al., 2016)<br>- **Low energy and low endurance measured by 30 seconds chair stand test N=1** (Chang et al., 2014) | **N= 2**<br>- **"weak" *(item extracted from* EORTC QLQ-C30) N=1** (Kristjansson et al., 2012)<br>- **"Weak" N=1** (Hogan et al., 2012) |

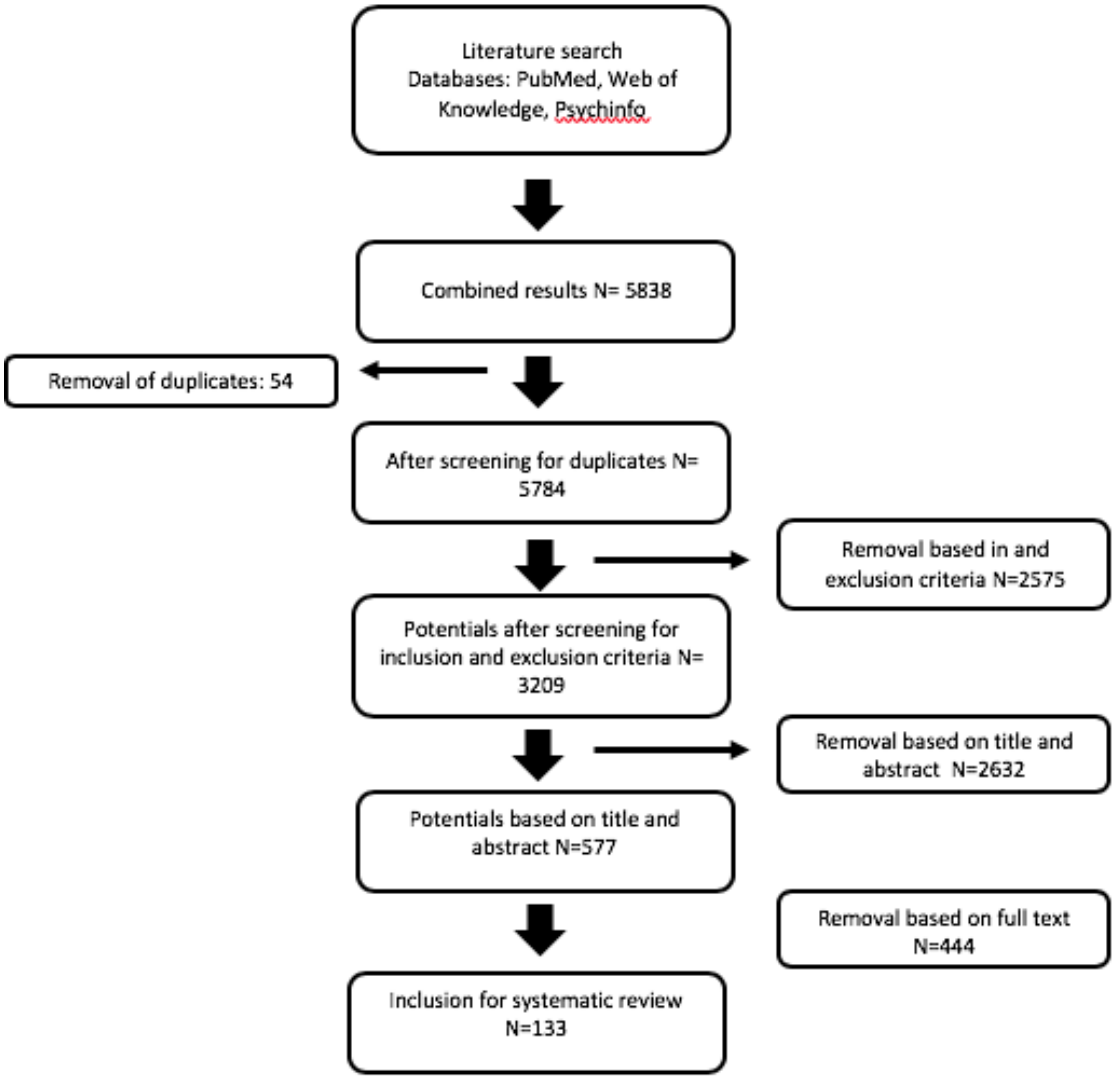
| | | | | | |
|---|---|---|---|---|---|
| | | - **"Tired" *(item extracted from the* EORTC QLQ-C3) N=1** (Kristjansson et al., 2012; Lee et al., 2017)<br>- **"Tired" *(item extracted from the SF-36)* N=3** (Clark et al., 2017; Lee et al., 2017; Woods et al., 2005; Zaslavsky et al., 2017)<br>- **"Low energy" N=3** (Hogan et al., 2012; Kamdem et al., 2017; Woo et al., 2012)<br>- **"Low energy" *(item extracted from the BDI)* N=1** (O'Connell et al., 2013)<br>- **"Distressed by feeling low in energy or slowed down" *(item extracted from the Hopkins)* N=1** (Gruenewald and Seeman, 2009)<br>- **"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<br>N=105 | | **N=4**<br>- **"Energetic" N=1** (Rockwood et al., 2005)<br>- **"Feeling fit" N=2** (Chan et al., 2010; Rockwood et al., 2005)<br>- **"Feel full energy" *(item extracted from GDS)* N=1** (Solfrizzi et al., 2017) | | **N=1**<br>- **Peak Aerobic Power (VO2peak) N=1** (Villareal et al., 2004) | |
| Single domain frailty instruments<br>N=53 | | **N=11**<br>- **"feeling full of pep" *(item extracted from the SF-36)* N=2** (Clark et al., 2017; Woods et al., 2005)<br>- **"feeling full of pep" *(item extracted from the Vitality scale)* N=1** (Lee et al., 2017)<br>- **"Feeling full of energy" *(items extracted from the Vitality scale)* N=1** (Lee et al., 2017)<br>- **"Full of energy" *(item extracted from the GDS)* N=3** (Ensrud et al., 2007; Ensrud et al., 2009; Forti et al., 2012)<br>- **"Feeling full of energy" *(item extracted from the SF-36)* N=3** (Clark et al., 2017; Sirola et al., 2011; Woods et al., 2005)<br>- **" 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




1

2 *Figure 1. Flow chart*

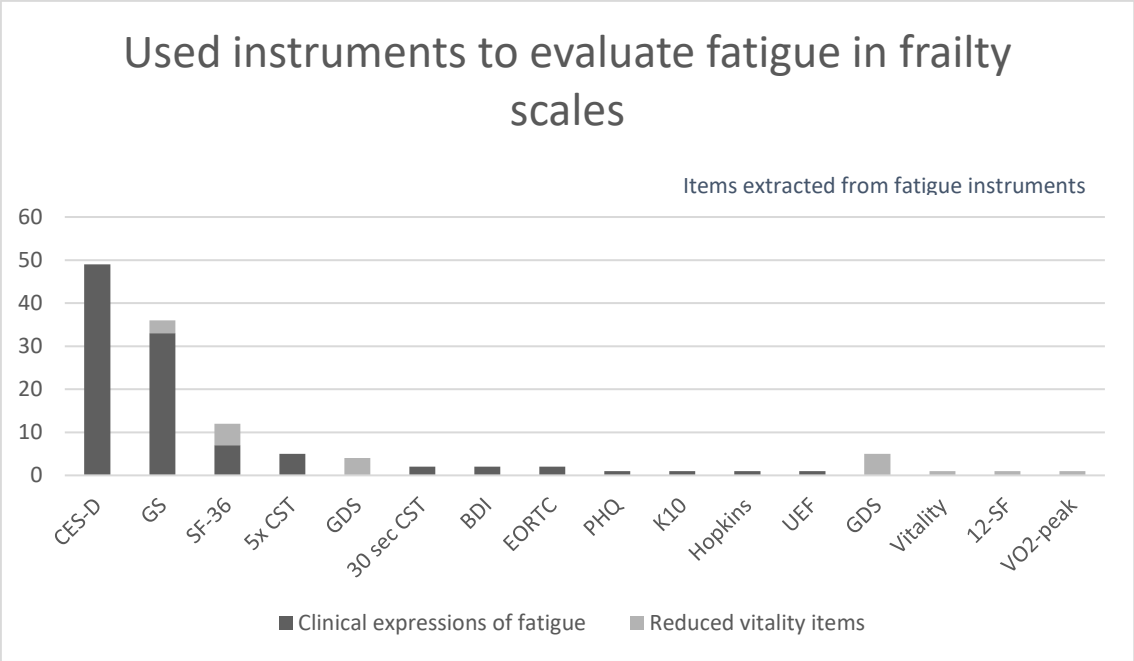



*Figure 2. Represents all fatigue items that have been extracted from different fatigue instruments in the frailty scales, a distinction has been made between clinical signs of fatigue (dark grey), and vitality items (light grey).*

*CES-D: Center for Epidemiologic Studies Depression Scale; GS: Generic Question; SF-36: 36-item Short Form Health; EORTC QLQ-C3: European Organization for the Research and Treatment of Cancer quality of life questionnaire*; *BDI: Beck Depression Inventory*; K10: Kessler Psychological Distress Scale; PHQ: Patient Health Questionnaire; 12-SF *12-Item Short Form Health survey; Hopkins: Hopkins checklist UEE: Upper Extremity Exhaustion*

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**Supplementary table 1. Overview of all included frailty instruments and fatigue items (e.g. Clinical expressions of fatigue and reduced Vitality items) in multi-domain frailty scales.**

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| **1. 70-item Frailty Index/Canadian Study of Health and Aging CSHA** (Rockwood et al., 2007a, Rockwood et al., 2006, Rockwood et al., 2005) | Tired all the time | | 1.4% | | 1.4% | Generic Question | Not reported | No |
| **2.40-item Frailty Index/CSHA** (Rockwood et al., 2006) | Feeling tired | | 2,5% | | 2,5% | Generic Question | Not reported | No |
| **3. 50-variable Frailty Index derived from Canadian Study of Health and Aging CSHA-FI (**Joseph et al., 2014) | I felt that everything I did was an effort | | 2% | | 2% | CES-D | Not reported | No |
| **4. Modified Frailty Index mFI** (Hodari et al., 2013) | | | | | | | | No |
| **5. 40- item Rockwood Frailty Index RFI/ Newcastle 85+ study** (Collerton et al., 2012) | | | | | | | | No |
| **6. 51-variable / Gothenburg H-70 study** (Rockwood et al., 2006) **original (**Steen and Djurfeldt, 1993) | Feeling tired | | 2% | | 2% | Generic Question | Not reported | No |
| **7. Modified 43-item Armstrong Index** (Hogan et al., 2012) **original** (Armstrong et al., 2010) | | | | | | | | No |
| **8. 83-item Full Frailty Index** (Hogan et al., 2012) | Fatigue: Can not complete day-to-day activities | | 1.2% | | 1.2% | Generic Question | Not reported | No |
| **9. 48-item Deficits index DI** (Kulminski et al., 2008) | Fatigue | | 2.1% | | 2.1% | Generic Question | Not reported | Yes |
| **10. 32-item Frailty Index – Cumulative Deficits FI-CD** (Pilotto et al., 2012) **original** (Ensrud et al., 2009a) | | | | | | | | No |

| **Full name of frailty instruments** | ***Category 1*** **Clinical expressions of fatigue used in the frailty scales** | ***Category 2*** **Vitality items** | **Weight of category 1** | **Weight of category 2** | **Total Weight** | **Used fatigue instruments** | **Rational** | **Physical construct Yes/No** |
|---|---|---|---|---|---|---|---|---|
| **11. 62-item Frailty Index** (Woo et al., 2006) | | | | | | | | No |
| **12. 47-item Frailty Index FI** (Woo et al., 2012) | | | | | | | | No |
| **13. 44- item Deficit Accumulation Index DAI** (Hastings et al., 2008) | | | | | | | | No |
| **14. CSHA rules-based definition of frailty/ Composite B/ Deficit Accumulation Index** (Purser et al., 2006, Salvi et al., 2012) **original** (Rockwood et al., 1999) | | | | | | | | No |
| **15. Canadian Study of health and Aging Clinical Frailty Scale CSHA – CFS** (Rockwood et al., 2005, Rockwood et al., 2007a) | Slowed up | Energetic and motivated Active/fit | 12.5% | | 37.5% | Generic Question | Not reported | Yes |
| **16. Chinese-Canadian Study of Health and Aging Clinical Frailty Scale Telephone Version CSHA-CFS TV** (Chan et al., 2010) | Slowed down | Fitter than anyone else at the same age | 16.7% | | 33.3% | Generic Question | Not reported | Yes |
| **17. Frailty Index Comprehensive Geriatric Assessment FI CGA** (Pilotto et al., 2012) **original** (Jones et al., 2004) | | | | | | | | No |
| **18. Multidimensional Prognostic Index MPI based on CGA** (Pilotto et al., 2012) **original** (Pilotto et al., 2008) | | | | | | | | No |
| **19. Adjusted Clinical Groups-diagnoses based computerized predictive model frailty tag ACG frail/outpatient CGA study at Israeli Health Maintenance Organization** (Sternberg et al., 2012) | | | | | | | | No |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **20. CGA-frailty** (Kristjansson et al., 2012) **original** (Balducci and Beghe, 2000) | | | | | | | | No |
| **21. HUBBARD scale/Chinese cohort** (Woo et al., 2012) **original** (Hubbard et al., 2010) | Exhaustion: daily walks for exercise<br><br>Feeling no energy | | 28,57 | | 28,57% | Generic Question | Not reported | Yes |
| **22. Functional domains model/Health and Retirement Study HRS** (Cigolle et al., 2009) **original** (Strawbridge et al., 1998) | | | | | | | | Yes |
| **23. Onco-Geriatric Screening Tool OGS** (Valéro et al., 2011) | | | | | | | | No |
| **24. Reference test to the Onco-geriatric screening tool (**Valéro et al., 2011) | | | | | | | | Yes |
| **25. Simple Frailty Score** (Robinson et al., 2013) | | | | | | | | Yes |
| **26. Expanded Frailty Model** (Amrock et al., 2014) | | | | | | | | Yes |
| **27. Electronic Frailty Model** (Amrock et al., 2014) | | | | | | | | No |
| **28. 15 variable Trauma- Specific Frailty Index TSFI** (Joseph et al., 2014) | I felt that everything I did was an effort | | 6.7% | | 6.7% | CES-D | Not reported | No |
| **29. CSBA index /Easy Prognostic Indicator** (Forti et al., 2012) **original** (Ravaglia et al., 2008) | | | | | | | | Yes |
| **30. Kihon checklist** (Fukutomi et al., 2013) | Feel exhausted for no reason | | 3,1% | | 3,1% | Generic Question | Not reported | Yes |
| **31. Barber Questionnaire** (Molina-Garrido and Guillen-Ponce, 2011) **original** (Barber et al., 1980) | | | | | | | | No |
| **32. Sherbrooke Postal Questionnaire** (Daniels et al., 2012, Metzelthin et al., 2010) **original** (Hébert et al., 1996) | | | | | | | | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **33. INTER-FRAIL** (Di Bari et al., 2014) | Easily exhausted | | 10% | | 10% | Generic Question | Not reported | Yes |
| **34. Vulnerable Elders Scale VES-13/Acove Frailty** (Kellen et al., 2010, Molina-Garrido and Guillen-Ponce, 2011, Smets et al., 2014, Sternberg et al., 2012) **original** (Saliba et al., 2001) | | | | | | | | No |
| **35. Modified VES-13/Modified Scoring** (Ma et al., 2009) | | | | | | | | No |
| **36. Groningen Frailty Indicator (GFI)** (Daniels et al., 2012, Kellen et al., 2010, Metzelthin et al., 2010, Olaroiu et al., 2014, Smets et al., 2014) **original** (Steverink et al., 2001) | | | | | | | | Yes |
| **37. Self-assessment version of GFI** (Peters et al., 2012) | | | | | | | | Yes |
| **38. Tilburg Frailty Indicator** (Daniels et al., 2012, Gobbens et al., 2012, Metzelthin et al., 2010) **original** (Gobbens et al., 2010) | Physical tiredness | | 6,67% | | 6,67% | Generic Question | The items in the physical domain of the TFI correlates significant with the Shortened Fatigue Questionnaire (SFQ) | Yes |
| **39. Modified Short Emergency Geriatric Assessment (SEGAm) instrument** (Oubaya et al., 2014) **original** (Schoevaerdts et al., 2004) | | | | | | | | Yes |
| **40. Identification of Seniors At Risk ISAR** (Salvi et al., 2012) **original** (McCusker et al., 1999) | | | | | | | | No |
| **41. Modified Changes in Health, End-Stage Disease and Symptoms and Signs of medical problems CHESS** | | | | | | | | No |

| **Full name of frailty instruments** | ***Category 1*** **Clinical expressions of fatigue used in the frailty scales** | ***Category 2*** **Vitality items** | **Weight of category 1** | **Weight of category 2** | **Total Weight** | **Used fatigue instruments** | **Rational** | **Physical construct Yes/No** |
|---|---|---|---|---|---|---|---|---|
| (Hogan et al., 2012) **original** (Hirdes et al., 2003) | | | | | | | | |
| **42. Comprehensive Geriatric Assessment** (Smets et al., 2014) **original** (Solomon, 1988) | | | | | | | | No |
| **43. Abbreviated CGA** (Smets et al., 2014) **original** (Overcash et al., 2005) | | | | | | | | No |
| **44. G8** (Smets et al., 2014) **original** (Soubeyran et al., 2008) | | | | | | | | No |
| **45. Frailty Index for Elders FIFE** (Tocchi et al., 2014) | Easily tired | | 10% | | 10% | Generic Question | Evidence based on literature | Yes |
| **46. Multidimensional Frailty Score MFS** (Kim et al., 2014b) | | | | | | | | No |
| **47. The Frailty Trait Scale FTS** (García-García et al., 2014) | I felt that everything I did was an effort | | 14.2% | | 28.6% | CES-D + 30 seconds chair stand test | Test is used to measure low energy level | Yes |
| **48. Physical frailty score** (Carrière et al., 2005) | Endurance 5 times sit to stand test | | 14,3% | | 14,3% | Five times sit to stand test | Items were strong predictors for disability | Yes |
| **49. Modified Physical Performance Test + $VO_2$peak + ADL** (Villareal et al., 2004) | Endurance 5 times sit to stand test | Peak Aerobic Power (VO2 Peak) | 8,3% | 8,3% | 16,67% | Five times sit to stand test + Peak Aerobic Power (VO2 Peak) | Chosen items correlate with degree of disability, loss of independence, and mortality | Yes |
| **50. Modified FRAIL Scale/ Chinese cohort** (Woo et al., 2012) **original** (Abellan Van Kan et al., 2008) | Reporting no energy | | 20% | | 20% | CES-D | Not reported | Yes |
| **51. Seven potential frailty criteria** (Rothman et al., 2008) | I felt that everything I did was an effort- Could not get going | | 14.2% | | 14,2% | CES-D | Association with adverse health outcomes Self-reported | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **52. Marigliano-Cacciafesta polypathology scale MCPS** (Martocchia et al., 2013) **original** (Amici et al., 2008) | | | | | | | | No |
| **53. Balducci** (Kenig et al., 2015) **original** (Balducci and Beghe, 2000) | | | | | | | | No |
| **54. Triage Risk Screening tool (TRST)** (Kenig et al., 2015) **original** (Meldon et al., 2003) | | | | | | | | No |
| **55. EASY-Care Two step Older people Screening Procedure (EASY-Care TOS)** (van Kempen et al., 2015) | Out of breath during normal activities | | Not specified | | Not specified | Generic Question | Association with high risk of adverse health outcomes | Yes |
| **56. Care partner derived FI based on CGA (CP-FI-CGA)** (Goldstein et al., 2015) | Exhaustion | | 2.25% | | 2.25% | Generic Question | Not reported | Yes |
| **57. Frailty Index for Acute Care based on the Inter-RAI (FI-AC)** (Hubbard et al., 2015) | Fatigue | | Not specified | | Not specified | Generic Question | Not reported | Yes |
| **58. Modified 15-variable emergency general surgery specific -frailty index (EGSFI**) (Jokar et al., 2016) | I felt that everything I did was an effort | | 6,67% | | 6,67% | CES-D | Association with development of postoperative complications | Yes |
| **59. Katz questionnaire** (Forcillo et al., 2017, Kleczynski et al., 2017, Zdradzinski et al., 2017) | | | | | | | | No |
| **60. 58- item FI-Clinical Long term Care (FI-Clinical-LTC** (Rockwood et al., 2015) | Tired all the time | | 1.7% | | 1.7% | Generic Question | Not reported | Yes |
| **61. 81-item FI-Combined** (Rockwood et al., 2015) | Tired all the time | | 1.25% | | 1.25% | Generic Question | Not reported | Yes |
| **62. 46-items frailty index** (Theou et al., 2017) **original** (Blodgett et al., 2015) | | | | | | | | No |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **63. Modified 37 Frailty Index (**Yeoh et al., 2017) **original** (Searle et al., 2008, Rockwood et al., 2007a) | I felt that everything I did was an effort<br>- Could not get going | | 5,4% | | 5,4% | CES-D | Not reported | Yes |
| **64. Novel preoperative frailty index** (Tomlinson et al., 2017) | | | | | | | | No |
| **65. 30-item Frailty index** (Kumar et al., 2017) **original** (Searle et al., 2008) | | | | | | | | No |
| **66. 40-item Frailty Index** (Searle et al., 2008) | I felt that everything I did was an effort<br>- Could not get going | | 5% | | 5% | CES-D | Association with health status that increase with age and cover a range of systems | Yes |
| **67. Gerontopole screeningtool** (Breccia et al., 2018, Demougeot et al., 2013, Bruyère et al., 2017) **original** (Subra et al., 2012) | Feeling tired in the past 3 months | | 16,7% | | 16,7% | Generic Question | Not reported | Yes |
| **68. Edmonton frail scale** (Blanco et al., 2017, Nguyen et al., 2017) **original** (Rolfson et al., 2006) | | | | | | | | Yes |
| **69. Fried + scale** (Afilalo et al., 2017) **original** (Folstein et al., 1975, Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 16,7% | | 16,7% | CES-D | Not reported | Yes |
| **70. Bern Scale** (Afilalo et al., 2017, Schoenenberger et al., 2013) | | | | | | | | Yes |
| **71. Columbia scale** (Green et al., 2015, Afilalo et al., 2017) | | | | | | | | Yes |
| **72. Essential Frailty Tool** (Afilalo et al., 2017) | 5 times sit to stand test | | 25% | | 25% | Five times sit to stand test | Not reported | Yes |
| **73. CLI Frailty Index** (Morisaki et al., 2017) | | | | | | | | No |
| **74. EMAS FI** (Swiecicka et al., 2017) **original** (Searle et al., 2008) | Feeling tired | | 2.55% | | 2.55% | Beck depression inventory<br>SF-36 | Not reported | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **75.Cognitive Frailty Index** (Won et al., 2018) | | | | | | | | No |
| **76. Evaluative Frailty Index for Physical Activity (EFIP)** (de Vries et al., 2013, Karssemeijer et al., 2017) | I felt that everything I did was an effort<br>- Could not get going – Feeling tired/lacking energy | | 4,8% | | 4,8% | CES-D | Items based on agreement of experts (geriatricians) | Yes |
| **77. Revised Frailty Index (rFi)** (Gani et al., 2017) | | | | | | | | No |
| **78. Leuven oncology frailty score (LOFS)** (Brouwers et al., 2015, Bailur et al., 2017) | | | | | | | | Yes |
| **79. Frailty Risk Score** (Lekan et al., 2017) | Fatigue | | 6,25% | | 6,25% | Generic Question | High prevalence and an important feature of frailty based on geriatricians | Yes |
| **80. Risk Analysis Index** (Hall et al., 2017a, Hall et al., 2017b) | | | | | | | | No |
| **81. Frailty Index** (Schoenenberger et al., 2013, Schoenenberger et al., 2018) | | | | | | | | Yes |
| **82. 42 Item frailty index** (Guler et al., 2017) **original** (Rockwood and Song, 2011) | Feeling tired | | 2,4% | | 2,4% | Generic Question | Fatigue is one of the most frequently reported deficits and correlates with the frailty status | Yes |
| **83. International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics (IANA/IAGG) criteria** (Solfrizzi et | | Do you feel full of energy? | | 2,8% | 2,8% | Geriatric depression scale | Not reported | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| al., 2017) **original** (Kelaiditi et al., 2013) | | | | | | | | |
| **84. Modified EASY-Care Two step Older people Screening Procedure TOPICS-MDS** (Geessink et al., 2017, Lutomski et al., 2013) | Out of breath after activity | | 2,6% | | 2,6% | Generic Question | Not reported | Yes |
| **85. 20-Item Frailty Index** (Chew et al., 2017) | | | | | | | | No |
| **86. Multimorbidity frailty index (mFI)** (Wen et al., 2017) | | | | | | | | No |
| **87. 35-Item Frailty Index** (Dent et al., 2017) | Feeling tired for no reason – Everything cost effort | | 5,7% | | 5,7% | Kessler Psychological Distress Scale K10 + SF-36 | Health deficits identified had a prevalence of at least 1% in the study population, and increased in prevalence with age | Yes |
| **88. Puts model** (Puts et al., 2005, Turusheva et al., 2017) | | | | | | | | Yes |
| **89. Functional Independence Measure** (Ryomoto et al., 2017) **original** (Tsuji et al., 1995) | | | | | | | | Yes |
| **90. The Tokyo Metropolitan Institute of Gerontology (TMIG) index** (Iki et al., 2017, Koyano et al., 1991) | | | | | | | | Yes |
| **91. Multidimensional Prognostic Index MPI based on SVaMA** (Pilotto et al., 2013, Pilotto et al., 2018) | | | | | | | | No |
| **92. 34- Item Frailty Index** (Martínez-Velilla et al., 2017) **original** (Rockwood et al., 2005) | | | | | | | | No |
| **93. Italian Frailty Index** (Abete et al., 2017) | I felt that everything I did was an effort<br>Could not get going | | | | 5% | CES-D | Not reported | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **94. Frail-NH scale** (Kaehr et al., 2015) | Fatigue | | 14,3% | | 14,3% | PHQ-9 >10 | Fatigue related to depression is associated with frailty | Yes |
| **95. Electronic Frailty Index (EFI)** (Hippisley-Cox and Coupland, 2017, Ravindrarajah et al., 2017) **original** (Clegg et al., 2016) | | | | | | | | No |
| **96. Conselice Study of Brain Aging Score/Modified easy prognostic score** (Lucicesare et al., 2010) **original** (Ravaglia et al., 2008) | | | | | | | | Yes |
| **97. Eastwood frailty criteria** (Eastwood et al., 2017) | | | | | | | | No |
| **98. 20-item Frailty Index** (Perttila et al., 2017) | | | | | | | | Yes |
| **99. Frailty based on clinical data and biomarkers** (Sanchis et al., 2015) | | | | | | | | No |
| **100. Adult Spinal Deformity Frailty Index** (Reid et al., 2018) **original** (Searle et al., 2008) | Tired – worn out | | 5% | | 5% | SF-36 | Not reported | Yes |
| **101. 35-item frailty index** (Castrejón-Pérez et al., 2018) **original** (Searle et al., 2008) | I felt that everything I did was an effort | | 5,7% | | 5,7% | CES-D | Not reported | Yes |
| **102. Modified Frailty Index** (Schaller et al., 2018) **original** (Rockwood et al., 2005) | | | | | | | | No |
| **103. Hospital Frailty Risk Score** (Gilbert et al., 2018) | | | | | | | | No |
| **104. 72-items Frailty Index** (Campitelli et al., 2016, Maxwell et al., 2018) **original** (Searle et al., 2008) | | | | | | | | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **105. 72-items Frailty Index** (McCarthy et al., 2018) | | | | | | | | Yes |

%: Percentage; CSHA: Cardiovascular Health study; FI: Frailty Index; SFQ: Shortened Fatigue Questionnaire; 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; RAND-36:36 item Health Survey, Medical Outcomes Study; SF-36: 36-item Short Form Health; K10: Kessler Psychological Distress Scale; PHQ-9: Patient Health Questionnaire; The weight calculation expressed as a percentage of the total number of fatigue items divided by the total number of items

**Supplementary table 2. Overview of all included frailty instruments and fatigue items (e.g. Clinical expressions of fatigue and reduced Vitality items) in single-domain frailty scales**

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| **1. Phenotype of frailty/Cardiovascular Health Study CHS** (Collerton et al., 2012, Kulminski et al., 2008, Makary et al., 2010, Nemoto et al., 2012, Kim et al., 2014a) **original** (Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Exhaustion was one of the most prevalent factors in the CHS study cohort | Yes |
| **2. Modified Phenotype of frailty** (Hogan et al., 2012) | Feeling unusually tired during the day – Feeling unusually weak – feeling unusually low energy | | 20% | | 20% | CES-D | Not reported | Yes |
| **3.Composite A/ Modified Phenotype of frailty** (Purser et al., 2006) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **4. Modified Phenotype of frailty** (Woo et al., 2012) | Reporting no energy | | 20% | | 20% | Generic Question | Not reported | Yes |
| **5. Modified Phenotype of frailty** (Kristjansson et al., 2012) | Feeling tired | | 20% | | 20% | EORTC QLQ-30 | Exhaustion measured by Cancer Quality of life questionnaire | Yes |
| **6. Modified Phenotype of frailty** (Ensrud et al., 2009a, Ensrud et al., 2009b) | | | 20% | | 20% | 30-item Geriatric Depression Scale | Not reported | Yes |
| **7. Modified Phenotype of frailty** (Ávila-Funes et al., 2009) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **8. Modified Phenotype of frailty /Mobilise Boston Study MBS** (Kiely et al., 2009) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **9. Modified Phenotype of frailty** (Savva et al., 2013) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **10. Modified Phenotype of frailty/MacArthur Study of Successful Aging MSSA** (Gruenewald and Seeman, 2009) | Distressed by feeling low in energy or slowed down | | 20% | | 20% | Hopkins checklist | Not reported | Yes |
| **11. Modified Phenotype of frailty** (Woods et al., 2005) | Feeling worn out-feeling tired | feeling full of pep - Having lots of energy | 10% | 10% | 20% | SF-36 | Rand 36 is used as an indicator of exhaustion. The items chosen in this tool are indicators that are used by widely | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | available instruments to identify frailty | |
| **12. Modified Phenotype of frailty/Rush Memory and Aging project** (Buchman et al., 2011) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 25% | CES-D | Not reported | Yes |
| **13. Modified Phenotype of frailty/Hispanic Established Populations for the Epidemiologic Studies of the Elderly EPESE** (Graham et al., 2009) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **14. Modified Phenotype of frailty/ Frail-CHS (Rockwood et al., 2007b, Rockwood et al., 2006)** (Rockwood, Andrew, et al. 2007; Rockwood et al. 2006) | Feeling tired all the time | | 20% | | 20% | Generic Question | Not reported | Yes |
| **15. Biologic syndrome Model/Health and Retirement Study** (Cigolle et al., 2009) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **16. Adapted Fried using questionnaire data from RAND-36/SF-36/ Helsinki Businessmen Study** (Sirola et al., 2011) | | Feeling full of energy all the time | 20% | | 20% | SF-36 | Fatigue is based on the RAND 36-item what is a good instrument to define frailty | Yes |
| **17. Gill Frailty Index** (Kim et al., 2014a) **original** (Gill et al., 2002) | | | | | | | | Yes |
| **18. Zutphen Elderly Study (**Chin A Paw et al., 1999) | | | | | | | | Yes |
| **19. Modified Physical Performance Test** (Brown et al., 2000) **original** (Reuben and Siu, 1990) | Endurance: 5 times CST | | Not specified | | Not specified | Five times sit to stand test | Not reported | Yes |
| **20. Short Physical Performance Battery** (Chang et al., 2014) | 30 Sec CST | | 25% | | 25% | 30 seconds chair stand test | Not reported | Yes |
| **21. Timed Up and Go** (Savva et al., 2013) **original** (Podsiadlo and Richardson, 1991) | | | | | | | | Yes |
| **22. Study of Osteoporotic fractures** (Bilotta et al., 2010, Ensrud, 2008, Kiely et al., 2009) **original** (Ensrud et al., 2007) | | Feeling full of energy | | 33% | 33% | 30-item Geriatric Depression Scale | Not reported | Yes |
| **23. Modified Study of Osteoporotic fractures index** (Forti et al., 2012) | | Feeling full of energy | | 33% | 33% | 30-item Geriatric Depression Scale | Not reported | Yes |
| **24. Expanded timed Up and go Test (ETUG) using inertial sensors** (Galán-Mercant & Cuesta-Vargas 2015) | | | | | | | | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **25. Upper extremity frailty (UEF)** (Toosizadeh et al., 2016, Joseph et al., 2017) | Upper extremity exhaustion | | Not specified | | Not specified | Performance test | Not reported | Yes |
| **26. Gait analysis based on trunk acceleration signals** (Martínez-Ramírez et al., 2015) | | | | | | | | Yes |
| **27. Self-reported assessment of frailty syndrome** (Nunes et al., 2015) | Could not perform daily activities due exhaustion- Routine activities require an effort | | 20% | | 20% | CES-D | Not reported | Yes |
| **28. 5 min walk test** (Forcillo et al., 2017, Kleczynski et al., 2017) | | | | | | | | Yes |
| **29. Hand grip strength** (Campo et al., 2017, Forcillo et al., 2017) | | | | | | | | Yes |
| **30. Adapted Phenotype Fried criteria** (Joseph et al., 2017) | Feeling that I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **31. Modified Fried criteria** (Martín-Sánchez et al., 2017) **original** (Fried et al., 2001) | Feeling that I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Based on clinicians | Yes |
| **32. Gait Speed** (Bruyère et al., 2017) **original** (Cruz-Jentoft et al., 2010) | | | | | | | | Yes |
| **33. SHARE Frailty Index** (Bruyère et al., 2017) **original** (Romero-Ortuno et al., 2010) | No energy to do the activities that were wanted to do | | | | 20% | Generic Question | Not reported | Yes |
| **34. EMAS- F (O'Connell et al., 2013, Swiecicka et al., 2017) original** (Fried et al., 2001) | Not enough energy to do anything<br><br>Too tired to do the things that are normally done | | 20% | | 20% | Beck Depression Inventory | Not reported | Yes |
| **35. sWHI Frailty Phenotype (Zaslavsky et al., 2017) original** (Fried et al., 2001) | Feeling tired in the pas 4 weeks | | 20% | | 20% | SF-36 | Fatigue is sensitive to capture severity of chronic conditions | Yes |
| **36. Short Form of the Kidney Disease Quality of Life questionnaire, Korean version** (Lee et al., 2017) | | Feeling full of pep - Having a lot of energy - Feeling tired | 20% | | 20% | Vitality scale | Not reported | Yes |

| Full name of frailty instruments | ***Category 1*** Clinical expressions of fatigue used in the frailty scales | ***Category 2*** Vitality items | Weight of category 1 | Weight of category 2 | Total Weight | Used fatigue instruments | Rational | Physical construct Yes/No |
|---|---|---|---|---|---|---|---|---|
| **37. Modified Phenotype of frailty** (Op Het Veld et al., 2017) **original** (Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **38. Modified Phenotype of frailty** (Kamdem et al., 2017) **original** (Fried et al., 2001) | Lack of energy or fatigue in past 4 weeks | | 20% | | 20% | Generic Question | Not reported | Yes |
| **39. Modified Phenotype of frailty** (Clark et al., 2017) **original** (Fried et al., 2001) | Feeling worn out-<br>Feeling tired | Feeling full of pep- Having lots of energy | 10% | 10% | 20% | SF-36 | Not reported | Yes |
| **40. Elderly mobility scale** (Kleczynski et al., 2017, Smith, 1994) | | | | | | | | Yes |
| **41. Indicators of the sarcopenia and osteopenia study** (Kaplan et al., 2017) | | | | | | | | No |
| **42. Psoas muscle area (PMA)** (Garg et al., 2017) | | | | | | | | No |
| **43. Social Frailty Index** (Makizako et al., 2015, Tsutsumimoto et al., 2017) | | | | | | | | No |
| **44. Frailty based on sensor data** (Greene et al., 2014) | | | | | | | | Yes |
| **45. Modified Phenotype of frailty (Nadruz et al., 2016)** (Nadruz et al. 2016) **original** (Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **46. Modified Phenotype of frailty** (Ribeiro et al., 2017) **original** (Fried et al., 2001) | | A lot of energy in the past 4 weeks | | 20% | 20% | 12-item Short Form Health Survey | Not reported | Yes |
| **47. Modified Phenotype of frailty** (Furtado et al., 2017, Kim et al., 2018) **original** (Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **48. Modified Phenotype of frailty** (Pao et al., 2018) **original** (Fried et al., 2001) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **49. Frailty Screening Questionnaire (FSQ)** (Ma et al., 2018) | I felt that everything I did was an effort<br>- Could not get going | | 20% | | 20% | CES-D | Not reported | Yes |
| **50. Liver Frailty Index** (Lai et al., 2017, Kuo et al., 2018) | Endurance: 5 times CST | | 25% | | 25% | Five times sit to stand test | Not reported | Yes |
| **51. 50. 23- item FI-Lab** (Howlett et al., 2014) | | | | | | | | No |
| **52. FI-OutRef** (Klausen et al., 2017) | | | | | | | | No |
| **53. Albumine level** (Forcillo et al., 2017) | | | | | | | | No |

%: Percentage; CSHA: Cardiovascular Health study; FI: Frailty Index; SFQ: Shortened Fatigue Questionnaire; 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; RAND-36:36 item Health Survey, Medical Outcomes Study; SF-36: 36-item Short Form Health; K10: Kessler Psychological Distress Scale; PHQ-9: Patient Health Questionnaire; The weight calculation expressed as a percentage of the total number of fatigue items divided by the total number of items

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