



Fatigue: Relevance and implications in the aging population



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ARTICLE INFO

Article history:

Received 24 February 2015

Received in revised form 14 July 2015

Accepted 15 July 2015

Available online 17 July 2015

Section Editor: Borg Holly M Brown

Keywords:

Fatigue

Older people

Disability

Frailty

Symptom assessment

ABSTRACT

Frailty has been identified as a promising condition for distinguishing different degrees of vulnerability among older persons. Several operational definitions have proposed fatigue as one of the features characterizing the frailty syndrome. However, such a subjective symptom is still not yet sufficiently explored and understood.

Fatigue is a common and distressing self-reported symptom perceived by the person while performing usual mental and physical activities, highly prevalent in older people, and strongly associated with negative health-related events. The understanding of fatigue is hampered by several issues, including the difficulty at objectively operationalizing, the controversial estimates of its prevalence, and the complex pathophysiological mechanisms underlying its manifestation. Despite such barriers, the study of fatigue is important and might be encouraged. Fatigue may be the marker of the depletion of the body's homeostatic reserves to a threshold leading to its psycho-physical functional impairment, mirroring the concept of frailty. Its subjective and symptomatic nature resembles that of other conditions (e.g., pain, depression), which equally affect the individual's quality of life, expose to negative outcomes, and severely burden healthcare expenditures.

In the present paper, we present an overview of the current knowledge on fatigue in older persons in order to increase awareness about its clinical and research relevance. Future research on this topic should be encouraged and developed because it could potentially lead to novel interventions against this symptom as well as against frailty and age-related conditions.

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1. Introduction

The proportion and absolute number of older adults has substantially been increasing worldwide, and demographic projections confirm such trends for the future. Persons aged 65 years and older represent the fastest growing segment of the population. For example, the 2010 United States Census reveals that 13.0% (i.e., 40.3 million) of the total population is represented by older persons, an estimate higher than what previously reported in 2000 (i.e., 12.4%) (Werner, 2011). These demographic developments are not only characteristic of the most developed countries, but they are also described in the less developed ones (United Nations, Department of Economic and Social Affairs, 2013).

The increase in life expectancy is an important public health goal and represents a marker of cultural, social, medical and scientific progress. However, such a goal has to be pursued in parallel with efforts to

preserve independent life at any age. Disability is frequently an irreversible condition, difficult to be managed due to its heterogeneous and complex nature. The disabling cascade is indeed a dynamic process. At old age, it is largely determined by the life-long impact of chronic conditions on the functioning of specific body systems. This pathway from pathology to disability is predisposed by individual risk factors and triggered by multiple personal or environmental events. Moreover, the disablement process itself can cause negative consequent effects, prompting to the onset of other diseases and dysfunctions, generating a detrimental vicious cycle (Verbrugge and Jette, 1994). Disability negatively impacts on the individual's quality of life (Groessler et al., 2007) and is responsible for relevant public health expenditures (Fried et al., 2001b). Given such characteristics, it is clear why the prevention of disability represents today a priority for public health authorities. There is a well-established and growing consensus among clinicians and researchers encouraging the early identification of the functional deterioration in older persons. To effectively counteract the disabling cascade, it is important to recognize its early stages, the underlying and potentially modifiable risk factors, and develop intervention strategies able to support the homeostatic efforts of the body so that the endogenous reserves may benefit and may still be conserved.

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The condition of pre-disability may represent the ideal target for implementing specific preventive strategies against disability and age-related conditions. It has been identified into the working concept of frailty, “the biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes” (Fried et al., 2001a). This theoretical concept has been operationalized in different definitions for being implemented in the clinical and research settings. Interestingly, several definitions have considered in their algorithms/criteria the fatigue symptom as one of the main features of frailty (Ensrud et al., 2008; Fried et al., 2001a; Morley et al., 2012). Fatigue may indeed well mirror the frailty syndrome because it may optimally capture the pathophysiological exhaustion of the organism functional reserves. It may resemble an alert launched by the organism running on the limit while performing usual psychological and/or physical activities.

If theoretically fatigue may represent a cornerstone of the frailty symptom, its translation into practice is more complex. Symptoms, such as fatigue, are uncomfortable or distressing bodily sensations experienced by the individual, and are not always easy to be objectivized (Kroenke, 2014). At the same time, symptoms are one of the main reasons for outpatient visits in primary care and responsible for relevant consumption of healthcare resources (Schappert, 1992; Speckens et al., 1996).

In the present article, we provide an overview of fatigue in older people with the aim of increasing awareness about its clinical relevance in the medical community and encouraging specific research.

2. The symptom of fatigue

Fatigue is one of the symptoms most frequently reported by older persons (Meng et al., 2010), often in the absence of a clear underlying cause. Fatigue significantly burdens the individual's quality of life and concurs at exposing him/her to the risk of negative health-related outcomes (Schultz-Larsen and Avlund, 2007). Despite its detrimental consequences (for the individual as well as for the society), the assessment and treatment of fatigue are still largely inadequate (if not completely ignored!). One of the possible explanations may surely be found in a sort of “ageism” considering fatigue as an inevitable sign of age with little expectation for relieving it (Tinetti and Fried, 2004). It is also noteworthy that, to date, the only opportunity for targeting fatigue is mainly represented by detecting its underlying causes. Nevertheless, if the diagnostic pathway fails to identify clear causes, fatigue may be easily left untreated for the lack of reliable symptomatic interventions. The incomplete understanding of the complex pathophysiological mechanisms underlying fatigue as well as the difficulty of objectively assessing this (often vague) symptom represent further barriers to the study and its clinical implementation.

Several scientific societies and institutions have encouraged higher consideration of the symptom of fatigue. For example, the United States National Institute on Aging (2007) organized an exploratory workshop focused at initiating a broad-based scientific dialogue on the clinical problem of “idiopathic” or “unexplained” fatigue in older adults. More recently, the American Geriatrics Society held its 5th Bedside-to-Bench Research Conference on the theme of “Idiopathic Fatigue and Aging”. The conference was specifically focused on physical fatigue as a disorder of energy balance, and aimed at drafting strategies for future research on the topic (Alexander et al., 2010).

Nevertheless, there are still relatively few studies targeting this issue. For example, a search of all articles, performed in PubMed in February 23, 2015 using the terms “fatigue” and “older adults”, has led to just 378 results.

3. The characterizations of fatigue

Fatigue is a complex and multidimensional symptom. The Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V)

defines fatigue 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. Physical fatigue leads to an inability to continue functioning at one's normal level of activity. Although widespread in everyday life, this state usually becomes particularly noticeable during heavy exercise. Mental fatigue, by contrast, most often manifests as somnolence (sleepiness)” (American Psychiatric Association, 2013). Here, several synonyms of fatigue are also provided (i.e., exhaustion, tiredness, lethargy, languidness, languor, lassitude, and listlessness).

Nevertheless, despite its inclusion in the DSM-V, the definition of fatigue is largely debated. In fact, several definitions of fatigue coexist in literature, each one with a specific connotation capturing a peculiar characteristic of the symptom. Such diverse operationalizations (as well as the frequent interchangeable use of them) are responsible for ambiguities and misunderstandings.

For example, “tiredness” is one among the most commonly used terms for indicating the symptom of “fatigue”. It has been described as a temporary lessening of strength and energy (Ream and Richardson, 1996). It represents a universal sensation (relieved by rest and sleep) expected to normally occur at certain times of the day and after activities (Avlund, 2010). In cardiology, it is frequently discussed as the so-called state of “vital exhaustion”, characterized by the presence of lack of energy, increased irritability, and feeling of demoralization (Appels, 1990).

Recently, the concept of “fatigability” has also been introduced for taking into account the inter-individual variability of fatigue following physical activity. Individuals may have similar levels of fatigue despite varying levels of activity. For example, older people tend to reduce their physical activity (self-pacing) in order to remain well below their threshold of fatigue onset, consequently requiring an age-related adaptation of the reference exercise intensity determining fatigue. Therefore, fatigability reflects the perceived inability to continue a standardized activity at the same intensity with resultant performance deterioration and degree of fatigue. It may indeed represent the normalization of fatigue according to the physical activity level determining it (Eldadah, 2010; Simonsick et al., 2014).

Fatigue can be distinguished as acute or chronic, according to the characteristics of its onset. Acute fatigue may be seen as a protective symptom, an alert that the organism is raising for the onset of a specific abnormality. Acute fatigue is usually characterized by rapid onset and short duration, linked to a single cause, and frequently perceived as the “normal” consequence of an evident causing condition. It may be alleviated by rest and has minimal effects on activities of daily living and quality of life. On the other hand, chronic fatigue has an insidious onset and persists over time. It often presents multiple or unknown underlying causes. Chronic fatigue is usually perceived as an “abnormal”, unusual and/or excessive symptom. It cannot be relieved by usual restorative techniques, and has major negative effects on the individual's activities of daily living and quality of life (Aaronsen et al., 1999). Chronic fatigue (defined as a self-reported persistent or relapsing fatigue lasting 6 or more consecutive months) has even been nosologically framed as part of a specific disease, the so-called “chronic fatigue syndrome” (CFS) (Fukuda et al., 1994), which finds overlapping with organic (especially immune system) and psychiatric disorders as well as potentially infectious pathogenesis.

A further example of the operationalization of fatigue for a specific condition is coming from a relevant body of literature in the oncology specialty. Fatigue has indeed led to the description of the cancer-related fatigue (CRF) syndrome. The CRF syndrome is operationally defined as the presence of clinically significant fatigue (lasting for at least 2 weeks), associated with five additional criteria (including non-restorative sleep and active disruption of daily activities), due to cancer, and unrelated to a psychiatric disorder (Sadler et al., 2002). It is remarkable how fatigue might be considered as a common and independent symptom as well as the core characteristic of a specific syndrome built around it.

4. Epidemiology

Given the lack of a “gold standard” instrument for the assessment of fatigue, data from literature are quite heterogeneous in the estimate of its prevalence/frequency. The presence of fatigue has been reported in 6% to 45% of individuals in the general population (Lewis and Wessely, 1992). In a cohort of 17,084 adult and older persons, the prevalence of fatigue was estimated to be 31.2%, more likely to affect women, and showing an increasing age-related trend (Meng et al., 2010). Similar results were consistently reported by other studies (Moreh et al., 2010). However, the prevalence of fatigue is largely related to the characteristics of the target population and the setting where the assessment is conducted. For example, the prevalence of fatigue may be particularly high in very frail and multimorbid elders as those living in long term care, even up to 98% (Liao and Ferrell, 2000). Furthermore, different temporal characteristics and level of fatigue have been observed comparing data obtained from subjects recruited in the general population with those from patients affected by fatigue-related clinical disorders, with the latter showing higher and more consistent levels of the symptom (Murphy and Smith, 2010; Murphy et al., 2013; Christodoulou et al., 2014). Also the difference in physical activity capacity among subjects included in study samples could influence the evaluation of fatigue and make the observations not directly comparable. This could contribute to explain the lack of an age-related increase in the prevalence of fatigue resulted in some reports (Chen, 1986; Bardel et al., 2009). The abovementioned concept of fatigability takes the activity context associated to fatigue perception into account. Thus, it may be considered a promising less-biased approach, also from an epidemiological perspective.

5. Causes

Fatigue is often observed in specific medical diseases (e.g., cancer, neurodegenerative disorders, rheumatologic disease, heart failure, stroke, hormonal disorders...). However, for many older persons, it can be difficult to ascribe fatigue to a single disease or provide a definitive explanation to it (even after an accurate diagnostic process). The conventional disease-centered categorization of symptoms seems indeed inadequate (Tinetti and Fried, 2004), as often occurring in geriatrics. In fact, a wide spectrum of distressing conditions of older persons may be hard to fit into discrete disease categories, mainly because generated by the life-long accumulation and interactions of multiple physical, biological, psychological, social and environmental factors.

As mentioned above, the mechanisms underlying the fatigue manifestation are not well understood. Fatigue may be influenced by multiple biological (e.g., changes in skeletal muscle function, cardiovascular impairment, inflammatory mediators, nutritional deficiencies) and psychological (e.g., mood disorders) factors (Avlund, 2010; Beyer et al., 2012; Gonzales et al., 2014, 2015). Fatigue may mirror the erosion of the physiological reserves of the body. In fact, fatigue may occur as consequence of an imbalance between the required effort and the capacity of the organism to successfully meet it. It is generated when the required resources are insufficient due to a disproportionate demand for the altered homeostatic mechanisms (Alexander et al., 2010). In this context, fatigue may well resemble the frailty syndrome (i.e., the condition of extreme vulnerability characterizing the older person with limited physiological reserves), and well serve as a potential marker of biological aging.

6. Consequences

Fatigue is strongly associated with poor physical performance (Vestergaard et al., 2009), independently of age (Mänty et al., 2014), and with multiple negative outcomes in the elderly, including hospitalizations, increased use of healthcare services, incident disability, and mortality (Avlund et al., 2001; Hardy and Studenski, 2008a,b;

Schultz-Larsen and Avlund, 2007). Furthermore, fatigue is one of the main factors associated with reduced capacity to conduct regular physical activities among community-living older adults (Gill et al., 2001). Daily experience of fatigue is strongly related to reduction of physical activity, especially in older adults and in the presence of comorbid conditions (e.g., osteoarthritis) (Murphy et al., 2013). In other words, fatigue may represent a key factor capable of both directly and indirectly affecting the individual's health status and quality of life.

7. Assessment

The assessment of fatigue is not easy, especially due to the subjective nature of this symptom. Although a number of different validated tools exist for measuring fatigue, no instrument can still be considered as the “gold standard”. In particular, it is evident that each of the available tools captures a specific dimension of fatigue. This leads to the fact that all of them are legitimate and predictive of negative outcomes, but the overall correlation between the measurement tools is quite modest (Flachenecker et al., 2002).

Available instruments assessing fatigue can be differentiated into uni- and multidimensional instruments. Unidimensional scales tend to focus on one specific aspect of the symptom, usually its severity. They are often brief and, as such, more indicated for screening purposes. Some of these instruments have been developed in populations affected by specific conditions. For example, the Brief Fatigue Inventory (BFI) is a well-known 9-item scale measuring fatigue severity which was originally designed in oncology (Mendoza et al., 1999). Differently, multidimensional scales are usually longer and provide detailed description of fatigue, informing about its intensity, nature and impact on daily activities. For example, the Multidimensional Fatigue Inventory (MFI-20) includes 20 items and explores multiple domains, providing a general description of the symptom, characterizing whether it is more physical and/or mental, estimating the related reduction of activities, and determining the associated motivation (Smets et al., 1995). Additional scales used to measure fatigue, such as the Edmonton Functional Assessment Tool, are usually appropriate for research rather than clinical purposes (Watanabe et al., 2011). Recently, the National Institutes of Health has developed the Patient-Reported Outcome Measurement Information System (PROMIS) to provide reliable and precise assessment of reported outcomes, including fatigue. For example, a modified 7-item PROMIS-fatigue Short Form questionnaire for daily assessment has shown to be accurate and sensitive to changes over time, providing an interesting opportunity for better evaluating the temporal modifications of this symptom (Christodoulou et al., 2014).

It is noteworthy that the fatigue symptom has been frequently operationalized from secondary analyses of available data collected for different purposes. For example, the measurement of fatigue has been done by retrieving answers to specific items included in questionnaires measuring depressive symptoms, sleep quality, or quality of life. The most evident example of this is represented by the operationalization of the “exhaustion” criterion included in the frailty phenotype proposed by Fried and colleagues, which used two items of the Center for Epidemiological Studies-Depression scale (Radloff, 1977) administered in the Cardiovascular Health Study. Although this is a legitimate choice, it cannot be ignored that the result of such operationalizations cannot be considered as robustly describing the symptom of interest, but should still be regarded as surrogates.

Attempts to improve the assessment of fatigue in older persons are represented by the operationalization of the new concept of fatigability. In the last few years, different measurement tools have been proposed and tested. For example, two performance-based models of fatigability aimed at evaluating 1) the performance deterioration, and 2) the perceived exertion during a predefined activity have been studied (Schnelle et al., 2012; Simonsick et al., 2014). At the same time, a recent self-reported tool (i.e., the 10-item Pittsburgh Fatigability Scale) has been developed and validated for older adults to measure perceived

fatigability. It is based on the level of physical and mental fatigue that subject expects or imagines to feel after completing a set of hypothetical activities related to daily life (Glynn et al., 2015). However, further studies in this area are still needed, especially for better appreciating the clinical relevance of these measures (e.g., predictive value for negative outcomes).

8. Lessons learned from depression and pain

The relatively poor interest given to the fatigue symptom in the medical community is quite surprising given the severe burden of it on the individual and the society. In particular, it is amazing how such subjective symptom does not receive the same attention given to other very similar and related conditions, such as depression and pain. Exactly as fatigue, pain and depression are also particularly frequent in older adults and associated with major negative health-related outcomes (Beekman et al., 1997; Eggermont et al., 2014). Moreover, fatigue, pain and depression are all subjective symptoms and present very similar methodological issues in their operationalizations.

A bidirectional association surely exists between fatigue and depression, although their causal relationship still remains unclear. Fatigue as well as depression are both characterized by physical, cognitive, and emotional dimensions. Depression plays a role in the manifestation of fatigue, and vice versa, fatigue is considered a component of depression. Such close relationship is clearly evident in the inclusion of the fatigue symptom as one of the possible clinical manifestation of the major depressive episode according to the DSM-V (American Psychiatric Association, 2013). At the same time, it is noteworthy that fatigue still remains one of the symptoms less responsive to antidepressant treatments (Arnold, 2008). Such apparent contradiction may support the hypothesis that fatigue and depression indeed share close but distinct etiologies.

Similarly, an association between fatigue and pain is evident as well (Fishbain et al., 2003). Fatigue is a major disabling complaint in patients with pain caused by chronic diseases, such as osteoarthritis (Murphy et al., 2013; Power et al., 2008). Improving the understanding about the causal relationship between pain and fatigue may be useful for developing and optimizing symptomatic treatments. Unfortunately, even in this case, the underlying mechanisms are not clear.

In the hypothetical triangle fatigue–pain–depression, the most studied association is for sure the one between pain and depression. The coexistence of pain and depression significantly increases the risk of negative clinical outcomes. Moreover, shared biological pathways have been described between the two (e.g., dysregulation of serotonin and norepinephrine associated with depression also influences the transmission of nociceptive signals) (Bair et al., 2003).

Fatigue, depression and pain frequently coexist and potentially generate a vicious cycle finally leading to negative outcomes. Nevertheless, the three still are distinct entities, each one requiring a specific assessment and probably individual intervention.

The history of fatigue may potentially follows what already occurred some years ago for pain and depression. The concept of pain has represented a longly debated issue in the scientific community. Today, its clinical relevance is widely recognized and this symptom is carefully studied in the clinical as well as in the research setting. This has been obtained by developing dedicated research, understanding of pathophysiological pathways, detecting possible targets for ad hoc pharmacological and non-pharmacological interventions, designing more informative assessment tools, and raising awareness about the relevance of the symptom. The American Pain Society (1991) presented one of the first programs to improve the treatment of acute and cancer pain. Subsequently in 1995, pain was proposed as the “fifth vital signs” (Campbell, 1996) to reinforce the recommendation of routinely assess it in the standard clinical practice. The under-treatment of pain was very frequent up to a couple of decades ago, especially among older individuals (Bernabei et al., 1998). Driven by public opinion concerns, higher attention has been dedicated to this issue. Specific and more

focused recommendations have started being diffused (AGS Panel on Persistent Pain in Older Persons, 2002). These essentially explained how to improve the assessment and clinical management of pain, keeping in mind the quality of life amelioration as primary outcome of the interventions.

Also for what concerns depression, clinical and research interest has steadily increased during the past decades (Blazer, 2003). In particular, special efforts have been made to translate into clinical practice the complex information coming from research on such subjective condition. As example, “major depression” has been operationalized as a diagnostic category according to the DSM criteria since its third edition, and the reliability of such diagnosis has been increasing in these last years. Nevertheless, the static and sterile description of diseases is often complicated in geriatrics by the heterogeneous and dynamic presentations. Consequently, higher attention has been given to the necessity of different operationalizations of late-life depressive syndromes, which may not meet the “standard” criteria for major depression but still capture pathological abnormalities of mood (e.g., minor, subsyndromal or subthreshold depression) (Meeks et al., 2011). The increased awareness about the negative effects played by depression is evident in the repeated recommendation for ad hoc screening procedures provided by, just for example, the Canadian Task Force on Preventive Health Care (MacMillan et al., 2005) as well as the United States Preventive Services Task Force (2009). In the absence of biological markers, screening has been made possible by developing standardized questionnaires and more carefully assessing the subject's health status and history. In this context, scales like the Geriatric Depression Scale (Yesavage et al., 1983) or EURO-D (Prince et al., 1999) have been developed and validated specifically for use in older people.

Despite these advances, both pain and depression still present major challenges and unclear issues to solve. Nevertheless, the recent history of these two symptoms in the clinical care may indeed represent an interesting model for building up strategies targeting other detrimental symptoms with the aim of improving the quality of life of older persons. Such process cannot exclude (but is really based on) the clarification of the underlying pathophysiological mechanisms. In this context, the already available evidence on depression and pain may support the complementary research on fatigue. In fact, the established pathophysiological mechanisms identified as contributors to depressive and pain symptoms may serve as reference for untangling and differentiating fatigue-specific pathways contributing to the diverse clinical manifestations. The influence of the depression and/or pain-related pathways on the homeostatic balance should be explored more carefully looking at the potential consequences on fatigue (and vice versa). It is noteworthy that by “triangulating” these three subjective symptoms (i.e., depression, pain, and fatigue), it might be possible to better understand their overlappings as well as peculiarities. It is possible that by fostering research on fatigue, parallel benefits in terms of knowledge might be also acquired in the fields of depression and pain. This will likely translate into the identification of novel therapeutic targets and development of improved symptomatic interventions.

Looking at the clinical setting, it is important to more carefully and systematically monitor the presence/absence/variation of fatigue in older persons. Such tremendously predictive parameter for negative health-related events may not only support clinical decisions and improve the appreciation of interventions benefits. The assessment of fatigue may indeed help at identifying subtle signs of treatable conditions (e.g., chronic pain, depressive symptoms) which may be reversed and concur at the amelioration of the individual's quality of life. It might already be important to pay more attention to those fatigue-related items included in the screening tools that are commonly used in the geriatric clinical and research settings (e.g., frailty tools, questionnaires for depressive symptoms). The identification of the problem may then lead to a more detailed assessment of fatigue and the consequent personalized plan of intervention. As for depression and pain, treatment successful intervention cannot preclude from the multidimensional evaluation

of the individual (including the clinical and biological domains as well as the mental, emotional, and social ones).

9. Future perspectives

Poor consideration about the fatigue symptom cannot be tolerated anymore. To date, it is clear how detrimental is fatigue for the individual and the society. It is important to improve current knowledge about the pathological implication of fatigue among older persons, encouraging its reporting to the general practitioner and healthcare professionals. Prevention is based on the education of the target population about the nature of the condition of interest and its characteristic features. This approach may indeed support the development of effective preventive interventions because allowing the implementation of appropriate counteractions at earlier stages of the disorders. On the other hand, the clinicians should be more vigilant about the presence of this symptom and try to objectivize, describe, treat, and follow if possible. As pain and depression assessments are routinely included in the clinical assessment of older persons, healthcare providers should start screening in a more systematic way the presence of fatigue.

The identification of fatigue in the older person may potentially serve as an entry criterion for a comprehensive geriatric assessment (GCA), an integrated process of diagnosis, assessment and management. In fact, its heterogeneous nature may require a multidomain evaluation in order to detect the underlying causes and propose person-tailored interventions. Covering multiple domains (e.g., physical, cognitive, affective, functional, socio-economical, environmental), CGA may allow a more effective identification of a hypothetical cause of fatigue and framing of concurrent conditions contributing to it. For example, when fatigue prompts to a hospital admission, the search for a specific diagnosis and treatment of a single cause (e.g., infectious disease, cancer) might be insufficient if not nested in a more comprehensive approach aimed at uncovering all the other possible determinants of it (e.g., affective disorders, sleep disorders, social issues). Such multidimensional process will lead to a better framing of the health status of the individual, potentially indicate complementary targets of intervention, and generate a more robust structure on which follow the patient over time.

Fatigue may play a precious role in the growing strategies aimed at preventing disabling conditions in our aging populations. In fact, it might represent a very sensible alert supporting the identification of frail individuals in the community-dwelling population. For example, in the primary care setting, general practitioners may better consider as abnormal such subjective symptom and potentially refer the individual to a second-level evaluation (possibly based on the CGA model). In other words, fatigue may indeed resemble an easy-to-assess and powerful marker of frailty (Zengarini et al., *in press*). Such process will be more robustly implemented when fatigue could be more reliably and objectively measured. The improved understanding of fatigue and the ability to identify different clinical manifestations of it may help researchers to describe multiple “fatigue profiles” (e.g., mainly physical or mental). This step may foster research aimed at identifying specific targets for future pharmacological and non-pharmacological interventions.

The lack of sufficient awareness about the clinical relevance of fatigue significantly affects the robustness of our knowledge on the topic. It is necessary to concentrate the research efforts in this field trying to 1) operationalize and standardize the assessment of the symptom, 2) appropriately measure the phenomenon in the population (especially in the older persons), 3) better understand its pathophysiological mechanisms, and 4) test potential interventions against it. All these ambitious and difficult tasks can be targeted and addressed only if the relevance of such potentially modifiable risk factor for negative outcomes in the elders will be sufficiently recognized.

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