Early detection of accelerated aging and cellular decline (AACD): A consensus statement

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ABSTRACT

The cellular hallmarks of accelerated aging and their clinical expression may be grouped using the terms 'accelerated aging and cellular decline' (AACD) and/or 'age-associated cellular decline'. This construct is designed to capture the biological background predisposing the development of age-related conditions. By classifying risk factors, early indicators, and clinical differentiators of AACD through expert consensus, this study aimed to identify the signs, symptoms, and markers indicative of AACD. In doing so, this work paves the way for future implementation of the AACD concept in the clinical and research settings.

An interdisciplinary panel of experts with clinical and research expertise was selected to participate in a virtual workshop to discuss AACD. A modified nominal group technique was used to establish consensus among the group. An extended group of international experts critically reviewed an early draft of the manuscript, and their feedback was then incorporated into the model.

Experts identified 13 factors predisposing to or clinically manifesting AACD. Among these, chronic diseases, obesity, and unfavorable genetic background were considered as the most important. There was a consensus that a gradual and nonspecific development often characterizes AACD, making its clinical detection potentially challenging. In addition, signs and symptoms might have multifactorial causes and overlapping origins, such as genetic and epigenetic predispositions. As a result, an initial checklist was outlined, listing clinical factors of special relevance (e.g., fatigue, low quality of sleep, and low mood) to represent early manifestations of the organism's exhaustion, which are also frequently neglected in the clinical setting.

Differentiating AACD from other conditions is essential. The use of a combination of biomarkers was proposed as a viable method in a two-step process of differentiation: 1) identification of early AACD clinical indicators, followed by 2) symptom and biomarker confirmation with a focus on system domains (to be potentially targeted by future specific interventions).

Although the AACD construct is not yet ready for routine use in clinical practice, its operationalization may support the early identification of age-related conditions (when this might still be amenable to reversion) and also encourage preventative interventions. Further investigation is needed to establish specific biomarkers that confirm independent risk factors for AACD and provide a more definitive structure to the concept of AACD (and age-associated cellular decline).

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1. Introduction

Aging of multicellular organisms is a highly complex biological processthat is associated with increasing deterioration of health and physical performance (Diot et al., 2016). The aging process acts simultaneously at three interconnected levels. At the cellular level, cells deteriorate as they lose their ability to function optimally. This process may lead to organ-specific dysfunction at the organ level, which may consequently become responsible for the development of age-related diseases, symptoms, and clinical signs at the organism level (Andreux et al., 2018).

While aging involves a time-dependent progressive decline in biochemical and physiological functions (Massudi et al., 2012), cellular changes precede subsequent clinical manifestations (Franceschi et al., 2019). Clinically, aging is therefore often associated with loss of resilience alongside a reduction in other functional domains (Campisi et al., 2019).

Resilience is assessed dynamically, with evaluation of time series able to capture capacity to recover from a stressor at the cellular, organ, and organism level (Gijzel et al., 2019). Loss of resilience is associated with reduced stamina. Individuals aged approximately 55 years sometimes complain of reduced muscle strength, decreased mobility, and fatigue. These complaints tend to increase with aging, especially after the age of 65 (Etman et al., 2012). It is important to note that the phenotype of the aging individual results from a combination of genetics and environmental factors. In this context, it is noteworthy that aging is a complex, time-related process responsible for the extreme biological heterogeneity of the population (Franceschi et al., 2019; Cesari et al., 2013). This fact is further complicated by the close relationship existing between time (i.e., aging) (Massudi et al., 2012) and clinical conditions (i.e., disease) (Lopez-Otin et al., 2013). Defining this relationship is challenging but essential for understanding the complexities of advanced aging development in the course of the individual's life (Cesari et al., 2013).

The role of prevention in reducing the burden of age-related conditions that our aging societies are experiencing (and will continue to experience) has been repeatedly advocated (Fries, 2000; Verbrugge and Jette, 1994). It is important to acknowledge the complexity of aging and age-related conditions through a system biology approach. Therefore, it is crucial not to dismiss the fact that the aging process plays a critical role in the onset, development, and characterization of age-related diseases. Clinically, a more in-depth evaluation able to give more value to the myriad of neglected signs and symptoms mirroring the underlying process of aging may pave the way towards more personalized interventions. For example, a decline in food intake is commonly observed in older individuals, partly due to the pathophysiological changes of aging (Azzolino et al., 2020). The resulting nutritional deficiencies may worsen the individual's clinical status and contribute to the acceleration of aging (Kaur et al., 2019). The age-related reduction of muscle mass and strength starting after the age of 40 [termed sarcopenia (Cruz-Jentoft et al., 2019)] may only be partially reduced by physical exercise. Interventions that can mitigate the age-related biological modifications of the skeletal muscle might be affected by lifestyle modifications.

The current understanding of aging in mammals includes the concept of hallmarks of aging. To qualify as a hallmark of aging, a trait must occur during normal aging, contribute to the aging process itself, and be potentially modifiable. At the same time, its experimental amelioration should provide the ability to facilitate healthy aging (Campisi et al., 2019). Biological hallmarks of aging have been identified as: genomic instability, telomere attrition, loss of proteostasis, deregulated nutrient sensing, altered intercellular communication, cellular senescence, stem cell exhaustion, epigenetic alterations, and mitochondrial dysfunction (Diot et al., 2016; Lopez-Otin et al., 2013).

The detection of early signs of accelerating aging, which potentially contributes to future adverse health-related events, could allow for corrective interventions and promote healthy aging (Lopez-Otin et al., 2013; Kaur et al., 2019). In this context, it might be important to define those health deficits (i.e., signs, symptoms, and biological abnormalities) suggestive of an underlying pathological trajectory of the aging process. Unifying these manifestations using an umbrella term may facilitate their inclusion and recognition in the clinical field and promote research in aging. This could also assist in raising awareness of many too often overlooked abnormalities of health status and potentially anticipate targeted interventions (Andreux et al., 2018).

In this article, the authors propose that the term 'accelerated aging and cellular decline' (AACD) [or 'age-associated cellular decline'] refers to the clinical expression of the hallmarks of aging (see below) (Cesari, 2020; Goodpaster, 2020).

Characterizing the clinical signs of AACD could help in identifying those individuals at risk of pathological/accelerated aging, irrespective of their chronological age or overt clinical profiles. The aim of this pilot expert opinion study was thus to provide an initial framework for the clinical identification of AACD and potentially pave the way towards the future operationalization of the AACD construct. This initiative sought to identify, through expert consensus, risk factors and early indicators that are currently neglected in the clinical setting, despite their mirroring biological markers of abnormal aging.

2. Methods

2.1. Selection of the expert panel

2.1.1. Interdisciplinary expert panel

The overall objective of the workshop was to identify (through a pre-meeting survey) and prioritize (during the workshop) key indicators of AACD in order to build a theoretical framework for this concept. Given the authors' belief that it would be easier to have a meaningful discussion and reach a consensus if the initial panel was limited, five specialists were recruited to sit on this expert panel to evaluate the preliminary theme and draft key principles. This initial panel of research scientists and geriatricians was identified from four different countries (Italy [MC, AC], USA [JG], Spain [LRM], and Switzerland [AB]). Members were selected based on clinical and research expertise in the fields of geriatrics (MC, LRM, AC, JG), public health and health economics (AB), and epidemiology (JG). They all agreed to participate in a virtual workshop.

2.1.2. Extended group of experts

An extended group of 13 international geriatric experts from 11 different countries (Japan [HA], USA [BG; JW], Mexico [MUPZ], Australia [RV], New Zealand [DW], Singapore [WSL], Italy [EM], Spain [MI], France [LC], Brazil [ABGdT], and the Netherlands [MOR]) then reviewed and critically commented on the draft framework that was initially developed by the interdisciplinary expert panel.

2.2. Consensus development

The modified nominal group technique (NGT) was used to establish consensus among the interdisciplinary expert panel. To facilitate the NGT in a virtual format, opinions from the expert panel were collated before the virtual meeting. The questions were developed and refined by the lead author to facilitate and direct the workshop discussions. The questions were then sent to advisors via an electronic survey as part of the pre-workshop assignment along with relevant background literature (Suppl. Table 1).

All surveys were created and distributed electronically using an online survey development and distribution platform ahead of the virtual workshop. The responses were collected and stored on a secure database, to be presented and discussed during the virtual workshop, conducted over a web-based conferencing platform. To allow more time for discussion and limit conflicting schedules, two parallel workshops were held. Each member of the panel attended one workshop, except for the meeting chair, who attended both. During the workshops, the

Table 1
Prioritized physical and environmental risk factors for accelerated aging and cellular decline.

Identified risk factors
Demographic/clinical characteristics
Clinical conditions (cardiovascular, renal, metabolic disease, cancer)
Obesity
Unfavorable genetic background[a]
Insulin resistance
Low physical capacity (e.g., slow gait speed, muscle weakness)
Environmental/behavioral
Smoking
Sedentary lifestyle
Low physical activity
Persistent physical or psychological stress
Low socioeconomic status
Alcohol abuse
Inadequate nutrition
Air pollution[a]

Risk factors presented in order of ranking by the interdisciplinary expert panel.
[a] Nonmodifiable risk factors.

predefined key topics and submitted responses were discussed, and attendees were allowed to prioritize responses using electronic polling software. The top five answers to each topic provided by each member of the interdisciplinary panel were analyzed following the workshops and discussed to identify the most relevant items for inclusion in the framework.

An initial report of outcomes from the workshops was drafted based on prioritization scores, and this was subsequently shared with the expert panel. Recommendations were first refined by the interdisciplinary expert panel and subsequently by the extended group of experts. The extended group of experts critically reviewed an early draft of the manuscript, and their feedback was then incorporated into the framework. The wider expert group ensured that the consensus reached during the workshop was in agreement with opinions held by a wider audience of experts with clinical and research backgrounds.

2.3. AACD terminology

Reference to AACD as accelerated aging and cellular decline evolved over time. The pre-meeting survey questions feature a definition of AACD as 'age-associated cellular decline' to reflect preliminary discussions between the interdisciplinary expert panel. After careful consideration and debate during the workshop, it was agreed the term 'accelerated aging and cellular decline' accurately captures the novel concept of abnormal trajectory of the aging process. For this reason, the acronym AACD is defined primarily as 'accelerated aging and cellular decline' while acknowledging the original definition of 'age-associated cellular decline'. In other words, the term 'age-associated cellular decline' is proposed to refer to the cellular origins of the hallmarks of aging, whereas 'accelerated aging and cellular decline' represents their longitudinal clinical expression (Cesari, 2020; Goodpaster, 2020).

3. Results

Refinement of the term AACD occurred following in-depth discussions with the authors as to how best to define the concept of the abnormal aging process. It was decided that 'accelerated aging and cellular decline' best encompasses the clinical expression determined by accelerated aging. It is important to note the evolvement of the term when referring to the pre-meeting survey questions (Suppl. Material).

3.1. Risk factors for AACD

The experts identified 18 potential predisposing factors for AACD (or age-associated cellular decline). Following discussions and

prioritization, five items were discarded, leaving 13 potential risk factors (Table 1), of which two were deemed nonmodifiable. Several environmental, clinical, and demographic characteristics were considered particularly important, although smoking was consistently viewed as the most prominent risk factor for AACD (Suppl. Fig. 3).

Age is considered a central factor influencing AACD, but was removed from the construct for two main reasons. Firstly, age has itself been recognised as potentially the strongest risk factor for the clinical conditions identified as risk factors for AACD, and may therefore obscure other elements. Secondly, the inclusion of age may lead to an ageist profile within the framework.

The presence of chronic diseases, physical or psychological stress, sedentary lifestyle, and obesity were also ranked highly. Clinical conditions such as diabetes, cardiovascular disease, cancer, and renal disease were noted as risk factors, with chronic inflammatory conditions associated with AACD (Chung et al., 2019).

Sex was not prioritized as a risk factor by the expert panel. However, there were opposing views regarding this decision. Some experts felt that men are on a worse trajectory of cellular decline than women for some conditions (Crimmins et al., 2019). In contrast, others noted that women may have longer lifespans (Crimmins et al., 2019) and may, therefore, accumulate a more considerable burden of AACD.

3.2. Detection of AACD

Detection of AACD is based on individual phenotypic expression. It is thus important to link the clinical manifestation to the underlying cellular changes responsible for early deviations from the optimal aging trajectory.

A total of 16 factors heterogeneously contributing to AACD were mentioned as being of particular interest. To provide a potentially unifying framework connecting biological mechanisms with the clinical phenotype, these factors were organized as clinical features, biological domains, and specific pathways (Table 2). The items identified in Table 2 include overlapping concepts, the impact of which on AACD assessment is difficult to predict or discern. Therefore, no specific weighting was assigned to each of the indicators at this stage. To fully quantify the AACD concept, individual indicator weighting must be determined empirically through further validation studies. As aging progresses, AACD is characterized by gradual and increasingly evident manifestations. Because of the low severity of clinical manifestations in the early stages, they might be easily overlooked, making early detection of AACD more challenging (Franceschi et al., 2019).

Following the panel discussions, it was agreed that to adequately consider AACD-related manifestations in adults who may not necessarily require clinical management, it is crucial to raise awareness about neglected signs and symptoms. To date, these are considered as clinically marginal, especially in apparently healthy individuals. However, their identification, measurement, and early management might be pivotal to promote a biology-driven approach in the management of AACD and potentially allow the implementation of *ad hoc* preventive solutions. In this context, the novel field of geroscience, which aims to understand the molecular and cellular mechanisms behind the association of aging with increased risk of multiple chronic conditions, is of

Table 2
Main framework of identifying accelerated aging and cellular decline.

Underlying cellular and subcellular networks	Domains	Clinical indicators
Cellular senescence *(mitogenesis)*		Fatigue
Mitochondrial abnormalities	Energy metabolism	Low quality of sleep
Metabolomic signaling (*insulin sensitivity*)	Immune system	Low mood
Inflammation pathway signaling	Central nervous system	Lack of motivation
Autophagy/mitophagy	Body composition	Subjective memory complaints
Oxidant/antioxidant balance		Poor exercise tolerance

particular interest (Sierra, 2019).

3.2.1. Biomarkers

When considering potentially relevant biomarkers, the US Food and Drug Administration definition of a "defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention" was used [*BEST (Biomarkers, EndpointS, and Other Tools) Resource,* 2016]. The panel envisaged that biomarkers could be used to confirm the presence/absence of AACD that is suggested by specific clinical manifestations.

Agreement on a definitive set of AACD biomarkers will be necessary for characterizing the target populations in future clinical investigations for possible interventions. The use of biomarkers to track the underlying aging process was discussed at length. In particular, the possibility of using biomarkers in combination with clinical tests to differentiate AACD from other conditions was mentioned. Raising awareness about clinically evident but often neglected aspects of the accelerated aging process (e.g., sedentary behavior, psychological stress, and malnutrition) through the use of biomarkers was also debated.

Interestingly, there is increasing evidence in favor of biomarkers capturing specific risk profiles [e.g., low concentrations of vitamin D (Caristia et al., 2019), high levels of oxidative stress indicators (Dodig et al., 2019; Liguori et al., 2018)]. Similarly, methods for measuring levels of frailty-associated biomarkers [e.g., specific microRNAs (Cardoso et al., 2018)] are already available for use today (Vasto et al., 2010).

The participating experts debated the use of inflammatory biomarkers, despite agreeing about the increasing evidence that these are useful biomarkers for capturing an individual's biological aging (e.g., the so-called 'inflamm-aging' theory) (Campisi et al., 2019; Vatic et al., 2020; Kane and Sinclair, 2019). Nevertheless, as inflammatory mediators are also increased in many conditions not necessarily linked to aging *per se* (Rea et al., 2018), the consensus was that they would be nonspecific for AACD. It was therefore suggested that a multidimensional panel of biomarkers should be preferred over the use of any single biomarker to capture the multifaceted nature of AACD. This was the preferred approach as it better represents the complexity of AACD and acknowledges the need for multidimensional strategies to assess it adequately. Currently, there is insufficient literature to specify the exact biomarkers that should be recommended for the definition of AACD. Several features of AACD have not yet been validated (e.g., cellular senescence, autophagy/mitophagy). As a result, further investigation into ways to measure cellular/subcellular components will be warranted to define the concept further.

3.3. Clinically relevant triggers for intervention

The interdisciplinary expert panel prioritization indicated that the most important clinical manifestations of AACD requiring intervention are related to a reduction in energy and engagement in physical and social activities (Pek et al., 2020). Items identified as relevant triggers also included those considered to be later-stage manifestations of AACD, such as decline in mobility and muscle function. Furthermore, slow recovery from an illness was mentioned during this discussion, and the topic of resilience was regarded as an important area to explore. Observation of resilience may offer an opportunity to monitor and detect systemic failures in specific organs as well as in the whole organism (Scheffer et al., 2018).

3.4. Differentiating AACD from other conditions

Many clinical constructs for identifying AACD in an individual are moving away from the age- and/or disease-driven approach towards more biology- and/or function-focused ones. The need for a novel construct to differentiate AACD from other conditions (e.g., frailty, intrinsic capacity, resilience) was debated. Both the interdisciplinary

panel and the extended group of experts felt this to be a key aspect.

It was agreed that the process of AACD is responsible for age-associated conditions such as frailty (Martin and O'Halloran, 2020). The World Health Organization recently presented the theoretical concept of 'vitality'. According to the provided definition, vitality would represent the biology of aging responsible for the clinical manifestation of the individual's intrinsic capacity (Beard et al., 2019). AACD may represent the 'other side of the coin' of the positive concept of vitality. AACD focuses on the loss of energy reserves in the individual due to aging. It is noteworthy that clinical practice is designed to detect abnormalities and deficits (e.g., diseases), and is not particularly apt for capturing reserves. The concept of AACD may thus be relatively easy to adopt in the clinical setting owing to the negative health attributes being currently neglected but still having a significant impact.

Recognition of AACD as a condition of the above-mentioned geroscience opens avenues towards possible geroprotective interventions to target the fundamental mechanisms of aging, such as mitochondrial dysfunction (Campisi et al., 2019; Kennedy et al., 2014). Furthermore, the presence of conditions such as obesity may be indicative of underlying cellular decline. Targeting these aging pathways may provide an opportunity to prevent a worsening in physiology and potentially revert to an improved health status (Campisi et al., 2019).

The preference ranking identified the absence of chronic pain as a critical point. Conditions characterized by chronic pain often exhibit ancillary symptoms similar to the clinical markers of AACD. Consistently, the extended group of experts suggested including the assessment of pain to isolate AACD from other conditions that have this symptom as an overarching feature (Booker and Herr, 2016).

Using a combination of biomarkers was also considered a viable method for future clustering and differentiation of eventual subgroups of AACD. The panels proposed that biomarkers could be adopted to confirm the results of a clinical composite scoring system. This may aid differentiation of specific subgroups of AACD in the future.

4. Discussion

Seeking to categorize the main features of AACD and define its critical indicators may help to identify at-risk populations and increase awareness surrounding the issue of the biological modifications caused by an accelerated aging process (Andreux et al., 2018). The identification of highly vulnerable individuals would enable the implementation of effective preventative strategies (Woolford et al., 2020). Highlighting research that pinpoints when the process of aging starts to accelerate abnormally may contribute to improved quality of life over the person's lifetime. Lifestyle modifications in an individual's life course, such as nutritional and physical activity interventions, were also thought to support the optimal trajectory of aging. Prompt implementation was considered to be the most effective in preventing subsequent consequences on physiology and function (Robinson, 2018).

In our discussions, the aging process still has to be considered a natural and universal phenomenon that cannot be reversed. However, there is potential to correct its trajectory when this deviates from the norm (Pichard et al., 2020; Barzilai et al., 2016; Fontana et al., 2014). Age was considered the pivotal factor influencing the onset of AACD, but defining a risk group based on chronological age could be argued as ageist. Furthermore, it might potentially distract from the real basis of the construct, which is defined by all the subclinical and clinical conditions affecting the biological status of the individual (Vasto et al., 2010).

The interdisciplinary panel agreed that important clinical triggers suggesting the presence of AACD can be found in the reported reduction of self-perceived energy and reduced engagement in physical and social activities. Diseases, physical or psychological stress, and sedentary lifestyle were also ranked highly for their contribution to AACD. It has been shown that diseases positively correlate with age because of the exponential increase of biological abnormalities accumulating in the

organism over time (Prasad et al., 2012). This association supports the presence of such conditions as useful alerts, indicating the underlying presence of AACD.

Biomarker availability was discussed by the expert panel as a means to differentiate AACD from other conditions. Despite recent advances, including research highlighting the pivotal role of oxidative stress in conditions closely associated with aging (e.g., cardiovascular disease, diabetes, cancer) (Vasto et al., 2010), the use of these biomarkers in exploring human aging remains limited. Although many *in vitro* markers are available, their lack of specificity means they cannot be used *in vivo* and may not be sufficiently specific to form the sole basis for AACD identification (Vasto et al., 2010).

The identification of AACD should be based on assessing multiple biological domains and mechanisms (as those mentioned in Table 2), which together provide a comprehensive overview of such a complex and heterogeneous condition. Further information may characterize the relative importance of multiple biological patterns, enabling the integration of these into a future composite score. A composite score may be demonstrative of the specific domains of interest that have been identified (Mitnitski et al., 2015), and this score may be used to define specific subgroups of AACD in the future.

Frailty is defined by a continuing decline in functional reserves, and there have been recent advances in refining this categorization further (Woolford et al., 2020). For example, the stratification of frail individuals using processes such as the comprehensive geriatric assessment has been linked with reductions in length of hospital stay and readmission rates. Frailty identification can be assessed by the means of multiple methods, including the phenotype model, the cumulative deficit model, and the Clinical Frailty Scale (Woolford et al., 2020). A large EU-funded project (FRAILOMIC) aimed to support subgroup categorization for frailty by analyzing 30,000 potential biomarkers to build a biological index. Although the data are still being analyzed, it appears that very few of those biomarkers would be able to add accuracy to the phenotypic markers currently used in clinical practice (Erusalimsky et al., 2016). Other studies have explored the overlap between different conditions, such as the commonality between frailty and multimorbidity (Yarnall et al., 2017). Increased age is associated with a higher prevalence of morbidities. Although many older adults with frailty have multimorbidity, the majority of people with multimorbidity are not frail.

Resilience was highlighted as an essential factor to consider in characterizing AACD. While Justice et al. (Justice et al., 2016) have mentioned that age can be an independent risk factor for adverse outcomes resulting from interventions, they also examined the challenges in quantifying the concept of resilience if insult or injury is unexpectedly experienced. They proposed a proof-of-concept approach encouraging the use of the term 'artificial' injuries in healthier middle-aged or older adults. They suggested evaluating recovery from wound healing after a skin biopsy or testing immune responses through vaccinations, pointing out that this approach would provide greater scientific control, from study population and initial conditions to selected intervention and outcomes. Similar approaches might be considered as we look into validating the initial AACD framework before its implementation in the clinical setting.

The use of the NGT in this study permitted establishing a consensus among the interdisciplinary expert panel. This method encouraged a proposal of a wide variety of potential risk factors for AACD during the anonymous idea-generation stage and precluded undue influence from any specific group members. As opinions of the expert panel were gathered before a virtual meeting, all the ideas generated were given equal attention regardless of who proposed them. The method was effectively carried out within single meetings and did not necessitate multiple rounds of responses. In this way, the sessions enabled discussion of the different biological markers, clinical indicators, and differentiators of the AACD construct, and explored reasons for these differences with a reduced risk of misunderstanding.

Limitations of using the NGT, however, still include the lack of flexibility. There was no opportunity for discussion outside of the pre-specified topics nor the chance for participants to re-evaluate ranking based on group results. In addition, the participation was limited to a small group of experts whose opinions may not have been representative of their fields. The purpose of the extended group review was to mitigate this weakness by bringing in a broader range of expertise and reducing the possibility of biased views. One point to note is that an NGT is generally implemented following a systematic review. However, given that the topic of AACD is a previously uncharacterized concept, a systematic review was not considered necessary for this consensus process.

The complexity of AACD suggests that the condition (consistent with the complex nature of the aging process) might be better framed through a multidimensional paradigm, encompassing clinical, functional, and biological parameters. In the future, the further characterization of AACD as a geroscience condition may render it eligible for geroprotective interventions targeting the biological pillars of accelerated aging. A major assumption in defining AACD is that there is an established norm by which to evaluate accelerated aging. Which particular reference groups should be used to develop quantitative criteria or thresholds for AACD remains to be determined.

In the next phase of development, it would be interesting to see whether a predictive tool can be developed to allow even more specific refinement of the clinical indicators exemplified in Table 2, as many of them result in heterogeneous clinical manifestations. These clinical indicators of AACD may cause all of the symptoms proposed to be associated with AACD. This aspect highlights the challenges of discriminating between numerous confounders, especially those that may be impacted by socioeconomic and cultural factors.

In conclusion, this consensus statement examines the signs and indicators of AACD, proposing an initial framework that can act as the basis for future discussions and promote the development of a specific self-assessment tool. Further studies are necessary to confirm and validate the proposed checklist of AACD clinical features, leading to the potential development of a more quantitative instrument, thus translating the concept of AACD into clinical practice. The present work also identifies the need for further research to ascertain additional biomarkers and quantify independent risk factors to allow a holistic, definitive capturing of AACD.

CRediT authorship contribution statement

Declaration of competing interest

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2021.111242.

References

Andreux, P.A., van Diemen, M.P.J., Heezen, M.R., et al., 2018. Mitochondrial function is impaired in the skeletal muscle of pre-frail elderly. Sci. Rep. 8 (1), 8548.

Azzolino, D., Arosio, B., Marzetti, E., Calvani, R., Cesari, M., 2020. Nutritional status as a mediator of Fatigue and its underlying mechanisms in older people. Nutrients 12 (2).

Barzilai, N., Crandall, J.P., Kritchevsky, S.B., Espeland, M.A., 2016. Metformin as a tool to target aging. Cell Metab. 23 (6), 1060–1065.

Beard, J.R., Jotheeswaran, A.T., Cesari, M., Araujo de Carvalho, I., 2019. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. BMJ Open 9 (11), e026119.

BEST (Biomarkers, EndpointS, and Other Tools) Resource, 2016. Silver Spring, MD.

Booker, S.Q., Herr, K.A., 2016. Assessment and measurement of pain in adults in later life. Clin. Geriatr. Med. 32 (4), 677–692.

Campisi, J., Kapahi, P., Lithgow, G.J., Melov, S., Newman, J.C., Verdin, E., 2019. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 571 (7764), 183–192.

Cardoso, A.L., Fernandes, A., Aguilar-Pimentel, J.A., et al., 2018. Towards frailty biomarkers: candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res. Rev. 47, 214–277.

Caristia, S., Filigheddu, N., Barone-Adesi, F., et al., 2019. Vitamin D as a biomarker of Ill health among the over-50s: a systematic review of cohort studies. Nutrients 11 (10).

Cesari, M., 2020. Age associated cellular decline: mechanisms and perspectives. Clinical Nutrition Highlights. 10 (1), 4–7.

Cesari, M., Vellas, B., Gambassi, G., 2013. The stress of aging. Exp. Gerontol. 48 (4), 451–456.

Chung, H.Y., Kim, D.H., Lee, E.K., et al., 2019. Redefining chronic inflammation in aging and age-related diseases: proposal of the senoinflammation concept. Aging Dis. 10 (2), 367–382.

Crimmins, E.M., Shim, H., Zhang, Y.S., Kim, J.K., 2019. Differences between men and women in mortality and the health dimensions of the morbidity process. Clin. Chem. 65 (1), 135–145.

Cruz-Jentoft, A.J., Bahat, G., Bauer, J., et al., 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48 (1), 16–31.

Diot, A., Morten, K., Poulton, J., 2016. Mitophagy plays a central role in mitochondrial ageing. Mamm. Genome 27 (7–8), 381–395.

Dodig, S., Cepelak, I., Pavic, I., 2019. Hallmarks of senescence and aging. Biochem. Med. (Zagreb). 29 (3), 030501.

Erusalimsky, J.D., Grillari, J., Grune, T., et al., 2016. In search of 'Omics'-based biomarkers to predict risk of frailty and its consequences in older individuals: the FRAILOMIC initiative. Gerontology. 62 (2), 182–190.

Etman, A., Burdorf, A., Van der Cammen, T.J., Mackenbach, J.P., Van Lenthe, F.J., 2012. Socio-demographic determinants of worsening in frailty among community-dwelling older people in 11 European countries. J. Epidemiol. Community Health 66 (12), 1116–1121.

Fontana, L., Kennedy, B.K., Longo, V.D., Seals, D., Melov, S., 2014. Medical research: treat ageing. Nature. 511 (7510), 405–407.

Franceschi, C., Garagnani, P., Morsiani, C., et al., 2019. The continuum of aging and age-related diseases: common mechanisms but different rates. Front Med (Lausanne) 5, 61.

Fries, J.F., 2000. Compression of morbidity in the elderly. Vaccine. 18 (16), 1584–1589.

Gijzel, S.M.W., Whitson, H.E., van de Leemput, I.A., et al., 2019. Resilience in clinical care: getting a grip on the recovery potential of older adults. J. Am. Geriatr. Soc. 67 (12), 2650–2657.

Goodpaster, B., 2020. The impact of age associated cellular decline on bioenergetics and functional impairment. Clinical Nutrition Highlights. 10 (1), 8–13.

Justice, J., Miller, J.D., Newman, J.C., et al., 2016. Frameworks for proof-of-concept clinical trials of interventions that target fundamental aging processes. J. Gerontol. A Biol. Sci. Med. Sci. 71 (11), 1415–1423.

Kane, A.E., Sinclair, D.A., 2019. Frailty biomarkers in humans and rodents: current approaches and future advances. Mech. Ageing Dev. 180, 117–128.

Kaur, D., Rasane, P., Singh, J., et al., 2019. Nutritional interventions for elderly and considerations for the development of geriatric foods. Curr Aging Sci. 12 (1), 15–27.

Kennedy, B.K., Berger, S.L., Brunet, A., et al., 2014. Geroscience: linking aging to chronic disease. Cell. 159 (4), 709–713.

Liguori, I., Russo, G., Curcio, F., et al., 2018. Oxidative stress, aging, and diseases. Clin. Interv. Aging 13, 757–772.

Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell. 153 (6), 1194–1217.

Martin, F.C., O'Halloran, A.M., 2020. Tools for assessing frailty in older people: general concepts. Adv. Exp. Med. Biol. 1216, 9–19.

Massudi, H., Grant, R., Braidy, N., Guest, J., Farnsworth, B., Guillemin, G.J., 2012. Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. PLoS One 7 (7), e42357.

Mitnitski, A., Collerton, J., Martin-Ruiz, C., et al., 2015. Age-related frailty and its association with biological markers of ageing. BMC Med. 13, 161.

Pek, K., Chew, J., Lim, J.P., et al., 2020. Social frailty is independently associated with mood, nutrition, physical performance, and physical activity: insights from a theory-guided approach. Int. J. Environ. Res. Public Health 17 (12).

Pichard, J., Brondelo, J.M., Becker, F., et al., 2020. Generation of human pluripotent stem cell lines (iPSCs) from mesenchymal stem cells (MSCs) from three elderly patients with osteoarthritis. Stem Cell Res. 44, 101721.

Prasad, S., Sung, B., Aggarwal, B.B., 2012. Age-associated chronic diseases require age-old medicine: role of chronic inflammation. Prev. Med. 54 (Suppl), S29–S37.

Rea, I.M., Gibson, D.S., McGilligan, V., McNerlan, S.E., Alexander, H.D., Ross, O.A., 2018. Age and age-related diseases: role of inflammation triggers and cytokines. Front. Immunol. 9, 586.

Robinson, S.M., 2018. Improving nutrition to support healthy ageing: what are the opportunities for intervention? Proc. Nutr. Soc. 77 (3), 257–264.

Scheffer, M., Bolhuis, J.E., Borsboom, D., et al., 2018. Quantifying resilience of humans and other animals. Proc. Natl. Acad. Sci. U. S. A. 115 (47), 11883–11890.

Sierra, F., 2019. Geroscience and the challenges of aging societies. Aging Med (Milton). 2 (3), 132–134.

Vasto, S., Scapagnini, G., Bulati, M., et al., 2010. Biomarkers of aging. Front. Biosci. (Schol Ed). 2, 392–402.

Vatic, M., von Haehling, S., Ebner, N., 2020. Inflammatory biomarkers of frailty. Exp. Gerontol. 133, 110858.

Verbrugge, L.M., Jette, A.M., 1994. The disablement process. Soc. Sci. Med. 38 (1), 1–14.

Woolford, S.J., Sohan, O., Dennison, E.M., Cooper, C., Patel, H.P., 2020. Approaches to the diagnosis and prevention of frailty. Aging Clin. Exp. Res.

Yarnall, A.J., Sayer, A.A., Clegg, A., Rockwood, K., Parker, S., Hindle, J.V., 2017. New horizons in multimorbidity in older adults. Age Ageing 46 (6), 882–888.