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## Conference on Nutrition, immune function and infectious disease Symposia/Award: Symposium Three

### Fatigue in older persons: the role of nutrition

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Fatigue is defined as a symptom leading to the inability to continue functioning at the expected activity level. It is a highly prevalent symptom, challenging to frame into monodimensional pathophysiological mechanisms. As a result, fatigue is often underestimated in the clinical setting and is wrongly considered an unavoidable consequence of ageing. Several potential mechanisms responsible for fatigue have been proposed, including sleep patterns, autonomic nervous system abnormalities and biological complexity. Inflammation and mitochondrial dysfunction are among the most promising mechanisms through which malnutrition may cause fatigue. Not surprisingly, fatigue is highly prevalent in inflammatory conditions (e.g. COVID-19 infection). The nutritional status may also represent a critical factor in the development and presentation of fatigue, which may mimic the exhaustion of the individual's metabolic reserves. For example, the insufficient dietary intake of energy and proteins may determine the catabolism of body fat and muscles, disrupt the homeostatic balance and cause the onset of fatigue. It is necessary to conduct research on fatigue. By characterising its pathophysiological mechanisms, it will be possible to (1) support the design and development of targeted interventions, (2) improve the quality of life of many persons by acting on the symptom and (3) reduce the direct and indirect costs of a burdening condition typical of advancing age. In the present review, we provide an overview of the role that nutrition may play as a determinant of fatigue in older people, also in the context of the COVID-19 pandemic.

#### Ageing: COVID-19: Frailty: Sarcopenia: Malnutrition

Older people are frequently characterised by a high clinical complexity resulting from multiple chronic morbidities and mutually interacting syndromes. Furthermore, the ageing process exposes the individual to the onset

of clinical conditions challenging to frame and define, such as fatigue.

Fatigue is a highly prevalent symptom in older people, responsible for the inability to properly function at the

**Abbreviation:** FACET, fatigue in centenarians.

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expected activity level. Despite its high prevalence and clinical impact, fatigue is often overlooked and underestimated, often considered an unavoidable result of ageing. In this context, the absence of a gold standard for its measurement and the subjectivity of the symptom hamper the routine assessment in the clinical setting. It is also noteworthy that the multiple operationalisations of fatigue existing in literature (i.e. tiredness, exhaustion, lassitude, anergia) also contribute to its poor understanding<sup>(1)</sup>.

Fatigue is included in the diagnostic and statistical manual of mental disorders-fifth edition, where it is defined 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'<sup>(2)</sup>. It is a complex symptom with multiple potential causal mechanisms. Among the many proposed in the literature, the most promising pathways at the basis of fatigue are probably those related to sleep disorders, autonomic nervous system abnormalities, frailty and malnutrition<sup>(1)</sup>. Nevertheless, the biological substratum of fatigue remains unclear and difficult to disentangle. This gap of knowledge negatively affects the management of the symptom for which, for example, symptomatic interventions are currently missing.

The recent COVID-19 pandemic has further enhanced the need for research to advance in the field, given the high and long-lasting prevalence of fatigue among patients infected by the SARS-CoV-2<sup>(3,4)</sup>. We have previously indicated nutrition as a critical factor underlying the manifestation of fatigue (Table 1). In the present review, we provide an overview of the role that nutrition may play as a determinant of fatigue in older people, also in the context of the COVID-19 pandemic.

### Nutrition as a major determinant of fatigue

Several age-related physiological, pathological and psycho-social changes (Table 2) have been indicated as responsible for the so-called *anorexia of ageing* (i.e. the loss of appetite and/or decreased food intake in late life<sup>(5)</sup>), a risk factor for malnutrition, sarcopenia, frailty, morbidity and mortality<sup>(6-8)</sup>. Interestingly, some determinants of the anorexia of ageing (i.e. inflammatory cytokines, sleep disorders, poor dentition, depression) are strongly associated with fatigue<sup>(1,9,10)</sup>. Indeed, poor nutritional status may represent a mediator (if not a causal factor) in the clinical expression of the symptom.

Fatigue can be envisioned as a disorder of energy balance, a sort of alert launched by the organism in the

**Table 1.** Potential determinants of fatigue in older people and in the context of COVID-19 pandemic

	Fatigue in older people	Post-COVID-19 fatigue
Inflammation	<ul style="list-style-type: none"> <li>● Low-grade systemic inflammation (i.e. inflamm-ageing)</li> </ul>	<ul style="list-style-type: none"> <li>● Abnormal release of pro-inflammatory cytokines (i.e. cytokine storm)</li> </ul>
Mitochondrial dysfunction	<ul style="list-style-type: none"> <li>● Hallmarks of ageing</li> <li>● Defective immune response to viral infections (i.e. immunosenescence)</li> </ul>	<ul style="list-style-type: none"> <li>● Increased inflammatory or oxidative state</li> </ul>
ANS abnormalities	<ul style="list-style-type: none"> <li>● Modifications of the cardiac function</li> </ul>	<ul style="list-style-type: none"> <li>● Cardiovascular damage</li> </ul>
Poor nutritional status	<ul style="list-style-type: none"> <li>● Anorexia of ageing</li> <li>● Undernutrition</li> </ul>	<ul style="list-style-type: none"> <li>● Anorexia (i.e. loss of taste and smell, loss of appetite)</li> <li>● Weight loss and cachexia</li> <li>● High catabolic conditions</li> </ul>
Obesity and physical inactivity	<ul style="list-style-type: none"> <li>● Inflammation</li> <li>● Metabolic and endocrine alterations</li> <li>● Reduced mobility</li> </ul>	<ul style="list-style-type: none"> <li>● Inflammation</li> <li>● Immobilisation</li> <li>● Lifestyle changes (i.e. sedentary behaviour)</li> </ul>
Sarcopenia	<ul style="list-style-type: none"> <li>● Accentuated age-related muscle decline</li> </ul>	<ul style="list-style-type: none"> <li>● Cachexia</li> </ul>
Sleep alterations	<ul style="list-style-type: none"> <li>● Daytime sleepiness,</li> <li>● Poor nocturnal sleep quality</li> <li>● Sleep apnoea</li> <li>● Depression</li> <li>● Mood disorders</li> </ul>	<ul style="list-style-type: none"> <li>● Daytime sleepiness</li> <li>● Social isolation</li> <li>● Psychological distress</li> <li>● Anxiety</li> <li>● Sleep apnoea</li> </ul>
Respiratory complications	<ul style="list-style-type: none"> <li>● Chronic obstructive pulmonary disease</li> </ul>	<ul style="list-style-type: none"> <li>● Dyspnoea</li> <li>● Acute respiratory distress syndrome</li> <li>● Lung fibrotic damage</li> </ul>

ANS, autonomic nervous system.

Adapted from Azzolino and Cesari<sup>(87)</sup> under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

**Table 2.** Major changes occurring with ageing

Physiological	Pathological	Psychosocial
Digestive system	Diseases	Depression
Hormonal	Medications	Financial status
↓ Taste and smell	Neurological disorders	Anxiety
↓ Energy expenditure	Swallowing problems	Sleep disorders
Early satiety	Poor dentition	↓ Ability to shop or prepare meals
Cytokines	Poor mobility	Loneliness
Xerostomia		

Adapted from Azzolino *et al.*<sup>(52)</sup> under the Creative Commons Attribution 4.0 International license (CC BY 4.0).

presence of limited and decreasing reserves. When energy and protein intakes become inadequate to meet the demands, catabolic pathways are activated, explaining (at least, in part) the onset of fatigue<sup>(11)</sup>. Interestingly, fatigue is one of the most common symptoms of hypothyroidism, which is characterised by metabolic derangements, myalgias and muscle weakness<sup>(12)</sup>.

We recently explored the association between malnutrition (assessed using the mini nutritional assessment short form) and the lack of energy in a population of 570 nursing home (NH) residents<sup>(13)</sup>. In both univariate and multivariate logistic regression analyses, the mini nutritional assessment short form score was inversely associated with the lack of energy. In particular, decreased food intake, reduced mobility and stressful conditions were strongly associated with anergia.

#### *Inflammation and mitochondrial dysfunction*

As mentioned earlier, malnutrition can influence fatigue via direct and indirect mechanisms, influencing critical biological pathways such as inflammation and mitochondrial dysfunction. Mitochondria represent the hub of energy production through oxidative phosphorylation, in which nutrients are processed to generate ATP<sup>(14)</sup>. Ageing is characterised by a state of low-grade systemic inflammation (i.e. the so-called *inflamm-ageing*) and mitochondrial dysfunction<sup>(15)</sup>. In particular, inflammation, along with other predisposing factors (e.g. inadequate intake of energy and proteins), could lead to mitochondrial dysfunction with the production of mitochondrial damage-associated molecular patterns<sup>(14,16,17)</sup>. Consequently, there is an increased production of cytokines, chemokines, nitric oxide and reactive oxygen species, further promoting mitochondrial damage and establishing a vicious circle<sup>(16)</sup> with the enhancement of wasting syndromes<sup>(17,18)</sup>.

The mitochondrial dysfunction caused by critical illness and physiological ageing increases lactate levels and decreases ATP production, leading to reduced stamina and onset of fatigue<sup>(10,14,19)</sup>. The acidosis occurring at the skeletal muscle level resulting from the increased mitochondrial lactate production can manifest as muscular fatigue<sup>(20)</sup>. An inflammatory state and mitochondrial dysfunction are common in a variety of diseases characterised by the presence of fatigue, including type 2 diabetes, cardiovascular conditions, chronic fatigue syndrome or amyotrophic lateral sclerosis<sup>(11,21,22)</sup>. Indeed, mitochondrial dysfunction may represent a

marker of ageing and a consequence of the age-related deterioration of the organism<sup>(15)</sup>.

Interestingly, fatigue has been suggested as a clinical manifestation of underlying abnormal ageing. A recent consensus statement proposed the so-called accelerated ageing and cellular decline condition to identify persons expressing accelerated/acceluated ageing with fatigue representing a dominant phenotypic characteristic<sup>(23)</sup>.

#### *Sarcopenia, frailty and fatigue*

Ageing is associated with a progressive loss of muscle mass and strength leading to a poor physical function, the so-called 'sarcopenia'<sup>(24)</sup>. Conversely, frailty is defined as 'a clinical state in which there is an increase in an individual's vulnerability for developing an increased dependency and/or mortality when exposed to a stressor'<sup>(25)</sup>. Malnutrition, sarcopenia and frailty frequently show a remarkable overlap, especially in the physical domain<sup>(26–28)</sup>. Of note, fatigue is included (more or less explicitly) in some instruments to screen for frailty<sup>(29–31)</sup>.

Fatigue is strongly associated with poor physical function<sup>(32)</sup> which is recognised as a core component of both sarcopenia and frailty. In particular, according to the European working group of sarcopenia in older people, poor physical function (i.e. low gait speed) is used to determine sarcopenia severity<sup>(24)</sup>. Recently, Justine *et al.*<sup>(33)</sup> reported associations of fatigue severity (assessed with the fatigue severity scale) with the SARC-F questionnaire (acronym for the poor Strength, need of Assistance with walking, impaired Rising from a chair, difficulty at Climbing stairs and history of Falls), calf circumference, muscle strength and gait speed. Wyness *et al.*<sup>(34)</sup> found an association of low gait speed with higher scores for physical fatigue, reduced activity and reduced motivation. They also reported that the presence of sarcopenia was related to reduced motivation.

The reduction of muscle strength, a key characteristic of sarcopenia, is another aspect that should be considered. In fact, after the fourth decade of life there is a progressive reduction in muscle strength of about 1.5% per year<sup>(35)</sup>. The European working group of sarcopenia in older people, in the defining algorithm of sarcopenia<sup>(24)</sup>, has given priority to the assessment of muscle strength over the muscle mass quantification both to promote the concept of sarcopenia in clinical practice and for its strong predictive capacity for adverse clinical

outcomes<sup>(24,36)</sup>. Patino-Hernandez *et al.*<sup>(37)</sup> found an association among low gait speed and handgrip strength (i.e. two out of three sarcopenia-defining variables) with fatigue. To date, muscle fatigue can be defined as 'the inability of the muscle to produce or maintain force'<sup>(38)</sup>. In other words, the force developed by the muscle necessary to produce fatigue is the result of the maximum force that the skeletal muscle can develop. Accordingly, any factor reducing the maximum muscle force can result in fatigue and the consequent reduced muscle function<sup>(39)</sup>. As previously mentioned, the diagnostic and statistical manual of mental disorders-fifth edition defines fatigue (i.e. physical fatigue) as 'a specific, work-induced burning sensation within one's muscles' leading to the inability to continue functioning at the normal level of activity<sup>(2)</sup>. It is therefore clear that skeletal muscle abnormalities play a major role in the manifestation of the symptom. It has been also suggested that fatigue without disability may represent an early stage of frailty<sup>(9)</sup>, representing a limitation to performance<sup>(40)</sup> and impacting the capacity to conduct regular physical activities in older persons<sup>(41)</sup>. Therefore, fatigue may be envisioned as the clinical manifestation of the reduction of the homeostatic reserves of the older individual. In other words, given that poor physical function has been strongly associated with fatigue and is a core component of some instruments to early identify older people at risk for frailty and sarcopenia, the presence of fatigue may represent an early clinical indicator of the organism exhaustion.

#### *Obesity and fatigue*

Obesity has been consistently associated with increased levels of fatigue<sup>(42–44)</sup>. Also in this case, inflammation and mitochondrial dysfunction seem to play a relevant role<sup>(14,45–47)</sup>. In fact, in those people with obesity, the presence of low-grade systemic inflammation as a consequence of the release of several pro-inflammatory mediators can result in insulin resistance and then mitochondrial dysfunction, with a disruption of energy production<sup>(45,46)</sup>. It is interesting to note that, with ageing, parallel to the muscle mass decline there is an increase in adiposity which can mask the presence of sarcopenia if nutritional status is assessed through anthropometric measures such as BMI<sup>(18,48)</sup>. Furthermore, obesity is strictly associated with sleep disorders and vice-versa<sup>(49)</sup>. Sleep alterations are widespread among older people and are strongly interrelated with fatigue. In fact, according to the diagnostic and statistical manual of mental disorders-fifth edition of mental disorders, mental fatigue frequently manifests as somnolence (i.e. sleepiness)<sup>(2)</sup>. Obesity and sleep disorders share some metabolic determinants (i.e. insulin resistance, decreased, glucose tolerance) as well as endocrine alterations (i.e. abnormal cortisol, leptin and ghrelin levels)<sup>(49–52)</sup>. Also in this case, obesity-related inflammation may alter sleep parameters with the consequent manifestation of fatigue<sup>(53)</sup>.

#### *Nutrition, fatigue and COVID-19*

Fatigue has been reported as the most complained and persistent symptom of the COVID-19 infection<sup>(3,4)</sup>.

Interestingly, some mechanisms potentially determining fatigue seem to be common to both older people and COVID-19 patients (Table 1). The COVID-19 infection is characterised by an increased inflammatory state (i.e. arriving up to the so-called 'cytokine storm' in the most severe cases)<sup>(54)</sup>. Indeed, COVID-19 infection results in a high catabolic response, predisposing to weight loss and muscle wasting, which may further explain the manifestation of fatigue<sup>(55)</sup>.

The COVID-19 infection is also characterised by loss of taste and smell (which can persist for several months) along with gastrointestinal alterations (i.e. nausea, vomiting, diarrhoea), enhancing the anorexia of ageing<sup>(56)</sup>. At the same time, obesity has been evoked as a predisposing factor for COVID-19 infection and disease severity. Again, the mediating mechanisms might be indicated in inflammation and mitochondrial function abnormalities<sup>(48,57–59)</sup>.

Finally, since muscle wasting and weakness occur as whole-body processes, they also involve muscles dedicated to breathing and swallowing, challenging their function<sup>(60)</sup>. For example, the resulting weakness of respiratory muscles may contribute to the so-called 'respiratory fatigue'<sup>(39)</sup> characterised by a decrease in expulsive airway clearance tasks (i.e. coughing and sneezing), and increased risk of respiratory infections.

#### **Nutritional strategies**

Given that some determinants of fatigue are the same of anorexia of ageing and sarcopenia, nutritional strategies aimed at counteracting muscle loss could be beneficial against fatigue. In this context, it might be important to compensate the eventual deficits of energy and protein intake to meet the individual's specific needs. It is noteworthy that, according to the recommendations<sup>(61,62)</sup>, older people need more protein to counteract muscle decline. In particular, the suggested amount of protein is 1–1.2 g/kg of body weight/day and up to 1.2–1.5 g/kg of body weight/day in the presence of acute or chronic illness<sup>(61,62)</sup>. In relation to energy provision, it has been proposed a guiding value of about 125.52 kJ/kg (30 kcal/kg) of body weight/day<sup>(63)</sup>. In addition, the amount of energy intake has to be adjusted according to the person's nutritional status, physical activity and diseases<sup>(63)</sup>.

The 'energy diet', proposed by the National Health Service for sleep and tiredness, may represent an interesting strategy<sup>(64)</sup>. Recommendations include eating at least five portions/day of fruit and vegetables and the consumption of starchy carbohydrates. The importance of iron-rich foods is also emphasised<sup>(64)</sup>. Special attention is also paid to alcohol intake and food fortification (to increase energy and nutrient density).

It is important to note that no single food (including the so-called 'superfoods') can provide an energy boost. All the vitamins and minerals needed by the organism can be provided by eating a healthy, balanced diet. Some groups of people at risk of nutrient deficiencies might be advised to take a supplement. Fatigue is observed in some conditions characterised by





micronutrient deficiencies<sup>(1)</sup>, and some vitamins and minerals are pivotal for mitochondrial functioning<sup>(14)</sup>. It has been hypothesised that antioxidant supplementation may reduce fatigue in animal models<sup>(10)</sup>, but the evidence in human subjects remains scarce<sup>(65)</sup>.

Most evidence for nutritional interventions against fatigue comes from the chronic fatigue syndrome. Several studies have demonstrated a potential benefit on fatigue from creatine supplementation, both stand-alone or in combination with exercise training<sup>(66)</sup>. Creatine is mainly stored in muscles, where it is converted into phosphocreatine through the enzyme creatine kinase. The phosphocreatine acts as an energy shuttle, transferring a high-energy phosphate group to adenosine diphosphate to regenerate ATP during the muscle contraction<sup>(67,68)</sup>.  $\beta$ -hydroxy- $\beta$ -methylbutyrate, a metabolite of leucine, has been also indicated as a promising agent. Several studies (mostly conducted in athletes) have reported that the  $\beta$ -hydroxy- $\beta$ -methylbutyrate supplementation may promote muscle health and increase resistance to fatigue<sup>(69)</sup>. Beneficial effects of acetyl L-carnitine on mental and physical fatigue have been reported by Malaguarnera *et al.*<sup>(70)</sup>. Low concentrations of vitamin D have also been associated with both mental and physical fatigue in older people<sup>(71)</sup>.

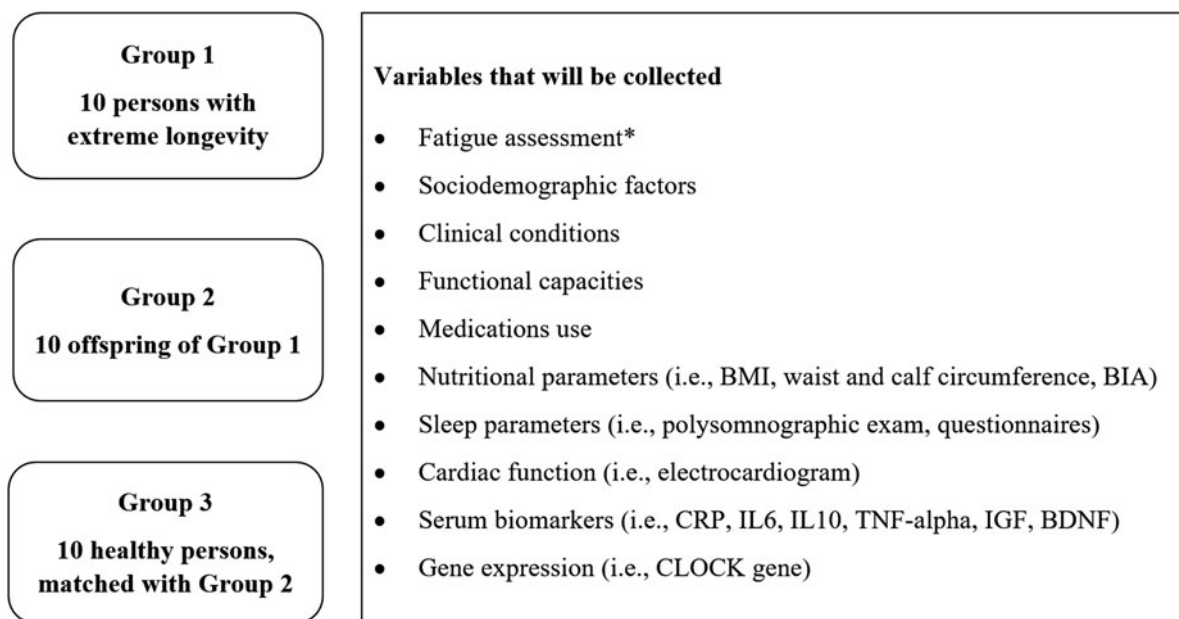
Coenzyme Q plays an important role in the mitochondrial electron transport chain, and coenzyme Q10 has showed antioxidant and anti-inflammatory properties<sup>(72)</sup>. NADH is also involved in the mitochondrial function<sup>(73)</sup> and regulation of inflammation<sup>(74)</sup>. Castro-Marrero *et al.*<sup>(75)</sup> have reported that NADH and coenzyme Q10 supplementations are able to reduce fatigue in patients with chronic fatigue syndrome.

Low concentrations of selenium have been associated with anxiety, depression and tiredness<sup>(76)</sup>. Selenium may

influence mitochondrial biogenesis<sup>(14)</sup> as well as the antioxidant defence, redox signalling and redox homeostasis<sup>(77)</sup>. With its antioxidant properties, selenium is involved in the dampening of the inflammatory responses by eliminating free radicals<sup>(78)</sup>. Oral supplementation with coenzyme Q10 plus selenium has shown to improve fatigue through the modulation of oxidative stress and inflammatory status in chronic fatigue syndrome<sup>(79)</sup>. Other studies reported improved well-being and diminished fatigue in patients with autoimmune hypothyroidism from selenium supplementation<sup>(80–82)</sup>. Some seleno-proteins (i.e. glutathione peroxidases, thioredoxin reductases) seem to be effective at controlling oxidative stress and inflammation<sup>(77,83,84)</sup>. Glutathione might also be of interest for reducing fatigue, given its immunomodulating capacity<sup>(85)</sup>. *n*-3 PUFA have been indicated as potentially beneficial in inflammatory conditions (mainly for their effect on mammalian target of rapamycin and insulin resistance)<sup>(86)</sup>, and might be worth to be explored in the management of fatigue.

### The fatigue in centenarians study

The fatigue in centenarians (FACET) pilot study has been established to preliminarily explore the complex mechanisms underlying fatigue in older persons. In particular, FACET focuses on three critical mechanisms (i.e. sleep patterns, nervous autonomic system, biological complexity) potentially at the basis of fatigue. It hypothesises possible interactions of fatigue with age and sleep, age and heart rate variability, age and biological complexity. In FACET, a total of thirty participants will be recruited. The sample will be composed of ten persons presenting extreme longevity (e.g. centenarians), ten direct offspring of them and ten apparently



**Fig. 1.** Variables that will be collected in the FACET study. BIA, bioelectrical impedance analysis; CRP, C reactive protein; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IGF, insulin growth factor; BDNF, brain-derived neurotrophic factor. \*Brief fatigue inventory<sup>(88)</sup>, SF-36 vitality subscale<sup>(89)</sup>, the multidimensional assessment of fatigue<sup>(90)</sup>, fatigue severity scale<sup>(91)</sup>.

healthy older persons (matched with the offspring by age and sex). The main eligibility criteria applied in the recruitment of the three groups are: (1) inability/unwillingness to provide written informed consent, (2) clinician's perception that the participant may not adhere to the study protocol, (3) type 2 diabetes, (4) use of benzodiazepines and/or  $\beta$ -blockers. A comprehensive assessment of participants is conducted by trained personnel (Fig. 1). Analyses are planned to be conducted in the whole sample and separately in the three groups of participants. The interaction terms defining the three study groups will be tested in the associations of interest to capture possible differences and similarities across groups.

FACET is a pilot experience to provide preliminary data to approach the fatigue symptom at the clinical and biological levels. It will be considered a successful experience if it will provide robust information for designing/optimising future research initiatives, particularly for the definition of targets of pharmacological and non-pharmacological interventions.

The FACET recruitment phase started on October 2021 and is expected to end in September 2022. The results will be released on spring 2023.

### Conclusions

Fatigue is a complex and multidimensional symptom. Although older adults frequently report it, its underlying mechanisms are still incompletely understood. Consequently, fatigue is commonly considered an unavoidable result of ageing and remains often neglected in clinical practice. Nutritional status may play a critical role in explaining the fatigue manifestation. In particular, fatigue may represent the clinical expression of an abnormal ageing process caused or mediated by inadequate nutrition. Increased efforts should be made to better characterise fatigue at the biological and clinical level to support the development of specific interventions against such a burdening symptom.

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### Conflict of Interest

Matteo Cesari has served as consultant and member of scientific advisory boards for Nestlé Health Science. The other authors declare no conflict of interest.

### Author Contributions

D. A. contributed to conceptualising and writing the manuscript. H. J. C. J., M. P., V. M. M. and M. C. edited and revised manuscript. All the authors approved the final version of manuscript.

### Authorship

The authors had sole responsibility for all aspects of preparation of this paper.

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