WHITE BOOK ON FRAILTY

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Global Aging Research Network

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A video on "BEWARE OF FRAILTY"

A short 40 seconds film was realized in collaboration with the IAGG and its GARN Network, to promote autonomy of old people. It was funded by the CNSA (Caisse Nationale de Solidarité pour l'Autonomie), a French state organization and is available in eleven versions:
English https://www.youtube.com/watch?v=T9-JPN_jY9I
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The film can be disseminated via any type of screen: social networks, websites, local TVs, or during events dedicated to old people. We also invite you to target a large public, networks, colleagues, local authorities and all those whose work to prevent dependency of older people.

SUMMARY

WHITE BOOK ON FRAILTY

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Frailty is a clinical state in which there is an increase in an individual's vulnerability for developing dependency and/or mortality when exposed to a stressor. Frailty can occur as the result of a range of diseases and medical conditions, but this syndrome can be delayed, if identified and managed early enough.

Established in 1950, the International Association of Gerontology and Geriatrics (IAGG) has always been committed to promoting the highest quality of life and well-being of all people as they experience aging at an individual and societal level. For this reason, IAGG launched the Global Aging Research Network (GARN) in 2011 to get together the world's best research centers dedicated to biological and clinical Gerontology.

The White Book on Frailty, endorsed by the IAGG GARN Network, aims to promote preventive interventions against disability and to provide information on how to adequately implement frailty into everyday clinical practice. To this effect, it will highlight current knowledge on the identification of target population, the assessment of frail old adults, and the development of tailored intervention programs. We now know that early detection and intervention is critical to addressing frailty.

The White Book presents a general overview of the topic and details the main frailty pathologies. Assessment tools and implementation initiatives are presented, in view of preventing and/or delaying disability and dependence, at home, in the community and in hospital settings.

We hope that each contribution will help raise awareness on frailty and its outcomes. We take this opportunity to thank the authors for their support and input. It is our wish that this book will encourage healthcare professionals around the world to develop actions at a local, regional, national and international level for the benefit of elder people.

Thank you very much for your consideration.

IAGG MISSION FOR FRAILTY OF OLDER PERSONS

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Frailty, a progressive physiologic decline in multiple body systems, is defined as a state of increased vulnerability to the stress that carries an increased risk of disability, functional decline, hospitalization and mortality in older adults. Referring to the general population studies in the world, the prevalence of frailty varies from 4.9% to 27.3%, and also that of pre-frailty varies from 34.6% to 50.9%.(1) Researchers have revealed that even when individuals with acute and chronic medical conditions were excluded, 7% of the population aged 65 and over and 20% of the population aged 80 and over are frail.(2) It means that frailty is an elderly specific geriatric syndrome.

Recognition of frailty or pre-frailty is important for clinical practitioners and also policy-makers because it poses a greater risk of adverse health outcomes such as falls, increased morbidity, physical and psychosocial dependence and death. Frailty leads to the increase in long-term care need for older persons. When we see the influence to the health policy, frailty leads to the increase in medical costs and imposes bad influence on healthcare financing. So, preventing the frailty is a very important issue now on the globe, as such an effort can result in the reduction of dependency, institutionalization, long-term care needs and medical/social expenditures.

Good news is that not all older persons get frail. And the better is that many states of pre-frailty and some frailty can be reversed to robust and pre-frail conditions. We must remember that frailty cannot be overcome by just combating with the traditional concepts of chronic diseases. We should treat and manage the frailty with a new concept and approach such as comprehensive functional assessments or multidisciplinary interventions.

In recent years IAGG has involved in research and training on frailty through IAGG GARN networks all over the world. The research findings of the networks imply that early detection and intervention is most important to prevent and protect frailty. The collaboration among the IAGG GARN institutes has been very precious. That is the just way the members of IAGG GARN work on it.

The mission of IAGG is to promote the highest levels of achievement of gerontological research and training worldwide in order to promote the highest quality of life and well-being of all people. For this mission, IAGG will continue to support the research and training activities of the IAGG GARN networks on frailty and the international cooperation for frailty.

(1) Choi J, Ahn A, Kim S, Won CW. Global Prevalence of Physical Frailty by Fried's Criteria in Community-Dwelling Elderly With National Population-Based Surveys.J Am Med Dir Assoc. 2015 Jul 1; 16(7):548-550.

(2) Wilson JF. Frailty - and its dangerous effects - might be preventable. Ann Intern Med. 2004; 141:489-492.

BEYOND THE BEDSIDE: FACTORS INFLUENCING THE PREVALENCE AND MANAGEMENT OF FRAILTY

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This White Book on Frailty appears at a critical time in the development of our understanding of the pathophysiology, clinical course, incidence and prevalence of this very important geriatric syndrome. While we work to enhance early detection of frailty and development of effective prevention and treatment strategies, we must also be mindful of important societal trends that may aggravate the incidence or severity of frailty and complicate its effective management. Two such changes are changes in the structure and function of families and the increasing gap in socioeconomic status between the "haves" and the "have not"s in many societies.

CHANGES IN THE STRUCTURE AND FUNCTION OF THE FAMILY

Anyone with experience in the care of older persons is aware of the critical importance of family supports in serving as the primary safety net for the social, psychological and financial needs of older persons. The capacity of the family to serve this traditional role is threatened.

Simultaneous increases in life expectancy and decreases in fertility are leading to more elders with fewer younger family members to support them. Increases in women's participation in the workforce and the fact that as the oldest old reach into their 90s and beyond, their children are also becoming old and have problems of their own further aggravate the difficulty. As divorce and cohabitation become more common, the traditional nuclear family fades and reformed or "blended" families emerge. And in developing nations dramatic migration of youth and young adults from rural areas to urban centers is leaving the older generations behind with weakened informal support systems.

These changes in the structure and function of the family place additional stresses on the health care workforce and community-based resources, especially regarding the support of frail elders with multiple needs.

DISPARITIES

The gap between the rich and poor is widening in both developed and developing countries. With respect to health care for the elderly, there is concern regarding the long term implications of this troubling divergence of "haves" and "have not"s. The cumulative disadvantage in wages, labor market participation, and wealth accumulation, is reflected in functional capacity and may lead to increases in the incidence of frailty as well as difficulties in bringing together the resources needing to provide comprehensive care for frail elders.

These trends in families and socio-economic equity suggest that major challenges are on the horizon for the management of frail elders and provide even greater impetus for acceleration of the development of effective strategies for the prevention and management of frailty.

I

GENERAL OVERVIEW

ONE PRECIOUS MODEL IN CHINA

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The ageing population represents a special challenge for China, a country with 1.3 billion people (about 18% of the global population). It has been estimated that by the end of 2010, older persons in China were 178 million (13.3% of the Chinese population). Although the longer life expectancy is a clear sign of scientific and cultural advancements, it still potentially exposes the public health systems to the risk of unsustainability due to the parallel increase of age-related disabling conditions. In particular, elders with partial or total disability in China were 33 million (19% of the older persons in China) in 2010.

In these last decades, mounting interest has been devoted by the scientific community to the so-called "frailty syndrome", as frailty is considered an ideal target for conducting preventive activities against disabling conditions in the elderly. Unfortunately, very little evidence on the topic is coming from China.

In the past five years, the Center of Gerontology and Geriatrics of West China Hospital dedicated in promoting the awareness, clinical practice and research about frailty in Chinese geriatricians. As a member of IAGG GARN, many geriatricians in the Center are trained through IAGG GARN networks all over the world about how to integrate the frailty in clinical practice. The collaboration of research work about frailty is in progress with Saint Louis University, the Gérontopôle in Toulouse, and Dalhousie University. Just as President Heung Bong CHA said, the just way the members of IAGG GARN work on the frailty is the collaboration. Our works in the Center provide one precious model for the collaboration. That is also one shortcut to help Chinese clinical practitioners early detect and intervene frailty.

MULTISECTORAL ACTION FOR A LIFE COURSE APPROACH TO HEALTHY AGEING

World Health Organization

Policy Paper EB 134/19

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The proportion of older people in the population is increasing in almost every country. By 2050, around 2000 million people in the world will be aged 60 years or over, with 400 million aged 80 years or over. Of them, 80% will be living in what are now low- or middle-income countries.

The transition to older populations will challenge society in many ways. Demand for health care, long-term care, social care and pensions is likely to increase, while the proportion of the population in traditional working ages will fall. But population ageing also presents many opportunities. Older people make important social contributions as family members, volunteers and active participants in the workforce. Indeed, older populations represent a substantial, but as yet underutilized, human and social resource.

Health in older age will be a crucial determinant of where the balance will lie between the costs and benefits associated with population ageing. Poor health undermines the ability of older people to remain actively engaged in society, limits their contribution and increases the costs of population ageing. Investing in health across the life course lessens the disease burden in older age, fosters the ongoing social engagement of older people (helping to prevent isolation) and has broader benefits for society by enabling the multiple contributions of older people.

Poor health in older age is a burden not just for the individual but also for his or her family and for society as a whole. The poorer the family or the setting, the greater the potential impact. Loss of good health can mean that an older person who was previously a family resource may no longer be able to contribute and may, instead, require significant support. This care is often provided by women who may need to give up other career aspirations to deliver it. The cost of health care for an older person can impoverish the whole family. These burdens are spread inequitably. Those with the least resources, or who live in the poorest areas, are most at risk.

Health in older age is determined by pathways or "trajectories" that develop across the life course. These trajectories are influenced by an integrated continuum of exposures, experiences and interactions. The impact of many factors is greatest at specific critical or sensitive periods of development. These can start very early in life, with experiences that can "program" an individual's future health and development. Subsequently, risk and protective factors across life have a cumulative effect on health trajectories.

Because of the cumulative nature of these influences, one of the hallmarks of ageing is diversity. Many older people will be healthy and well educated and will want to continue to play an active role in society. Others of the same age may be poor, illiterate and have no financial security. Policies to enable older people to maximize their capabilities must address the broad spectrum of needs in these diverse populations.

CHALLENGES AND RESPONSES

Health systems

Current health systems, particularly in low- and middle-income countries, are not adequately designed to meet the chronic care needs that arise from this complex burden of disease. These needs span the life course and the care continuum: from prevention to detection, early diagnosis, treatment, rehabilitation, long-term care and palliative care.

In many places, health systems will need to move from focusing on the delivery of curative interventions for single acute problems to a more comprehensive continuum of care that links all stages of life and deals with multiple morbidities in an integrated manner.

Towards the end of life, many people will eventually require assistance beyond that habitually required by a healthy adult. Most of these individuals prefer this "long-term care" to be provided in their home, and this is often delivered by family members. For those with severe functional decline, institutional care may be required. There are few standards or guidelines on the most appropriate care, family carers often lack an understanding of the challenges they face, and care may be disconnected from health services. This can leave the needs of the older person inadequately addressed, with carers facing a greater burden than is necessary and acute care services being inappropriately used to fill gaps in chronic care. Furthermore, changing social patterns mean that it may not be sustainable to rely on families alone to meet many of these needs. The relative number of older family members is dramatically increasing; older people are less likely to live with younger generations and are more likely to express a desire to continue living in their own home; and women, the traditional family carers, may have changing career expectations. New systems of long-term care are therefore urgently required, to provide a continuum of care that is tailored to a continuum of need. These should be focused on the individual, closely linked to health systems and designed to maintain the best possible function, well-being and social participation.

Workforce

Health system limitations are compounded by major workforce gaps. Few members of either the formal or informal workforce are adequately trained to meet the specific needs of older people, and demographic change means that as the number of older people rises, the relative number of people in traditional working ages will fall.

New social models

Rigid ideas about the life course and ageist stereotypes limit our ability to find innovative solutions. For example, social systems often artificially categorize people into life stages based on chronological age (e.g. student, adult, retired). These concepts have little biological basis. With people living 10 or 20 years longer, a range of life options that would only rarely have been achievable in the past become possible. A life course approach to healthy ageing views life as a continuum, recognizes and enables the valuable contributions of people at all ages, strengthens links between generations and develops strategies to build capabilities across all stages of life.

Ageing is interrelated with other major global trends, including migration, changing roles of women, urbanization, technological change and globalization. These and other aspects of the physical and social environment can strongly influence both the health of an older person and his or her capacity to participate actively in society. Innovation will be a crucial component of successful strategies to address the challenges of population ageing.

Gender

Gender exerts a powerful influence on health and ageing across the life course and in older age. Traditionally, women have provided most of the unpaid care for family members across the life course (from child care to elder care). This is often to the detriment of their own participation in the paid workforce and has many consequences in older age. These include a greater risk of poverty, more limited access to quality health and social care services, a higher risk of abuse, poor health in later life and reduced access to pensions.

Knowledge

There are major knowledge gaps that prevent us from taking appropriate and effective action on ageing and health. Even basic questions such as "are people living longer healthy lives, or are the additional years gained experienced in poor health?" cannot yet be answered. Other major gaps include understanding the causes and management of key conditions such as dementia. Even where strong evidence exists, barriers remain to its translation into policy and practice.

Current approaches to the development of policies and health interventions often exclude older people, even though they may be the main users or targets. Older people and those with comorbidities are routinely excluded from clinical trials, so our understanding of which treatment options are best in older ages is limited. Much routine data collection either excludes older people or aggregates all people over a certain age (such as 70 years and above), so we often cannot accurately assess health need or whether this is being met.

Leadership

While global attention on population ageing and health is rapidly increasing, existing responses are disjointed and outdated. There is no global strategy and no global action plan. Both the Madrid International Plan of Action on Ageing (1) and the WHO contribution Active ageing: a policy framework (2) are over 10 years old, and Member States need more up-to-date guidance to help them prioritize their actions in a rapidly changing world. To ensure that this guidance is grounded in the best available evidence, there is an urgent need for a platform that brings together key ex-

perts to advise decision-makers on global action priorities. There is also an urgent need to coordinate global responses on ageing and health between key agencies.

RECOMMENDATIONS

Advocacy

Population ageing is one of the biggest demographic transitions the world has ever faced. Good health is central to ensuring that social and economic benefits are fully realized, and the development of sustainable health and social care systems is crucial if costs are to be controlled. There is a need for powerful international and national advocacy to ensure that the centrality of health is understood and that the opportunities arising from it are fully appreciated. As a step towards this goal, World Health Day 2012 had the theme "Good health adds life to years", to bring global attention to bear on issues related to ageing and health. The Secretariat continues to convey these messages in many forums, but these perspectives need to be given even greater prominence in global development and research agendas.

Convening and coordinating

The Secretariat partners with many other organizations, including the International Association of Gerontology and Geriatrics and the International Federation on Ageing, to link experts and decision-makers in this field. But a more formal expert advisory mechanism is needed, to inform the Director-General and other stakeholders about key knowledge gaps and priorities for research and action in the field of ageing and health.

A comprehensive global strategy on ageing and health, followed by a global ageing and health action plan with measurable outcomes, is needed to shape future global priorities in this area.

Support to Member States

The Secretariat currently supports Member States by providing guidance on key issues and promoting uptake of this evidence into policy and action at country level. This work is carried out by all levels of the Organization. The project on "Knowledge translation on ageing and health" supports Member States in identifying priorities for action and developing evidence-based policy options. The approach was piloted in Ghana in 2013 and will be applied in China in 2014. The Secretariat is also working to support the development of physical and social environments that foster active and healthy ageing through the WHO Global Network of Age-friendly Cities and Communities. This network encourages the exchange of experience and mutual learning between cities and communities that are creating inclusive and accessible "age-friendly" environments. It currently has over 150 member cities and communities in 21 countries worldwide, as well as 10 affiliated country programs.

However, more support is needed. This includes:

- defining the best steps that countries at different levels of development can take to build an integrated continuum of care spanning primary health care, inpatient care, long-term care and end-of-life care;
- identifying evidence-based strategies to create environments that foster healthy and active ageing and enable intergenerational collaboration;
- developing models and standards for monitoring and quantifying the health of older people;
- elaborating strategies for capacity-building and workforce development to address the health needs of older people;
- identifying sustainable financing models to ensure access to services.

Knowledge generation and management

WHO will release the first global report on ageing and health in 2015. This will constitute a crucial resource for Member States, defining what is currently known, outlining case studies of innovative responses and making clear the gaps in our knowledge. Nonetheless, there is an urgent need to ensure that these knowledge gaps are included in global research agendas.

As a first step, data gathered by the Organization need to be collected across the whole life 22.course and disaggregated by sex and age, to distinguish between different stages of ageing. The standards and practices recommended by WHO for data collection by Member States should also promote disaggregation by sex and age across the whole life course. Furthermore, objective indicators are urgently needed for monitoring the health of older adults, including determinants and consequences, and encouragement should be given to research that identifies the most cost-effective interventions.

REFERENCES

1. Political Declaration and Madrid International Plan of Action on Ageing. New York: United Nations; 2002 (http://undesadspd.org/Ageing/Resources/MadridInternationalPlanofActiononAgeing.aspx, accessed 4 December 2013).

2. Active ageing: a policy framework. Geneva: World Health Organization; 2002.

ACTION GROUP ON PREVENTION OF FRAILTY OF THE EUROPEAN INNOVATION PARTNERSHIP (EIP) ON ACTIVE AND HEALTHY AGEING

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The European Innovation Partnership on Active and Healthy Ageing was launched in 2012 as a Commission response to demographic changes in the EU, in the framework of Europe 2020 strategy. Three years since it was launched, the Partnership is helping to identify and develop new approaches for supporting change, placing patients at the centre of the health and social care systems and moving away from hospital-centred, reactive, disease-focused care, towards a proactive, community-based model of prevention and continuous care management, with the participation of the patient and informal care-givers.

Within the Partnership, a specific Action Group on Prevention of Frailty started to work in June 2012. After two invitations for commitments launched by the Commission, 160 partners expressing a total of 131 commitments are working together in a multidisciplinary Action Group.

The aim of this group of partners is to provide older people with safe, effective, compassionate, high-quality care and to encourage care services to improve the organisational context supporting everyday life and clinical practice encountered by frail older people and their care-givers. To do this, the group of EIP partners working on prevention of frailty is implementing innovative solutions to better understand the underlying factors of frailty, is exploring the association between frailty and adverse health outcomes in older people and is working to better prevent and manage the frailty syndrome and its consequences.

The Partnership reflects a growing awareness that better care and sustainability of health services calls for innovative ways to address the needs of the elderly. It has encouraged a wide range of stakeholders to join forces, to improve cooperation, and to foster political commitment, so as to encourage innovative solutions towards a better quality of life as citizens grow older. It identifies a set of actions that have started as early as 2012 and will deliver measurable outcomes within the 2012-2020 timeframe.

WORK DEVELOPMENT

The group of partners working on prevention of frailty is currently implementing an agreed common Action Plan. This was based on the objectives, activities, timing and deliverables specified in the 131 commitments sent in by a group of stakeholders. This Action Plan frames the work to be applied by all partners who adhere to this group.

The groups' ambition is to create critical mass to push the frailty prevention approach towards is tipping point in the following domains. Specifically, their objectives and activities address the challenges that fall in any of the following domains:

1. Frailty in general
2. Cognitive decline
3. Functional decline
4. Nutrition
5. Care givers and dependency
6. Physical activity

The strength and added-value of working in the Partnership has been that every member's individual work contributes to the achievement of a grander common objective. Together they explore common solutions for the key challenges related to frailty, physical and cognitive decline as well as risks factors such as malnutrition or lack of physical activity for older people.
The group of partners has in particular focused their work on certain areas where actions related to frailty have the potential to advance at a quicker pace (by joining efforts) such as:

Advocacy
- Informing the opinion on frailty interventions at levels where priorities are determined and decisions are taken.
- Bring attention to the issue of frailty in older people being a common EU public health problem.

Protocols and programmes on screening and prevention
- Preventing occurrence of frailty and avoiding its predictable negative consequences.
- Preventing factors, such as malnutrition or lack of regular physical activity, which have impact on different components of the frailty syndrome.
- Supporting adequate nutrition and physical activity.
- Prevention, screening and early assessment of risk factors.

Care management and assessment
- Supporting evidence based interventions through appropriate pathways of Health and Social Care to avoid incident frailty, its progression to disability and its negative consequences.
- Diminishing avoidable and recurrent hospitalizations.
- Training professionals to improve their knowledge and skills and keep pace with new needs.
- Supporting care-givers in their tasks of caring for their dependant relatives.
- Identifying those patients whose outcomes have the higher costs for the health system.
- Identifying those most at risk and those who will benefit most from the interventions.
- Supporting a multi-disciplinary approach to care and management.
- Evaluating current interventions and supporting what really works.
- Supporting care and preventive interventions that can be better delivered within the community.
- Sharing good practices ready to scale up.
- Implementing guidelines to improve management and prevention of frailty.

Research
- Improving methodology for the screening and identification of pre-frail status.
- Basic research development on any of the six (jointly-identified) domains of frailty.

WHAT EVIDENCE HAS THIS WORK PROVIDED?

Framing the idea of the "frailty prevention approach" has been the fundamental outcome of the work done by the partners in the EIP. Through the work that has been conducted on advocacy, screening, research and coordination of care, the partners have contributed to establish a common European approach to tackle frailty in older people.
In almost 3 years of collaboration the partners have contributed to establish a common European approach to provide older people with safe, effective, compassionate, high-quality care and to encourage care services to improve in this regard by tackling frailty in older people.

Although the activities are still in the early stage, the partners have already achieved some results, such as:
- A more comprehensive and clear understanding of frailty and its priorities: the exchange of knowledge and expertise among partners has resulted in the identification of clear benchmark on 6 main areas of intervention: frailty in general, physical decline, cognitive decline, nutrition, dependency and care givers, physical exercise.
- More reliable trials: many partners had the opportunity to test their protocols and tools in broader settings, allowing strengthening the reliability of both protocols and tools.
- Shaping a new model for screening, treatment and monitoring of frailty and functional decline.
- A more suitable training offer for healthcare professionals: different Group members have proposed improved training courses for nurses, social workers and PhD students on frailty topics.
- A collection of good practices in frailty prevention. The final text gathers 98 good practices coming from 14 Member States. It offers a grasp of what are the main achievements and what kind of experiences are being carried out in some European regions around the topic of frailty and functional decline. The numerous and varied examples of Good Practices, promote the visibility of a wide range of interventions undertaken in clinical settings, research centers and in the community, aimed to reduce age-related frailty, disability and suffering associated to it.
- Contribution to the policy debate at EU level, providing technical inputs to the European Commission on frailty and functional decline in particular through the international conferences on Frailty in April 2013 and June 2014.

Some of the preliminary results and the collection of good practices can be a source of inspiration for further management improvement and policy development. In the coming years efforts aimed at raising effectiveness of care delivery will be crucial. Working closely and sharing ideas and solutions can help the EU as a whole to find and implement new strategies to tackle frailty.

EU Member States are at different stages in their efforts to address the need for help and care of frail and most vulnerable older people. Whereas some are still developing their first strategies, others have accumulated more than four decades of experiences. The potential in the area of frailty prevention for the EU to add value by facilitating the transfer of know-how is therefore particularly large.

The wealth of evidence that partners have brought to the table provides a sound basis on how innovations in assessment and management of health and social needs can be used in new approaches of prevention and care for older people, and how these can be implemented in daily life.

Through a process of informed deliberation the EIP process has selected cases that involve clear examples in which policy intervention could reduce frailty and cognitive decline. These cases should be seen as illustrative examples rather than constituting a comprehensive overview of all the actual work being developed and all the thinking behind the different projects and interventions.

CONCLUSIONS

Framing the idea of the "frailty prevention approach" has been the fundamental result of the work done since the EIP was launched three years ago. In this respect, the need to tackle frailty in the older people across EU is now accepted by a large number of stakeholders spanning policy makers, professionals and researchers across EU Member States.

The EIP partners are committed to work towards solutions that can be easily implemented and replicated by others in Europe. This aspect emphasizes the spirit of the Partnership in a broader context and strengthens the work already done by many of them. These 3 years of work have established a solid ground on which to build common and effective approaches to tackle frailty in old age. But still further work and policy support and resources are needed so that tackling frailty in older people is no longer an issue of public debate.

Finding new tools and strategies to prevent and treat frailty in all its dimensions will not only improve dramatically the quality of life of old people, but will also reduce both the number and the length of hospitalisation and institutionalisation. The final results will be alleviation in the budgetary pressure of our health and social care systems, allowing Members States to more efficiently allocate the resources for the health and care of their citizens.

In the coming years efforts aimed at raising effectiveness of care delivery will be crucial. Working closely and sharing ideas and solutions can help the EU as a whole to find and implement new strategies to tackle frailty.

The Partnership provides a platform for national and regional authorities and key stakeholders to coordinate and mobilize actions in strategic areas, identify good and relevant practices, finally replicate and scale-up the most needed and successful solutions.

INTRODUCING FRAILTY AND THE FRAILTY PROCESS WITHIN THE DISABLEMENT MODELS

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Two main approaches have been proposed to assess frailty, the model of Fried (Fried et al, 2001) and the model of Rockwood (Rockwood et al, 1994). The Fried's paper "Frailty in Older Adults: Evidence for a Phenotype" has been cited more than 3,800 times since 2001 and the Rockwood's paper "Frailty in elderly people: an Evolving Concept" has been cited more than 350 times since 1994, illustrating the great popularity of the concept of frailty in gerontology over the past 20 years. Although quite different, these two models have in common not to have been involved in the debates of 1980s and 1990s on models and classifications of health conditions, such as the International Classification of Impairments, disabilities and handicaps (ICIDH), published by the World Health Organization (WHO) in 1980 as a classification of the consequences of disease (WHO, 1980), or the International Classification of Functioning, Disability and Health published by the same WHO twenty years later (WHO, 2001). The result, for these models, is that there is some ambiguity in what is covered by the concept of frailty, especially in regard to the concepts of impairments and functional limitations of the disablement process. Does frailty measure the same things than impairments and functional limitations or is it clearly distinct from the concepts of disability? This is especially true for the Rockwood's model that offers a four-point scale, ranging from the absence of any problem in physical and cognitive functioning to total dependence on a third person (care giver) for daily living activities.

In the Fried's model, there is in theory a clear distinction between frailty and disability. In this approach, not only frailty is distinct from disability, but it is also from the accumulation of diseases (comorbidity). Frailty is presented as a major risk factor for disability and death (Fried et al, 2001). The state or states of frailty would concern individuals not suffering disability and loss of independence or not yet. In practice, as in the illustration given by Fried and his colleagues, it is more complicated because individuals with disabilities or dependent in daily life activities are not excluded from the analyses. As most individuals with disabilities or dependent in daily life activities are found in the pre-frail or frail categories, it is difficult to say what is the specific contribution of frailty in the prediction of worsen disability or mortality. Accordingly, the French study of frailty (Sirven, 2013) distributes the entire population of 50 years and over in all three categories, robust, pre-frail and frail, ignoring the factors previously identified as determining the loss of independence as, for instance, disabling diseases, functional limitations and activity restrictions. It is clear that such studies, replacing the concepts of disability by the concepts of frailty, cannot bring a lot more knowledge about the loss of independence that studies based only on concepts of disability.

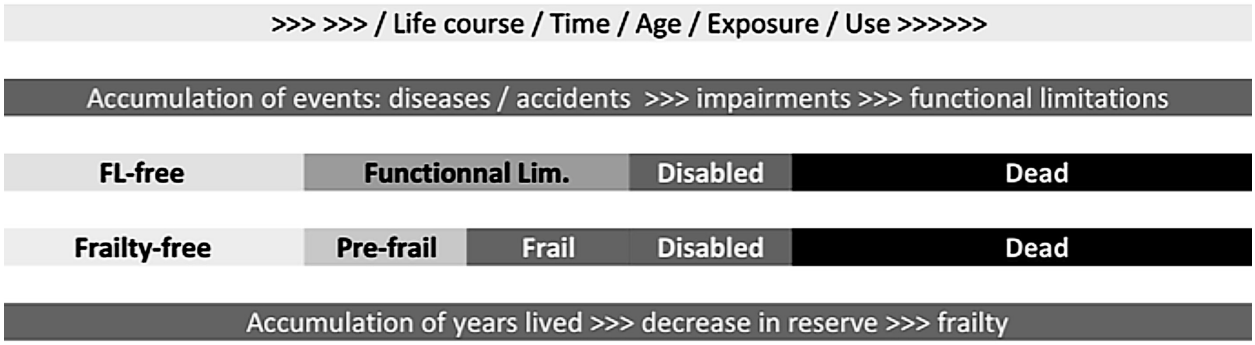
Actually, Fried and colleagues suggest that frailty measures or indicates a decline in physiological reserves and resistance to stress regardless of existing pathologies. It would be, in other words, a measure of the biological senescence or an assessment of the remaining health capital. If the international classification of disability (WHO, 1980) and related models well apprehend the disablement process as

a consequence of illness and/or accidents, they ignore the possibility of a biological process leading to the decrease physiological reserves. This is where the concept of frailty is interesting because it allows a second pathway that can lead to disability and loss of independence (Figure 1). The first, the "disablement process" is based on accidental or medically clearly identified causes, disabling diseases, impairments, functional limitations, etc. The second, the frailty process, requires no clearly identifiable medical causes. It reflects at the level of the whole organism, reduced physiological reserves over time which may be due to small or great causes that it is not necessarily needed to identify.

Of course the two processes must interact constantly. The state of physiological reserves should depend, in a measure to be determined, of past morbid events and the development of new disease must depend in part on the state of physiological reserves. When seeking to attribute, in advanced statistical models, disability to morbid causes, accidents and/or disabling diseases, a significant proportion of disability remains unexplained. The integration of the concept of frailty in such models should be quite useful as the unexplained part of disability increases with age.

The success of the international classification of disability (WHO, 1980) has led to a first revision, paying much more attention to non-medical and non-accidental causes of disability (WHO, 2001). Similarly, the current success of the concept of frailty leads to its extension to other domains such as social or psychological frailty. The example of the Fried's frailty model, described above, reminds us that the introduction of a new concept only values if it is not just renaming existing concepts differently.

Figure 1: Two processes leading to the loss of independency: the disablement process and the frailty process



REFERENCES

- Fried LP, Tangen CM, Walston J et al. Frailty in Older Adults: Evidence for a Phenotype. J Gerontol A Biol Sci Med Sci (2001) 56 (3): M146-M157.
- Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people: an evolving concept. Cam Med Assoc J 1994; 150: 489-495.
- Sirven N. Fragilité et prévention de la perte d'autonomie: Une approche en économie de la santé. Questions d'économie de la santé 184, Institut de Recherche et de Documentation en Economie de la Santé, Paris 2013.
- World Health Organization. International Classification of Impairments, Disabilities, and Handicaps. A manual of classification relating to consequences of disease. World Health Organization, Geneva 1980.
- World Health Organization. International Classification of Functioning, Disability and Health. World Health Organization, Geneva 2001.

HOW MIGHT DEFICIT ACCUMULATION GIVE RISE TO FRAILTY?

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Abstract: Frailty is a multiply determined vulnerability state. People who are frail are at risk of many adverse health outcomes, including death. For any individual, this risk can only be expressed probabilistically. Even very fit people can suddenly die or become catastrophically disabled, but their risk of both is much lower than a very frail person, who might nevertheless suddenly succumb without worsening health. Frailty occurs with ageing, a stochastic, dynamic process of deficit accumulation. Deficits occur ubiquitously at subcellular levels, ultimately affecting tissues, organs and integrated organ action, especially under stress. Some people are disposed to accumulate deficits at higher rates, but on average, deficit accumulation varies across the life course and likely is mutable. In this way, the clinical definition of frailty is distinct from the statistical definition, which sees frailty as a fixed factor for an individual. Recent, early animal work links subcellular deficits to whole body frailty. In humans, clinically detectable health deficits combine to increase the risk of adverse health outcomes. The rate of deficit accumulation occurs with remarkable regularity around the world, as does a limit to frailty. Of note, when 20+ deficits are counted, these characteristics are indifferent to which deficits are considered. The expression of risk in relation to deficit accumulation varies systematically. For example, at any given level of deficit accumulation, men are more susceptible to adverse health outcomes than are women. Likewise, in China, the lethality of deficit accumulation appears to be higher than in Western countries. In consequence, it may be necessary to better distinguish between frailty and physiological reserve; the latter may apply chiefly in relation to microscopic deficits. The expression of frailty risk in relation to deficit accumulation depends on the environment, including both the physical and social circumstances in which people find themselves.

Key words: Frailty, deficit accumulation, frailty index, aged, frailty phenotype, physiological reserve, mathematical gerontology, stochastic dynamics.

As is well known, two general approaches are used to characterize frailty (1-3). One sees frailty as a phenotype, with five key clinical features (4), that sometimes are expanded to include impairments in cognition and mood (5), or at other times reduced to just impaired nmobility (6) or grip strength (7). Another sees frailty arising as a consequence of the accumulation of deficits (8). The two approaches have in common the idea that frailty is a multiply determined vulnerability state, putting people at risk for a range of adverse health outcomes, including death. They also view frailty as an individual characteristic, and one that can change over the life course. (This is in contrast to the statistical definition of frailty, which sees it as a fixed individual factor (9), similar to Beard's notion of a

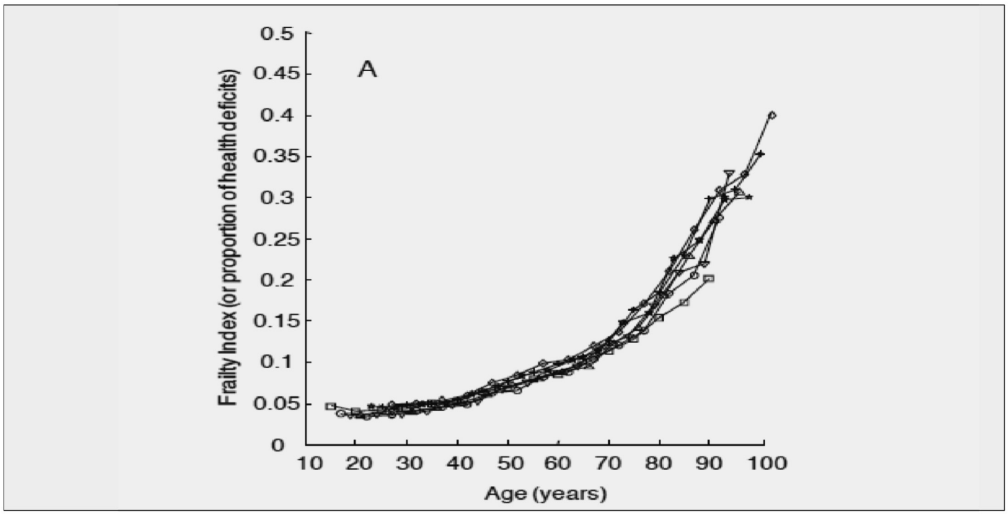
longevity factor (10)). The two also share the idea that frailty underlies the variable vulnerability to adverse outcomes of people of the same chronological age. This last means that both approaches to measuring frailty have been validated in relation to mortality prediction; this is a reasonable, if rough standard, but there is more to frailty than mortality prediction, a point elaborated below. Acknowledging that this is only one view, the purpose of this paper is to consider how deficit accumulation might give rise to frailty. It will do this by first sketching clinical deficit accumulation and then considering how this might link to deficit accumulation at the subcellular and tissue level.

FRAILTY AS CLINICAL DEFICIT ACCUMULATION – THE FRAILTY INDEX

The strong case for frailty as deficit accumulation reads like this. As people age, they are more likely to die. But not everyone of the same age has the same risk of death. What accounts for the relationship between age and death? As people age, they are more likely to have things wrong with them. The more things they have wrong with them, the more likely they are to die. Not everyone of the same age has the same number of things wrong with them, and it is this variability in the number of things they have wrong with them which accounts for the variable likelihood of death of older adults of the same age.

There is reasonable evidence for this view that variable deficit accumulation is associated with variability in the risk of adverse health outcomes (11). To interpret the evidence a few methodological points need to be reviewed. First, the notion of "things people have wrong with them" has been operationalized as "health deficits". A health deficit can be any symptom, sign, laboratory measurement, disease or disability. In contrast to the highly specified items that make up the frailty phenotype, what gets counted as a health deficit is hardly specified at all. In fact, the only criteria are that any candidate health deficit for inclusion in a frailty index should increase with age, have a prevalence of at least 1%, have <5% missing data, are related to an adverse outcome and cover several organ systems.

Figure 1
Mean value of Frailty Index at each study cycle as a function of age (n=14.127, population weighted)
(Reproduced from CMAJ, Rockwood et al., 2011)



In addition, enough deficits should be considered so that all relevant bodily systems can be covered, as well as their impact on function. The health deficits qualitatively should cover more than just co-morbidities; as they assay impact on function they should include items such as measures of mobility, strength, physical activity and health attitude. Quantitatively, as few as 20 items can be considered, but in general, more robust estimates are found when the frailty index includes 50 or more potential health deficits; after about 70 such deficits, there appears to be little gain in precision. When many deficits exist which meet these criteria, they can be sampled at random with little impact on overall risk classification (12), although the more items that are selected, the narrower the confidence limits (13). By virtue of the liberal criteria for inclusion as a deficit, many clinical and population datasets have enough information in them for deficit accumulation to be studied using existing data. Likewise, a typical Comprehensive Geriatric Assessment carries enough information for frailty to be operationalized – and graded – even without performance measures, or the

precise items used in the frailty phenotype or like operational definitions that require (14). In either setting deficits can be counted in a frailty index.

A frailty index is the measure by which the risk of adverse health outcomes is calculated. A frailty index counts deficits and standardizes the deficit count for an individual in relation to the total number of deficits considered. In short, the frailty index score for any individual is the ratio of deficits present in that individual to the number of deficits counted. Consider, for example, that a health survey data set has 50 variables that each meet the criteria for being considered as a health deficit.

Someone who had none of these would have a frailty index score of 0/50 = 0. (This is also referred to as the "zero state" of frailty and has particular significance, discussed below.) Someone with 35 things wrong would have a frailty index score of 35/50 = 0.70. As it turns out, this, and not 1.0, is the likely maximum frailty index score.

Around the world, across different data sets, and using different variables and different numbers of the same variables to calculate a frailty index, community-dwelling people accumulate deficits at about the same rate – about 3% per year, on a log scale (15). Deficit accumulation in theory starts before birth. Empirically, it can be demonstrated from about age 15 onwards. (Figure 1). Figure One, which reports a 40-item frailty index, shows its distribution over 7 successive waves of a cohort study. Several features are remarkable. First, the distribution is about the same each year, with the notable exception of slightly fewer people each year who have nothing wrong with them. Next, even though the cohort has aged 14 years, the upper limit of the frailty index for the 99% of the population does not exceed 0.67 (16). That is because, on average, the risk of death is closely linked to the value of the frailty index. The fact that the maximum value is much less than 1.0 reflects the common sense clinical observation that an individual might be as sick as they can be without having every known disease.

Although health deficits should cover both impairments in a range of body systems and some evidence that these deficits are impactful, some commentators insist that no definition of frailty should include mention of disability (17, 18). As with other groups (19-28), this is not a convention to which we subscribe. Amongst other reasons, the great majority of older adults have some degree of disability, especially when the "physical activity" criterion of the frailty phenotype is operationalized as impairment in household chores, mowing the lawn or gardening (29). Excluding disability from the evaluation of frailty also undermines the strategy of staging frailty, which is essential for clinical decision making. Given that people with a greater degree of frailty are more at risk of adverse outcomes than those with a lesser degree of frailty, and that the notion of frailty is meant in part to explain why some people of the same in the stochastic nature of deficit accumulation, as well as in the variable environments in which older adults might find themselves. What is more, even systems with no redundancy and no ability to repair – a radioactive decay curve illustrates an extreme example (30) – will show variable survival.

Figure 2

The probability of death as a function of the number of the Frailty Index during 4, 8 and 12 years amongst Canadians aged 55 years and older at baseline. (The data came for the NPHS and adapted from Mitnitski et al., 2007, Exp Geront)

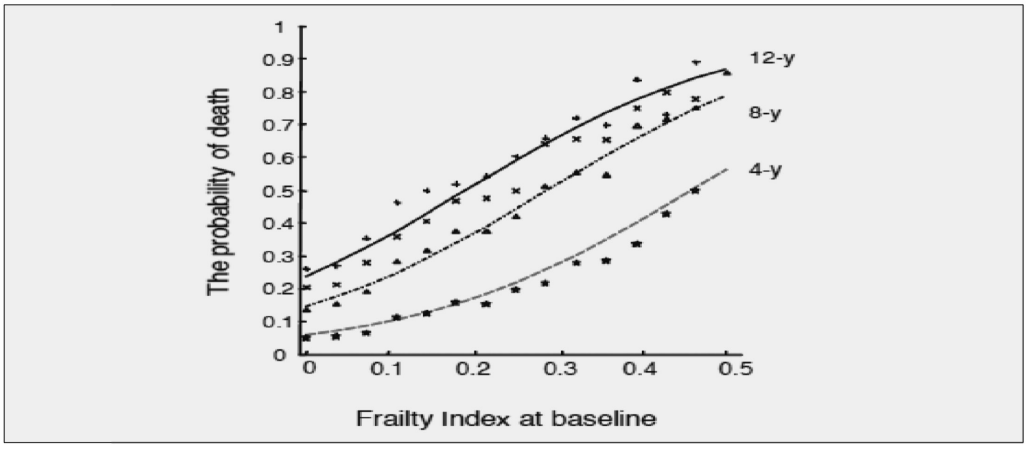
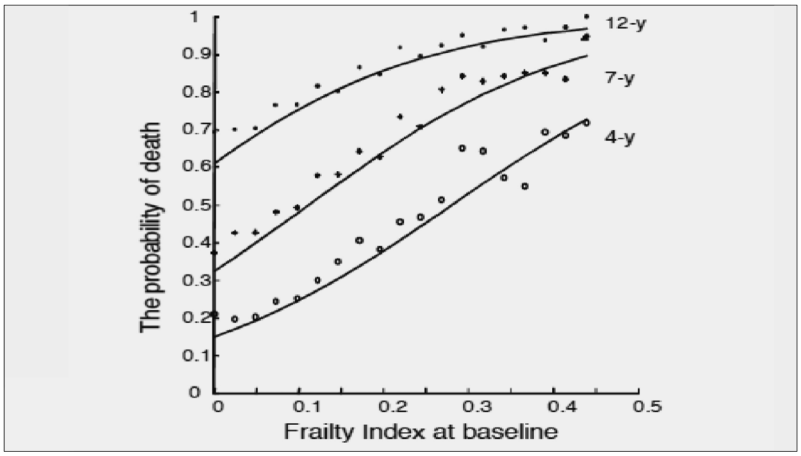


Figure 3
The probability of death as a function of the Frailty Index during 4, 7 and 12 years Chinese people aged 55 and over. [Reproducted from BMC Geriatric, Shi et al., 2011]



HOW DO DEFICITS COME ABOUT?

Frailty occurs with ageing, a stochastic dynamic process of deficit accumulation. A standard view of ageing is that deficits arise first (31) at subcellular levels, and ultimately affect tissues, organs and integrated organ action – i.e. function - especially under conditions of stress. A variety of examples exist, including many which overlap between key age-related diseases, such as Alzheimer's disease and diabetes mellitus, which affect glucose metabolism and are related to longevity in lower order animals (32). Against this background, it might be tempting to see deficit accumulation simply as a matter of scale. Indeed, recent animal work has shown that the accumulation of deficits in other systems (such as changes in sodium handling or plasma glucose levels) is associated with both structural and functional changes in myocytes, and with impaired mobility (33). It should be noted however that the scale varies amongst the items considered as health deficits in a frailty index. Some may well reflect relatively specific processes having become disordered (e.g. low bone density) whereas others are much less specific (e.g. "heart disease"). Still others integrate across a large number of organ systems, such as impaired mobility. These last have been named "clinical state variables" (34). The term was chosen to be exactly analogous to a state variable in a physical system, such as temperature, which reflects the average of the kinetic energies of the atoms which make up that system. The link between subcellular deficits and state variables needs to be better understood, so that a more quantitative and less metaphorical language can be employed.

Another consequence of the difference in scale between subcellular deficits and how function might be impacted is that is important to distinguish between levels of deficits. At any level, the presence of a deficit reflects that the capacity to resist or repair the insult which gave rise to the deficit has been overwhelmed. As we have seen, in humans, macroscopic deficit accumulation is tightly associated with mortality at the group level, where the relationship between the mean frailty index and the risk of death increases exponentially with typically very high fit, manifest, for example, by $r^2>0.95$. Even so, at the individual level, the outcomes of a given level of frailty range from improvement to stability to worsening to death. These probabilities occur with great regularity, described as a change in the Frailty Index which corresponds to a Poisson distribution (35). Although mortality risk, for example, increases with age, even very fit people can suddenly die or become catastrophically disabled, but their risk of both is much lower than a very frail person, who might nevertheless suddenly succumb without worsening health. These probabilities are in, turn influenced systematically by other factors, including social ones (such as social vulnerability) (36-38) or the country in which a person lives. For example, in Canada, the frailty index mortality curve is convex to the baseline (Figure 2) (39) whereas in China, it is concave to the baseline (40) (Figure 3). Systematic variability in the risk of an adverse outcome in relation to the number of deficits also varies in relation to factors more intrinsic to the individual, such as the level of exercise or education (41, 42). What this variable tolerability appears to reflect is how deficits impact intrinsic repair capacity, which typically is termed "physiological reserve" or "physiological redundancy" and which perhaps can be measured separately (43). Given variable life circumstances, it can be expected that some people are disposed to accumulate deficits at higher rates than others do, but on average, the tendency to deficit accumulation is variable, and likely mutable, and varies across the life course (44).

CONCLUSIONS

Frailty is a multiply determined vulnerability state which is related to ageing. Conceptually, it can be related to ageing in body systems and their integrated action, and that too can be related to subcellular deficit accumulation, although this needs to be tested empirically, as has begun with animal work. Considering frailty in relation to deficit accumulation allows the interval nature of the frailty index to be exploited to make frailty modeling more precise. It also poses an important challenge in clinical research, which is translate from the elegant reproducibility of the mathematics to the more divergent manifestations that frailty can take in humans.

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REFERENCES

1. Abellan van Kan G, Rolland Y, Bergman H, et al., The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008;12:29-37.
2. Crome P, Lally F. Frailty: joining the giants. CMAJ. 2011;183:889-90.
3. Martin FC, Brighton P. Frailty: different tools for different purposes? Age Ageing. 2008;37:129-31.
4. Fried LP, Tangen CM, Walston J, Frailty in older adults: evidence for a phenotype. J Gerontol. 2001;56:146-157.
5. Sternberg S, Schwartz A, Karunananthan S, Bergman H, Clarkfield A. The identification of frailty: A systematic literature review. Journal of the American Geriatrics Society. 2011;59(11):2129-2138.
6. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. J Am Geriatr Soc 2008;56:2211-2216.
7. Ling CH, Taekema D, de Craen AJ, Gussekloo J, et al. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. CMAJ. 2010;182(5):429-35.
8. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. Scientific World Journal. 2001:1:323-336.
9. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography. 1979;16:439-54.
10. Beard RE, 1971. Some aspects of theories of morality cause of death analysis, forecasting and stochastic processes. In Brass, W. (Ed., Biological aspects of demography. Taylor & Francis, London, pp.557-68
11. Rockwood K, Mitnitski A. Frailty in relation to deficit accumulation and geriatric medicine in relation to frailty. Clinics in Geriatric Medicine 2011;27:17-26.
12. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54(6):975-9.
13. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci. 2007;62(7):738-43.
14. Jones D, Song X, Mitnitski A, Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. Aging Clin Exp Res. 2005;17:465-471.
15. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc. 2005;53: 2184-2189.
16. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mech Ageing Dev 2006;127:494-6.
17. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. Clin Geriatr Med. 2010;26:275-286.
18. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):255-63
19. Gu D, Dupre ME, Sautter J, Zhu H, Liu Y, Yi Z. Frailty and mortality among Chinese at advanced ages. J Gerontol B Psychol Sci Soc Sci. 2009 Mar;64(2):279-89.
20. Hastings SN, Purser JL, Johnson KS, Sloane RJ, Whitson HE. Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. J Am Geriatr Soc. 2008;56:1651-7.
21. Kulminski, AM., Yashin, AI., Ukraintseva SV, et al. 2006. Accumulation of health disorders as a systemic measure of aging: findings from the NLTCS data. Mech. Ageing Dev. 127(11):840-848.
22. Yang Y, Lee LC. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the U.S. older adult population. J Gerontol B Psychol Sci Soc Sci. 2010;65B(2):246-55.
23. Woo J, Tang NL, Suen E, Leung JC, Leung PC. Telomeres and frailty. Mech Ageing Dev. 2008 Nov;129(11):642-8.
24. Armstrong JJ, Stolee P, Hirdes JP, Poss JW. Examining three frailty conceptualizations in their ability to predict negative outcomes for home- care clients. Age Ageing. 2010;39(6):755-8
25. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. J Am Med Dir Assoc. 2010 Jun;11(5):344-55.
26. Pol RA, van Leeuwen BL, Visser L, Izaks GJ, van den Dungen JJ, Tielliu IF, Zeebregts CJ. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. Eur J Vasc Endovasc Surg. 2011 Dec;42(6):824-30.
27. Steverink N, Slaets JPJ, Schuurmans H, Lis van M: Measuring Frailty. Development and testing of the Groningen Frailty Indicator (GFI). Gerontologist 2001, 41:236-237.
28. Martin FC, Brighton P: Frailty: different tools for different purposes? Age Ageing 2008, 37(2):129-131.
29. Eckel SP, Bandeen-Roche K, Chaves PH, Fried LP, Louis TA. Surrogate screening models for the low physical activity criterion of frailty. Aging Clin Exp Res. 2011;23(3):209-16.
30. Gavrilov LA and Gavrilova NS. Models of systems failure in Aging. In P Michael Conn (ed): Handbook of Models for Human Aging, Burlington, MA: Elsevier Academic Press, 2006, pp45-68.
31. Kirkwood TB. Frailty only occurs with ageing, a stochastic dynamic process of deficit accumulation. Cell 2005;120:437-447.

32. Gerozissis K, 2010. The Brain-insulin connection, metabolic diseases and related pathologies. In Craft S, Christen Y. (Eds.), Diabetes, Insulin and Alzheimer's Disease. Springer-Verlag, Berlin Heidelberg, pp.21-42.
33. Parks RJ, Fares E, Macdonald JK, et al., A procedure for creating a frailty index based on deficit accumulation in aging mice. J Gerontol A Biol Sci Med Sci. 2011 Oct 21 [Epub ahead of print].
34. Rockwood K, MacKnight C. Fitness, frailty and the mathematics of deficit accumulation. Rev Clin Gerontol. 2007;17:1-12.
35. Mitnitski A, Bao L, Rockwood K. Going from bad to worse: a stochastic model of transitions in deficit accumulation, in relation to mortality. Mech Ageing Dev. 2006;127(5):490-3.
36. Andrew MK, Mitnitski AB, Rockwood K. Social vulnerability, frailty and mortality in elderly people. PLoS One. 2008;3(5):e2232.
37. Lang IA, Hubbard RE, Andrew MK, et al., Neighborhood deprivation, individual socioeconomic status, and frailty in older adults. J Am Geriatr Soc. 2009;57(10):1776-80.
38. Woo J, Goggins W, Sham A, Ho SC. Social determinants of frailty. Gerontology. 2005;51(6):402-8.
39. Mitnitski A, Song X, Rockwood K. Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. Exp Gerontol. 2007 Nov;42(11):1109-15.
40. Shi J, Song X, Yu P, Tang Z, Mitnitski A, Fang X, Rockwood K. Analysis of frailty and survival from late middle age in the Beijing Longitudinal Study of Aging. BMC Geriatr. 2011 Apr20;11:17.
41. Hubbard RE, Fallah N, Searle SD, Mitnitski A, Rockwood K. Impact of exercise in community-dwelling older adults. PLoS One. 2009;4(7):e6174.
42. Fallah N, Mitnitski A, Searle SD, Gahbauer EA, Gill TM, Rockwood K. Transitions in frailty status in older adults in relation to mobility: a multistate modeling approach employing a deficit count. J Am Geriatr Soc. 2011;59(3):524-9.
43. Rockwood K, Rockwood MR, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. J Am Geriatr Soc. 2010 Feb;58(2):318-23
44. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 2011;183(8):E487-94.

II

FRAILTY IN CLINICAL PRACTICE

FRAILTY: THE SEARCH FOR UNDERLYING CAUSES

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Frailty is a state of increased vulnerability, which increases the risk of adverse health outcomes and/or death (1), after a stressor event. It is a dynamic process and may be reversible or attenuated by interventions focused on the underlying causes of frailty. Many of the causes of frailty are not necessarily age-related and irreversible. Most of them like physical inactivity, malnutrition or depression, are treatable and even reversible with appropriate treatment, education and follow-up (1). The management of frailty involves:

1) to screen frail older adults in clinical practice,
2) to assess them by looking after the causes of frailty and
3) to propose strong and long-term useful interventions.

A comprehensive geriatric assessment (CGA) is a multidimensional and multidisciplinary evaluation designed to determine the underlying causes of frailty. The older person is central to the process. The purpose is to plan and carry out a personalized multi-domain intervention plan. This intervention plan will vary because frailty has different causes in different people.

SOCIAL, ENVIRONMENTAL AND FINANCIAL SUPPORT

The social evaluation includes aspects such as level of education, marital and living status, informal support available from family or friends, formal support and financial situation. In addition, living arrangements (home comfort, facilities and safety), use of telehealth technology, transport facilities and accessibility to local resources should also be evaluated. It is also important to assess the ability to fulfill societal, community and family roles, as well as participate in recreational or occupational tasks.

The existence of a strong social support network can frequently be the determining factor of whether the patient can remain at home. Elders may also qualify for being offered care resources, depending upon their income. The use of home care support services, home healthcare technologies, community programs, may be useful for avoiding social isolation and maintaining elderly adults at home.

MEDICAL DOMAIN AND MEDICATIONS

Frailty is not synonymous of comorbidity but many frail older adults have multiple chronic conditions such as chronic heart failure, diabetes mellitus, osteoporosis, osteoarthritis, chronic pulmonary disease or chronic renal failure. A thorough medical examination is necessary to identify relevant comorbid conditions, review their management, and determine their impact to prioritize medical and pharmacological interventions. A detailed history and complete physical examination including a complete review of system are necessary to identify new symptoms indicative of a new diagnosis or a worsening existing condition. It is essential to ensure that there is a diagnosis or an explanation for all newly discovered symptoms and signs, and to look for reversible medical problems. The medical history should also include documentation and quantification of alcohol and tobacco consumption. Because they have multiple chronic conditions, many frail older people have also a long list of medications, often prescribed by different health care providers. By following the guidelines for the management of chronic disease, the prescription of an extensive list of medications could be justified. But polypharmacy has negative consequences for older adults, with

a risk of non-compliance, drug interactions, and adverse drug reactions. Furthermore, prescriptions are often inappropriate in this population (anticholinergic drugs or long acting benzodiazepines for example); but some drugs are also insufficiently prescribed because of concerns about frailty (such ACE inhibitors in heart failure). A review of medication lists (including over-the-counter medications and herbal products), their indications, effects and doses is important. The utilization of validated guidelines such as Beers Criteria (2) or STOPP and START criteria (3) can be helpful to optimize medical prescriptions.

NUTRITION

Compared to the general population the elderly are more vulnerable to inadequate nutrition because of number of reasons such as limited dentition, diminished appetite, depression, dementia, limited functional status to purchase or prepare food, or lack of financial resources. Undernutrition and weight loss are strongly associated with frailty in elderly patients, but are still under-diagnosed. Simple measures such as protein-calorie supplementation have been associated with positive outcomes in older persons, especially when associated with exercise resistance programs (1). At a minimum, a nutritional assessment involves the evaluation of the current weight and height (and the determination of the Body Mass Index (BMI)), recent changes in body weight, food intake, and calculation of the MNA (Mini Nutritional Assessment) score (4). These criteria are useful to diagnose an under-nutrition or at-risk of under-nutrition. The diagnosis of under-nutrition should lead to further investigations to understand the underlying causes but also its consequences (such as sarcopenia or falls). If needed, a dietary assessment is added.

COGNITIVE STATUS

The evaluation of cognitive function includes a thorough history (with the patient and his/her caregiver), a detailed mental status examination, and neuropsychological testing. Many instruments can be used for cognitive assessment, such as the MMSE (Mini Mental State Examination) (5), the Memory Impairment Screening (MIS) and the clock-drawing test. In case of cognitive impairment, nutritional complications, falls or behavioral complications must be investigated.

FUNCTIONAL AND PHYSICAL STATUS

A major goal in the care of older adults is maintaining their functional and physical status (e.g walking, or bathing themselves, but also driving or cooking). Many exercise programs have demonstrated efficacy in improving physical function in older person and preventing disability. These exercise programs may not only improve the physical function of the patient but also their mood, nutritional status and be integrated in social activities.

Functional status refers to a person's ability to perform tasks that are required for living. An older adult's functional status can be assessed by the Katz ADL (Activities of Daily Living) scale (6), and the Lawton IADL (Instrumental Activities of Daily Living) scale (7).

In addition to measures of ADLs, physical performances might be measured by the SPPB (Short Performance Physical Battery) (8). Measures of physical performance may identify older persons with a preclinical stage of disability who may benefit from interventions to prevent the development of disability. The physical assessment should also include the frequency and duration of usual exercise and physical activities (walking, housework) in which the patient is already engaged. An assessment of fall history, fall risk, gait or balance problem should be integrated into the history and physical examination of all frail patients and can be indicative of neurologic or rheumatologic disease.

MOOD DISORDERS

Depression in the elderly may present atypically and remained under-diagnosed and inadequately treated. It is a serious health concern, strongly associated with frailty, and leading to unnecessary suffering, impaired functional status, increase mortality and excessive use of health care resources. A variety of screen tests are available for depression. Among them, mini-GDS (Geriatric Depression Scale) scale or GDS scale can be easily administered (9). If the frail person is depressed, she should be treated.

SENSORY ABILITIES

The majority of older adults will experience some changes in their sensory abilities. These changes may lead to further complications such as falls, social isolation, medication errors or poor quality of life. Vision and hearing testing are essential in older frail patients. An ophthalmologic evaluation including visual acuity measurement (distance vision and near vision) and Amsler grid testing (for macular degeneration) can be easily performed in routine. Hearing impairment can be assessed using the Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S). In case of hearing impairment, an otoscopic examination and a review of medications (looking for potentially ototoxic drugs) are recommended. Vision and hearing testing are required before any cognitive assessment.

Finally, additional components may also be evaluated such as urinary continence, sexual function, sleeping disorders, or vaccinations.

The objective of this comprehensive geriatric assessment is to propose and implement a personalized multi-domain intervention, to prevent disability. This intervention is developed with the patient, by taking into account his goals and preferences, and determining priority actions.

REFERENCES

1. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013 Jun;14(6):392-7.
2. Resnick B, Pacala JT. 2012 Beers Criteria. J Am Geriatr Soc. 2012 Apr;60(4):612-3.
3. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008 Feb;46(2):72-83.
4. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutr Burbank Los Angel Cty Calif. 1999 Feb;15(2):116-22.
5. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry. 1983 Jul;40(7):812.
6. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA J Am Med Assoc. 1963 Sep 21;185:914-9.
7. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179-86.
8. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994 Mar;49(2):M85-94.
9. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982 1983;17(1):37-49.

NUTRITION AND FRAILTY: A REVIEW OF CLINICAL INTERVENTION STUDIES

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Abstract: Frailty is one of the major health concerns in aging. It is considered a geriatric syndrome characterized by muscle weakness, sarcopenia and fatigue. It is also associated with several adverse health outcomes, including disability. Literature shows that there are a number of studies conducted to define the relationship between frailty and nutrition. The majority is from cross sectional, longitudinal, and cohort studies. Few intervention studies using micronutrients, macronutrients, nutritional supplement, or food regimens have been found. This review examines the nutrition intervention studies targeted towards older adults with frailty, and evaluates the effectiveness of nutrition interventions on frailty indicators. Twenty-four intervention studies from six electronic databases met the inclusion criteria. Sixteen were randomized controlled clinical trials; one was a quasi- experimental design, whilst the rest were controlled trials. Participants included in the studies differed in terms of age and frailty status. The studies were inconsistent in intervention type, duration, and targeted outcomes. Most of the studies indicated that modification of nutrition quality, either by giving supplements or by improving diet intake, could improve strength, walking speed, and nutritional status in majority of frail or pre-frail older adults. However, there was limited evidence on the effectiveness of intervention on inflammatory status and other biomarkers related to frailty due to limited number of studies targeting frailty biomarkers as a major outcome.

Key words: Frailty, nutrition, supplement, randomized controlled trials, intervention studies.

BACKGROUND

Frailty is a geriatric syndrome involving multi-system disorders, neuromuscular dysfunction, abnormalities in energy metabolism, immune dysfunction, inflammation, and endocrine regulation (1-3). It has been associated with increased risk of negative health outcomes including decline in quality of life (1, 2, 4) and disability (5). The concept of frailty is multidimensional based on the relation between physical, psychological, social and environmental factors (1, 3).

Literature has recorded a high variability in the prevalence of frailty. The prevalence of frailty and prefrailty among older adults in the United States of America were 12% and 59.9% respectively, whilst the corresponding figures were 21.6%, and 60.3% respectively in United Kingdom (3). In Spain frailty was 8.4% and prefrailty was 41.8% in older populations (6). Similar findings were found in Asian countries, specifically in Thailand where the prevalence was 4.9% for frailty and 40.0% for prefrailty (7). The difference was probably due to the variability on sample, assessment methodology, criteria and heterogeneity in pattern of diseases and lifestyles including diet.

The relationship between diet and chronic age related diseases has been reported in literature (5). However, the relationship between diet and mechanism of how nutrition contributes to frailty is still not clear and needs further

investigation (8). Nutritional status, dietary behavior, type of food, and nutrients consumed are important parameters that should be thoroughly studied to determine the relationship between frailty and nutrition (8). Malnutrition has been significantly associated with many of the frailty components such as impairments in cognitive and physical function (9, 10). The results of studies investigating the relationship between body mass index (BMI) and frailty are more controversial (5). For example, Balum and colleagues reported a significant association between frailty and obesity (11), Hubbard and colleagues reported a U-shape relationship between BMI and frailty (12), whereas Frisoli and colleagues found no significant association (13).

Diet quality, healthy food choices, food sufficiency, and food diversity are significantly correlated with frailty (2, 14, 15). A higher protein consumption was associated with a lower risk of the incidence of frailty (16). Serum levels of carotenoid, vitamin D, vitamin B6, and folate levels differed between non-frail, prefrail and frail older women (10). However, interventional effect of related micronutrients or dietary patterns in the experimental studies were few compared to cross sectional, longitudinal, or cohort studies.

In this review we aimed to report and evaluate the nutritional intervention studies that have been conducted on frail older adults, and to determine which type of nutritional intervention significantly contributed to improving frailty. As yet, there are no published reviews on nutritional intervention studies and frailty that have been reported.

METHODS

A thorough search for nutritional intervention studies on older adults with frailty using multiple electronic bibliographic databases (Medline, CINAHL, Scopus, Science Direct and Springerlink), was conducted. Key words including frailty with nutrition, diet, supplement, macronutrients, micronutrients and food were used to trace more studies. The search was not limited to any time period but the oldest studies were from the early1990s and onwards. The databases search resulted on hundreds of studies. A screening on the title, abstract, and methodology was done to identify the studies that met the inclusion criteria for further analysis.

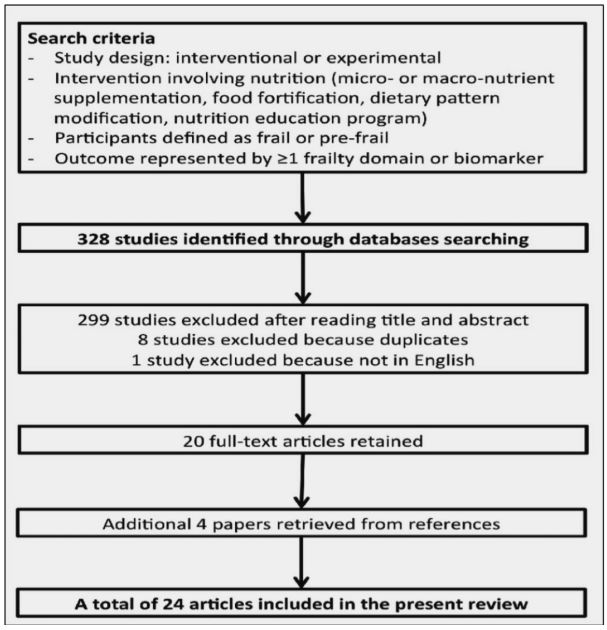
Inclusion and Exclusion Criteria

The inclusion criteria included:

(1) only original studies
(2) study design was experimental i.e. clinical trials or quasi studies;
(3) study participants were defined as "frail" or "prefrail";
(4) intervention targets had at least one of the frailty indicators: nutritional status, physical function, cognitive function and mood, physical activity, mobility, energy, psychology and frailty biomarkers;
(5) intervention involved mainly nutrition alone or mixed with others; and
(6) full-text published in English.

Studies that did not fulfill the inclusion criteria were excluded. All the selected studies were reviewed in terms of methodology, study design, intervention type and duration, participants enrolled in the studies, targeted outcome and main findings. Figure 1 summarizes the procedures of articles selection.

Figure 1
Articles selection flow chart



RESULTS

Twenty-four nutritional intervention studies met the inclusion criteria, with 2216 older adults identified as frail and prefrail, distributed unevenly in twelve countries including USA, Canada, Australia, Netherland, China, France, Germany, Sweden, Poland, Japan, Finland and Korea. The majority of the study design was a randomized controlled clinical trial, followed by controlled trial; two were placebo controlled and blinded, one was quasi experiment. The sample size ranged from 47 to 243, one study included women only, while the rest included both genders, mainly community dwelling older adults, except for four of the trials that were done on institutionalized older adults. The outcome measures reported were mainly physical functions (walking speed and strength) and nutritional status compared to frailty biomarkers. Summary of clinical trials in the present review included study design, intervention period, assessment tools main findings and outcomes as listed in table 1.

Types of nutrition intervention

Various types of nutritional interventions were used according to the requirements of the study. Nine studies used a specific nutritional supplement formula, with calories ranging from 200 to 400 kcal per day. Other studies used i) daily food fortification with protein supplement, ii) nutritional education and counseling for healthy food and dietary habits, iii) an additional evening meal, dietary counseling, and an educational program for healthy food choices and iv) micronutrients (vitamin D, omega three fatty acids, and multivitamin) supplementation as the nutritional intervention.

Effectiveness of intervention

The measures used to evaluate effectiveness of the intervention varied among the studies. Nutritional status, body weight, body composition, basal metabolic rate (BMR) and biomarkers were inconsistent due to variability in participants' nutritional status at baseline and the types of intervention used. Eleven of the sixteen studies that targeted frailty status reported improvement in one or more of the frailty domains, whilst the others reported improvement on other outcomes. Most of the studies that measured frailty parameters reported significant improvement on these parameters.

DISCUSSION

The published reviews on frailty were mainly addressing frailty assessments and risk factors. Intervention studies in relation to frailty are limited. Thus, in this review we focused on evaluating the effectiveness on frailty status. The aim of this review was to answer a research question of whether certain types of dietary intervention, nutritional or micronutrients supplementations have an impact on frailty status. The evaluation of the studies acknowledged the higher level of evidence from RCT as compared to controlled trials that includes: frailty assessment tools, frailty indicators, nutritional status assessment and the nutrition intervention itself.

The level of evidence of the reviewed studies is high as all of them are clinical trials, but sixteen studies involved randomization and this provided further strength in the level of evidence (14). The rest of the studies are controlled studies. A well-designed RCT is considered as a level A in evidence based practice, however, the power of the study also need to be considered (14). The quality of these studies' methodology is discussed in the following paragraphs.

Frailty definition tool

Frailty assessment has been the main concern in the intervention studies and has been used to assess outcomes. In clinical research, the frailty phenotype proposed by Fried and colleagues is very popular and well accepted for frailty assessment (5, 17). The Frailty Index (based on the accumulation of deficits) has also been recommended for intervention studies (17). However, in the reviewed studies, the frailty phenotype was used only in 2 of the studies (18, 19), and the Frailty Index had not been used in any of the studies. Moreover, in many of the studies frailty assessment was not defined. Participants' selection criteria were not clear and it was only stated as older adults with frailty were selected to participate. Nevertheless, in the study by Kim and colleagues mobility (gait speed) was used to define older adults with frailty (20). Zak and colleagues used an operationalization of frailty based on five criteria which was different from the original phenotype by Fried and colleagues (21). In the study by Olin and colleagues, level of dependency was used as a tool to determine frailty status (9). It could be concluded that frailty assessment was not consistently carried out in most of the studies. This might be due to the fact that the frailty phenotype was published in 2001, the Frailty Index later, and a systematic review evaluating different frailty tools only in 2011 (17). Prior to these publications, evidence for recommendations of frailty assessment was not sufficiently available.

The frailty indicators

Frailty has several indicators which include nutritional status, physical function, cognitive function, mood, physical activity, mobility, energy, psychology (9, 22) and biological markers (12). In the reviewed frailty intervention studies, one or more of these indicators had to be included in the intervention outcomes. The most frequently studied frailty indicators in the reviewed studies were nutritional status and physical function (18, 23, 24-30). In addition to nutritional and physical functional status, physical activity was also added to frailty indicators assessment in some recent studies (18, 19).

A more comprehensive assessment for frailty indicators was performed in a study among 139 older adults with frailty which includes, the changes in cognitive function, psychological status, physical function and physical activity (31). Psychological status, nutritional, physical and cognitive function has been used in the frailty assessment as early as 1994 (30). Moreover, some of the studies limited frailty indicators in the nutritional status to only diet intake, body composition, and serum micronutrients (32, 33, 34). Generally, the rest of the studies examined two or more of the frailty indicators namely physical activity, nutritional, cognitive and physical function.

Frailty biomarkers such as homocysteine and serum level of vitamin B12 were studied in only two studies (20, 35). These studies reported improvement in the oxidative stress, immune function and inflammatory status indicating an im-

provement in frailty status. Future studies need to consider the inclusion of biomarkers to indicate early changes in the biological system following intervention.

Nutritional status assessment

As nutrition and its related impact were the main issues in frailty, comprehensive nutritional status assessments are important to report in order to highlight the effects of the intervention on frailty. These include anthropometric measurements, biochemical data (especially micronutrients level), albumin, clinical assessments using the Mini Nutritional Assessment tool (MNA) or Subjective Global Assessment (SGA) and dietary intake.

As shown in Table 1, nutritional assessments were conducted using several methods. Some studies reported detailed nutritional assessments, which examined nutritional status as the main outcome. In the study by Lammes et al. (2012), nutritional status was assessed by using MNA, resting metabolic rate to estimate the energy intake, anthropometric measurements, BMI, fat mass and body density using four skinfolds (33). On the other hand, several studies involved limited nutritional status assessments such as BMI and diet (18, 20, 27). MNA (a highly sensitive and accurate tool for nutritional assessment in older adults) has repeatedly been used as a tool for clinical nutritional status assessment (9, 19, 21, 23-25).

Type of the nutrition intervention

The nutrition intervention used in the studies included, a single type of (n=2), multivitamins (n=4), nutritional supplement formula (n=8), adding an extra meal (n=1), meals on wheels (MOW) (n=1), mixed with exercise (n=7) and individualized dietary counseling (n=4). The results and outcomes varied due to the type and duration of nutrition intervention and nutritional status before the intervention. The studies that used energy supplements in the intervention reported significant improvements in one or more of the frailty indicators or nutritional status, while nutritional advice and counseling (20, 33) showed no significant improvement. However, Nykanen and colleagues reported improvement in frailty status with individual dietary counseling (19). Probably because the study involved older adults who were at risk of malnutrition, showed improvement in frailty status by improving their nutritional status. This may explain that older adults who were at risk of malnutrition, showed improvement in frailty status by improving their nutritional status. On the other hand, adding an extra meal to the habitual diet showed significant improvements on dietary intake (34). But, in the study by Olin et al. (2008) no significant improvement was found (9), which might have been due to the difference in the participants ages between the two studies. In the mixed intervention of nutrition and exercise, the exercise groups showed more improvement compared to the nutrition groups, which revealed the stronger effect of exercise on frailty when compared to nutrition. The intervention period is varied according to the study objectives, ranging from one day to one year. However, the justification for the intervention period was not mentioned in the published articles.

In general, nutrition intervention showed significant effects on frailty indicators in most of the studies. Nutritional status before the intervention had an impact on the results, with intervention appearing to be effective in older adults with malnutrition. The comprehensive nutritional status and the assessments are substantial constituents of any intervention study. Improvement in nutritional status might possibly have led to improvement in frailty status. Mixed intervention nutrition and exercise might have been more effective than nutrition only.

Further research is recommended to include normal weight older adults with frailty to determine the effect of the intervention of frailty status without affecting malnutrition, which would confound the research results. Some micronutrients deficiency such as vitamin D and B12 were studied to examine their effect on frailty in cross sectional and longitudinal studies, although the experimental studies are very sparse. So, experimental studies with adequate dose and intervention period are needed to determine the effectiveness of vitamin D on frailty.

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Table 1
Frailty and Nutrition intervention study

Authors	Study design	Intervention	Intervention period	Intervention arms	Subjects characteristics	Frailty assessment tools	Main findings	
Hutchins et al (2013)	RCT Blinded Placebo	Omega 3 (2gm of EPA, DHA)	Six months	Two arms	126 postmenopausal women	Fried et al 2001 criteria	Improvement in walking speed	NUTRITIONAL INTERVENTION IN FRAILTY
Kim et al (2013)	RCT	200 ml -400kcal nutritional supplement.	12 weeks	Two arms	87 community dwelling frail elderly	Their own definition Nutrition and mobility	Improvement in gait speed and time up and go (TUG)	
Lammes et al (2012)	RCT	Nutritional advice with or without exercise	3 months	Four arms	96 frail elderly aged 75 and above		Increase in RMR in the exercise group only	
Nykanen et al (2012)	CT	Individual dietary counseling	1 year	Two arms	159 community dwelling at risk of malnutrition 75 years and above (frail and prefrail)	Fried criteria	Improvement in the frailty status	
Rydwik et al (2010)	RCT	Physical training and individual dietary counseling	3 months intervention. 9 months follow up	4 arms	96 community dwelling frail elderly	Weight loss and low physical activity	Increase of the habitual physical activity level No significant effects on ADL	
Zak et al (2009)	RCT Blinded Placebo	300 kcal nutritional supplement (NUTRIDRINK) / exercise	7 weeks	4 arms	80 frail elderly (both community dwelling and institutionalized)	5 points inclusion criteria	Improvement in muscle strength were found in (EG/ E+NS)	
Olin et al (2008)	CT	Additional evening meal (530kcal)	6 months	2 arms	49 service flat frail elderly aged 75 and above	Level of dependency	No changes on body weight, and cognitive function	
Rydwik et al (2008)	RCT	Physical and nutritional intervention program	6 months	4 arms	96 frail community dwelling elderly aged 75 and above		No effect by the Nutrition intervention	
Smoliner et al (2008)	CT	Food fortification	12 weeks	2 arms	65 institutionalized (malnourished or at risk)	Not defined	Improvement in protein intake and Body composition	
Roy & Payette (2006)	Quasi-experimental	Meals on wheels (MOW) program	8 weeks	2 arms	51 frail elderly		Increase in the dietary intake	
Wouters et al (a) (2005)	CT Placebo	250 ml, 300 kcal nutritional supplement	6 months	2 arms	33 frail elderly 65 years and above, BMI<25	Not defined	Significant difference in proliferation, no significant difference in IL2 between groups	
Wouters et al (b) (2005)	CT placebo	250 ml, 300 kcal nutritional supplement	6 months	2 arms	67 frail elderly	Not defined	Significant changes in the serum biomarkers. Improvement in some of cognitive test	
Bonnefoy et al (2003)	RCT	400 kcal \ day Protein – energy supplement with exercise	9 months	4 arms	57 frail elderly, from retirement houses	Not defined	Improvement of the muscle functional test in the supplement group	

Authors	Study design	Intervention	Intervention period	Intervention arms	Subjects characteristics	Frailty assessment tools	Main findings	
Latham et al (2003)	RCT Multicentral	Vitamin D / exercise	Single dose of Vitamin D 10 weeks exercise	4 arms	243 frail elderly	Winograd et al., 1991 criteria	Exercise group showed increases risk of musculoskeletal injury	NUTRITIONAL INTERVENTION IN FRAILTY
Payette et al (2002)	RCT	400ml, 400 kcal nutritional supplement	16 weeks	2 arms	83 frail elderly at risk for under nutrition	Not defined	Improvement in total energy intake, weight, muscle strength, functional status, days spent in bed	
Paw et al (2002)	RCT	Micronutrient supplement / exercise	17 weeks	4 arms	139 frail elderly	Not defined	None	
Kwok et al (2001)	RCT	Low lactose milk powder	7 weeks	2 arms	47 institutionalized frail elderly	Not defined	Improvement in dietary intake only	
Marijke 2001	RCT placebo controlled	Enriched food and exercise	17 weeks	4 arms	157 frail elderly	Weight loss Low physical activity	Significant improvement on physical function and fitness in the exercise groups, Consumption of enriched products did not affect performance, fitness, or disability scores	
De jong et al (A) (2000)	CT	Nutrients dense products/ exercise	17 weeks	4 arms	159 frail community dwelling elderly	Weight loss Low physical activity	None	
De jong et al (B) (2000)	RCT	Nutrients dense products/ exercise	17 weeks	4 arms	143 frail elderly	Weight loss Low physical activity	Increase in the lean body mass in the exercise groups	
Singh et al (2000)	RCT	Multinutrient liquid	10 weeks		50 frail institutionalized elderly	Not defined	Significant decrease in diet intake	
Gray et al (1995)	RCT	200 kcal nutritional supplement	12 weeks	2 arms	50 frail elderly	Not defined	Significant weight gain	
Fiatrone et al (1994)	RCT	Nutritional supplement and exercise	10 weeks	4 arms	100 frail institutionalized elderly	Not defined	Increase in the physical function in the exercise groups	

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REFERENCES

1. Crentsil V. Mechanistic contribution of carnitine deficiency to geriatric frailty. Ageing Res Rev 2010;9(3):265-8.
2. Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC, et al. Dietary quality is related to frailty in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2013;68(4):483-9.
3. Bowen ME. The Relationship Between Body Weight, Frailty, and the Disablement Process. J Gerontol B Psych Sci Soc Sci 2012;67(5):618-26.
4. Rockwood K, Mitnitski A. How might deficit accumulation give rise to frailty. J Frailty Aging 2012;1:8-12.
5. Guyonnet S SM, Ghisolfi A, Ritz P, Vellas B. Nutrition frailty and prevention of disabilities with aging. J Frailty Aging 2014 in press.
6. Garcia-Garcia FJ, Avila GG, Alfaro-Acha A, Andres MA, Aparicio ME, Aparicio SH, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. J Nutr Health Aging 2011;15(10):852-6.

7. Chen C-Y, Wu S-C, Chen L-J, Lue B-H. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr 2010;50:S43.
8. Bischoff HA, Staehelin HB, Willett WC. The effect of undernutrition in the development of frailty in older persons. J Gerontol A Biol Sci Med Sci 2006;61(6):585-9.
9. Olin AÖ, Koochek A, Cederholm T, Ljungqvist O. Minimal effect on energy intake by additional evening meal for frail elderly service flat residents—a pilot study. J Nutr Health Aging 2008;12(5):295-301.
10. Bartali B, Frongillo EA, Bandinelli S, Lauretani F, Semba RD, Fried LP, et al. Low nutrient intake is an essential component of frailty in older persons. J Gerontol A Biol Sci Med Sci 2006;61(6):589-93.
11. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. J Am Geriatr Soc 2005;53(6):927-34.
12. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. J Gerontol A Biol Sci Med Sci 2010;65(4):377-81.
13. Frisoli Jr A, Chaves PH, Ingham SJM, Fried LP. Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: results from the Women's Health and Aging Study (WHAS) II. Bone 2011;48(4):952-7.
14. Bernstein MA, Tucker KL, Ryan ND, O'Neill EF, Clements KM, Nelson ME, et al. Higher dietary variety is associated with better nutritional status in frail elderly people. J Am Diet Assoc 2002;102(8):1096-104.
15. Tieland M, Borgonjen-Van den Berg KJ, van Loon LJ, de Groot LC. Dietary protein intake in community-dwelling, frail, and institutionalized elderly people: scope for improvement. Eur J Nutr 2012;51(2):173-9.
16. Beasley JM, LaCroix AZ, Neuhouser ML, Huang Y, Tinker L, Woods N, et al. Protein intake and incident frailty in the Women's Health Initiative observational study. JJ Am Geriatr Soc 2010;58(6):1063-71.
17. De Vries N, Staal J, Van Ravensberg C, Hobbelen J, Olde Rikkert M, Nijhuis-Van der Sanden M. Outcome instruments to measure frailty: a systematic review. Ageing Res Rev 2011;10(1):104-14.
18. Hutchins-Wiese H, Kleppinger A, Annis K, Liva E, Lammi-Keefe C, Durham H, et al. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. J Nutr Health Aging 2013;17(1):76-80.
19. Nykänen I, Rissanen TH, Sulkava R, Hartikainen S. Effects of individual dietary counseling as part of a comprehensive geriatric assessment (CGA) on frailty status: A population-based intervention study. J Clin Gerontol Geriatr 2012;3(3):89-93.
20. Rydwik E, Frändin K, Akner G. Effects of a physical training and nutritional intervention program in frail elderly people regarding habitual physical activity level and activities of daily living—A randomized controlled pilot study. Arch Gerontol Geriatr 2010;51(3):283-9.
21. Zak M, Swine C, Grodzicki T. Combined effects of functionally- oriented exercise regimens and nutritional supplementation on both the institutionalised and free-living frail elderly (double-blind, randomised clinical trial). BMC Public Health 2009;9(1):39.
22. Olin AÖ, Koochek A, Ljungqvist O, Cederholm T. Nutritional status, well-being and functional ability in frail elderly service flat residents. Eur J Clin Nutr 2005;59(2):263-70.
23. Kim C-O, Lee K-R. Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. J Gerontol A Biol Sci Med Sci 2013;68(3):309-16.
24. Smoliner C, Norman K, Scheufele R, Hartig W, Pirlich M, Lochs H. Effects of food fortification on nutritional and functional status in frail elderly nursing home residents at risk of malnutrition. Nutrition 2008;24(11):1139-44.
25. Bonnefoy M, Cornu C, Normand S, Boutitie F, Bugnard F, Rahmani A, et al. The effects of exercise and protein–energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. Br J Nutr 2003;89(05):731-8.
26. Bonnefoy M, Cornu C, Normand S, Boutitie F, Bugnard F, Rahmani A, et al. The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. BBr J Nutr 2003;89(5):731-8.
27. Payette H, Boutier V, Coulombe C, Gray-Donald K. Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial. J Am Diet Assoc 2002;102(8):1088-95.
28. Kwok T, Woo J, Kwan M. Does low lactose milk powder improve the nutritional intake and nutritional status of frail older Chinese people living in nursing homes? J Nutr Health Aging 2000;5(1):17-21.
29. Gray-Donald K, Payette H, Boutier V. Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. J Nutr 1995;125(12):2965-71.
30. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 1994;330(25):1769-75.
31. Paw MCA, De Jong N, Schouten E, Van Staveren W, Kok F. Physical exercise or micronutrient supplementation for the wellbeing of the frail elderly? A randomised controlled trial. Br J Sports Med 2002;36(2):126- 31.
32. De Jong N, Paw MCA, De Groot LC, Hiddink GJ, Van Staveren WA. Dietary supplements and physical exercise affecting bone and body composition in frail elderly persons. Am J Public Health 2000;90(6):947.
33. Lammes E, Rydwik E, Akner G. Effects of nutritional intervention and physical training on energy intake, resting metabolic rate and body composition in frail elderly. A randomised, controlled pilot study. J Nutr Health Aging 2012;16(2):162-7.
34. Roy M, Payette H. Meals-on-wheels improves energy and nutrient intake in a frail free-living elderly population. J Nutr Health Aging 2005;10(6):554-60.
35. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID, et al. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc 2003;51(3):291-9.
36. Rao M. Nitric oxide scavenging by curcuminoids. J Pharmacy Pharmacol 1997;49(1):105-7.

REASONING ABOUT FRAILTY IN NEUROLOGY: NEUROBIOLOGICAL CORRELATES AND CLINICAL PERSPECTIVES

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Abstract: To date, the frailty syndrome has surprisingly attracted limited attention in the field of neurology and neuroscience. Nevertheless, several concepts closely related to frailty, such as vulnerability, susceptibility, and homeostatic reserves, have been increasingly investigated and documented at level of neuronal cells, brain networks, and functions. Similarly, several aspects commonly assessed in the neurological practice, including cognitive functioning and emotional/affective status, clearly appear to be major determinants of the individual's vulnerability and resiliency to stressors. Therefore, they should be carefully considered in the clinical approach to frail subjects. Moreover, dysfunctions of these domains, if timely detected, may be suitable to be targeted by interventions providing beneficial effects to the overall health status of the individual. In the present article, we discuss the neurobiological processes potentially contributing to frailty. Moreover, we reason about the clinical manifestations allowing the prompt and easy recognition of frail persons in the neurological practice.

Key words: Frailty, cognitive impairment, dementia, brain aging, emotional status.

Frailty is defined as a multidimensional condition of increased vulnerability to stressors, posing the subject at risk of negative health-related outcomes, including falls, hospitalization, institutionalization, and disability (1). This concept is triggering a growing scientific and clinical interest as it may allow the identification of a pre-disability state still amenable to interventions and, thus, potentially reversible. To date, surprisingly, such entity attracted limited attention in the field of neurology and neurosciences. The word "frailty" has appeared on neurological and neuropsychiatric journals in only 17 out of nearly 450 articles (3.8%) published in 2013 (research updated to August 15th, 2013). Nevertheless, several concepts closely related to frailty are extensively investigated in neurosciences.

First, as stated above, frailty may be intended as a state of increased vulnerability/susceptibility. Such condition has been increasingly documented at level of neurons, brain networks, and functions. Despite sharing several pathophysiological pathways at different biological levels (i.e. synaptic, glial, mitochondrial, inflammation, and protein misfolding), each neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis) seems to primarily affect defined neuronal subsets and populations, suggesting underlying specific cellular vulnerabilities (2). Based on these observations, it can be hypothesized that these diseases may result from specific combinations of genetic predispositions and environmental stressors causing dysfunctions in susceptible neurons. Similarly, brain aging is considerably heterogeneous being characterized by various degrees of involvement of specific brain systems (notably a medial temporal lobe system and a fronto-striatal system) (3). Accordingly, some brain functions (e.g. semantic memory) are relatively preserved with age, while other abilities (e.g. processing speed, working memory, and episodic memory) more consistently decline (4). The routine neurological practice offers numerous clinical examples of such brain vulnerability. Vascular lesions, though small and limited, can

cause overt dementia syndromes when involving strategic cerebral structures. Furthermore, individuals with impaired cognitive performance may experience the occurrence of psychotic disturbances and/or an abrupt worsening of cognitive abilities when subjected to general anesthesia. Taken together, this evidence indicates that several brain components, networks, and functions are intrinsically vulnerable, potentially contributing to individual vulnerability to stressors (e.g. stressful events, neuropathological changes).

On the other hand, frailty may also be interpreted as a condition of reduced resilience/reserve. The concept of reserve has been introduced for explaining differences across individuals when facing similar age-related brain modifications and pathologies. It combines both structural (e.g. number of neurons and synapses) and functional (e.g. use of pre-existing or compensatory mechanisms) aspects that may increase tolerance to pathology. Epidemiological studies suggest that lifelong experiences and leisure activities in later life may increase such reserves. This has been mainly documented in the field of cognition (i.e. "cognitive reserve") (5). For example, individuals with higher educational and occupational attainment have been found to have a reduced risk of developing Alzheimer's disease (6-7). Subjects with higher reserve may maintain adequate functioning of strategic networks in critical situations (i.e. neuronal knock-out related to head trauma, anesthesia, dehydration, electrolyte dysfunction, and metabolic syndromes) and tolerate a greater amount of structural and functional disease-specific pathology (e.g. Alzheimer's disease). Therefore, changes in lifestyle and interventions may be useful to delay age-related cognitive decline or dementia.

In recent years, several proxies of cognitive reserve have been proposed including educational level, work complexity, social networks as well as engagement in cognitively-stimulating activities, leisure time activities, and physical exercise. In parallel, the neural mechanisms potentially underlying such reserve have been increasingly investigated and elucidated.

Beside of defining the biological basis of frailty, a great effort is also devoted to the identification of clinical parameters allowing the easy identification of the frail person. This may consent to promptly implement preventive interventions against disability and other negative outcomes. Several operational definitions have been developed in order to translate into practice the theoretical concept of frailty. So, how can we detect frailty in the neurological practice? What clinical symptom/sign can help us identifying frail subjects at risk of negative events that may still beneficiate from appropriate interventions? In our opinion, two domains should be carefully considered, namely cognitive abilities and affective/emotional status. These factors greatly influence the individual's vulnerability and resiliency to stressors. They have been consistently found to significantly influence the risk towards relevant adverse outcomes. Moreover, if promptly detected, the impairment of these domains may be still manageable and suitable to be targeted by preventive interventions providing beneficial effects to the overall health status of the individual.

Cognitive impairment, independently from specific clinical diagnosis (i.e. dementia, mild cognitive impairment), is increasingly recognized as a potential contributor to the clinical vulnerability of older persons, resulting as a strong predictor of several adverse health-related outcomes (8). In particular, a decline of cognitive performance has been found to increase the risk of mortality, disability, and institutionalization, independently of potential confounders (e.g. socio-demographic characteristics, incident dementia, depression, and comorbidities). Several hypotheses may explain the association between cognitive impairment and frailty. Impaired cognitive functioning may interfere in recognizing symptoms of diseases, affect adherence to therapeutic interventions, and influence the adoption of healthy lifestyle behaviors. Similarly, cognitive deficits may limit vocational achievements resulting in socioeconomic disadvantage and, consequently, in reduced access to health care. Finally, the decline of each cognitive domain may result in a relevant limitation in planning and implementing adaptive behaviors and strategies in response to stressful events. According to these considerations, there is a growing consensus proposing to include cognitive impairment as a component of the operational definitions of frailty (9-10). A factor potentially limiting its adoption in the clinical translation of the frailty syndrome is represented by the timeliness of its detection. In fact, if cognitive decline is recognized too late (when an extensive neurodegeneration has already occurred), it may be not substantially modifiable by preventive actions and may potentially evolve toward a condition of overt dementia. To date, we still need accurate clinical tools allowing the prompt identification of at-risk subjects. Moreover, the limited/controversial validity of the proposed pre-dementia phases (e.g. mild cognitive impairment, subjective cognitive decline) still limits their implementation in the routine clinical practice (11).

Consistently, emotional and affective dimensions strongly influence the individual's vulnerability and should then necessarily be taken into account when addressing the multidimensional syndrome of frailty. Pathological emotional responses (e.g. anxiety and depression) have been found to considerably affect the onset, course over time, and severity of several medical conditions (e.g. ischemic heart disease, essential hypertension, tumors, and infectious diseases) as result of well-established interactions with nervous, endocrine, and immune systems. Subjects with affective disorders may more likely adopt unhealthy behavioral conducts resulting in increased risk of diseases and reduced compliance to proposed interventions. Moreover, chronic

mood disorders are frequently associated with a subsequent impairment of specific cognitive abilities (e.g. executive functions), leading to further reduction of individual resiliency. Differently from cognitive disorders, emotional and affective disturbances may be more responsive to diverse non-pharmacological (e.g. psychotherapy) and pharmacological interventions. These strategies may positively influence the overall health status by improving the capacity to cope with stressors and dysfunctions.

In conclusion, we believe that "frailty" should represent a source of inspiration in the field of neurology. This concept stresses the multidimensionality of aging and age-related medical conditions, the urgent necessity to identify at-risk subjects potentially benefiting from preventive actions, and the possibility of significantly influence the trajectories toward the "successful" aging. In this context, cognition and emotional/affective status appear to be major determinants of individual vulnerability and resiliency. The dysfunctions of these domains should be therefore carefully investigated and managed. Inspired by the process of attempting the translation of "physical frailty" in clinical settings, neurologists will need to develop and validate use-friendly assessment tools (necessarily encompassing cognitive and emotional aspects) in order to allow a prompt detection of frail subjects in their practice.

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REFERENCES

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752–62.
2. Saxena S, Caroni P. Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration. Neuron 2011;71(1):35–48.
3. Jagust W. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. Neuron 2013;77(2):219–34.
4. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. Psychol Aging 2002;17(2):299–320.
5. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 2012;11(11):1006–12.
6. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004;3(6):343–53.
7. Mangialasche F, Kivipelto M, Solomon A, Fratiglioni L. Dementia prevention: current epidemiological evidence and future perspective. Alzh Res Ther 2012;4(1):6.
8. Houles M, Canevelli M, Abellan van Kan G, Ousset P, Cesari M, Vellas B. Frailty and cognition. J Frailty Aging 2012;1(2):56–63.
9. Avila-Funes JA, Amieva H, Barberger-Gateau P, Le Goff M, Raoux N, Ritchie K, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. J Am Geriatr Soc 2009;57(3):453–61.
10. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment- A review of the evidence and causal mechanisms. Ageing Res Rev 2013;12(4):840–51.
11. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. Eur Psychiatry J Assoc Eur Psychiatr 2008;23(5):321–30.

MOLECULAR CROSSROADS OF FRAILTY AND HIV

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Abstract: An epidemiological transition is occurring regarding Human Immunodeficiency Virus (HIV) infection. This phenomenon, explained by several mechanisms (e.g.: physiologic changes, pharmacologic advances, sexual behaviors), is demonstrated by a significant increase in the number of patients aged 50 years and older diagnosed with this infection. The immunological changes observed in HIV-infected patients may prompt the appearance of an accelerated aging process as well as that of comorbidities and other pathological entities commonly diagnosed in older adults. Frailty is a biologic syndrome characterized by a multi-systemic decrease of the individual's physiologic and homeostatic reserves, leading to diminished resistance against stressors and increased vulnerability. The purpose of this review is to describe the common molecular changes seen in both frailty and HIV-1 infection, offering an in-depth analysis of their pathophysiology and specifying common processes where their pathways meet.

Key words: Frailty, elderly, HIV, AIDS.

INTRODUCTION

Nowadays, a significant epidemiological transition is occurring regarding Human Immunodeficiency Virus-infected patients around the world. This change is characterized by an increased prevalence of HIV-1 infection among patients aged 50 and older (1). A variety of factors have influenced this change, including the access to highly active antiretroviral therapy (HAART) and the increase in the number of newly- diagnosed cases in this group of age. For example, in the United States, the Centers for Disease Control (CDC) estimates that approximately 30% of people currently living with HIV/AIDS are 50 years and older. In 2010, 15-25% of new diagnoses of HIV/AIDS occurred in individuals older than 50 years, while in the year 2000 they only represented 10%. (2). In Mexico, according to the National Center for Prevention and HIV/AIDS Control (CENSIDA), 19,877 cases of HIV-1 infection were reported between 1983 and 2012 in patients 50 years of age and older, representing 12.6% of the entire affected population (3). Consequently, it is projected that from 2015 to 2020, patients belonging to this group of age will represent more than 50% of the infected population worldwide. One aspect that has gained importance over the last few years is the presence of frailty.

"Frailty" has emerged as a condition associated with an increased risk of functional decline among the older persons. Frailty can be differentiated from aging, disability, and comorbidity. It is a biologic condition in which the individual's physiologic and homeostatic reserves are decreased and

its resilience diminished, resulting in a state of increased vulnerability to the adverse effects of a variety of environmental factors, expressed as an increased risk for hospitalization, institutionalization, and mortality (6). In the absence of biological markers, various operational definitions aimed at identifying elderly persons vulnerable to adverse health related outcomes have been proposed. Fried et al. proposed a definition that conceptualizes frailty as a clinical syndrome integrated by the combination of the following five components: weight loss, exhaustion, low physical activity, slow gait speed, and low grip strength (6). Subjects meeting three or more of these criteria were considered to be "frail"; those meeting one or two criteria were considered "pre-frail" or "intermediate" while those meeting none were "non-frail". However, the best way to identify frailty remains controversial. Although the Fried et al.'s definition is widely used, inclusion of other common age-related conditions into the previously described phenotype has been a topic of considerable debate. For example, Rockwood et al. understand frailty in the context of the accumulation of deficits, where the individual's frailty index score reflects the proportion of potential deficits present at a given time translating the likelihood of the patient being frail (7). However that may be, the conceptual frame of frailty implies a connection between all its components and supports the perception of frailty as a multifactorial entity.

On the other hand, unlike the typical definition of the term 'syndrome' used in medical literature, the term 'geriatric syndrome' has a different meaning (8). A geriatric syndrome is defined as the "accumulated effect of impairments in multiple domains" that could lead to a variety of adverse health-related outcomes including falls, incontinence or delirium (6, 8). It is precisely this accumulation of deficits and their physiologic correlations that represent frailty.

As the ever-increasing cohort of HIV-1 positive patients aged 50 and older continues to grow, researchers around the world have formulated interrogations and hypotheses regarding interconnections between frailty and HIV-1 infection in elderly patients. Several associations between these two entities have been suggested in previous research (9, 10). From a molecular perspective, both may share similar changes that could lead to a series of inter-related multi-systemic implications. Indeed, HIV infection has been proposed as a "premature aging model" (11), where a variety of biological systems are compromised, including the musculoskeletal, cardiovascular, neurologic, hematologic, endocrine, and immune systems (12). Furthermore, the aging process coupled with HIV infection situates these patients at a high-risk for adverse health-related outcomes and increased morbimortality (13). In this review, we explore the molecular mechanisms and changes observed in both HIV-1 infection and frailty following a system-based analysis in order to describe how each change contributes to the clinical manifestations that place these patients' health and outcomes at stake.

CHANGES IN THE IMMUNE SYSTEM AND INFLAMMATION

The innate immune system, considered the organism's first line of defense, confers an immediate-yet-unspecific response against stressors such as infectious processes and physical injuries. On the other hand, the adaptive immune system offers a more specialized defense mechanism due to its ability to mount pathogen-specific responses and develop immunological memory in case of subsequent infections (14). In order to serve their purpose, both immune systems have under their command a variety of cellular components implicated in mounting an effective response. If a disturbance to the immune system occurs, its protective response suffers alterations as well (15).

HIV infection is characterized by a progressive failure of the immune system, which shares some of the characteristics seen in the immune system of elderly subjects. As the individual ages, his ability to generate a robust and accurate immune response deteriorates over time. The term "immunosenescence" refers to this deterioration of the immune system also present in frailty, mimicking a state of immunosuppression that has a negative impact on the patient's morbimortality (15). Both HIV-1 infected patients and frail persons share common immune cellular changes (Table 1). Even though several immune alterations are present in frailty and HIV-1 infection, changes in lymphocyte count and function are the most prominent ones (16). Both conditions are accompanied by thymic involution, leading to a decreased production of T-cells (17). This anatomical alteration of the thymus is compensated by an increased proliferation of memory T-cells at the expense of naïve lymphocytes, which in the long run is associated with reduced T-cell function (18). Both frail and HIV-1 positive patients show a marked increase in the production of $CD28^-$, $CD57^+$ memory $CD8^+$ T-cells with reduced ability to produce interleukin 2 (IL-2) (19). In addition to a compromised production of T-cells, the telomeric shortening evidenced in $CD4^+$ T-lymphocytes causes premature apoptosis that further contributes to immunosuppression. $CD4^+$ T-cell dysregulation has also been associated with an increased risk of developing a frailty-related phenotype (FRP) among HIV-1 infected patients who were not already frail at diagnosis (20).

Table 1

Common immune cellular changes between frailty and HIV

Thymic involution
↓ $CD4^+$ T-cell and its repertoire
↓ Naïve $CD4^+$ T-cell
$CD4^+$ T-cell telomeric shortening
$CD4^+$ T-cell premature apoptosis
↑ Expression of CCR-5
↑ $CD28^-$, $CD57^+$ memory $CD8^+$ T-cells
↑ Inflammatory cytokines (IL-6, TNF-α)
↓ Secretion of IL-2

HIV: Human Immunodeficiency Virus; CCR-5: CC chemokine receptor 5; IL: Interleukin; TNF: Tumor Necrosis Factor

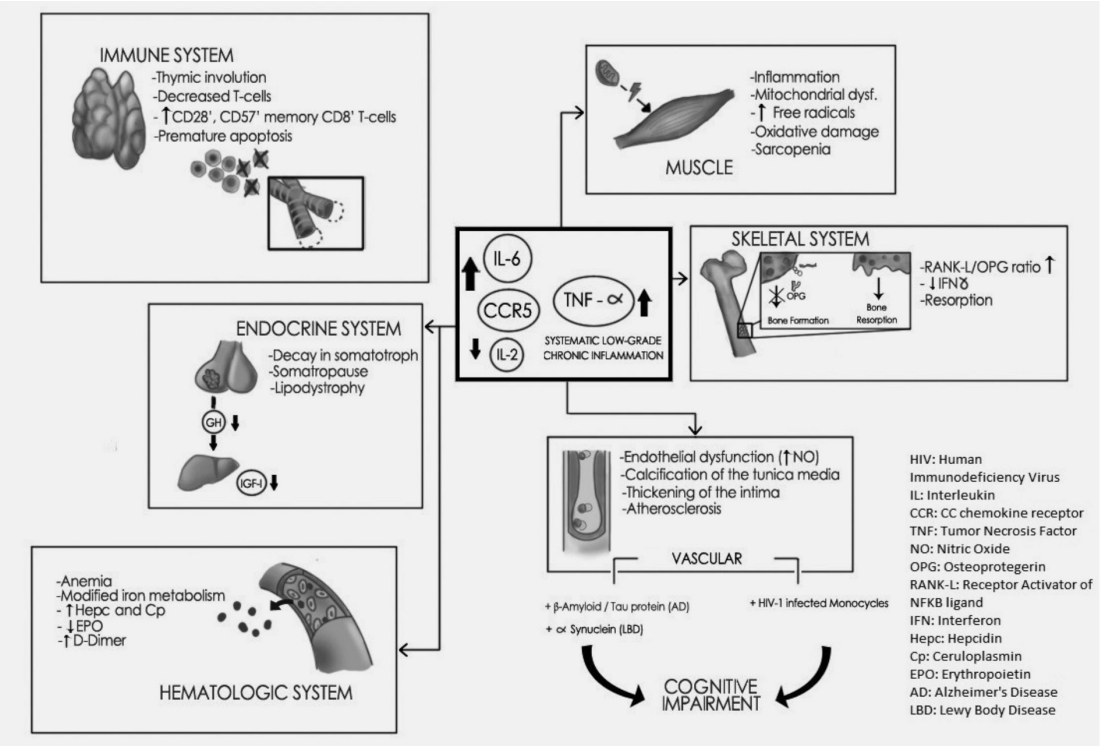
Inflammatory changes have been widely documented in both frailty and HIV infection, and there is strong evidence that they play a central role in the pathogenesis of both conditions (16). The accumulation and deposit of senescent cells in various tissues have been proposed to be strong contributors of long- lasting secretion of proinflammatory cytokines during the aging process (21). This chronic state of low-grade systemic inflammation seen in the elderly is called "inflammaging", and it is characterized by an elevated amount of circulating inflammatory cytokines, particularly interleukin 6 (IL-6). This inflammation-related aging process is caused by the activation of several genomic cellular systems involved in the resistance to oxidative stress and apoptosis (22). T-cells also contribute to inflammation by expressing chemokine CC receptor-5 (CCR5) and at the same time by showing a type-1 pro-inflammatory phenotype (23, 24). These receptors are not only expressed in the aging individual but also in HIV-1 infected patients (25). Common inflammatory changes between frailty and HIV-1 infection, summarized in Table 1, have been strongly associated with increased all-cause mortality (16, 19).

CHANGES IN BONE HOMEOSTASIS

The human skeletal system is responsible for major functions related to support, protection and movement, as well as for endocrine functions such as calcium metabolism and hematopoiesis. Bone tissue goes through a continuous cycle of self-regeneration that replaces old bone with new bone, and a cautious balance between these two phenomena must exist in order to maintain bone integrity. This complex process in which osteoclasts resorb bone and osteoblasts produce and deposit new bone is called "remodeling" (26). As the individual ages, such balance suffers alterations that lead to less bone formation and greater bone resorption. A variety of studies have described a considerably higher prevalence of osteoporosis in both frail and HIV-1 infected patients (27).

Figure 1

Common molecular changes among frailty and HIV-1 infection



The increased production of inflammatory cytokines, particularly TNF-α, plays a key role in the development of bone homeostasis changes, especially in osteoclast activity (28-30). Both, patients with HIV-1 infection and frail patients show an increased expression of TNF-α, which in turn promotes bone resorption within bone metabolic units. Due to this elevated production of proinflammatory cytokines, the balance between bone formation and resorption is largely disrupted (31).

Another of the best-studied mechanisms related to TNF-α and osteoclast activation is the expression of Receptor Activator of NFKB Ligand (RANK-L). In basal conditions, a member of the TNF superfamily called osteoprotegerin (OPG) binds to RANK-L inhibiting its transcription process and thus reducing the production of osteoclasts (27). In HIV-1 infection, OPG production by lymphocytes is diminished while RANK-L remains present in a considerable amount. This leads to an elevated RANK-L/OPG ratio, promoting osteoclasts formation and ultimately contributing to osteoporosis. The increase in TNF-α expression also causes a downregulation of IFN-γ expression, which has the capacity to inhibit RANK-L. The attenuation of this inhibitory mechanism delivers the ideal scenario for RANK-L to perpetuate the progression of osteoporosis. The very same mechanism of bone turnover can be evidenced in the aging individual, being one of the most important physiopathologic factors in postmenopausal osteoporosis (32, 33).

On the other hand, specific components of antiretroviral therapy have also been implicated in the pathogenesis of reduced bone mineral density (BMD) in HIV-infected persons. Randomized controlled trials comparing BMD in protease inhibitor (PI) versus non-PI treatment regimens have shown mixed results. Several studies have revealed that PI-containing regimens led to decreased spine BMD while others showed no difference in total body or hip BMD between treatment groups. Despite the mixed effects on BMD, cumulative exposure to boosted PI was found to be associated with increased risk of fracture (HR 1.11; 95% confidence intervals 1.05-1.18; $p<0.001$) (34). In particular, treatment with lopinavir/ritonavir led to a 17% increase in the risk of incident hip, vertebral, or wrist fracture (34). Multiple studies have assessed the impact of ART initiation on BMD and have generally shown a 2-6% loss after 48-96 weeks of therapy, regardless of the type of ART initiated. This degree of bone loss is larger than what would be expected by aging alone and is comparable to the bone loss seen in women aged 50-59 over 2 years (35, 36).

CHANGES IN MUSCLE

Consequences of aging in the muscular system have been extensively described in the literature. The decline in skeletal muscle mass is commonly observed in the elderly. This qualitative and quantitative progressive loss of muscle mass is called "sarcopenia", which in turn has a significant impact on the individuals' mobility and strength which translates into an increased risk of adverse health-related outcomes (37). The model of frailty described by Fried et al. is strongly influenced by the musculoskeletal system function, whose impairment results in a decreased resting metabolic rate, decreased strength and power, and decreased VO2 max (37). Even with the use of HAART, HIV-1 infected individuals are at increased risk of wasting and sarcopenia (6). In fact, data suggest that changes in muscle mass occur at a similar rate over 5 years in HIV- infected adults and non-infected elderly (38). Several factors have been implicated in muscle damage, including inflammation and mitochondrial dysfunction.

The state of chronic inflammation observed in both frail patients and untreated HIV-1 infected patients has significant repercussions in the muscle system since myocytes are highly responsive to cytokines (39). Furthermore, muscle homeostasis appears to be dependent on a balanced expression of cytokines such as IL-6 and TNF-α (40). This essential balance is disrupted by catabolic stimuli, which include low-grade chronic inflammation. Such disruption will eventually lead to sarcopenia in both frail and HIV-1 infected individuals, causing serious implications on their prognosis as stated in data from the Framingham Heart Study, which reported that IL-6 production was a significant predictor of mortality over a 6- year period (41).

Mitochondrial dysfunction is also a part of the multifactorial etiology of sarcopenia. Mitochondria are the cellular organelles responsible for adenosine triphosphate (ATP) production, and as such, are considered the main source of energy at a cellular level. Many reactions and processes in the organism are dependent of ATP, and muscle contraction is not an exception. The pathways by which mitochondrial dysfunction is related to sarcopenia in frail and HIV-1 infected patients will be described below. As it was previously mentioned, sarcopenia is a highly prevalent phenomenon in older adults as well as in frail individuals. Muscle is not only responsible for movement and strength but also works as the body's main reservoir of protein and as an essential site of glucose disposal (42). The process of aging causes a reduction in mitochondrial size and DNA content, as well as a decrease in mitochondrial protein synthesis (39). This flawed functioning could be associated with oxidative damage caused by the excess of free radical production (39). Over time, the accumulation of oxidative damage reduces ATP production in muscle, causing impaired muscle contraction and affecting the individual's capacity for movement and strength. HAART has also been implicated in premature and accelerated aging via direct effects on mitochondria. Antiretroviral drugs cause accumulation of damaged mitochondrial DNA, induce morphologic changes

and increase oxidative stress (10). This mechanism of mitochondrial damage is common for both frailty and HIV-1 infection.

Growth hormone also plays a major role in the development of sarcopenia in frail older adults and HIV infected patients. Due to its predominant endocrine nature, it will be discussed in the section dedicated to endocrine changes. Another factor of great importance in the pathophysiology of sarcopenia is the decline of α-motor neuron input. Nevertheless, there are very few reports of HIV-1 positive patients with a documented motor neuron disorder (43). This lack of evidence makes it difficult to associate motor neuron disease with sarcopenia in HIV-1 infected individuals. However, neuromuscular impairment is considered a cornerstone in the development of sarcopenia in the context of frailty, which is the reason why it should not be overlooked while reviewing the different mechanisms of muscle damage. All these inter-related mechanisms highlight the importance of sarcopenia as a critical factor in the development of the impairment of strength, mobility, balance, and gait.

CHANGES IN THE HEMATOLOGIC SYSTEM

Anemia is the most frequently diagnosed hematologic disorder. This disorder can be found in both frail and HIV-1 infected patients and is associated with higher mortality and diminished health-related quality of life (44-46). Anemia is a manifestation of several phenomena including hemorrhage, diminished erythropoiesis, hemolysis, and nutritional deficiencies (i.e. iron, folic acid, vitamin B12), among others. However, in order to discuss anemia in HIV and frailty we need to retake inflammation as the core causative mechanism. There is convincing evidence that supports a strong link between IL-6 and anemia (47). The chronic low-grade pro-inflammatory state characterized by increased levels of IL-6 observed in HIV infection and frailty modifies iron metabolism, which is essential for the homeostatic regulation of the hematologic system (48). Because of the deregulation of pro-inflammatory cytokines, iron is diverted from the blood flow into the reticuloendothelial system where it is no longer available for the erythrocyte (49, 50). Iron maldistribution is the consequence of an IL-6-induced type II acute phase response that results in the expression of Hepcidin (Hepc) and Ceruloplasmin (Cp), contributing to a restriction in iron availability and affecting hemoglobin production (51).

Proinflammatory cytokines also have an inhibitory effect on erythropoietin (EPO), the glycoprotein hormone responsible for erythropoiesis (52). HIV-1 infected patients express a myriad of circulating antibodies, including autoantibodies to endogenous erythropoietin (anti-EPO). Diminished erythropoiesis due to either inhibition or destruction of EPO is a known mechanism of anemia in frailty and HIV, respectively (53).

CARDIOVASCULAR CHANGES

Several changes in the cardiovascular system have been described in the aging individual as well as in HIV infected patients. Previous work has shown these changes to be associated with an increased risk of cardiovascular disease, posing a threat to health related quality of life of both groups of patients. More than two decades ago, Joshi et al. and Paton et al. described atherosclerotic changes in post-mortem analyses of young HIV-infected patients, setting the initial evidence of vascular dysfunction in HIV infection (54, 55). Recent studies have also suggested a link between HAART and acute myocardial infarction (AMI) risk among HIV-positive patients; however, the mechanisms are not entirely known yet. History of cardiovascular disease, such as AMI, angina, and congestive heart failure is more prevalent among frail elderly patients, being congestive heart failure the most strongly associated with frailty (56). Possible factors by which HIV infection contributes to these changes have been recently postulated and include inflammation, $CD4^+$ T-cell depletion, altered coagulation, dyslipidemia, impaired arterial elasticity, and endothelial dysfunction (57). Some of these structural and functional cardiovascular changes can also be seen in the aging individual, including increased vascular stiffness and endothelial dysfunction (58). Vascular stiffness results from calcification of the tunica media, thickening of the intima, and an increase in collagen content, which intertwines and forms a rigid matrix that results in atherosclerotic disease (59).

Endothelial dysfunction, another core cardiovascular alteration, is present in HIV-positive patients as well as in frail elderly patients (60, 61). Individuals with both of these conditions develop dysregulations of nitric oxide synthesis (NO). However, even though both HIV and frailty present this endothelial change, NO synthesis behaves differently in each condition. In the setting of HIV infection, production of NO increases and is further enhanced by TNF-α monocyte activation (62).

The coagulation system is involved in frailty and HIV infection, and its alterations may be causative agents of cardiovascular sequelae. It has been recognized that both conditions feature a procoagulant state with an increase of several biomarkers, particularly D-dimer (63, 64). Evidence obtained from previous research demonstrates that the increase in D-dimer observed in both HIV-1 infection and frailty correlates with adverse health-related outcomes, increasing both morbidity and mortality (65, 66). Moreover, the increase of these coagulation/fibrinolysis biomarkers was associated with physical performance decline, specifi-

cally that of lower extremities, disability for activities of the daily living and poorer cognitive performance (67).

Due to the influence of these changes, the cardiovascular system is significantly compromised in both groups of patients, increasing the risk of complications such as AMI. Further evidence is needed to describe the exact molecular changes of the cardiovascular system in the frail individual; however, physiological changes observed with aging may represent strong indicators of what is observed in frailty.

CENTRAL NERVOUS SYSTEM CHANGES

Atherosclerosis, a key factor for the development of cardiovascular disease, also plays a major role in central nervous system (CNS) alterations observed in frailty. The brain is one of many end organs affected by atherosclerosis and stiffening of large and small vessels (68). The interaction between vessel pathology and other factors associated with neurodegenerative changes may result in cognitive decline and dementia in the aging individual. Current neurogeriatric views consider Alzheimer's disease (AD), small and large vessel disease, and Lewy-body disease as the three main conditions related to dementia and cognitive decline. Even though they are considered to be different pathological entities, these three conditions may coexist; an example of this interaction is the evidence that large-vessel atherosclerosis may contribute to AD (69, 70). Frailty is associated with low cognitive performance and has been proposed as a risk factor for mild cognitive impairment and AD (71, 72). Only recently has it been proposed that frailty is an independent risk factor for incident vascular dementia (73). These findings support the importance of cerebral blood supply and highlight the role of vascular factors in the pathogenesis of dementia.

Central nervous system involvement in HIV infected patients comprises a wide range of neurocognitive disorders, which are collectively known as HIV-associated neurocognitive disorders (HAND), being the HIV-associated dementia (HAD) its most severe manifestation. Vascular dysfunction may contribute to a lesser extent to the pathogenesis of HAND; however, the main recognized developmental mechanism of HAD/HAND is neuronal cell damage by infected monocytes that cross the blood-brain barrier to further differentiate into macrophages responsible for the neuronal insult (74). Even though the mechanisms by which neurocognitive impairment presents and develops in HIV-1 infection and frailty may not be exactly the same, recognizing both entities as possible sources of CNS damage in the setting of these conditions is imperative.

CHANGES IN THE ENDOCRINE SYSTEM

The endocrine system contributes to homeostasis by secreting hormones into the blood stream. Its functions depend on connections -or axes- between several organs and glands. The pathophysiologic processes of the two conditions discussed in this review are strongly linked with endocrine system dysfunction. As the individual ages, the somatotroph axis is one of the hormonal pathways that demonstrates a significant decay and thus has been implicated in several catabolic phenomena present in older adults. The term "somatopause" was coined in order to describe the decline in the activity of the GH-IGF-1 axis as well as its metabolic consequences. Frailty is directly related to somatopause as both conditions share common alterations and sequelae (75). The decrease in GH and IGF-1, along with the abnormally high levels of inflammatory mediators, contribute to the development of frailty (76). IGF-1, whose synthesis by the liver is GH-dependent, has been proposed as the most important mediator of muscle and bone growth (77). Several studies suggest that low circulating levels of IGF-1, as well as reduced responsiveness to its action by musculoskeletal tissues, play an essential role in age-related osteopenia and sarcopenia, changes also observed in frail elders (78).

Individuals with HIV-1 infection experience endocrine dysregulations related to hypothalamic and pituitary dysfunction (79). Just as in frailty, the somatotroph axis is affected in HIV-1 infection (80). Data obtained from recent studies suggest that the development of early functional impairment in HIV-1 infected patients is associated with low IGF-1, which leads to the decrease of muscle mass and bone mineral density. These indicators are initial manifestations of somatopause (81). Another mechanism in which the somatotroph axis is involved in the setting of HIV-1 infection is the development of lipodystrophy. Patients with HIV-associated lipodystrophy show decreased levels of GH and IGF-1 (82). Recent investigations on the relationship between body composition and frailty in HIV-infected older adults have concluded that infected frail subjects tend to exhibit central obesity and characteristic fat redistribution consistent with lipodystrophy.

Several other changes related to the decay of the somatotroph axis are worth noting. Recently, IGF-1 has been attributed a role in the pathogenesis of numerous conditions seen during aging such as atherosclerosis, cardiovascular disease, cognitive decline, and dementia (83). These conditions can be observed in HIV-1 infection as well. However, further research must be carried out in order to determine the definitive mechanism by which they occur.

Sex hormones are also affected due to changes in the pituitary-gonadal axis and most notably observed in men. As HIV progresses to AIDS, testosterone levels usually decrease. With the arrival of HAART, the incidence of

hypogonadism in HIV-infected men has declined from 40 to 20%. Hypogonadism may be accompanied by decreased muscle and strength, generalized fatigue, reduced libido, mood alterations, gynecomastia, normocytic anemia, and diminished BMD (84). Hypogonadal men with HIV-associated weight loss treated with physiologic testosterone therapy show improvement in lean body mass (LBM), muscle strength, BMD, and health-related quality of life. Hypogonadism may also be involved in the pathogenesis of wasting syndrome, as it is present in up to 50% of men and women with wasting and has been directly correlated with decreased in both LBM and fat (85).

Given the multi-systemic nature and metabolic complexity of frailty and HIV, it is unlikely that alterations of a single axis (i.e. the somatotroph axis) can explain the entire metabolic dysregulation present in these conditions. Nevertheless, the importance of somatopause has been widely recognized as a determinant factor in aging and HIV infection.

CONCLUSION

HIV infection in older adults has important medical, psychological, and socioeconomic implications. These patients show a higher prevalence of comorbidities and, those who remain untreated, a more rapid progression to AIDS. The physiopathological similarities found between HIV-1 infection and frailty could behave as synergic phenomena that may potentially impact these patients' health status and translate into a more profound deterioration. Due to the vast commonalities between these two conditions, frailty could escape even a well- trained clinical eye and remain unnoticed. Failure to identify and address frailty in HIV-1 positive patients could result in the appearance of serious adverse health-related outcomes or potentiate those already present. Even though HIV and frailty share similarities at a molecular level, pharmacologic treatment of the first has shown no benefit on the course of the second. No current consensus is available on the treatment of frailty; however, prevention via identification of risk factors and protective countermeasures (i.e. management of weight loss, physical activity, adequate caloric and protein intake, among others) could theoretically improve outcomes in pre-frail and frail individuals. In the meantime, surveillance of this ever- increasing population is required since life expectancy of an HIV-1 infected frail patient could be even more compromised in spite of adequate HAART treatment.

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REFERENCES

1. Perez JL, Moore RD. Greater effect of Highly Active Antiretroviral Therapy on survival in people aged > or = 50 years compared with younger people in an urban observational cohort. Clin Infect Dis 2003;36:212-218.
2. Centers for Disease Control and Prevention. HIV/AIDS among persons aged 50 and older: CDC HIV/AIDS facts. 20011, Washington, DC: US Department of Health and Human Services.
3. SS/DGE. National Census of AIDS Cases. Data up to April 2013. SS/CENSIDA.
4. Kirk JB, Goetz MB. Human immunodeficiency virus in an aging population, a complication of success. J Am Geriatr Soc 2009;57:2129- 2138.
5. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection: what is known and future research directions. Clin Infect Dis 2008;47:542-553.
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-M156.
7. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007;62:738-743.
8. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm - issues and controversies. J Gerontol A Biol Sci Med Sci 2007;62:731-737.
9. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis 2008;47:542-553
10. Smith RL, de Boer R, Brul S, et al. Premature and accelerated aging: HIV or HAART? Front Genet 2012;3:328. doi: 10.3389/fgene.2012.00328. Epub 2013 Jan 28.
11. Pathai S, Lawn SD, Gilbert CE, et al. Accelerated biological aging in HIV- infected individuals in South Africa: a case-control study. AIDS 2013;27:2375-2384.
12. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011;62:141-155.
13. Önen NF, Abayomi A, Enbal S, et al. Frailty among HIV-infected persons in an urban outpatient care setting. J Infect 2009;59:346-352.
14. Kuchel GA. Aging and homeostatic regulation. In: Halter J, Ouslander J, Tinetti M, Studenski S, High K, Asthana S (ed) Hazzard's Geriatric Medicine and Gerontology, 6th edn. 2009. McGraw Hill, pp 621-629.
15. Deeks SG, Verdin E, McCune J. Immunosenescence and HIV. Curr Opin Immunol 2012;24:501-506.
16. Yao X, Li H, Leng SX. Inflammation and Immune System Alterations in Frailty. Clin Geriatr Med 2011;27:79-87.
17. Sauce D, Larsen M, Fastenackels S, et al. Evidence of premature immune aging in patients thymectomized during early childhood. J Clin Invest 2009;119:3070-3078.

18. Akbar AN, Henson SM. Are senescence and exhaustion intertwined or unrelated processes that compromise immunity? Nat Rev Immunol 2011;11:289-295.
19. Aberg, JA. Aging, inflammation and HIV infection. Top Antivir Med 2012;20:1-5.
20. Desquilbet L, Margolick JB, Fried LP, et al. Relationship between a frailty-related phenotype and progressive deterioration of the immune system in HIV-infected men. J Acquir Immune Defic Synr 2009;50:299- 306.
21. Coppé JP, Patil CK, Rodier F, et al. A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. PLoS ONE 2010;5:e9188.
22. Navarrete-Reyes, AP. Montaña-Álvarez M. Inflammaging: Aging inflammatory origin. Rev Invest Clin 2009;61:327-336.
23. De FU, Wang GC, Fedarko NS, et al. T-lymphocytes expressing CC chemokine receptor-5 are increased in frail old adults. J Am Geriatr Soc 2008;56:904-908.
24. Qin S, Rottman JB, Myers P, et al. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. J Clin Invet 1998;101:746-754.
25. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor account for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996;86:367-377.
26. Guyton AC, Hall J. Parathyroid hormone, calcitonin, calcium & phosphate metabolism, vitamin D, bone & teeth. In: Guyton AC, Hall J. (ed). Guyton and Hull textbook of medical physiology. 11th edn. 2001. Philadelphia, Pensylvania., pp 978-995.
27. Saccomanno MF, Ammassari A. Bone disease in HIV infection. Clin Cases Miner Bone Metab 2011;8:33-36.
28. Stone B, Dockrell D, Bowman C, et al. HIV and bone disease. Arch Biochem Biophys 2010;503:66-77.
29. Ofotokun I, Weitzmann MN. HIV-1 infection and antiretroviral therapies: risk factors for osteoporosis and bone fracture. Curr Opin Endocrinol Diabetes Obes. 2010;17:523-529.
30. Yin MT, Shane E. Low bone-mineral density in patients with HIV: pathogenesis and clinical significance. Curr Opin Endocrinol Diabetes 2006;13:497-502.
31. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: A practical review and recommendations for HIV care providers. Clin Infect Dis 2010;51:937–946.
32. Yun TJ, Chaudhary PM, Shu GL, et al. OPG/FDCR-1, a TNF receptor family members, is expressed in lymphoid cells and is up-regulated by ligating CD40. J Immunol 1998;161:6113-6121.
33. Li Y, Toraldo G, Li A, et al. B cells and T cells are critical for the preservation of bone homeostasis and attainment of peak bone mass in vivo. Blood 2007;109:3839-3848.
34. Bedimo R, Zhang S, Dreschler H, et al. Risk of osteoporotic fractures associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012;26:825-831
35. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral régimen. J Acquir Immune Defic Syndr 2009; 51:554-61.
36. Warming L, Hassager C, Christiansen C. Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 2002; 13:105-112.
37. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing 39:412–423.
38. Tang AM, Jacobson DL, Spiegelman D, et al. Increasing risk of 5% or greater unintentional weight loss in a cohort of HIV-infected patients, 1995 to 2003. J Acquir Immune Defic Syndr 2005;40:70–76.
39. Yarasheski, K. Age-related skeletal muscle decline is similar in HIV- infected and uninfected individuals. J Gerontol A Biol Sci Med Sci. 2011;66:332–340.
40. Drey, M. Sarcopenia-pathophysiology and clinical relevance. Wien Med Wochenschr 2011;161:402–408.
41. Cannon JG. Intrinsic and extrinsic factors in muscle aging. Ann NY Acad Sci 1998;854:72–77.
42. Roubenoff R, Parise H, Payette H, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community dwelling men and women: the Framingham Heart Study. Am J Med 2003;115:429–435.
43. Cooper C, Dere W, Evans W, et al. Frailty and sarcopenia: definitions and outcome parameters. Osteoporos Int 2012;23:1839–1848.
44. Roubenoff R, Hughes VA. Sarcopenia: current concepts. J Gerontol A Biol Sci Med Sci 2000;55:716-724.
45. Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. Am J Med 2004;116:27-43.
46. Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV infection: clinical impact and evidence-based management strategies. Clin Infect Dis 2004;38:1454-1463.
47. Dong X, Mendes de Leon C, Artz A, et al. A population-based study of hemoglobin, race, and mortality in elderly persons. J Gerontol A Biol Sci Med Sci 2008;63:873–878.
48. Boelaert JR, Weinberg GA, Weinberg ED. Altered iron metabolism in HIV infection: mechanisms, possible consequences, and proposals for management. Infect Agents Dis 1996;5:36-46.
49. Wisaksana R, Sumantri R, Indrati AR, et al. Anemia and iron homeostasis in a cohort of HIV-infected patients in Indonesia. BMC Infect Dis 2011;11:213. doi: 10.1186/1471-2334-11-213.
50. Ganz T. The role of hepcidin in iron sequestration during infections and in the pathogenesis of anemia of chronic disease. Isr Med Assoc J 2002;4:1043-1045.
51. Vyoral D, Petrak J. Hepcidin: a direct link between iron metabolism and immunity. Int J Biochem Cell Biol 2005;37:1768-1773.
52. William B. Biological Interactions of Aging and Anemia: A Focus on Cytokines. J Am Geriatr Soc 2003;51:18-21.
53. Tsiakalos A, Kordossis T, Ziakas PD, et al. Circulating antibodies to endogenous erythropoietin and risk for HIV-1-related anemia. J Infect 2010;60:238-243.
54. Joshi VV, Pawel B, Connor E, et al. Arteriopathy in children with acquired immune deficiency syndrome. Pediatr Pathol 1987;7:261-275.
55. Paton P, Tabib A, Loire R, et al. Coronary artery lesions and human immunodeficiency virus infection. Res Virol 1993;144:225-231.
56. Freiberg M, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med 2013;173:614-622.
57. Newman AB, Gottdiener JS, McBurnie MA, et al. Association of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci 2001;56:158-166.
58. Lakkata EG, Schulman S. Age-associated cardiovascular changes are the substrate for poor prognosis with myocardial infarction. J Am Coll Cardiol 2004;44:1097-1104.
59. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 1993;73:413–467.

60. Kline ER, Sutliff RL. The roles of HIV-1 proteins and antiretroviral drug therapy in HIV-1-associated endothelial dysfunction. J Investig Med 2008;56:752-769.
61. Taddei S, Virdis A, Mattei P, et al. Aging and endothelial function in normotensive subjects and patients with essential hypertension. Circulation 1995;91:1981–1987.
62. Bukrinksy M, Schmidtmayerova H, Zybarth G, et al. A critical role of nitric oxide in human immunodeficiency virus type 1-induced hyperresponsiveness of cultured monocytes. Mol Med 1996;2:460-468.
63. Pontrelli G, Martino AM, Tchidjou HK, et al. HIV is associated with thrombophilia and high D-dimer in children and adolescents. AIDS 2010;24:1145-1151.
64. Kanapuru B, Ershler W. Inflammation, coagulation and the pathway to frailty. Am J Med 2009;122:605-613.
65. Pieper CF, Rao KM, Currie MS, et al. Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. J Gerontol A Biol Sci Med Sci 2000;55:649-657.
66. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008;5:203.
67. McDermott MM, Greenland P, Green D, et al. D-dimer, inflammatory markers, and lower extremity functioning in patients with and without peripheral arterial disease. Circulation. 2003;107:3191-3198.
68. O' Rourke MF, Hashimoto J. Mechanical factors in arterial aging. J Amer Coll Cardiol. 2007;50:1–3.
69. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813–817.
70. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging pathological correlations in vascular cognitive impairment. Stroke 2009;40:48-52.
71. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The Three-City Study. J Am Geriatr Soc 2009;57:453-461.
72. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. J Am Geriatr Soc 2008;56:2211–2216.
73. Avila-Funes JA, Carcaillon L, Helmer C, et al. Is frailty a prodromal stage of vascular dementia? Results from the Three-City Study. J Am Geriatr Soc 2012; 60:1708-1712.
74. Lindl KA, Marks DR, Kolson DL, et al. HIV-associated neurocognitive disorder: Pathogenesis and Therapeutic Opportunities. J Neuroimmune Pharmacol 2010;5:294-309.
75. Perrini S, Laviola L, Carreira MC, et al. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J Endocrinol 2010;205:201-210.
76. Joseph C, Kenny AM, Taxel P, et al. Role of endocrine-immune dysregulation in osteoporosis, sarcopenia, frailty and fracture risk. Mol Aspects Med 2005;26:181-201.
77. Goldspink G. Loss of muscle strength during aging studied at the gene level. Rejuvenation Res 2007;10:397-405.
78. Kveiborg M, Flyvbjerg A, Rattan SI, et al. Changes in the insulin-like growth factor-system may contribute to in vitro age-related impaired osteoblast functions. Exp Gerontol 2000;5:1061–1074.
79. Bhasin S, Singh AB, Javanbakht M. Neuroendocrine abnormalities associated with HIV infection. Endocrinol Metab Clin North Am 2000;30:749-764.
80. Jain S, Desai N, Bhangoo A. Pathophysiology of GHRH-growth hormone- IGF1 axis in HIV/AIDS. Rev Endocr Metab Disord 2013;14:113-118.
81. Erlandson KM, Allshousee AA, Jankowski CM, et al. Functional impairment is associated with low bone and muscle mass among persons aging with HIV infection. J Acquir Immune Defic Syndr 2013;63:209- 215.
82. Koutkia P, Canavan B, Breu J, et al. Growth hormone releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. JAMA 2004;292:210.
83. Ceda GP, Dall'Aglio E, Maggio M. Clinical implications of the reduced activity of the GH-IGF-I axis in older men. J Endocrinol Invest 2005;28:96-100.
84. Salehian B, Jacobson D, Swerdloff RS, et al. Testicular pathologic changes and the pituitary-testicular axis during human immunodeficiency virus infection. Endocr Pract 1999;5:1-9.
85. Dobs A. Role of testosterone in maintaining lean body mass and bone density in HIV infected patients. Int J Impot Res 2003;15:21-25.

COGNITIVE FRAILTY: FRONTIERS AND CHALLENGES

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An international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) recently convened in Toulouse, France to establish a definition for cognitive frailty in older adults. This effort was motivated by growing awareness that many people with physical frailty are also prone to cognitive problems. In "Cognitive Frailty: Rationale and Definition" (1), an initial working definition was developed, and a framework proposed for future studies of cognitive frailty.

This group should be commended for addressing the construct of cognitive frailty and an obvious gap in the clinical gerontology literature. Physical frailty is a widely recognized problem in the elderly. While age-associated cognitive dysfunction has been studied for many years, for the most part it was not conceptualized in a manner that is consistent with current definitions of physical frailty. In fact, cognition has typically not been conceptualized in this manner, and only recently has the term cognitive frailty been employed. Rockwood et al published one of the first studies to examine factors associated with frailty in the elderly (2). Frailty was conceptualized as a multidimensional construct with both physical and cognitive origins. Panza et al. used the term cognitive frailty in the title of their review of pre-dementia syndrome vascular risk factors (3). In a subsequent paper, Panza et al, attempted to specify different models of frailty in pre-dementia and dementia syndrome (4). The prognostic accuracy of frailty assessment inventories for mortality among hospitalized elderly people was examined subsequently, with results suggesting that both cognitive and physical factors were important in predicting outcome (5). We reviewed 199 manuscripts cited in PubMed in which cognitive frailty was mentioned in either the title or as a keyword. In the vast majority of these manuscripts, frailty was examined as a manifestation of cognitive dysfunction. Only recently has cognitive frailty itself become the focus of inquiry.

The term cognitive frailty is attractive as it suggests a parallel with physical frailty. The concept of physical frailty is relatively well understood in the context of aging, and has been operationalized in studies conducted over the past two decades (6-8). However, as Kelaiditi et al. point out, the operational definition of physical frailty remains unresolved (1). The situation is even more problematic for cognitive frailty, as past investigators have focused on a variety of different phenomena.

The term has often been used as a general descriptor for cognitive impairment occurring as people reach advanced age. Sometimes cognitive frailty refers to cognitive disturbances or pre-dementia occurring in association with other medical conditions (9). However, Kelaiditi et al. state that cognitive frailty must be considered as being independent of dementia or pre-existing brain disorders (1). Accordingly, there seems to be several different perspectives on the nature of cognitive frailty. The fact that the construct is ambiguous and lacking a precise operational definition clearly reinforces the authors' effort to establish a common language for future studies of cognitive frailty.

An obvious question emerges: How is cognitive frailty different from cognitive reserve? Cognitive reserve refers to the capacity of a given individual to resist cognitive im-

pairment or decline. Educational level and prior cognitive abilities have been shown to be important determinants of cognitive reserve (10-12). Cognitive reserve has been linked with resilience of brain function and structure in the presence of disease, injury, or other factors that alter physiological functioning (13). While cognitive and brain reserve undoubtedly have some common underpinnings, the relationship between these types of reserve is still not fully understood.

Kelaiditi et al maintain that "cognitive frailty is characterized by reduced cognitive reserve". Accordingly, cognitive frailty could be viewed as simply the inverse of cognitive reserve. The authors indicate that while cognitive reserve is an important element of cognitive frailty, it is also dependent on the existence of physical frailty; i.e., "the simultaneous presence of both physical frailty and cognitive impairment". They distinguish this category of older non-demented adults from cognitive impairment in the absence of physical frailty. The importance of this categorization is that it emphasizes an important and often under- recognized relationship between systemic physical illness, brain dysfunction, and cognitive impairment. It is now well established that cognitive disturbances occur secondary to various medical conditions, such as cardiovascular disease, diabetes and HIV (14-19).

The value of excluding brain disorders from cognitive frailty may be less well justified. By limiting cognitive frailty to people with physical frailty, Kelaiditi et al create four discrete categories of older non-demented adults, which may have some clinical value. However, with respect to the concept of cognitive frailty, there are many examples of people who are vulnerable to subsequent functional decline based on the existence of subtle cognitive and/or brain abnormalities below the threshold for clinical detection. In fact, a major thrust of current research on neurodegenerative disease focuses on the discovery of vulnerability and early markers of future functional decline. While physical disorders such as diabetes and cardiovascular risk factors contribute to this vulnerability, a variety of neurobiological and behavioral risk factors also exist that create functional vulnerability (20-22), and ultimately cognitive frailty. In fact, excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Furthermore, people with physical frailty who develop cognitive frailty presumably do so as their brain begins to develop neuropathological changes. Accordingly, there is value in dichotomizing cognitive frailty between people with or without pre-existing brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

Defining cognitive frailty depends on determining its diagnostic criteria. Other than physical frailty, the primary criteria proposed by Kelaiditi et al. is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance that would lead to dementia. Using these criteria, it is not clear whether people with cerebrovascular disturbances would meet these criteria or not. The authors make a point of also noting that "under different circumstances cognitive frailty may also represent a precursor of neurodegenerative processes". This is a critical point that reinforces the need to go beyond the definition of cognitive frailty as occurring in the absence of brain dysfunction. It is also likely that a CDR = 0.5 is too narrow to fully capture the heterogeneity of cognitive frailty. For example, people without cognitive impairment that rises to the level of a CDR=0.5 may still be vulnerable to functional decline under certain conditions. This occurs commonly during hospitalization, in response to extreme stress, or to changes in the physical environment in the elderly.

In fact, it is the vulnerability to alterations in cognitive function under such conditions that may be the essential determinant of cognitive frailty. There are many people in society with cognitive limitations who would not be considered to be frail, unless they exhibit a tendency to functionally decompensate when their resources are challenged. The key to operationalizing cognitive frailty may ultimately depend of developing diagnostic challenges that would enable clinicians to determine this tendency. This will depend on determining which neurocognitive measures are most useful for detecting this vulnerability and for assessing the severity of cognitive frailty.

In sum, "Cognitive Frailty: Rationale and Definition" (1) provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. While closely linked to cognitive reserve, the construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability to cognitive functional decline among people with or without physical frailty, though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors. Growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, measured with walking speed or the Short Physical Performance Battery (SPPB) (23), is independently associated with cognitive decline (24-36). The SPPB tests, including walking, balance and chair stands, require the complex interplay of sensory, cognitive, and motor functions. These systems may be altered early in the path to cognitive decline (36, 37), and possibly to cogni-

tive frailty. Low walking speed and low SPPB score are also associated with elevated inflammatory cytokines and low Brain-Derived Natirurectic Factor (BDNF) (38-40), all of which are predictors of cognitive decline (41, 42).

Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Following the expert consensus, prospective studies will be needed to assess the reliability and predictive validity of the operational measure of cognitive frailty. We laud the efforts of the IANA/IAGG consensus group in laying the foundation for the emerging concept of cognitive frailty and strongly encourage future studies aimed at advancing this clinical domain.

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REFERENCES

1. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ouset P, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salva A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten, Vellas B (2013) Cognitive Frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. J Nutr Health Aging 2013;9:726-734.
2. Rockwood K, Stolee P, McDowell I (1996) Factors associated with institutionalization of older people in Canada: testing a multifactorial definition of frailty. J Am Geriatr Soc 44(5):578-582.
3. Panza F, D'Introno A, Colacicco AM, et al (2006) Cognitive frailty: Predementia syndrome and vascular risk factors. Neurobiol Aging 27(7):933-940.
4. Panza F, Solfrizzi V, Frisardi V, et al (2011) Different models of frailty in predementia and dementia syndromes. J Nutr Health Aging 15(8):711-719.
5. Pilotto A, Rengo F, Marchionni N, et al (2012) Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. PLoS One. 7(1):e29090.
6. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B (2010) The assessment of frailty in older adults. Clin Geriatr Med 26(2):275-286.
7. Abellan van Kan G, Rolland Y, Andrieu S, et al (2009) Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 13(10):881-889.
8. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B (2008) The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 12(1):29-37.
9. Chouliara Z, Kearney N, Stott D, Molassiotis A, Miller M (2004) Perceptions of older people with cancer of information, decision making and treatment: a systematic review of selected literature. Ann Oncol 15(11):1596-1602.
10. Satz P, Morgenstern H, Miller EN, et al (1993) Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). J Acquir Immune Defic Syndr 6(5):503-511.
11. Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 8(3):448-460.
12. Stern Y, Albert S, Tang MX, Tsai WY (1999) Rate of memory decline in AD is related to education and occupation: cognitive reserve? Neurology 53(9):1942-1947.
13. Satz P, Cole MA, Hardy DJ, Rassovsky Y (2011) Brain and cognitive reserve: mediator(s) and construct validity, a critique. J Clin Exp Neuropsychol 33(1):121- 130.
14. Okonkwo OC, Cohen RA, Gunstad J, Tremont G, Alosco ML, Poppas A (2010) Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. Cerebrovasc Dis 30(4):362-373.
15. Cohen RA, Poppas A, Forman DE, et al (2009) Vascular and cognitive functions associated with cardiovascular disease in the elderly. J Clin Exp Neuropsychol 31(1):96-110.
16. Gunstad J, Cohen RA, Paul RH, Tate DF, Hoth KF, Poppas A (2006) Understanding reported cognitive dysfunction in older adults with cardiovascular disease. Neuropsychiatr Dis Treat 2(2):213-218.
17. Devlin KN, Gongvatana A, Clark US, et al (2012) Neurocognitive effects of HIV, hepatitis C, and substance use history. J Int Neuropsychol Soc 18(1):68-78.
18. Cohen RA, de la Monte S, Gongvatana A, et al (2011) Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. J Neuroimmunol 233(1-2):204-210.
19. Cohen RA, Harezlak J, Schifitto G, et al (2010) Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. J Neurovirol 16(1):25-32.
20. Elie M, Cole MG, Primeau FJ, Bellavance F (1998) Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 13(3):204-212.
21. Robertsson B, Blennow K, Gottfries CG, Wallin A (1998) Delirium in dementia. Int J Geriatr Psychiatry 13(1):49-56.
22. Woods AJ, Mark VW, Pitts AC, Mennemeier M (2011) Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R 3(5):426- 432.
23. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB (1995) Lower- extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 332(9):556-561.
24. Camargo EC, Beiser A, Tan ZS et al (2012) Walking Speed, Handgrip Strength and Risk of Dementia and Stroke: The Framingham Offspring Study. American Academy of Neurology, 64th Annual Meeting, New Orleans, April 21-28, 2012.
25. Dodge HH, Mattek NC, Austin D, Hayes TL, Kaye JA (2012) In-home walking speeds and variability trajectories associated with mild cognitive impairment. Neurology 78(24):1946-1952.
26. McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, Teri L (2011) Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed «up & go» test. Phys Ther 91(8):1198-1207.
27. Fitzpatrick AL, Buchanan CK, Nahin RL, DeKosky ST, Atkinson HH, Carlson MC, Williamson JD (2007) Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. J Gerontol A Biol Sci Med Sci 62(11):1244-1251.

28. Deshpande N, Metter EJ, Bandinelli S, Guralnik J, Ferrucci L. Gait speed under varied challenges and cognitive decline in older persons: a prospective study. Age Ageing 2009; 38(5):509-514.
29. Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, Yaffe K, Newman AB (2005) Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. Neuroepidemiology 24(1-2):8- 14.
30. Soumare A, Tavernier B, Alperovitch A, Tzourio C, Elbaz A (2009) A cross- sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci 64(10):1058-1065.
31. Abellan Van KG, Rolland Y, Andrieu S, Bauer J, Beauchet O, et al (2009) Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 13(10):881-889.
32. Wang L, Larson EB, Bowen JD, van BG (2006) Performance-based physical function and future dementia in older people. Arch Intern Med 166(10):1115-1120.
33. Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, Lipsitz LA (2009) A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. J Gerontol A Biol Sci Med Sci 64(9):994-1001.
34. Zimmermann LJ, Ferrucci L, Kiang L, Lu T, Guralnik JM, Criqui MH, Yihua L, McDermott MM (2011) Poorer clock draw test scores are associated with greater functional impairment in peripheral artery disease: the Walking and Leg Circulation Study II. Vasc Med 16(3):173-181.
35. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, Lipton RB (2008) Gait dysfunction in mild cognitive impairment syndromes. J Am Geriatr Soc 56(7):1244-1251.
36. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X (2007) Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry 78(9):929-935.
37. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA (2007) Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 69(5):483-489.
38. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, Marsh AP, Kritchevsky SB, Nicklas BJ (2009) Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci 64(4):455-461.
39. Hsu FC, Kritchevsky SB, Liu Y, Kanaya A, Newman AB, Perry SE, Visser M, Pahor M, Harris TB, Nicklas BJ (2009) Association Between Inflammatory Components and Physical Function in the Health, Aging, and Body Composition Study: A Principal Component Analysis Approach. J Gerontol A Biol Sci Med Sci 64(5):581- 589.
40. Scalzo P, Kummer A, Bretas TL, Cardoso F, Teixeira AL (2010) Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol 257(4):540-545.
41. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E, Kramer AF (2010) Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci 30(15):5368-5375.
42. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T (2003) Inflammatory markers and cognition in well- functioning African-American and white elders. Neurology 61(1):76-80.

FRAILTY AND CHRONIC RESPIRATORY DISEASES

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Abbreviations
AIRWAYS ICPs: Integrated Care for Airway Diseases (EIP-AHA)
CRD: Chronic Respiratory Diseases
EIP on AHA: European Innovation Partnership on Active and Healthy Ageing
EU: European Union
COPD: Chronic Obstructive Pulmonary Disease
GARD: WHO Global Alliance against Chronic Respiratory Diseases
NCD: Non-communicable Chronic Disease
UN: United Nations
WHO: World Health Organization
6MWD: Six-Minute Walking Distance

INTRODUCTION

As populations continue to grow older, efforts to support the process of ageing well are important goals (1). Ageing is intertwined with socioeconomic inequalities, providing an under-appreciated cause of poverty and hinders economic development, particularly of underserved populations and women. Active and Healthy Ageing (AHA) is a major societal challenge common to all countries and to all populations (2) AHA allows people to realize their potential for physical, social (economic, cultural, spiritual and civic affairs) and mental wellbeing throughout the life course (3). AHA needs to be promoted very early in life to be successful, contributing to general wellbeing of citizens and sustainability of social support systems.

Frailty is a common threaten to both physical and psychological/mental wellbeing in the elderly and is a major determinant of adverse outcomes including functional decline.

Frailty is increasingly seen as a multidimensional process that may include disruption in the health status, mental wellbeing or impact the equilibrium of the person with its surrounding physical environment and social networks.
Chronic respiratory diseases (CRD) represent a model of chronic diseases across the life course. As any non-communicable disease (NCD), they can be associated to frailty. Both conditions, CRD and frailty, are key targets of good practices emerging from the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). In order to foster discussion about key determinants of CRD and frailty and to highlight good practices for replicability and scaling-up, a meeting EIP on AHA was organized by the Région Languedoc-Roussillon and Region Centro Portugal, Lisbon July 1-2, 2015.

CHRONIC RESPIRATORY DISEASES

CRDs are chronic diseases of the airways and the other structures of the lungs. Major preventable CRD include asthma and respiratory allergies, chronic obstructive pulmonary disease (COPD), occupational lung diseases, sleep apnea syndrome and pulmonary hypertension. CRDs are major NCDs and affect over one billion people in the world (4) (Table 1). The burden of preventable CRD has major adverse effects on the quality of life and disability of affected individuals; they cause premature death and create large adverse and underappreciated economic effects on families, communities and societies in general. Among the EU member states, asthma accounted for an average of 53 hospital admissions per 100 000 population in 2009 and the average COPD-related admission rate was 184(5). The annual direct and indirect costs in the 28 EU countries due to COPD or asthma are estimated at €48 billion and €34 billion respectively (5).

Table 1: Prevalence of chronic respiratory diseases (WHO estimates) from (2)

Disease	Year of estimate	Prevalence
Asthma	2004	300 million
COPD	2007	210 million
Allergic rhinitis	1996-2006	400 million
Sleep apnea	1986-2002	>100 million
Others	2006	>50 million

Chronic respiratory diseases negatively impact active and healthy ageing (AHA). Breath difficulties and poor blood gas exchange are key determinants of metabolic health, leading to physiological inefficiencies, susceptibility to the onset or fast progression of diseases and poor physical and mental performance.

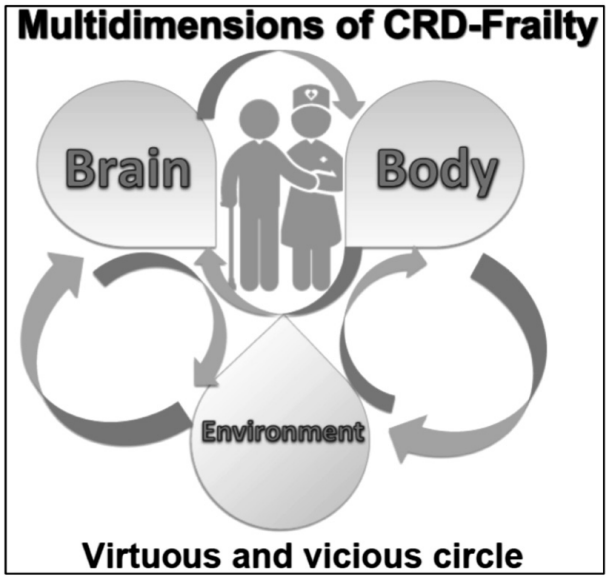
COPD is a heterogeneous disease with various clinical presentations. It is a characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response (neutrophilic) in the airways and the lungs to noxious particles and gazes. Worldwide, the most common risk factor is tobacco smoking. In many countries, outdoor, occupational and indoor air pollution (mainly biomass fuel combustion) are major risk factors. In addition, any factor that affects lung growth during pregnancy and early childhood (infection) may increase the risk for COPD (6). COPD is a major public health problem in subjects over 40 years of age and will remain a challenge for the future. COPD has an estimated annual death rate of over 4 million people globally. COPD is a major source of disability. Physical disability stemming from exercise-induced dyspnea, muscular deconditioning, and other factors has a major impact on the quality of life of the patients. The six-minute walking distance (6MWD) is a patient-important outcome in research and clinical practice to evaluate exercise capacity in COPD and cardiovascular disorders (7). Many individuals with COPD have low body weight associated with impaired pulmonary status, reduced diaphragmatic mass, lower exercise capacity and higher mortality than those who are adequately nourished (8). COPD is associated with social disability (9).
Asthma is defined as an airflow obstruction that is reversible spontaneously or after treatment. Inflammation (eosinophilic) of the airways and non-specific bronchial hyper-reactivity are features of asthma (10). Asthma and allergic diseases occur along the life cycle from early childhood (11). Asthma is a global health problem. Patients from all countries, all ethnic groups, all ages suffer from asthma. The prevalence of asthma can be higher than 20% of the population in some age groups. Asthma affects social life, sleep, school and work. Long-standing asthma can cause disability and COPD. Various social and economic effects are associated with asthma including absenteeism and presenteeism (12).

FRAILTY IN CHRONIC RESPIRATORY DISEASES

Frailty is a progressive physiological decline in multiple organ systems marked by loss of function, loss of physiological reserve and increased vulnerability to disease (13). It is considered as an early stage in the pathway towards disability characterised by a progressive functional decline which, differently from disability, is still amenable for preventive interventions and is reversible. Frailty appears to be secondary to multiple conditions using multiple pathways leading to a vulnerability to a low-power stressor. Biological (inflammation, loss of hormones), and clinical (e.g. sarcopenia, osteoporosis) factors are involved in the mechanisms leading to frailty and social factors (isolation, financial sit-

uation) play a significant role in modulating both the time of its clinical onset and its evolution and prognosis (14, 15). Many chronic diseases are associated with increasing frailty and functional decline in older people, with concomitant personal, social, and public health implications (16). Pre-frail participants have more comorbidity and are at higher risk for disability than non-frail participants (17). Older people suffering from frailty often receive fragmented chronic care from multiple professionals. There is an urgent need for coordination of care and a multidimensional approach in developing interventions aimed at reducing frailty, especially in lower educated groups (18, 19). Patients with CRDs are ageing and it is therefore of importance to consider frailty as an important outcome in order to reverse it (Figure 1).

Figure 1: The vicious circle between chronic respiratory diseases and frailty



Unrecognized CRDs can be detected in frail elderly patients (20).

COPD may be associated with frailty. Sarcopenia affects up to 15% of patients with stable COPD and impairs function and health status (21).

Gait speed in Impact of COPD treatment: Gait speed, a key marker of frailty is a consistent predictor of adverse outcomes. Gait speed is mainly determined by exercise capacity but reflects global well-being as it captures many of the multi-systemic effects of disease severity in COPD rather than pulmonary impairment alone. Gait speed slows down with increasing COPD severity. It correlates with age, clinical symptoms, pulmonary functions, and quality of life scores. Gait speed may be used as a functional capacity indicator (22). The usual gait speed is correlated with the 6MWD (23). In community-dwelling elderly people, has been demonstrated in patients with COPD that usual gait speed is a consistent predictor of adverse outcomes (24). The changes in usual gait speed and 6MWD were associated with increased 12-month mortality in patients with severe COPD suggesting that gait speed may inform clinicians when to initiate end-of-life communications and palliative care (25). The increasing evidence on gait speed is promising as a simple test that can inform the clinician about many important functional aspects of the COPD patient (26).

CRDs are associated with social life and work impairment and the social component of frailty may be of relevant importance in some patients with asthma and/or COPD, especially in old age adults.
It remains to be proven, however, whether optimizing treatment of frail COPD patients with multi-morbidities and polypharmacy improves health outcomes. Integrated care services in frail community-dwelling COPD patients improved clinical outcomes such as survival and decreased the ED visits, but it did not reduce hospital admissions (27).

Frailty may be common in asthma in the elderly (28) but no studies have demonstrated it.

CRDs may represent a model of frailty across the life course. CRDs are diseases often occurring early in life and they represent a model of chronic diseases across the life course. They impact social life and are inducing frailty across the life course. Understanding how frailty can occur and be prevented across the life course is likely to have a major impact on the prevention of frailty in old age adults with chronic diseases with a major impact in health and social care as well as costs.

THE EUROPEAN INNOVATION PARTNERSHIP ON ACTIVE AND HEALTHY AGEING

To tackle the potential of ageing in the EU, the European Commission -within its Innovation Union policy- launched the EIP on AHA (DG Santé, DG Connect) (29). It pursues a triple win for Europe (https://webgate.ec.europa.eu/eipaha/):

- Enabling EU citizens to lead healthy, active and independent lives while ageing.
- Improving the sustainability and efficiency of social and health care systems.
- Boosting and improving the competitiveness of the markets for innovative products and services, responding to the ageing challenge at both EU and global levels, thus creating new opportunities for businesses.

The Action Plan A3 of the EIP on AHA is helping to prevent functional decline and frailty, targeting multi-dimensions including the physical and mental/cognition components, as well as environment-related determinants, like malnutrition. The Action Plan B3 of the EIP on AHA is promoting integrated care models for chronic diseases, including the use of remote monitoring. The objective of Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) (30) is to launch a collaboration to develop multi-sectoral care pathways for CRDs in European countries and regions as part of the EIP on AHA (Area 5 of the Action Plan B3) and to scale up globally with WHO GARD (4) in order to (i) reduce the burden of the CRDs and (ii) promote AHA. AIRWAYS ICPs does not duplicate existing EU prevention programmes in CRDs (e.g. anti-smoking) but will strengthen them where appropriate.

THE MEETING ON AIRWAYS ICPS AND FRAILTY, LISBON, JULY 1-2, 2015

On behalf of the EIP on AHA Reference Site Network, the Languedoc Roussillon (31) and Centro Portugal regions have organised a meeting on CRDs and frailty in collaboration with the Directorate General of Health of Portugal and WHO GARD (4). This meeting reviewed the achievements of AIRWAYS ICPs and link the EIP on AHA Action Plan B3 initiative and the Action Plan A3 (frailty). Moreover, this meeting initiated a proposal attempting to link frailty across the life course in patients with CRDs. In particular, it followed a previous EIP on AHA Reference Site Network meeting in Montpellier (October 24, 2014) (32) on an operational definition of AHA.

REFERENCES

1. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry. 2006;14(1):6-20.
2. Rechel B, Grundy E, Robine JM, Cylus J, Mackenbach JP, Knai C, et al. Ageing in the European Union. Lancet. 2013;381(9874):1312-22.
3. Kuh D, Cooper R, Hardy R, Richards M, Ben-Shlomo Y. A life course approach to healthy ageing. Oxford: Oxford; 2014.
4. Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007:148 pages.
5. Gibson G, Loddenkemper R, Lundback B, Sibille Y. The new European Lung White Book: Respiratory health and disease in Europe: ERS Publications; 2013.
6. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. Am J Respir Crit Care Med. 2013;187(4):347-65.
7. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Int Med J. 2009;39(8):495-501.
8. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane database Syst Rev. 2012;12:CD000998.
9. Liu Y, Croft JB, Anderson LA, Wheaton AG, Presley-Cantrell LR, Ford ES. The association of chronic obstructive pulmonary disease, disability, engagement in social activities, and mortality among US adults aged 70 years or older, 1994-2006. Int J COPD. 2014;9:75-83.
10. Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. Curr Opin Pulm Med. 2015;21(1):1-7.
11. Samolinski B, Fronczak A, Kuna P, Akdis CA, Anto JM, Bialoszewski AZ, et al. Prevention and control of childhood asthma and allergy in the EU from the public health point of view: Polish Presidency of the European Union. Allergy. 2012;67(6):726-31.
12. Fletcher M, Jha A, Dunlop W, Heron L, Wolfram V, Van der Molen T, et al. Patient reported burden of asthma on resource use and productivity across 11 countries in Europe. Adv Ther. 2015;32(4):370-80.
13. Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario. Lancet. 2015;385(9968):e7-9.
14. Berrut G, Andrieu S, Araujo de Carvalho I, Baeyens JP, Bergman H, Cassim B, et al. Promoting access to innovation for frail old persons. IAGG (International Association of Gerontology and Geriatrics), WHO (World Health Organization) and SFGG (Societe Francaise de Geriatrie et de Gerontologie) Workshop--Athens January 20-21, 2012. J Nutr Health Aging. 2013;17(8):688-93.
15. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Determinants of frailty. J Am Med Dir Assoc. 2010;11(5):356-64.
16. Sinclair A, Morley JE, Rodriguez-Manas L, Paolisso G, Bayer T, Zeyfang A, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc. 2012;13(6):497-502.
17. Danon-Hersch N, Rodondi N, Spagnoli J, Santos-Eggimann B. Prefrailty and chronic morbidity in the youngest old: an insight from the Lausanne cohort Lc65+. J Am Geriatr Soc. 2012;60(9):1687-94.
18. Hoogendijk EO, van Hout HP, Heymans MW, van der Horst HE, Frijters DH, Broese van Groenou MI, et al. Explaining the association between educational level and frailty in older adults: results from a 13-year longitudinal study in the Netherlands. Ann Epidemiol. 2014;24(7):538-44 e2.
19. Tavassoli N, Guyonnet S, Abellan Van Kan G, Sourdet S, Krams T, Soto ME, et al. Description of 1,108 older patients referred by their physician to the "Geriatric Frailty Clinic (G.F.C) for Assessment of Frailty and Prevention of Disability" at the gerontopole. J Nutr Health Aging. 2014;18(5):457-64.
20. Bertens LC, Reitsma JB, van Mourik Y, Lammers JW, Moons KG, Hoes AW, et al. COPD detected with screening: impact on patient management and prognosis. Eur Respir J. 2014;44(6):1571-8.
21. Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax. 2015;70(3):213-8.
22. Ilgin D, Ozalevli S, Kilinc O, Sevinc C, Cimrin AH, Ucan ES. Gait speed as a functional capacity indicator in patients with chronic obstructive pulmonary disease. Ann Thorac Med. 2011;6(3):141-6.

23. DePew ZS, Karpman C, Novotny PJ, Benzo RP. Correlations between gait speed, 6-minute walk distance, physical activity, and self-efficacy in patients with severe chronic lung disease. Respir Care. 2013;58(12):2113-9.
24. Kon SS, Patel MS, Canavan JL, Clark AL, Jones SE, Nolan CM, et al. Reliability and validity of 4-metre gait speed in COPD. Eur Respir J. 2013;42(2):333-40.
25. Benzo R, Siemion W, Novotny P, Sternberg A, Kaplan RM, Ries A, et al. Factors to inform clinicians about the end of life in severe chronic obstructive pulmonary disease. J Pain Sympt Manag. 2013;46(4):491-9e4.
26. Karpman C, Benzo R. Gait speed as a measure of functional status in COPD patients. Int J COPD. 2014;9:1315-20.
27. Hernandez C, Alonso A, Garcia-Aymerich J, Grimsmo A, Vontetsianos T, Garcia Cuyas F, et al. Integrated care services: lessons learned from the deployment of the NEXES project. Int J Integr Care. 2015;15:e006.
28. Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, et al. Asthma in the elderly: Current understanding and future research needs--a report of a National Institute on Aging (NIA) workshop. The J Allergy Clin Immunol. 2011;128(3 Suppl):S4-24.
29. Bousquet J, Michel J, Standberg T, Crooks G, Iakovidis I, Gomez M. The European Innovation Partnership on Active and Healthy Ageing: the European Geriatric Medicine introduces the EIP on AHA Column. Eur Geriatr Med. 2014;5(6):361-2.
30. Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). Eur Respir J. 2014;44(2):304-23.
31. Bousquet J, Bourquin C, Augé P, Domy P, Bringer J, Camuzat T, et al. MACVIA-LR Reference Site of the European Innovation Partnership on Active and Healthy Ageing. Eur Geriatr Med. 2014;5(6):406-15.
32. Bousquet J, Kuh D, Bewick M, Strandberg T, Farrell J, Pengelly R, et al. Operational definition of active and healthy ageing (AHA): Report of the meeting held in Montpellier October 21,22-2012. Eur Geriatr Med. 2015;7:in press.

DIABETES AND FRAILTY: AN UP TO DATE SYNOPSIS

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Abstract
Diabetes mellitus (DM) is a disabling chronic condition with a tremendous health, social, and economic burden within our ageing communities. The main impact of diabetes in older adults stems from its effect on function, both physical and cognitive, that finally impairs their quality of life, although the impact on survival is modest.
Frailty is a powerful predictor of disability and other adverse outcomes including mortality, disability, and institutionalization in older adults.
We explore the intimate relationship between diabetes and frailty and recognise their huge societal and personal health burden.
Key words: diabetes, sarcopaenia, frailty, older people

INTRODUCTION

Diabetes mellitus (DM) is a highly prevalent metabolic condition (up to 30%) that is associated with disability and reduced life expectancy in older people (1-4). As many as 40% of people with DM remain undiagnosed (5).

Frailty has emerged during the last two decades as the most powerful predictor of disability and other adverse outcomes including mortality, disability, and institutionalization in older adults (6). Frailty can be described as a state of increased vulnerability to stressors, which results from decreased physiological reserve in multiple systems that causes limited capacity to maintain homeostasis (7). The prevalence of frailty in older adults has been described to be between 7-30% depending on the nature of the populations and the criteria used (8).

Sarcopaenia, the loss of muscle mass associated with ageing, appears to be an important contributor to the pathophysiological pathway leading to frailty and its effects are exacerbated by diabetes which is known to accelerate loss of muscle mass.
This review explores these interrelationships.

DIABETES MELLITUS

DM is a syndrome characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat, and protein metabolism, associated with an absolute or relative deficiency in insulin secretion and/or insulin action. The development of type 2 diabetes in older adults represents the progressive worsening of multiple age-related metabolic disturbances plus a contribution from environmental, genetic, and behavioural factors (9).

Older people with diabetes have higher rates of premature death and coexisting medical conditions than those without diabetes (10). They are also at a greater risk of several common geriatric syndromes such as polypharmacy,

depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain (11). Diabetes is a risk factor for the development of frailty, more than doubling the risk (OR: 2.18) after 3.5 years of follow-up. Overall, it is associated with a decline in quality of life and a decrease in leisure activities (12,13).

SARCOPAENIA

Sarcopaenia, the progressive decline in muscle mass and consequently strength and function may be due to progressive atrophy, loss of muscle fibres (14), and a reduction in "muscle quality" due to the infiltration of fat and other non-contractile material alongside changes in muscle metabolism and insulin resistance (15). The main effect of a loss of muscle mass is reduced muscle strength and power, which are important factors to maintain stability and gait, and necessary to perform ADLs (16). Impaired muscle strength is highly predictive of incident disability and all-cause mortality in this population, and sarcopaenia has been considered to be an integral component of frailty (17).

FRAILTY

Frailty is a complex clinical condition lacking consensus on a standardised definition, however Fried and colleagues have put forward a definition of a clinical phenotype of frailty which has been widely used (18) and is based on three main questions relating to weight loss, exhaustion, and physical activity levels supported by two practical tests involving hand grip strength and gait speed determinations.

A biological model, the "cycle of frailty", that included sarcopaenia, neuroendocrine and inmune dysfunction as potential causes has been proposed. Frailty is not an inevitable consequence of the ageing process, but appears to be a dynamic process and also potentially reversible. Early recognition of frailty and early intervention should therefore be a major focus for care of older people.

SARCOPAENIA IS AN INTERMEDIARY

The maintenance of skeletal mass and function is a due to multiple factors including hormonal, inflammatory, neurological, nutritional, and activity components (16). The development of sarcopaenia can be a result of alterations in multiple physiological systems, as well as from decline in activity and specific diseases. Briefly these are:

Nutritional factors:

Older people with diabetes may be at increased risk of malnutrition, and there is probably a causal relationship between malnutrition and functional decline in this group (19). Other factors can also contribute to poor nutrition in older people such as renal impairment and vitamin deficiencies.

Hormone imbalance:

Age-related alterations in hypothalamic-pituitary-testicular, hypothalamic—pituitary-adrenal and GH-IGF-1 axes are known to be associated with frailty via influences on muscle strength, bone strength and mobilit (16). There is accumulating evidence that several factors that have been shown to play a key role in the protein synthesis of muscle mass, such as IGF-1 and testosterone, are decreased in diabetes (20,21).

Vitamin D levels are lower in diabetes which may contribute to B cell dysfunction, insulin resistance and inflammation (22). Also, studies suggest that vitamin D levels correlate with muscle mass and strength and low levels of vitamin D are associated with falls and functional decline (23), and the frailty syndrome (24).

Insulin and insulin resistance:

Insulin resistance may lead to impairment of muscle strength, and during ageing, insulin resistance appears to be involved in muscle protein loss. Loss of control of the anabolic action of insulin on ageing muscle may be a key factor favouring sarcopaenia (16). Handgrip muscle strength is also significantly associated with fasting insulin level or insulin resistance. Other relevant observations include insulin-induced inhibition of protein degradation, an increase in protein synthesis and inhibition of proteolysis and a role in other key steps in protein regulation (25-27).

Inflammation and anti-inflammatory response:

An increase in proinflammatory cytokines may be associated with sarcopaenia and frailty (28,29). Diabetes is also associated with elevated cytokine levels, and higher level of cytokines can induce insulin resistance.

Obesity:

Obesity is a causative factor for the development of type 2 diabetes and frailty; with higher fat mass and lower muscle mass, physical activity becomes progressively more difficult, promoting further muscle mass loss. This cycle potentially leads to "sarcopaenic obesity", a major risk factor for the onset of physical disability (30).

Advanced glycation end products (AGEs):

AGEs formation accompanies diabetes mellitus and may play a role in the pathogenesis of sarcopaenia, through AGE-mediated increases in inflammation, endothelial dysfunction in the microcirculation of skeletal muscle and through cross-linking of collagen in skeletal muscle (31).

Mitochondrial dysfunction:

Defects in mitochondrial oxidation and phosporylation have been demonstrated both in older adults without diabetes, and in young obese and non-diabetic offspring of people with type 2 diabetes (32,33). These abnormalities could lead to a vicious cycle in which mitochondrial dysfunction, elevation of intramyocellular lipids, impaired lipid oxidation and insulin resistance amplify each other, leading to sarcopaenia.

OTHER FACTORS

Microvascular Complications of Diabetes:

Alterations in neurotransmission and motor unit remodelling seen in diabetic polyneuropathy may provide a basis for changes in motor performance (34). Diabetes-related renal impairment and may increase the risk of frailty due to inactivity, loss of muscle mass, comorbid conditions and decline in physical and cognitive function.

Atherosclerosis and Diabetes:

Diabetes-related macrovascular disease can increase morbidity and mortality and also exacerbate physical inactivity (13). Atherosclerotic change and endothelial dysfunction are key underlying features involved in this process.

Peripheral vascular disease may also affect muscular performance, and tends to be more diffuse in individuals with diabetes. The effect of impaired oxygen supply on striated muscle may be direct, or indirect via the peripheral nerves (35).

Cognitive decline:

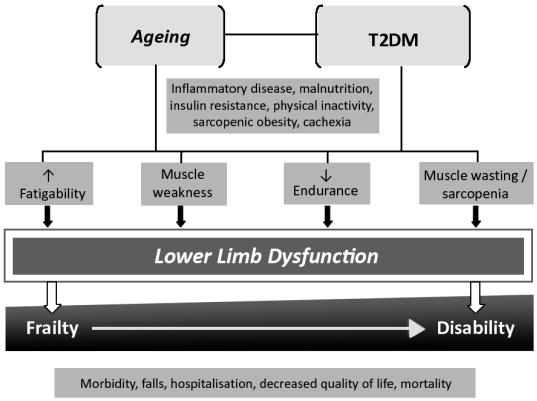
Both frailty and diabetes is associated with an increased risk of mild cognitive impairment (MCI) and diabetes increases the risk of dementia; repeated hypoglycaemic episodes are also more likely to develop dementia (36). Multiple mechanisms such as the formation of AGEs, cerebrovascular disease which may exacerbate β amyloid neurotoxicity and decreased cholinergic transport across the blood-brain barrier (37-38) may explain part of this linkage. The term "type 3 diabetes" has also been used to suggest that AD is a form of diabetes based on findings such as hyperinsulinaemia linked to recent onset Alzheimer's in subjects without diabetes (39). Vascular risk factors such as hyperglycaemia interact with ApoE4 to increase the risk of cognitive decline above and beyond the effect of ApoE4 alone, and this association has been supported by recent data (40).

CONCLUSIONS

Diabetes, sarcopaenia and frailty are associated with disability, morbidity and mortality. Diabetes accelerates the ageing process and could provide a pathophysiological environment for the development of frailty, with the close relationship between diabetes and sarcopaenia as a common factor (Figure 1). Diabetes can contribute to frailty by increasing the incidence of the core components of frailty: weakness, exhaustion, slowness and low physical activity level. Diabetes can also contribute to frailty through its associated complications; atherosclerosis, microvascular disease, neuropathy and dementia/cognitive impairment.

We believe that early recognition of frailty and sarcopaenia in older adults with diabetes should be a mandatory process in order to promote early multi-modal interventions based on physical exercise, nutritional education and which are aligned to glycaemic and other metabolic targets essential to proper functioning.

Figure 1: Schematic representation - combined effects of ageing, diabetes and sarcopaenia on lower limb dysfunction: moving towards Frailty (Marley J. Sinclair AJ et al, 2014)



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REFERENCES

1. Wilson PNF. Epidemiology of diabetes in the elderly. Am J Med 80: (suppl, 15A):3-15, 1982
2. Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20-74 years. Diabetes 36:523-34, 1987
3. Manton Kg, Stallard ES, Liu K. Forecasts of active life expectancy: policy and fiscal implications. J Gerontol 48 (special Issue): 11-26, 1993
4. Resnick HE, Harris MI, Brock DB, Harris TB. American Diabetes Association diabetes diagnostic criteria, advancing age, and cardiovascular disease risk profiles: results from the Third National Health and Nutrition Examination Survey. Diabetes Care. 2000 Feb;23(2):176-80.
5. Halter JB 2003. Diabetes mellitus in older adults: underdiagnosis and undertreatment. J Am Geriatr Soc. 2000 Mar; 48 (3): 340-1.
6. Fried LP, Ferruci L, Darer J, Williamson JD, Anderson G: Understanding the concepts of disability, frailty and comorbidity: implications for improved targeting and care. J Gerontol Biol Sci Med Sci 2004; 59: 255-263.
7. Fried LP, Kronmal RA, Newman AB, Bild DE, Mitelmark MB, Polak JF et al. Risk factors for 5-years mortality in older adults: the Cardiovascular Health Study. JAMA 1998; 279: 585-92.
8. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60(8):1487-1492.
9. Meneilly, G.S. and Elahi, D. (2005) Metabolic alterations in middle-aged and elderly lean patients with Type 2 diabetes. Diabetes Care, 28, 1498–9.
10. Mac Leod KM, Tooke JE: Direct and indirect costs of cardiovascular and cerebrovascular complications of type II diabetes. Pharmacoeconomics 8 (Suppl. 1):46-51, 1995
11. Standards of medical care in diabetes-2015. American Diabetes Association. Diabetes Care, January 2015; Vol 38 (Suppl 1).
12. García-Esquinas E, Graciani A, Guallar-Castillón P, López-García E, Rodríguez-Mañas L, Rodríguez-Artalejo F. Diabetes and Risk of Frailty and Its Potential Mechanisms: A Prospective Cohort Study of Older Adults. J Am Med Dir Assoc. 2015 May 16. pii: S1525-8610(15)00296-0. doi: 10.1016/j.jamda.2015.04.008. [Epub ahead of print]
13. Sinclair A, Dunning T, Rodriguez-Mañas L. Diabetes in older people: new insights and remaining challenges. Lancet Diabetes Endocrinol. 2015 Apr;3(4):275-85.
14. McNeil CJ, Doherty TJ, Stashuk DW, Rice CL (2005). Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. Muscle Nerve 31: 461-467.
15. Cree MG, Newcomer BR, Katsanos CS, Sheffield-Moore M, Chinkes D, Aarsland A, Urban R, Wolfe RR (2004). Intramuscular and liver triglycerides are increased in the elderly. J Clin Endocrinol Metab 89: 3864-3871.
16. Rolland Y, Czerwinskil S, Abellan Van Kan G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging. 2008 Aug-Sep; 12(7): 433–450.
17. Cesari M, Leeuenburgh c, Lauretani F, Onder G, Bandinelli S, Maraldi C et al. Frailty syndrome and skeletal muscle-Result from the InCHIANTI study. Am J Clin Nutr 2006; 83(5): 11421148.
18. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001 Mar;56(3):M146-56.
19. Turnbull PJ, Sinclair AJ. Evaluation of nutritional status and its relationship with functional status in older citizens with diabetes mellitus using the mini nutritional assessment (MNA) tool-a preliminary investigation. J Nutr Health Aging. 2002 May;6(3):185-9.
20. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014 Oct;2(10):819-29.
21 Kitty Kit Ting Cheung, Andrea On Yan Luk, Wing Yee So, Ronald Ching Wan Ma, Alice Pik Shan Kong, Francis Chun Chung Chow, Juliana Chung Ngor Chan. Testosterone level in men with type 2 diabetes mellitus and related metabolic effects: A review of current evidence. Diabetes Investig. 2015 March; 6(2): 112–123.
22. Ozfirat Z, Tahseen AC. Vitamin D deficiency and type 2 diabetes. Postgrad Med J 2010; 86: 18-25
23. Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. J Am Geriatr Soc. 2003 Sep; 51 (9): 1219-26.
24. Shardell M, Hicks GE, Miller RR, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci 2009. vol 64 A, Nffl 1, 69-75.
25. Louard RJ, Fryburg DA, Gelfand RA, Barrett EJ. Insulin sensitivity of protein and glucose metabolism in human forearm skeletal muscle. J Clin Invest. 1992 Dec;90(6):2348-54.
26. Newman E, Heslin MJ, Wolf RF, et al. The effect of systemic hyperinsulinemia with concomitant amino acid infusion on skeletal muscle protein turnover in the human forearm. Metabolism. 1994 Jan; 43 (1): 70-8.
27. Guttridge DC. Signaling pathways weigth on decisions to make or break skeletal muscle. Curr Opin Clin Nutr Metab Care 2004;7:443-50
28. Payette H, Roubenoff R, Jacques PF, et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopaenia in very old community-living men and women: the Framingham Heart Study. J am Geriatr Soc 2003; 51:1237-43.
29. Visser M, Pahor M, Taeffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci. 2002; 57(5):M326-M332.
30. Baumgartner RN. Body composition in healthy aging. Ann N Y Acad Sci. 2000 May; 904:437-48.
31. Payne GW. Effect of inflammation on the aging microcirculation: impact on skeletal muscle blood flow control. Microcirculation. 2006 Jun; 13 (4): 343-52.
32. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science. 2003 May 16;300(5622):1140-2.
33. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med. 2004 Feb 12;350(7):664-71.

34. Allen MD, Stashuk DW, Kimpinski K, Doherty TJ, Hourigan ML, Rice CL. Increased neuromuscular transmission instability and motor unit remodelling with diabetic neuropathy as assessed using novel near fibre motor unit potential parameters. Clin Neurophysiol. 2015 Apr;126(4):794-802.
35. Rodríguez-Mañas L, Bouzon CA, Castro M. Peripheral arterial disease in old people with diabetes. In: Diabetes in Old Age, 3rd edition (Ed: AJ Sinclair), Wiley 2009.
36. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009 Apr 15;301(15):1565-72
37. Roriz-Filho JS, Sá-Rodriguez TM, Rosset I, et al. (Pre)diabetes, brain aging, and cognition. Biochimica et Biophysica Acta 1792 (2009) 432-443.
38. Pasquier F, Boulogne A, Leys D , Fontaine P. Diabetes mellitus and Dementia. Diabetes Metab 2006;32:403-414.
39. Kuusisto J, Koivisto K, Mykkanen L, et al. Association between features of the insulin resistance syndrome and Alzheimer´s disease independently of apolipoprotein E4 phenotype: cross sectional population based study. BMJ. 1997 Oct 25; 315 (7115): 1045-9.
40. Hsiung GY, Sadovnik AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. Can Med Assoc J 2004;171: 863-7.

FRAILTY FROM AN ORAL HEALTH POINT OF VIEW

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Abstract: Frailty commonly affects older persons, increasing their risk for adverse outcomes. Oral health is affected by those conditions related to the mouth and teeth, including caries, periodontal diseases, dysgeusia, presbyphagia and oral cancer among others. Oral health problems can be classified as development defects and acquired problems. These latter are related to infection or trauma, have a cumulative effect throughout life and their consequences are lifelong. Such acquired problems can be classified as primary or secondary, both interacting in a complex manner. Recovery to a previous state of tissue integrity is often impossible from these conditions. These complex interactions have negative impacts on the individual's general health and quality of life. Oral status is an important contributor to general health, and has been linked to several chronic conditions such as cognitive impairment, diabetes, cardiovascular diseases, strokes, and cancer. An individual's oral health is mostly stable throughout life. Tooth loss may be considered as the final outcome, resulting as a consequence of history of caries and periodontitis, as well as failure of prevention and treatment. The loss of a tooth may thus represent the first step of a vicious cycle. In fact, without intervention, one missing tooth may lead to further teeth loss, thus reducing the capability to chew and consume nutrients (essential for life and adequate physiological function), and finally contributing to the development of age-related chronic diseases.

Key words: Oral health, frailty, oral health problems, periodontal diseases, periodontitis.

INTRODUCTION

Frailty is a state of diminished physiologic reserve and is associated with enhanced susceptibility to adverse outcomes in older persons (1-4). The prevalence of this condition increases with age (5-7). Oral health has been related to several chronic conditions, demonstrating its important role as major contributor to general health. Oral health problems have a cumulative effect throughout life (8-11). They may onset at young age (8), subsequently affecting the nutritional status at older age (12-14). Oral health problems are indeed often underestimated in youth with consequences becoming clinically evident at more advanced ages. Oral health conditions often anticipate the clinical manifestation of chronic diseases, contributing to their development.

FRAILTY

The concept of frailty has been studied for over 30 years (1-4). Sometimes, it has been wrongly used as synonymous of comorbidity, disability, and/or aging (4, 15, 16). Frailty exposes the individual at the risk of adverse outcomes, including falls, institutionalization, and death (17, 18). Frailty consequences are considered as the result of excessive demands in an individual with diminished physiologic reserves (3, 19). Frailty may simulate a phase of accelerated aging.

Frailty has been identified in elders, with a prevalence of about 20% in community-dwelling older persons (15, 20). It often occurs in conjunction with other chronic conditions,

indicating a possible relationship between frailty and comorbidities as well as an eventual interaction among them.

ORAL HEALTH

Oral health refers to a cluster of conditions related to the mouth and teeth, the most common of which are dental caries (21-23). It also includes periodontal diseases (e.g. gingivitis and periodontitis), xerostomia, presbyphagia, dysphagia and oral cancer, among others (Table 1).

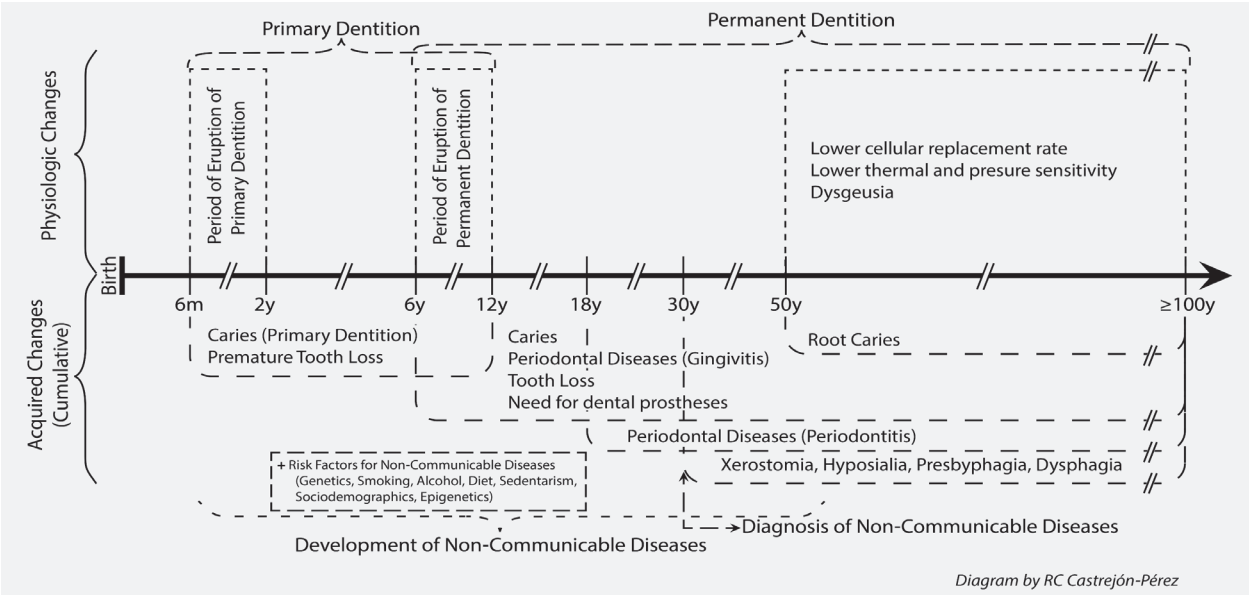
There are two basic types of oral health problems, those related to development defects and those acquired during the course of life (or cumulative changes; Table 1), sometimes simultaneously occurring with specific physiologic mechanisms (Figure 1).

Such physiologic modifications can be divided into two groups according to the affected period of life. During the first 12 years of life, the changes are associated with the eruption of teeth (both primary and permanent dentition). After the sixth decade of life (24), these changes are related to a lower cellular replacement rate in the mucosa, which can lead to changes in pressure and thermic sensibility, as well as in taste (i.e. dysgeusia; Figure 1). Another major change occurring at older age is the yellowing of the teeth due to the protective response of dentinoblasts (24).

The acquired (cumulative) modifications negatively affecting oral health may frequently be due to infections (e.g. caries and periodontal diseases) as well as to trauma. The onset of such changes may begin at very young age (e.g. even before one year of age with caries in primary dentition and premature tooth loss) (8, 9). The consequences may then be lifelong (e.g. tooth loss and need of dental prostheses; Figure 1) (8, 10, 24). With aging, new conditions (e.g. periodontitis after 18 years of age or xerostomia after 30 years of age) may be acquired (25, 26), exposing the individual at different and heterogeneous outcomes, such as tooth loss, caries or root caries, need of dental prostheses, and presbyphagia. Interestingly, specific oral disorders (e.g. xerostomia and hyposialia) are closely related to the use of certain drugs (e.g. anticholinergics, antidepressants and antihistamines) as well as to polypharmacy, conditions particularly frequent among elders (25-28).

Figure 1

Physiologic and cumulative oral modifications occurring during the life course



The acquired changes occurring in oral health can be classified as primary (or affecting intact tissues [e.g. caries and periodontal diseases]), and secondary (in which they are the consequence of primary acquired problems; Table 1). Primary and secondary changes interact in a complex manner (Figure 2), and recovery to a previous state of tissue integrity is often impossible after their onset. Instead, rehabilitation is required. The complex interaction between primary and secondary changes has a negative impact on the individual's general health and quality of life (Table 2), potentially leading to the generation of a vicious cycle that can only be halted by the adoption of hygiene and lifestyle modifications. For example, in the context of periodontal diseases, recovery from gingivitis is possible, but periodontitis will always leave sequels.

ORAL HEALTH AND FRAILTY

Limited evidence is available about the possible relationship between oral health and frailty. Despite differences in the adopted methodology, the findings of existing studies are quite consistent. In particular, it is well established that individuals with fewer teeth (29-31) and edentate persons who are not wearing dentures (32) present a higher risk of being frail. In a longitudinal study of older persons aged 70 years and older (follow-up: 3 years), the number of residual teeth was strongly associated with a lower risk of developing frailty (29).

Table 1

Oral health conditions

- Genetic and Development Oral Health Problems
  - Amelogenesis imperfecta
  - Dentinogenesis imperfecta
  - Cleft lip
  - Cleft palate
- Acquired Oral Health Problems
  - Primary (onset on intact tissues)
    - Caries
    - Periodontal diseases
      - Gingivitis
      - Periodontitis
  - Secondary (onset as sequel of primary acquired problems)
    - Dental fracture
    - Tooth loss
    - Root remains
    - Edentulism
    - Non-functional dental prostheses
    - Halitosis
    - Oral cancer
- Others
  - Xerostomia
  - Hiposialia
  - Presbyfagia
  - Dysgeusia
  - Temporo-Mandibular Disorders

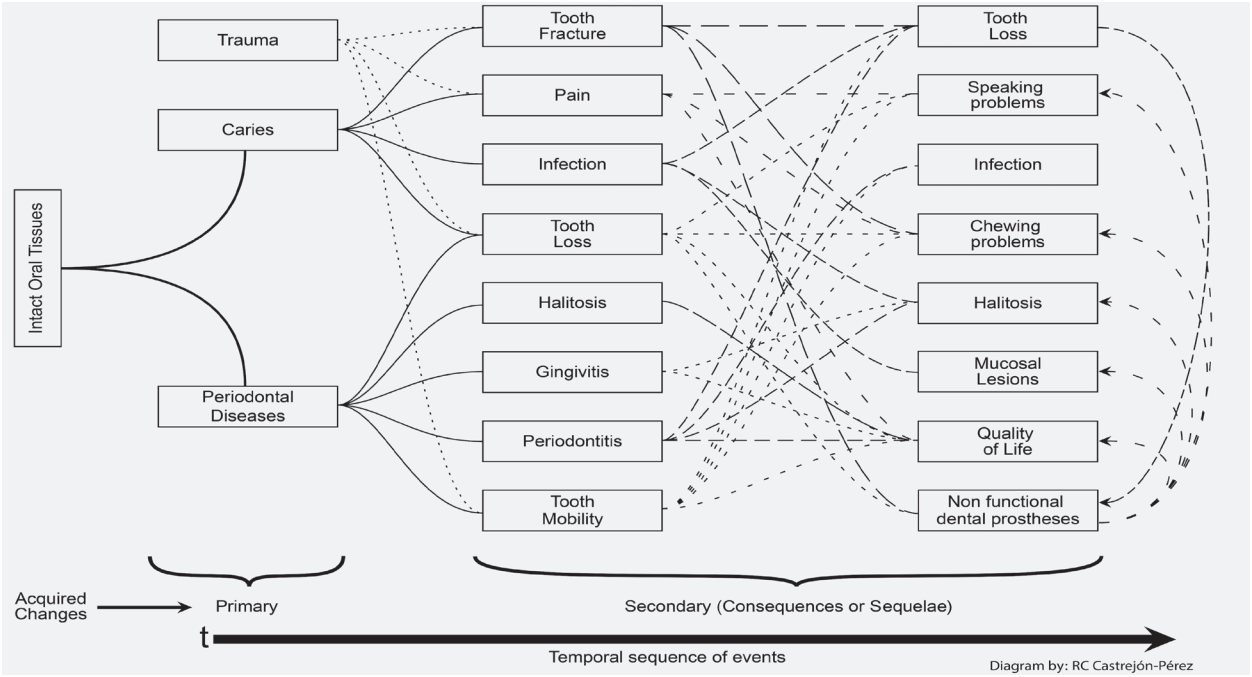
Table 2

Consequences of oral health problems and associated chronic conditions

Oral health problem	Consequences	Chronic condition associated	Component of the proposed model linking oral health and frailty
Caries	Dental fracture Pain Tooth loss Root remains Edentulism	Cognitive impairment Arthritis	Utilization of Dental Services Functional Psychosocial
Gingivitis	Bleeding gums Progression to periodontitis Halitosis	Cognitive impairment Arthritis	Utilization of Dental Services Functional Psychosocial
Periodontitis	Bleeding gums Acute and chronic infections Acute and chronic inflammation Halitosis Dental mobility Tooth loss Edentulism Chewing problems Speaking problems	Diabetes Cardiovascular diseases Arthritis Embolism Cognitive impairment Respiratory infections Obesity Osteoporosis	Utilization of Dental Services Psychosocial Physiologic/biologic
Tooth loss	Chewing problems Speaking problems Need for dental prostheses (partial dentures) Loss of support for facial muscles	Diabetes Cognitive impairment Arthritis Nutritional implications (changes in food selection) Frailty Cancer	Utilization of Dental Services Psychosocial Functional
Root remains	Acute and chronic infections Chewing problems Halitosis	Chronic inflammation Nutritional implications (changes in food selection) Cognitive impairment	Utilization of Dental Services Psychosocial Functional Physiologic/biologic
Edentulism	Chewing problems Speaking problems Need for dental prostheses (complete dentures) Dysgeusia Thermic and pressure sensibility changes	Diabetes Cardiovascular diseases Nutritional implications (changes in food selection) Arthritis Frailty Cancer	Utilization of Dental Services Psychosocial Functional
Non-functional dental prostheses	Chewing problems Speaking problems Dysgeusia Dysphagia Thermic and pressure sensibility changes Caries Periodontal diseases Mucosal lesions	Nutritional implications (changes in food selection) Frailty Cognitive impairment	Utilization of Dental Prostheses Psychosocial Functional
Xerostomia and hiposialia	Caries Periodontal diseases Opportunistic infections Chewing problems Speaking problems	Cardiovascular diseases (hypertension) Depression Polypharmacy Arthritis	Functional Physiologic/Biologic
Mucosal lesions	Pain Chewing problems Oral cancer	Cognitive impairment	Functional Physiologic/Biologic
Dysphagia	Chewing problems Malnutrition Bronchoaspiration	Cognitive impairment (Parkinson disease) Neurological impairment Depression Stroke	Functional Psychosocial

Figure 2

Complex interactions between primary and secondary cumulative oral changes



These findings support the hypothetical model here proposed linking oral health and frailty, in which four components are identified: functional, psychosocial, physiologic/biologic, and utilisation of dental services (33). The oral health (acquired) problems, either primary or secondary, contribute to each component to different degrees (Table 2) with tooth loss seeming to be the major contributor to health deterioration. This pattern has been observed in several studies showing that the number of teeth has not only nutritional implications (12, 13, 34-36), but is also associated with atherosclerosis (37), chronic obstructive pulmonary disease (38), fatigue (30), reduced quality of life (39), and higher risk of head and neck cancer (40) and cognitive impairment (41).

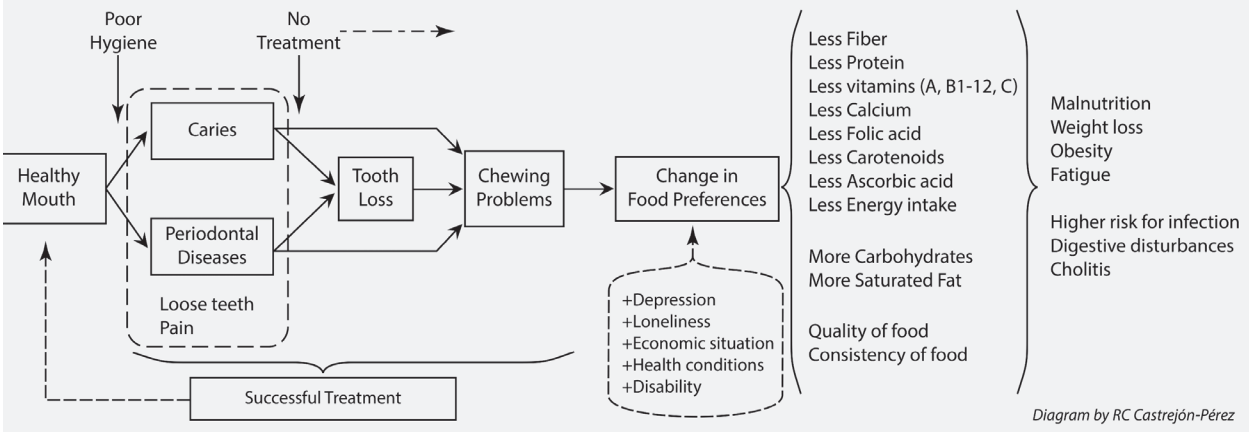
It must be emphasised that tooth loss is the final outcome frequently resulting after a natural history of caries and periodontitis. As such, missing teeth represent the failure of prevention and treatment and reflect the necessity for dental prostheses, which, in cases of failure, will then lead to a new chain of adverse outcomes (e.g. mucosal lesions). In Figure 2, we can observe that caries, periodontal diseases, and trauma all converge to tooth loss. Tooth loss is responsible for speaking and chewing problems, as well as for low quality of life. The utilisation of non-functional dental prostheses may also affect the individual's capacity to comfortably speak and chew. Chewing problems are the main reason for changes in food choices (14, 34, 36, 42, 43), potentially resulting in impaired nutritional status (14, 36, 44) (Figure 3).

ORAL HEALTH AND GENERAL HEALTH

Oral health is an important constituent of the overall health status (22, 45, 46). Oral conditions have been related to cognitive impairment (41, 47-49), diabetes (50), cardiovascular disease (51-55), stroke (56), respiratory infections (53), obesity (55), osteoporosis (56), and arthritis (58-62). Additionally, they have shown to exert a negative impact on the individual's quality of life (63-66), and are associated to polypharmacy (25, 27, 28) (Table 2).

Several pathways may be described to explain the associations between oral and non-oral health conditions. As an example, in Figure 3, we present the mechanisms linking oral health problems and malnutrition, probably the most straightforward and direct relationship. This model begins with a healthy mouth in which the presence of caries or periodontal diseases leads to tooth loss. Consequently, the individual may develop chewing problems and modifications in food preferences, finally resulting in lower nutrient and caloric intake. Some individuals cope with chewing limitations by switching to unhealthier food, which may lead to obesity or weight loss. In cases where an individual's energy intake becomes insufficient, detrimental effects may become evident on his/her capacity to conduct daily activities (67-71).

Figure 3
Possible pathway from oral health problems to malnutrition



FRAILTY FROM AN ORAL HEALTH VIEW

As mentioned above, an individual's oral health is quite stable throughout life, and acquired changes (in particular, tooth loss; Figure 1) are often related to infections or traumas. The loss of a tooth may then represent the first evident sign of a starting decline; one missing tooth can lead to the loss of additional teeth, especially if no intervention (or an inadequate one) is implemented.

Most missing teeth require dental prostheses, which must be functional. If they are not functional, they will promote the development of mucosal lesions and further tooth loss and may result in chewing problems. The process of progressive loss of teeth not only puts the individual at higher risk for malnutrition, but also exposes to the risk of inadequately respond to stressors. This scenario is very similar to what happening in the context of frailty.

In summary, oral health problems have a cumulative effect throughout life (Figures 1 and 2) and can be of such a low intensity that early in life, their effects may be ignored. However, if these problems are not promptly addressed, they may progress until the treatment becomes very complex (Figure 2). Some of the consequences will contribute at the development of additional chronic conditions, generating a network of interacting and self-feeding mechanisms progressively and rapidly deteriorating the individual's health status. As such, oral health could possibly represent an indicator, a risk factor, or even an outcome of general health at the same time. For example, oral health could be a marker of cognitive impairment as there are reports showing that persons with cognitive impairment are more likely to present caries (either coronal or root caries), periodontal diseases and have more missing teeth (47, 49), probably due to poor personal hygiene. Oral health may be used as a risk factor for malnutrition, as discussed above. This means that in a person with poor nutrition, it is important to explore oral health and identify possible issues in his/her food selection (12, 34, 35, 43, 72). Finally, oral health may act as outcome. For example, in adults taking multiple medications causing xerostomia (e.g. anticholinergic and antihypertensives) the risk of caries and periodontal diseases might be increased (25, 26, 28).

CONCLUSION

Dental loss may represent the initial point for decline in general health. It is a major outcome requiring immediate counteractions before the detrimental process becomes irreversible. Such preliminary step in a vicious cycle mining the maintenance of adequate health status strongly resembles the concept of frailty commonly adopted in geriatrics. It is noteworthy that the pathway we have described is not monofactorial, but results from the interaction of several other domains (e.g. genetics, economics, lifestyle habits…). At the same time and in the same way, the oral health assessment becomes crucial for the understanding and correct framing of any chronic condition.

As oral health is a part of an individual's general health status, multidisciplinary studies are needed to assess the contribution of oral health measures to specific conditions (e.g. diabetes, cardiovascular disease, cognitive impairment). The number of teeth may serve as a good marker for general health, as it reflects the net accumulation of several experiences over time, from poor hygiene habits to the occurrence of caries, periodontal diseases, and trauma. Furthermore, teeth count is a clinical-friendly information that can be easily retrieved during the comprehensive assessment of the older person, providing useful insights (e.g. possible nutritional issues) for the design of the most appropriate intervention.

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REFERENCES

1. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm - isues and controversies. J Gerontol A Biol Sci Med Sci. 2007;67A(7):731-7.
2. Bortz WM, 2nd. The physics of frailty. Journal of the American Geriatrics Society. 1993;41(9):1004-8.
3. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people: an evolving concept. CMAJ 1994;150(4):489-95.
4. Topinkova E. Aging, disability and frailty. Ann Nutr Metab. 2008;52 Suppl 1:6-11.
5. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006;61(3):262-6.
6. Lipsitz LA. Physiological complexity, aging, and the path to frailty. Sci Aging Knowledge Environ. 2004;2004(16):pe16.
7. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities. Arch Intern Med. 2002;162(20):2333-41.
8. Holst D, Schuller AA. Oral health in a life-course: birth-cohorts from 1929 to 2006 in Norway. Community Dent Health. 2012;29(2):134-43.
9. Isaksson H, Alm A, Koch G, Birkhed D, Wendt LK. Caries prevalence in Swedish 20-year-olds in relation to their previous caries experience. Caries Res. 2013;47(3):234-42.
10. Lu HX, Wong MC, Lo EC, McGrath C. Trends in oral health from childhood to early adulthood: a life course approach. Community Dent Oral Epidemiol. 2011;39(4):352-60.
11. Steele JG, Sanders AE, Slade GD, et al. How do age and tooth loss affect oral health impacts and quality of life? A study comparing two national samples. Community Dent Oral Epidemiol. 2004;32(2):107-14.
12. Nowjack-Raymer RE, Sheiham A. Numbers of natural teeth, diet, and nutritional status in US adults. J Dent Res. 2007;86(12):1171-5.
13. Sahyoun NR, Lin CL, Krall E. Nutritional status of the older adult is associated with dentition status. J Am Diet Assoc. 2003;103(1):61-6.
14. Sheiham A, Steele J. Does the condition of the mouth and teeth affect the ability to eat certain foods, nutrient and dietary intake and nutritional status amongst older people? Public Health Nutr. 2001;4(3):797-803.
15. Fried LP, Tangen CM, Waltson J. Frailty in older adults: evidence for a phenotype. J Gerontol. 2002;56(A):M146-M56.
16. Walston J. Frailty--the search for underlying causes. Sci Aging Knowledge Environ. 2004;2004(4):pe4.
17. Espinoza S, Walston JD. Frailty in older adults: insights and interventions. Cleve Clin J Med. 2005;72(12):1105-12.
18. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):255-63.
19. Powell C. Frailty: help or hindrance? J Royal Soc Med. 1997;90 Suppl 32:23-6.
20. Ahmed N, Mandel R, Fain M. Frailty: An emerging geriatric syndrome. Am J Med. 2007;120(9):748-53.
21. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century--the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol. 2003;31 Suppl 1:3-23.
22. Petersen PE, Ueda H. Oral Health in Ageing Societies. Integration of oral health and general health report of a meeting convened at the WHO, Centre for Health Development in Kobe, Japan 1-3 June 2005. Geneva: World Health Organization, 2006
23. Beaglehole R, Editions M. The oral health atlas: Mapping a neglected global health issue: FDI World Dental Federation; 2009.
24. McKenna G, Burke FM. Age-related oral changes. Dent Update. 2010;37(8):519-23.
25. Hopcraft MS, Tan C. Xerostomia: an update for clinicians. Aust Dent J. 2010;55(3):238-44; quiz 353.
26. Nederfors T. Xerostomia and hyposalivation. Adv Dent Res. 2000;14:48- 56.
27. Locker D. Xerostomia in older adults: a longitudinal study. Gerodontology. 1995;12(1):18-25.
28. Thomson WM, Chalmers JM, Spencer AJ, Slade GD. Medication and dry mouth: findings from a cohort study of older people. J Public Health Dent. 2000;60(1):12-20.
29. Castrejón-Pérez RC. [Estudio longitudinal sobre condiciones de salud bucal y calidad de vida como predictores de fragildiad en personas de 70 años y más]. Distrito Federal, México: Universidad Nacional Autónoma de México; 2012.
30. Avlund K, Schultz-Larsen K, Christiansen N, Holm-Pedersen P. Number of teeth and fatigue in older adults. J Am Geriatr Soc. 2011;59(8):1459-64.
31. de Andrade FB, Lebrao ML, Santos JL, Duarte YA. Relationship between oral health and frailty in community-dwelling elderly individuals in Brazil. J Am Geriatr Soc. 2013;61(5):809-14.
32. Castrejón-Pérez RC, Borges-Yáñez SA. Association between the use of complete dentures and frailty in edentuolous Mexican elders. J Frailty Aging. 2012;1(4):183-8.
33. Castrejón-Pérez RC, Borges-Yáñez SA, Gutierrez-Robledo LM, Avila- Funes JA. Oral health conditions and frailty in Mexican community-dwelling elderly: a cross sectional analysis. BMC Public Health. 2012;12:773
34. Touger-Decker R, Mobley CC. Position of the American Dietetic Association: oral health and nutrition. J Am Diet Assoc. 2007;107(8):1418-28.
35. Brennan DS, Spencer AJ, Roberts-Thomson KF. Tooth loss, chewing ability and quality of life. Qual Life Res. 2008;17(2):227-35.
36. Sheiham A, Steele JG, Marcenes W, et al. The relationship among dental status, nutrient intake, and nutritional status in older people. J Dent Res. 2001;80(2):408-13.
37. Shaboodien G, Uyar IS, Akpinar MB, et al. Carotid and popliteal artery intima-media thickness in patients with poor oral hygiene and the association with acute-phase reactants. Cardiovasc J Afr. 2013 12;23:1-5.
38. Barros SP, Suruki R, Loewy ZG, Beck JD, Offenbacher S. A cohort study of the impact of tooth loss and periodontal disease on respiratory events among COPD subjects: modulatory role of systemic biomarkers of inflammation. PloS One. 2013;8(8):e68592.
39. Jain M, Kaira LS, Sikka G, et al. How do age and tooth loss affect oral health impacts and quality of life? A study comparing two state samples of gujarat and rajasthan. J Dent (Tehran). 2012;9(2):135-44.
40. Wang RS, Hu XY, Gu WJ, Hu Z, Wei B. Tooth loss and risk of head and neck cancer: a meta-analysis. PloS One. 2013;8(8):e71122.
41. Kaye EK, Valencia A, Baba N, Spiro A, 3rd, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc. 2010;58(4):713-8.
42. Locker D. Changes in chewing ability with ageing: a 7-year study of older adults. J Oral Rehabil. 2002;29(11):1021-9.
43. Koehler J, Leonhaeuser I-U. Changes in Food Preferences during Aging. Ann Nutr Metab. 2008;52(1):15-9.

44. Walls AW, Steele JG, Sheiham A, Marcenes W, Moynihan PJ. Oral health and nutrition in older people. J Public Health Dent. 2000;60(4):304-7.
45. Petersen PE, Kandelman D, Arpin S, Ogawa H. Global oral health of older people--call for public health action. Community Dent Health. 2010;27(4 Suppl 2):257-67.
46. Petersen PE, Yamamoto T. Improving the oral health of older people: the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol. 2005;33(2):81-92.
47. Noble J, Borrell L, Papapanou P, Elkind M, Scarmeas N, Wright C. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. J Neurol Neurosurg Psychiatry. 2009;80(11):1206-11.
48. Chalmers JM, Carter KD, Spencer AJ. Oral diseases and conditions in community-living older adults with and without dementia. Spec Care Dentist. 2003;23(1):7-17.
49. Syrjala AM, Ylostalo P, Ruoppi P, et al. Dementia and oral health among subjects aged 75 years or older. Gerodontology. 2012;29(1):36-42.
50. Drumond-Santana T, Costa FO, Zenobio EG, Soares RV, Santana TD. [Impact of periodontal disease on quality of life for dentate diabetics]. Cad Saude Publica. 2007;23(3):637-44.
51. Arbes SJ, Jr., Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. J Dent Res. 1999;78(12):1777-82.
52. Karnoutsos K, Papastergiou P, Stefanidis S, Vakaloudi A. Periodontitis as a risk factor for cardiovascular disease: the role of anti-phosphorylcholine and anti-cardiolipin antibodies. Hippokratia. 2008;12(3):144-9.
53. Scannapieco FA. Position paper of The American Academy of Periodontology: periodontal disease as a potential risk factor for systemic diseases. J Periodontol. 1998;69(7):841-50.
54. Syrjala AM, Ylostalo P, Hartikainen S, Sulkava R, Knuuttila M. Number of teeth and selected cardiovascular risk factors among elderly people. Gerodontology. 2010;27(3):189-92.
55. Borges-Yanez SA, Irigoyen-Camacho ME, Maupome G. Risk factors and prevalence of periodontitis in community-dwelling elders in Mexico. J Clin Periodontol. 2006;33(3):184-94.
56. Boehm TK, Scannapieco FA. The epidemiology, consequences and management of periodontal disease in older adults. J Am Dent Assoc. 2007;138 Suppl:26S-33S.
57. Moedano DE, Irigoyen ME, Borges-Yanez A, Flores-Sanchez I, Rotter RC. Osteoporosis, the risk of vertebral fracture, and periodontal disease in an elderly group in Mexico City. Gerodontology. 2011;28(1):19-27.
58. Felton DA. Edentulism and comorbid factors. J Prosthodont. 2009;18(2):88-96.
59. Blaizot A, Monsarrat P, Constantin A, et al. Oral health-related quality of life among outpatients with rheumatoid arthritis. Int Dent J. 2013;63(3):145-53.
60. Agnihotri R, Gaur S. Rheumatoid arthritis in the elderly and its relationship with periodontitis: A review. Geriatr Gerontol Int. 2013 doi: 10.1111/ggi.12062.
61. Rajkarnikar J, Thomas BS, Rao SK. Inter-relationship between rheumatoid arthritis and periodontitis. Kathmandu Univ Med J (KUMJ). 2013;11(41):22-6.
62. Yokoyama T, Kobayashi T, Ito S, et al. Comparative Analysis of Serum Proteins in Relation to Rheumatoid Arthritis and Chronic Periodontitis. J Periodontol. 2013 May 7.
63. Locker D, Matear D, Stephens M, Jokovic A. Oral health-related quality of life of a population of medically compromised elderly people. Community Dent Health. 2002;19(2):90-7.
64. Locker D, Quinonez C. Functional and psychosocial impacts of oral disorders in Canadian adults: a national population survey. J Can Dent Assoc. 2009;75(7):521.
65. Locker D, Quinonez C. To what extent do oral disorders compromise the quality of life? Community Dent Oral Epidemiol. 2011;39(1):3-11.
66. Sheiham A. Oral health, general health and quality of life. Bull World Health Organ. 2005;83(9):644.
67. Borges-Yanez SA, Maupome G, Martinez-Gonzalez M, Cervantez-Turrubiante L, Gutierrez-Robledo LM. Dietary fiber intake and dental health status in urban-marginal, and rural communities in central Mexico. J Nutr Health Aging. 2004;8(5):333-9.
68. Cervantes L, Montoya M, Núñez L, Borges A, Gutiérrez L, Llaca C. Aporte dietético de energía y nutrimentos en adultos mayores de México. Nutrición Clínica. 2003;6(1):2-8.
69. Sahyoun NR, Krall E. Low dietary quality among older adults with self-perceived ill-fitting dentures. J Am Diet Assoc. 2003;103(11):1494-9.
70. Furuta M, Komiya-Nonaka M, Akifusa S, et al. Interrelationship of oral health status, swallowing function, nutritional status, and cognitive ability with activities of daily living in Japanese elderly people receiving home care services due to physical disabilities. Community Dent Oral Epidemiol. 2013;41(2):173-81.
71. Makhija SK, Gilbert GH, Clay OJ, Matthews JC, Sawyer P, Allman RM. Oral health-related quality of life and life-space mobility in community- dwelling older adults. J Am Geriatr Soc. 2011;59(3):512-8.
72. N'Gom P I, Woda A. Influence of impaired mastication on nutrition. J Prosthet Dent. 2002;87(6):667-73.

THINKING ABOUT COGNITIVE FRAILTY

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Over recent years a number of concepts have arisen to describe the cognitive decline, beyond healthy aging, that has been observed in substantial numbers of older persons whose impairments fall short of meeting of the criteria for dementia. This decline may or may not be linked to an early dementing process. Among these well-known entities are Age Associated Memory Impairment (AAMI), Cognitive Impairment, Not Demented (CIND), Mild Cognitive Impairment (MCI of various types such as amnestic, with executive dysfunction, multi-domain, etc.) and more recently, with the emergence of Psychiatry's Diagnostic and Statistical Manual 5th Edition (DSM 5), Minor Neurocognitive Impairment (MNCI). Each entity uses similar but distinct clinical diagnostic criteria and may be linked to underlying specific brain diseases.

A new concept, Cognitive Frailty (CF), has recently emerged in the Geriatrics literature (1, 2). Most recently Keleiditi and colleagues (11) have proposed the elements that comprise this clinical construct, and suggest a basic operational definition of the condition. Raising interesting points they indicate that cognitive frailty should be:

1) linked to a reduction in cognitive 'reserve',
2) independent of specific brain diseases but at the same time co-exist with the presence of physical frailty (in this concept, cognitive frailty is to be distinguished from the presence cognitive impairment found in non- physically frail individuals such as physically robust mild Alzheimer's Disease [AD] patients).
3) represented by a score of 0.5 on the well-established Clinical Dementia Rating Scale (CDR), a score that often is associated with a pre-dementia state, but is not with frank dementia.

Appearing in the geriatrics literature, the term Cognitive Frailty (CF) evokes a parallel or link to physical frailty, a major geriatric syndrome with negative health outcomes. Some studies now suggest that cognitive impairment (presumably of non-specific etiologies) provides added value for the prediction of negative health outcomes in physically frail elders (3, 4). Thus CF may be unlike the previously noted mild cognitive impairment entities whose principal goal appears to be to reveal the earliest clinical stages of dementing illnesses. Rather than foreshadowing or predicting underlying, specific brain diseases, CF may be a concept which identifies a proclivity toward cognitive functional decline, a loss of resiliency and adaptability to challenge, that could lead to negative health outcomes such as diminished executive abilities and increased dependency, both of which could exacerbate other negative physical health outcomes associated with frailty. However, while this is of interest, at this point we know little about the pathophysiology underpinning this condition, which Keleiditi et al. suggest can be independent of specific brain disease; nor do we know much about how it might be remediated. Thus the proposed Keleiditi el al. criteria that define the concept of CF deserve further consideration and some additional suggestions for clarification and eventual clinical application.

First let us consider the basic mechanism underpinning CF which has been suggested as a reduction of cognitive reserve. This point could benefit from further development. It is clear that brain diseases, particularly the dementias, can dramatically alter cognitive reserve as can severe systemic illness. Yet a majority of elders do not develop these conditions, so let us first consider the case of usual aging, non-brain diseased individuals. As employed by Keleiditi and colleagues, cognitive reserve implies a passive process similar to the concept of 'brain reserve capacity' first proposed by Katzman (5), and Satz (6) who define reserve in terms of the amount of brain damage (e.g. aging changes, micro-

vascular changes, white matter loss) that can be sustained before reaching a threshold of detectable clinical expression. Analogously, according to Keleiditi et al., the appearance of CF would be established with the slightly abnormal CDR score of 0.5. In contrast, a possibly more attractive model of cognitive reserve, one that is more 'active' could be used. Such a model would suggest that the brain actively attempts to manage damage or age-related changes by either using pre-existing cognitive processing approaches or by using compensatory mechanisms (7, 8). Thus, an active model of cognitive reserve implies that underlying it are neural networks and neuronal connectivity that are more efficient, have a greater capacity or are more flexible in individuals with greater reserve than those with less. Consequently, high brain reserve persons may be more capable of coping with challenges imposed by age-related brain changes or systemic or brain disease. Significant variability exists in cognitive reserve among individuals and epidemiologic studies have suggested that good proxies for amount of cognitive reserve include measures of economic attainment, level of education, IQ, and degree of literacy (9). This type of information might be useful to clinicians trying to estimate cognitive reserve and find ways of augmenting it even in the later years.

To better understand the possible neurological mechanisms underlying diminished cognitive reserve and increased CF, studies using the latest neuroimaging techniques need to be employed. With the advent of more sophisticated brain imaging techniques such as functional MRI, diffusion tensor imaging (DTI), optical imaging, among others, and in combination with the use of new, highly sensitive cognitive tasks during imaging, activity in the functional imaging of cognitive reserve and compensatory cognitive operations in healthy younger and older persons has been rapidly growing (10). Functional neuroimaging is providing many useful insights into the field of cognitive aging in addition to improving information on localization of particular cognitive operations. Functional neuroimaging of aging subjects has provided evidence for increased recruitment of the prefrontal cortex in diverse cognitive tasks. The prefrontal cortex is probably the area with most plastic capacity in the brain (11). It has also revealed that functional interactions between prefrontal cortex and other brain regions such as the mesial temporal lobe, important in encoding new information, are associated with better memory performance in older adults (12). These changes are likely compensatory in nature. Reuter- Lorenz et al. (13) have provided data supporting the observation that older adults display regions of greater prefrontal activity than younger adults when cognitive task demand is low, suggesting that older adults recruit more neural circuits than younger adults at lower levels of task demand. As demand increases, younger adults also begin to engage additional neural circuitry, whereas older adults plateau and then begin to decline, probably because they are no longer able to engage task-related circuitry, that is, they can no longer compensate for the challenge of the added cognitive load.

One could consider then, as a more neurologically based marker of CF, the inability to exhibit a minimal level of compensation for a cognitive task that had been previously established to produce a compensating response in most healthy older persons. In translating such experimental findings to the clinic, an office proxy for the imaging evidence could be employed such as the successful completion of the cognitive task in a specified amount of time. An approach of this type would have a markedly improved validity over the more arbitrary selection of a particular CDR score as a cut off point for CF, and would likely be easier to administer by primary care practitioners and their assistants than the CDR. Its prognostic value would need to be determined by subsequent longitudinal studies but it could have the advantage of providing a longer lead time before negative health outcomes became imminent.

It is foreseeable that through the future use of state of the art cognitive testing and imaging techniques, improved understanding of the neural mediation of various aspects of cognitive reserve can be attained. The imaging approach to measuring cognitive reserve could be important for understanding an aged individual's true clinical status which would reflect a combination of underlying, age-related brain changes and that individual's cognitive reserve in the context of those changes. Individuals with similar clinical appearances could differ substantially in their neural measures of reserve and this could have significant implications for a timely prognosis and intervention.

Next we should consider if CF can exist independently of brain disease and if it must co-occur with physical frailty. A major question in the study of brain aging has concerned the boundary between age-related change and disease. More recently the questions of what distinguishes 'normal' or 'usual' aging from CF and how frailty is different from disease have arisen. Our ability to answer these questions has improved as a consequence of the development of better imaging techniques and cognitive characterizations of patients, but it is certainly not complete. Many gerontologists and geriatricians suggest that aging is not just the aggregation of disease but that other time-related factors and subtle but pervasive accumulation of damage to homeostatic mechanisms can account for aging changes and that some brain structures are more vulnerable to them than others. In making the distinction between age-related brain changes and age-related brain disease, Small and colleagues (14) have been able to demonstrate, using human and non-human primate species, that memory decline is different in aging than in Alzheimer's disease (AD) and is mediated by

damage to different hippocampal structures in each condition, e.g., the entorhinal cortex in AD and the dentate gyrus in normal aging. Their work supports the proposition that aging per se and AD are distinct but possibly related processes since sporadic AD appears to be age-dependent with the risk of it increasing exponentially after age 65 until about age 95, yet there are very old individuals who do not develop AD.

Locating CF in relationship to 'normal' or 'usual' aging cognition and to disease is a more complicated theme and has been viewed differently by clinicians from different disciplines. Employment of new imaging and cognitive testing techniques should bring forth more evidence for and clarity to subtle brain dysfunctions. If we assume that a CF process can develop intrinsically in the brain, perhaps from a loss of protective factors still operative in healthy aging, and as a result of non-disease specific, age-related physiologic degradation of neural network communications evidenced by a reduction of cognitive reserve and an inadequate compensatory response to a challenge, we can affirm that in at least some cases CF can be dissociated from an identifiable disease processes such as, for example, pre-dementia AD. As imaging of occult brain disease (e.g. tau and amyloid imaging in asymptomatic AD) improves and we can clinically confirm the presence of pre-clinical disease with clinically reliable biomarkers (e.g. aβ42, p-Tau), we will be able to separate those individuals who are developing intrinsic CF as evidenced by challenge test results, from those who harbor occult disease and may also underperform during a challenge paradigm. This would have important intervention implications for the healthier individual as the absence of disease would permit the frail but non-diseased brain to respond with greater resilience to cognitive and behavioral stimulation of its inherent plasticity.

CF will be worsened by the presence of brain and systemic disease, pre-clinical or not, as cognitive reserve and compensatory mechanisms by cognitive circuitry would be additionally challenged by disease-specific neurodegenerative, vascular or metabolic/hormonal processes with a predilection for particular brain circuits and areas beyond those that are likely to be affected in non-disease aging. Examples of these are the early damage to the entorhinal cortex and posterior cingulate in AD, and in systemic hypertension by the deep white and deep grey matter lesions due to damage of the thin, deep, penetrating arteries of the posterior and anterior circulation. Consequently, disease-specific damage would add to the physiologic degradation of age-vulnerable areas such as the pre-frontal cortex, a structure likely to be involved in reduced reserve and compensatory capacity in basic CF.

Finally, the relationship between the state of CF and disease needs to be considered. As with much of the preceding discussion, little is factually known at present about this topic and many of the ensuing comments will necessarily be conjectural, yet eventually testable. It is appealing to hypothesize that cognitive frailty is an intermediary between "usual aging" and brain disease. For example, the molecular changes in neurons, glial cells and white matter that characterize the subtle loss of functionality from "usual" aging to CF are but part of a continuum of change that as further degradation takes place may permit pathogenic mechanisms of a particular disease to become more fully activated and expressed. The additional burden of systemic disease and physical frailty may actually hasten the process. This could at least partially explain why the emergence of sporadic, late onset AD seems to accelerate exponentially with age as individuals become more frail and ill. If this were the case, then it would be important to identify basic CF in its beginnings and develop interventions to retard or attenuate it in order to help diminish the risk of acquiring age-related brain diseases in older age.

Lastly, we should consider the fact that CF may indicate higher risk for adverse long term health outcomes. Based on the assumption that frailty is driven by the same basic age-related processes in all organs and systems in the body, its presence in the brain is bound to have functional consequences as it develops and these can lead to undesirable health outcomes short of dementia such as diminished executive ability, limited concentration, reduction in decision-making capacity, attenuated motivation, and a more precocious lowered autonomy which can alter the quality of life of older persons. However, it is important to note that all organs or systems in the body will not have developed the same degree of frailty at the same point in the individual's history. A number of recent studies have shown links between cognitive deficits and physical frailty (3, 4). The pattern emerging from these studies suggests that gait speed and grip strength are the components of frailty most strongly associated with cognitive function. Executive dysfunction and impaired attention are the cognitive domains most consistently linked to frailty. This may be best understood by the strong relationship of gait to the functioning of prefrontal executive and motor circuits. More subtle brain dysfunction such as reduction in cognitive compensation mechanisms under challenge conditions has not been examined as a predictor of gait speed or strength or longitudinally as a possible indicator of future negative health outcomes.

In conclusion, CF is a new clinical concept recently put forth in the Geriatrics literature and appears linked to physical frailty, a major geriatric syndrome with negative health outcomes. In contrast to other established clinical entities describing minor cognitively impaired states, whose main purpose appears to be to reveal the earliest clinical stages of specific dementing illnesses, CF seems more functionally oriented intending to identify an aging syndrome that can

be linked to functional cognitive and physical decline and possibly to preventable negative health outcomes. As it currently stands CF is in need of further development as several authors have recently noted (15-17). Whereas cognitive impairment per se appears to have some prognostic value for worse health outcomes in frail elders (3, 4), CF presently has no clearly identified supporting brain theory or demonstrated pathogenic mechanisms that differentiate it from healthier aging or specific brain disease, at least at the network or circuit level. It also lacks proven valid, sensitive and specific methods of detection at the clinical level. Studies will have to be conducted to confirm that identified CF actually leads to specific negative cognitive outcomes as described here earlier as well as contributes to the worsening of physical frailty. Further development of the construct could lead to a useful clinical entity that due to its possible reversibility, based on the non- diseased brain's potential for plastic response, might engender useful and timely interventions. This, however, will require substantial effort and adequate resources.

The present review offers some suggestions on how that development might proceed.

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REFERENCES

1. Panza F, Solfrizzi V, Frisardi V. Different models of frailty in pre-dementia and dementia syndromes. J Nutr Health Aging 2011; 15:711-719.
2. Keleiditi, E, Cesari M, Canevelli M, et al. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. J Nutr Health Aging 2013; 9:726-734.
3. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment: A review of the evidence and causal mechanisms.» Aging Res Rev 2013; 12:840- 51.
4. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three city study. J. AM Geriatr Soc 2009;57:453-61.
5. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology 1993; 43:13-20.
6. Satz P. Brain reserve capacity on symptom onset after brain injury. Neuropsychology 1993; 7:273-295.
7. Stern, Y, Habek C, Moeller J, et al. Brain networks associated with cognitive reserve in healthy young and old adults. Cereb Cortex 2005; 15:394-402.
8. Stern Y, Moeller J, Anderson K, et al. Different brain networks mediate task performance in normal aging and AD: Defining compensation. Neurology 2000; 55:1291-97.
9. Valenzuela MJ, Sachdev P. Brain reserve and dementia: A systematic review. Psychological Medicine 2005; 35:1-14.
10. Cabeza R, Anderson ND, Locantore JK, et al. Aging gracefully: Compensatory brain activity in high-performing older adults. Neuroimage 2002; 17;(3):1394-1402.
11. Grady CL, Maisog, JM, Horwitz B. Age-related changes in cortical blood flow activation during visual processing of faces and location. J Neurosci 1994;14:1450-1462.
12. Fernandes MA, Pacurar A, Moscovitch M. Neural correlates of auditory recognition under full and divided attention in young and old adults. Neuropsychologia 2006; 44:2452-64.
13. Reuter-Lorenz PA and Cappell KA. Neurocognitive aging and the compensation hypothesis. Current Directions in Psychological Science 2008; 17:177-82.
14. Small SA, Tsai, WY, DeLaPaz R, et al. Imaging hippocampal function across the human life span: Is memory decline normal or not? Ann Neurol 2002; 51:290-295.
15. Woods AJ, Cohen M, Pahor M. Commentary, Cognitive Frailty: Frontiers and Challenges. J Nutr. Health Aging, 2013; 17; 9:741-3.
16. Buchman AS, Bennett DA. Commentary, Cognitive Frailty. J Nutr Health Aging, 2013; 17;9:738-9.
17. Dartigues JF, Amieva H. Letter to the Editor, Cognitive Frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging 2014; 18;1:95.

FRAILTY AND PAIN: TWO RELATED CONDITIONS

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Abstract: Frailty is a multidimensional syndrome, involving functional, nutritional, biological and psychological aspects. This condition, defined as a decreased resistance to internal and external stressors, is predictive of adverse health outcomes, including disability and mortality. Importantly, the frailty syndrome is usually considered a reversible condition, thus amenable of specific preventive interventions. Persistent pain in older adults is very common and has multiple determinants. This symptom represents a determinant of accelerated aging. In the present paper, we discuss available evidence examining the association between these two conditions. Despite the high prevalence of these two conditions and their shared underlying mechanisms, our search only retrieved few relevant studies. Most of them reported a relationship between pain (or analgesics consumption) and different operational definitions of frailty. Pain may represent a relevant risk factor as well as a potential target for interventions against the frailty syndrome, but further studies are needed.

Key words: Frailty, pain, elderly, preventive medicine, comorbidity.

INTRODUCTION

Improving the burden of disability and the quality of life of elders is a key challenge in our aging societies. Frailty is an age-related multidimensional syndrome associated with poor health outcomes such as institutionalization and mortality (1). For some older adults, frailty represents a pre-disability phase potentially amenable for targeted intervention so as to delay the onset or prevent functional decline. Furthermore, frailty is a dynamic and time-related syndrome (2, 3). Thus, assessing the natural history and the determinants of frailty is of major interest for improving its early detection and structuring a proper management (4). In this perspective, poor outcomes such as disability (which is often irreversible at old age) may be delayed or avoided.

Pain is a very common symptom in older persons (2, 5), with a substantial impact on health status, functional prognosis, and extra costs for public health administrations (3, 6-8). Persistent pain may be related to and determine the acceleration of the aging process. In other words, it might indeed represent the primum movens of the natural history of frailty. Assuming that pain is a risk factor of frailty, this

symptom would represent a primary target for interventions aimed at reversing the frailty condition.

In the present review, we provided a brief presentation of the frailty syndrome, followed by an overview of the theoretical relationship between frailty and pain, to end with future perspectives in the field.

FRAILTY

The frailty syndrome, as a theoretical concept, is well established in the literature and universally accepted by researchers and clinicians (9). One of the most common definitions of frailty describes it as a state of enhanced vulnerability with insufficient homeostatic reserves to efficiently cope against stressors (10). Most notably, frailty is a multidimensional syndrome that paves the way for adverse health outcomes, such as mortality and disability (1). The frailty syndrome may be delineated as a functional and biological pattern of decline accumulating across various physiological systems, because of impaired regulations and repairing mechanisms. Yet, several aspects of the heterogeneous and complex frailty syndrome are still imperfectly understood, limiting its implementation in clinical practice. Further, the importance of the comprehensive geriatric assessment for describing the risk profile of the individual is well established and crucial for preventing the onset of disability (1, 11-15). In fact, personalized interventions (primarily aimed at correcting nutritional, physical and/or medical issues) have been indicated as potentially capable of restoring robustness in frail elders (15). Interestingly, the frailty issue has gone well beyond the geriatrics boundaries, and several other medical specialties are today interested on this topic.

Nevertheless, despite its crucial importance, early detection of frailty remains particularly challenging. Several instruments have been designed and validated to translate the theory of frailty into clinical practice. To date, the Frailty Phenotype (1) and the Frailty Index (13) are probably the most known and widely used. The Frailty Phenotype was proposed by Fried and colleagues and validated in the Cardiovascular Health Study. It consists of 5 criteria

Table 1

Studies exploring the relationship between frailty and pain

Study	Design	Pain assessment	Frailty assessment	Setting	n	Main objective	Main results
Koponen et al. (26)	CS	Musculoskeletal pain severity	Frailty phenotype	Community	605	Analgesic use-Frailty	Frail subjects used more analgesics
Shega et al. (34)	CS	Pain severity, pain duration	Frailty index	Community	4,694	Pain severity-Mortality	No significant relationship between frailty and pain
Shega et al. (27)	CS	Persistent body pain, pain severity	Frailty index	Community	4,968	Persistent pain-Frailty	More severe pain in pre-frail and frail subjects
Miguel et al. (28)	CS	No direct pain assessment; diagnosis of osteoarthritis	Frailty phenotype	Community	58	Analgesic use-Frailty	Frail elders use more analgesics
Chang et al. (29)	CS	History of pain	Frailty phenotype Edmonton Frail Scale	Community	275	Pain-Frailty	Pain more frequent in frail subjects
Lin et al. (30)	CS	SF-36	Frailty phenotype	Community	933	Disabilities-Frailty	More disabling conditions (including pain) in frail elders
Saxton et al. (31)	CS	SF-36	Frailty index	Surgical patients	226	Post-surgery complications-Frailty	Inverse relationship between pain and postsurgical complications
Chen et al. (35)	CS	Analgesic use	Frailty phenotype	Community	2,238	Analgesic use-Frailty	Higher use of analgesics in frail subjects
Weauver et al. (32)	CS	SF-36, pain duration, pain severity	Frailty index	Community	744	Pain-Frailty	More severe pain in frail elders
Blyth et al. (33)	CS	SF-12, pain severity, analgesic use	Frailty phenotype	Community	1,705	Pain-Frailty	More severe pain in frail subjects
Misra et al. (36)	CS	Symptomatic knee osteoarthritis	SOF scale	Community	3,707	Knee osteoarthritis-Frailty	More osteoarthritis symptoms in frail subjects
Wise et al. (37)	CS	No direct pain assessment; radiographic evaluation of osteoarthritis	Frailty phenotype	Community	4,130	Osteoarthritis-Frailty	More severe osteoarthritis in frail subjects

CS: cross-sectional study; SF-36, SF-12: Health Related Quality of Life Short Form scale (36 or 12 items, respectively); SOF: Study of Osteoporotic Fracture index.

measuring the risk-profile of the older subject. Differently, the Frailty Index proposed by Rockwood and colleagues estimates the age-related accumulation of deficits through the arithmetical evaluation of signs, symptoms, clinical conditions, and disabilities. These two instruments should not be considered as equivalent but rather as complementary in the clinical geriatric assessment (9). From these two main instruments, some additional tools have been elaborated over the last decade. For example, the Study of Osteoporotic Fractures (SOF) index (16) has simplified the frailty phenotype, reducing the key criteria from five to three. Additionally, the Groningen Frailty Indicator (GFI) (17) is a validated, 15-item questionnaire that with its multidimensional (i.e. physical, cognitive, social, and psychological) assessment of the older person may resemble the Frailty Index approach.

Xue and colleagues have highlighted the role of precursor signs of frailty (4). Treating these symptoms is surely a promising catalyst for breaking the vicious circle of frailty and preventing adverse health outcomes like disability. The evaluation and management of persistent pain have been given a growing interest among clinicians and researchers dealing with age-related conditions. However, although pain may represent a potential cause of frailty, it still remains an understudied and undertreated symptom, especially at old age. Instead, it indeed is a key symptom negatively affecting quality of life and potentially triggering the disabling cascade of frail elders.

PAIN

Chronic pain has been estimated to affect 100 million people in the United States (18), and is particularly prevalent in the older adults. A recent study (8) estimated that over half of community-dwelling older adults in the United States (18.7 million) reported bothersome pain in the last month. Moreover, pain has been reported as one of the most common symptoms among frail older persons (1, 19), especially in specific settings like nursing homes where estimated prevalence may be even higher than 70% (5). The increased prevalence of age- related degenerative diseases may at least partially explain such alarming figures. For example, the increased incidence of specific conditions such as diabetes, herpes zoster and lumbar radiculalgia with aging can be associated with higher rates of neuropathic pain (due to both central or peripheral nerve injuries). Unlike nociceptive pain, neuropathic pain may be triggered by non-painful stimuli (i.e., allodynia). The medical management of these symptoms is often poor and the quality of life of elders with neuropathic pain has shown to be significantly impaired (20). For these reasons, neuropathic pain often results in anxiety, mood and sleep disorders (21). Persistent pain (regardless of the etiological factors) has a systemic impact, also with cognitive, cardiovascular or behavioural consequences (22).

The multidimensional consequences of pain may actually overlap the consequences of the frailty status triggered by pain. For example, pain is closely associated with each of the the five frailty criteria included by Fried and colleagues in the Frailty Phenotype. Persistent pain may result in incapacitating exhaustion (23) and decreased physical activity (24, 25). Patel et al. (8) recently showed that pain is associated with decreased physical performance (i.e., handgrip strength and usual gait speed) in a nationally representative study of older adults in the United States. Furthermore, pain-induced anorexia and loss of appetite is common in older persons. Furthermore, cognitive, behavioural and social limitations caused by the pain symptom should not be underestimated as frequently acknowledged in the operationalization of the frailty condition.

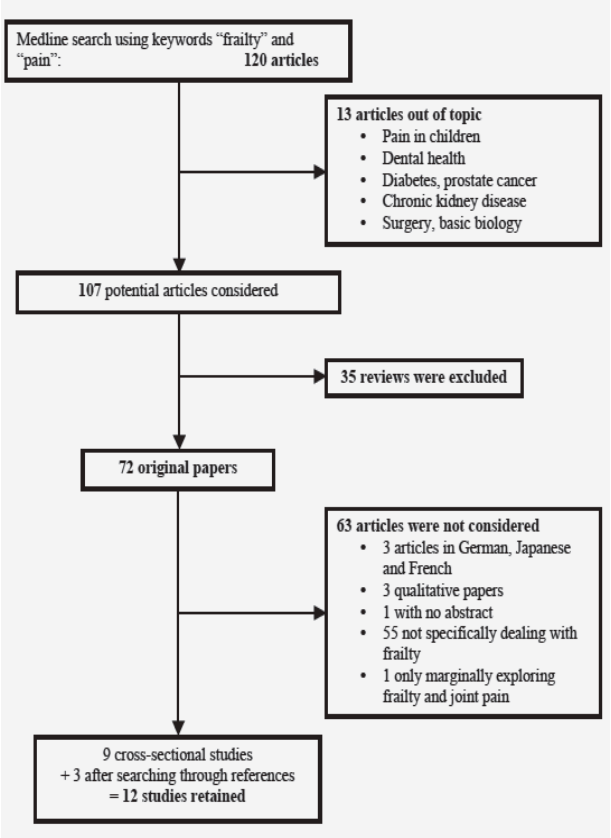
FRAILTY AND PAIN: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

Although the relationship between frailty and pain is supported by credible shared mechanisms, evidence in the field is still sparse and scarce. In order to provide an overview of such still partially explored field (i.e., relationship between frailty and pain), we conducted a Medline search, using the keywords "frailty" and "pain" from 1989 to 2014 (last update: 21/10/2014). In Figure 1, the flow chart describing the selection of studies of interest is presented.

One hundred and twenty studies were retrieved. Of these articles, thirteen were excluded because out of the topic (e.g., dealing with pain in children, dental health, chronic kidney disease, general biology, chemotherapy in prostate and breast cancer). Among the 107 remaining papers, 35 review articles were then excluded. Then, three non-English language papers, one with no available abstract, three qualitative articles, 55 papers did not take into consideration the frailty status, and one paper that only marginally explored frailty and joint pain were also excluded. Finally, 9 cross-sectional studies were retained (Table 1) (26-34). Other three studies were subsequently obtained after searching through the references of the selected articles (35-37).

Figure 1

Flow chart describing the selection process of the articles of interest.



Five cross-sectional studies specifically examined the relationship between frailty and pain. Blyth et al. in the Concord Health and Ageing in Men Project (CHAMP) study (33) investigated the association between intrusive pain and frailty in 1,705 community-dwelling Australian older men (mean age 77 years). Frailty was defined according to the Frailty Phenotype criteria. Intrusive pain was assessed using one item from the SF-12 quality of life questionnaire (38). Frailty status was significantly and incrementally associated with reporting intrusive pain, with unadjusted odds ratios (OR) for pain of 3.9 (95% Confidence Interval [95%CI] 2.7-5.6; p<0.0001) in frail men, compared to robust men. The results were consistent even after adjusting for multiple potential confounders including depression.

Shega et al. (27) explored the association between pain and frailty in the Canadian Study of Health and Aging. Frailty was defined according to a modified version of the Frailty Index (33 self-reported items). Pain was evaluated using five questions. Among 4,968 participants (mean age 80 years) self-reported "moderate or severe" pain was significantly associated with a higher frailty score than "no or very mild" pain.

Chang et al. (29) reported a cross-sectional association between frailty and history pain in a sample of 275 community- dwelling residents in Taiwan (65 years and older). Frail elders were found to more likely present history of pain than robust elders (p=0.03 using the Frailty Phenotype and p=0.006 according to the Edmonton Frail Scale) (39).

In 933 Taiwanese community-dwelling elders, Lin et al. (30) found very similar results. The prevalence of pain assessed with the Health Related Quality of Life short form-36 questionnaire (http://www.sf-36.org/demos/SF-36.html) was 47.7%, 56.6%, and 70.8% in robust, pre-frail, and frail elders, respectively (p<0.001).

Among Mexican Americans aged 65 years and older, Weaver et al. (32). studied the relationship between self- reported pain interference and severity with the Frailty Index. Again, frailty was associated with both pain interference (p<0.01) and severity (p<0.001).

Two other cross-sectional studies that examined the cross-sectional association between frailty and analgesic intake were also retained from our search (26, 35). Both indirectly suggested a relationship between frailty and pain, considering that frail elders tend to present a higher consumption of analgesic medications. Koponen et al. (26) reported a higher prevalence of analgesic drugs prescription in frail individuals (OR 2.96; 95%CI 1.38-6.36, p<0.001), among 605 community-dwelling elderly subjects (aged 75 years and older). It is noteworthy that in this population, musculoskeletal pain was found to be the most common complaint in frail people and acetaminophen the most prescribed drug. Chen et al. (35) reported a statistically significant higher prevalence of pain in frail (87.9%) vs. prefrail (65.2%) or robust (40.7%) community dwelling subjects (n=1,085). They also highlighted greater analgesics consumption in frail elders, distinguishing analgesics for osteoarthritis from other pain drugs (p<0.001 for both).

Miguel et al. (28) conducted a cross sectional study of 58 elderly subjects with osteoarthritis. Higher drug consumption was found in frail elders (compared with robust subjects), but no information was available regarding the used analgesics. However, pain and stiffness were not significantly overrepresented in frail or prefrail elders.

Saxton and Velanovitch (31) investigated the role of preoperative frailty (assessed with the Frailty Index) on postoperative complications after general surgery interventions, in 226 older adults. Frailty was associated with a higher risk of complications (OR 1.48, 95%CI 1.10-1.99; p=0.02). No difference in body pain was reported in frail patients according to the onset of postoperative complications.

CONCLUSIONS

To date, only twelve cross-sectional studies have more or less directly examined the relationship between frailty and pain. Overall, the results of our search support the existence of a cross-sectional relationship between these two conditions. Growing evidence has highlighted the importance of

early detection of frailty with appropriate screening tools in many clinical specialties. On the other hand, persistent pain, especially in older adults, has to be considered as a multidimensional condition with systemic consequences. Pain and frailty might share common mechanisms and appear to be associated in various populations of elders.

The importance of pain assessment in elders is still underappreciated. We do not know whether a better management of persistent pain in elders might impact the course of frailty syndrome. It is also unclear whether the improvement of frailty may also provide positive effects on pain. Further research is surely needed in such promising field for better understanding the inner foundations of the relationship between pain and frailty in the elderly. Results from such initiatives may indeed pave the way of future interventions against age-related and disabling conditions.

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REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults, evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-56.
2. Gill TM, Gahbauer EA, Han L, et al. Trajectories of disability in the last year of life. New Engl J Med 2010;362:1173–1180.
3. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–263.
4. Xue QL. The Frailty Syndrome: Definition and Natural History. Clin Geriatr Med 2011;27(1):1–15.
5. Abdulla A, Adams N, Bone M, et.al, Guidance on the management of pain in older people. Age Ageing 2013;42 Suppl 1:i1-57.
6. Thomas E, Mottram S, Peat G, et al. The effect of age on the onset of pain interference in a general population of the older adults: prospective findings from the North Staffordshire Osteoarthritis Project (NorstOP). Pain 2007;129:21-7.
7. Cavalieri TA. Pain management in the elderly. J Am Osteopath Assoc 2002;102(9):481-485.
8. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: findings from the 2011 National Health and Aging Trends Study. Pain 2013;154(12):2649-57.
9. Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing 2013;43(1):10-2.
10. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-62.
11. Hubbard RE, Fallah N Searle SD, Mitniski A, Rockwood K. Impact of exercise in community-dwelling older adults. PloS One 2009;4(7):e6174.
12. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. J Gerontol B Psychol Sci Soc Sci 1998;53:9–16.
13. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people: an evolving concept. CMAJ 1994;150:489–495.
14. Jones D, Song X, Mitnitski A, Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. Aging Clin Exp Res 2005;17: 465–471.
15. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323–336.
16. Kiely DK, Cupples LA, Lipsitz LA, Validation and comparison of two frailty indexes: the mobilize Boston study. J Am Geriatr Soc 2009;57:1532–1539.
17. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? J Gerontol A Biol Sci Med Sci 2004;59:962–965.
18. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press, 2011.
19. Rastogi R, Meek BD. Management of chronic pain in elderly, frail patients: finding a suitable, personalized method of control. Clin Interv Aging 2013;8:37.
20. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2009;27(2):95-112.
21. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage 2005;30(4):374-85.
22. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. Pain Med 2011;12(7):996-1004.
23. Whitson HE, Thielke SM, Diehr P, et al. Patterns and predictors of recovery from exhaustion in older adults: the cardiovascular health study. J Am Geriatr Soc 2011; 59(2): 207–213.
24. Patel KV, Dansie EJ, Turk DC. Impact of chronic musculoskeletal pain on objectively measured daily physical activity: a review of current findings. Pain Manag 2013;3(6):467-74.
25. Dansie EJ, Turk DC, Martin KR, Van Domelen DR, Patel KV. Association of Chronic Widespread Pain with Objectively Measured Physical Activity in Adults: Findings from the National Health and Nutrition Examination Survey. J Pain. 2014;15(5):507-15.
26. Koponen MP, Bell JS, Karttunen NM, et.al. Analgesic Use and Frailty among Community-Dwelling Older People. Drugs Aging. 2013;30:129– 136.
27. Shega JW, Dale W, Andrew M, Paice J, Rockwood K, Weiner DK. Persistent pain and frailty: a case for homeostenosis. J Am Geriatr Soc 2012;60(1):113-7.
28. Miguel Rde C, Dias RC, Dias JM, da Silva SL, Menicucci Filho PR, Ribeiro TM. Frailty syndrome in the community-dwelling elderly with osteoarthritis. Rev Bras Reumatol 2012;52(3):331-347.
29. Chang CI, Chan DC, Kuo KN, Hsiung CA, Chen CY. Prevalence and Correlates of Geriatric Frailty in a Northern Taiwan Community. J Formos Med Assoc 2011;110(4):247–257.
30. Lin CC1, Li CI, Chang CK, et al. Reduced Health-Related Quality of Life in Elders with Frailty: A Cross-Sectional Study of Community-Dwelling Elders in Taiwan. PLoS One 2011;6(7):e21841.
31. Saxton A, Velanovich V. Preoperative Frailty and Quality of Life as Predictors of Postoperative Complications. Ann Surg 2011;253:1223–1229.

32. Weaver GD, Kuo YF, Raji MA, et.al. Pain and disability in older Mexican-American adults. J Am Geriatr Soc 2009;57(6):992-9.
33. Blyth FM, Rochat S, Cumming RG, et al. Pain, frailty and comorbidity on older men: the CHAMP study. Pain 2008;140(1):224-30.
34. Shega JW, Andrew M, Kotwal A, et al. Relationship between persistent pain and 5-year mortality: a population-based prospective cohort study. J Am Geriatr Soc 2013;61(12):2135-41.
35. Chen CY, Wu SC, Chen LJ, et al. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr 2010;50(Suppl. 1):S43–7.
36. Misra D, Felson DT, Silliman RA, et al. Knee osteoarthritis and frailty: findings from the multicenter osteoarthritis study and osteoarthritis initiative. J Gerontol A Biol Sci Med Sci 2014;10:1093;102.
37. Wise BL, Parimi N, Zhang Y, et al. Frailty and hip osteoarthritis in men in the MrOS cohort. J Gerontol A Biol Sci Med Sci 2014;69(5):602-8.
38. Ware JE, Kosinski M, Keller SD. A 12-items short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
39. Rolfson DB1, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35(5):526-9.

USE OF BIOMARKERS

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Abstract: Expanding the concept of frailty to the clinical settings has raised the concern about the accuracy of the current definitions for identifying frail individuals (not populations). The usual tools to assess frailty show, among other characteristics, a low sensitivity and a low Positive Predictive Value. One approach to overcome this challenge is using biological biomarkers to improve those characteristics, making feasible and accurate the assessment of frailty in clinical settings. Many biomarkers of frailty have been identified but few of them have been assessed as clinical markers with controversial results. Taking into account that frailty is caused by the failure in different systems, it is worthy to check if the combination of several of these biomarkers could be of help. In this effort, the EU-funded project FRAILOMIC is trying to assess the ability of different sets of biomarkers for improving the accuracy of classical definitions in determining the risk, the diagnosis and the prognosis of frailty.

Key words: Frailty, aging, elderly, screening, assessment.

The traditional way of assessing frailty has been based until now in using several instruments that measure performance- based tasks jointly to the assessment of indicators of nutrition and physical activity. This approach has been rather successful in the epidemiological settings, allowing the demonstration of frailty as an important population-based risk factor for several adverse outcomes. But it looks insufficient in clinical settings, where the individual risk is the matter and where the characteristics of the instruments as diagnostic tools must be refined (1). From a clinical point of view, to detect frailty is of outstanding importance in preventing disability. When the frailty threshold has been surpassed and the disability has emerged, recovery from disability is unlikely (2), especially as the age of the patient, the degree of disability or its duration increase (3). Although the usual spontaneous evolution is to progress from non-frail to frail and disabled, a significant percentage of people improves in terms of functional status (4), with no clearly identified predictive factors of this evolution. However, some results from the Women´s Health and Aging Study II (WHAS II) suggest that some ill-defined characteristics could predict a differential risk (5). But to make accurate diagnosis of frailty is not only an issue of interest for risk prediction purposes, targeting those patients who will benefit from a specific approach compared to others who are not going to benefit from it, becoming frailty one of the cornerstones of decision-making in elderly patients. To know which patients will respond to the different treatments now available, mainly exercise and nutrition (6-8), is also of interest. Mainly when it looks that we are now in the border of an era where multimodal and pharmacological interventions targeting frailty will be available (9, 10).

Although it is well known that the evolution from frailty to disability and its clinical consequences depends on several factors, including genetic and other biological factors, their utility as biological biomarkers (BMs) of frailty and of the risk to become frail, to develop disability and to respond to treatment, remains far from desirable for the day to day clinical practice. In fact, there are no studies addressing these issues.

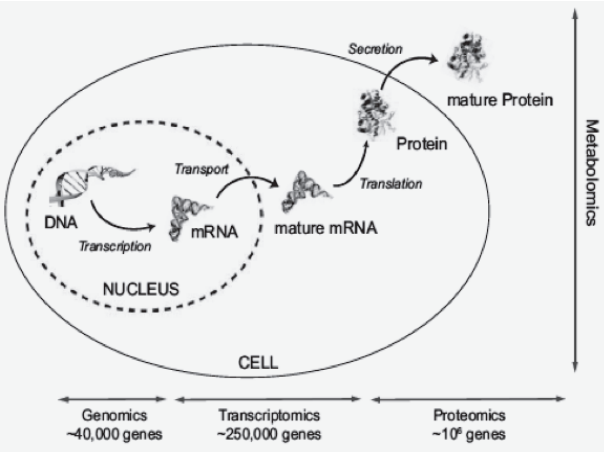
BIOLOGICAL BIOMARKERS OF FRAILTY

The most accepted physiological framework to explain frailty and its consequences was proposed by Walston and Fried (1999). Its fundamentals are sarcopenia and the energetic misbalance. They also established a feed-back between them: the so-called "frailty cycle". This cycle stems from the physiological changes associated with ageing, producing an imbalance between anabolism and catabolism. This state embraces multiple systems and especially those related to hormonal changes and the development of a pro-inflammatory state: the changes in sexual hormones (low testosterone in males but also high estradiol in women), the dysfunction of GH-IGF-1 axis, the increase in the ratio cortisol/DHEA-s, the combination of several hormonal deficits, and the increase in IL-6, IL-1 and TNF alpha circulating levels (Penninx et al., 2004), CRP and D-Dimer (Walston et al., 2002) and pro- inflammatory cytokines (Leng et al., 2002). These findings suggest that changes associated with sarcopenia and with the balance between production and use of energy may be among the most relevant factors associated with frailty: dysregulation of inflammatory cytokines and hormones, oxidative stress, nutrition, physical inactivity and mithochondrial dysfunction. In addition, the role of vascular disease (atherosclerosis) has been underscored by several authors (Strandberg & Pitkäla, 2007). The presence of clinical cardiovascular disease, but also subclinical cardiovascular disease has been shown to be associated to frailty. The possibility of detecting early biomarkers of vascular (endothelial) dysfunction rises as an important clue to the detection of early stages of frailty as to an improved diagnoses and/or prognostic capacity.

In addition to these classical BMs, more recently other BMs have come to the field of frailty. As an example, the role for Hypoxia Inducible Factors proteins-HIF (and mainly α subunits of HIF) and their signaling pathway has emerged as a main control of key pathways that are essential for cell physiology, in a variety of processes related with human ageing. The relevance of HIFα resides in the pivotal role played by their target genes in several of the above mentioned physiological systems involved in frailty: the cell metabolism and energy balance (e.g., NOS2, PHD3, GLUT1, GLUT4, GAPDH, PGK1, trasferrin, etc.), angiogenesis and cell proliferation (e.g., VEGF, TGFα, TGFβ3, IGF2, OCT3/4), the length of the telomere (hTERT), etc. At the same time HIF-1α has been identified as an important modifier of longevity in animal models (11). In addition other potential BMs have also raised as it is the case of a common signature of miRNA expression in 7 different human aging model systems (12) or the telomere length. Within this complex framework, the "omic sciences" represent a significant aid to the study of potential BMs by allowing a comprehensive approach from the genome to the metabolome (Fig. 1).

Figure 1

The "omic" sciences



In summary, early detection of subclinical changes or deficits at the molecular, cellular, and or physiologic level is key to preventing or delaying the development of frailty, and its consequences too. However, data evaluating the role of these substances in providing significant support to the clinical diagnosis of frailty or any of its associated risks are scarce.

THE FRAILOMIC INITIATIVE

It is noteworthy that one of the main characteristics of frailty is that its pathophysiological routes embrace several physiological systems (13). However, until now the approach to the study of the relationships between BMs and frailty has been done one by one, ignoring the multiplicity of relationships that probably account for the role of BMs in determining frailty. In addition, the usual tools to diagnose frailty used in the epidemiological studies show some characteristics (including a low sensitivity and a low positive predictive value) (14) that do not allow to use them for clinical purposes. These are some of the gaps that the recently launched Frailomic Initiative will try to fill (15). The principal aim of the Frailomic Initiative is to develop validated sets of measures comprising both classical and omics-based laboratory biomarkers (Table 1) to predict the risk of frailty, improve the diagnostic accuracy of frailty in day-to-day clinical practice, and assess the benefits of a prognostic forecast of frailty on the onset of disability and other adverse outcomes. In order to identify predictive biomarkers, the European Union-funded Frailomic Initiative follows an "omics" approach (genomics, transcriptomics, proteomics and metabolomics), using existing large datasets from previous "omics" initiatives. These studies have

created a wealth of data that, so far, have not been used in the field of frailty research until now. In addition, the participation of well-established cohorts aimed to the study of the processes of aging, frailty and disability will allow a tight assessment, due to the excellent phenotyping of the functional characteristics of those populations.

The approach taken by the Frailomic Initiative will allow clinicians to go beyond the traditional disease-based approach to healthcare strategy and toward a strategy based on comprehensive quality-of-life, since the impact will be on reducing disability. Secondary objectives of the Frailomic Initiative include assessing interactions among putative biomarkers, nutrition, exercise and their effects on the natural history of frailty. In addition, the potential therapeutic usefulness of identifying frailty status in special older populations such as those with metabolic syndrome, diabetes and cardiovascular disease will be examined. The Frailomic Initiative aims to provide useful tool kits for care providers that will allow them to assess the risk of an older individual for developing frailty (i.e., "risk biomarkers") as well its identification (i.e., "diagnostic biomarkers"), clinical course (i.e., "prognostic biomarkers"), and likely response to treatment (i.e., "predictive biomarkers") thus bridging the gaps between epidemiology and clinical practice.

Conflict of interest: None

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Table 1

Non-classical Biomarkers of frailty assessed in the Frailomic Initiative

Biological process	Biomarker	Rationale for selection	Method of analysis
Metabolism / Muscle function			
	ACE	Association of genotype with muscle mass, response to muscle power training and longevity	Openarray (SNP)
	ACTN3	Association of genotype with response to muscle power training, muscle mass and risk of falling in older females	Openarray (SNP)
	CNTF	Association of genotype and grip strength in older Caucasian women	Openarray (SNP)
	GDF8	Association of genotype with muscle mass in elerly women	Openarray (SNP)
	IL6	Implicated in muscle repair after exercise. Association between genotype and human longevity	Openarray (SNP and mRNA)
	mtDNA	Association between genotype and longevity in different populations	Openarray (SNP)
	VDR	Association of genotype with muscle strength and rate of falling in the elderly	Openarray (SNP)
Metabolism/ Insulin/IGF1 signaling pathway		Reducing the activity of this pathway protects from ageing-associated pathologies and extends life-span in animal model systems	
	AKT1	Association of genotype with human longevity	Openarray (SNP and mRNA)
	FOXOs	Association of genotype with human longevity	Openarray (SNP and mRNA)
	mTOR		Openarray (SNP and mRNA)
Metabolism /Stress response			
	HIF1	Modulation of life-span in C. elegans	Openarray (mRNA); ELISA
	PGC1α	Association of genotype with diabetes, with age of onset of neurodegenerative diseases and with longevity	Openarray (SNPs)
	SIRT1	Over-expression delays ageing phenotypes and extends life-span in model organisms; genotype associated with lipid profiles in humans	Openarray (SNP and mRNA)
	SOD2	Reduced expression associated with ageing phenotypes; genotype associated with survival in very old women	Openarray (SNP and mRNA)
Response to stress			
	TP53	Increased expression is associated with ageing phenotypes in mice	Openarray (mRNA)
	SESN2	Inactivation in Drosophila results in an ageing phenotype	Openarray (mRNA)

Biological process	Biomarker	Rationale for selection	Method of analysis
Cardiovascular homeostasis			
	AGT	Association of genotype with hypertension	Openarray (SNP)
	NOS3	Association of genotype with disability in the elderly	Openarray (SNP)
Inflammation			
	AGEs	Increased in ageing, diabetes and cardiovascular diseases; increased levels associated with reduced grip strength	ELISA
	sRAGE	Decreased in diabetes; inverse association with atherosclerosis	ELISA
	CCL11	Increased with ageing; elevated levels associated with decreased cognitive function and lower grip strength	ELISA
	LGALS3	Association of genotype with cognitive function at old age	Openarray (SNP)
	JAG1	Secreted by senescent endothelial cells	ELISA
	VCAN	Secreted by senescent endothelial cells	ELISA
Regulation of cell proliferation			
	IGFBP6	Secreted by senescent endothelial cells	ELISA
	Telomere	Association of telomere length with age-associated diseases and life-span	HT-QFISH
Regulation of gene expression			
	miR-24, miR- 130, miR-94	Longevity-associated miRNAs	miRNome profiling
	miR-17, miR- 19b, miR-20a, miR-106a	Ageing and senescence associated miRNAs	miRNome profiling
	mir-31miR-10a-5p, miR-10b-5p, miR-22-3p, miR-133b, miR-328-3p, let-7g-5p	Osteoporosis related circulating miRNAs	miRNome profiling

REFERENCES

1. Rodriguez-Mañas L, Fried LP. Frailty in the clinical scenario. Lancet. 2014 Nov 6. pii: S0140-6736(14)61595-6. doi: 10.1016/S0140-6736(14)61595-6.
2. Ferrucci L1, Cavazzini C, Corsi A, et al. Biomarkers of frailty in older persons. J Endocrinol Invest. 2002;25(10 Suppl):10-5.
3. Fried LP, Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. J Am Geriatr Soc 1997; 45: 92-100.
4. Xue QL, Walston JD, Fried LP, Beamer BA. Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: the women's health and aging study. Arch Intern Med. 2011; 171: 1119-21.
5. Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci. 2008; 63: 984-90.
6. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA. 2014; 311: 2387-96.
7. Cesari M, Vellas B, Hsu FC, et al. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. J Gerontol A Biol Sci Med Sci. 2015 Feb;70(2):216-22.
8. Kelaiditi E1, van Kan GA, Cesari M. Frailty: role of nutrition and exercise. Curr Opin Clin Nutr Metab Care. 2014; 17: 32-9.
9. Rodríguez-Mañas L, Bayer AJ, Kelly M, et al. An evaluation of the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes--the MID-Frail study: study protocol for a randomised controlled trial. Trials. 2014; 15: 34.
10. Vellas B, Pahor M, Manini T, et al. Designing pharmaceutical trials for sarcopenia in frail older adults: EU/US Task Force recommendations. J Nutr Health Aging. 2013; 17: 612-8.

11. Leiser SF, Begun A, Kaeberlein M. HIF-1 modulates longevity and healthspan in a temperature-dependent manner. Aging Cell. 2011; 10: 318- 26
12. Hackl M, Brunner S, Fortschegger K, et al. miR-17, miR-19b, miR-20a, and miR-106a are down-regulated in human aging. Aging Cell. 2010; 9: 291-6
13. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci. 2009 Oct;64(10):1049-57.
14. Garcia-Garcia FJ, Carcaillon L, Fernandez-Tresguerres J, Alfaro A, et al. A new operational definition of frailty: the Frailty Trait Scale. J Am Med Dir Assoc 2014; 15: 371.e7-371.e13.
15. Lippi G, Jansen-Duerr P, Viña J, et al. Laboratory biomarkers and frailty: presentation of the FRAILOMIC initiative. Clin Chem Lab Med 2015 DOI 10.1515/cclm-2015-0147

III

INTERVENTIONS AGAINST FRAILTY

RAISING AWARENESS ON THE URGENT NEED TO IMPLEMENT FRAILTY INTO CLINICAL PRACTICE

THE ORLANDO FRAILTY CONFERENCE GROUP (see Appendix)

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Abstract: Frailty has been linked to longer hospital stays and increased mortality in hospitalized patients. Frailty was found at the most common condition leading to death, followed by organ failure, cancer, other causes, advanced dementia, and sudden death. Yet despite evidence linking frailty to poor outcomes, frailty is not implemented clinically in most countries. Since many people are not identified as frail, they frequently are treated inappropriately in health care settings. Participants in the international conference on frailty emphasized the importance of raising awareness about frailty among geriatricians, general practitioners, and other primary care providers in order to implement frailty in clinical practice. The following recommendations were agreed upon: 1. Prioritize the identification of frail older persons in community settings, hospitals, and specialty clinics in order to ensure that people with frailty are treated appropriately and have access to interventional studies; 2. Build frailty clinics as a means of providing optimal management of frail elders; 3. Develop intervention programs incorporating physical and cognitive exercise, social support, and nutrition for people in the earliest stages of frailty in order to slow or reverse frailty; 4. Build stronger basic and clinical research programs in order to better understand the underlying causes of frailty, identify therapeutic targets, and develop new treatment strategies.

Key words: Frailty, prevention, primary care, public health, disability.

INTRODUCTION

According to the United Nations, by 2050 there will be 2 billion people worldwide over the age of 60, more than three times as many as in 2000 (1). While this reflects improvements in the health of people worldwide and increased longevity, it also presents challenges for individuals, families, and societies as the numbers of people with frailty, chronic diseases and disabilities also increases (2).

Frailty has been conceptualized as a physiological syndrome reflecting decreased reserve and resilience, which may lead to progressive functional decline, vulnerability to stressors, and an elevated risk of adverse outcomes, including death. It is a major cause of dependency, yet research suggests that it may be possible to prevent disability and dependency by targeting frail and pre-frail older adults with simple screening tools and effective and sustained interventions (3).

Frailty has been recognized as an important condition by the Institute of Medicine (IOM) (4) and the European Union (EU), although a consensus conference held in 2011 concluded that while frailty has a clear conceptual framework and is useful in clinical settings, there is no single operational definition of frailty that can satisfy all experts and more research is needed (5). Thus, another consensus conference was convened in October, 2012, in Orlando Florida. At this conference, frailty experts met to develop a consensus statement along with delegates from the International Association of Geriatrics and Gerontology (IAGG), the Ameri-

can Medical Directors Association (AMDA), the American Federation of Aging Research (AFAR), European Union Geriatric Medicine Society (EUGMS), International Academy of Nutrition and Aging (IANA), Society on Sarcopenia, Cachexia, and Wasting Disorders (SSCWD), the EU, and the Gateway Geriatric Education Center (GEC) (6).

Strong evidence supports the definition of frailty as a syndrome with a distinct etiology and consisting of a constellation of signs and symptoms that increase vulnerability to stressors and that, taken together, are better at predicting an adverse outcome than any individual characteristic. Fried and colleagues have proposed that the signs and symptoms of frailty result from dysregulated energetics involving multiple molecular and physiological pathways, which lead to sarcopenia, inflammation, decreased heart rate variability, altered clotting processes, altered insulin resistance, anemia, altered hormone levels, and micronutrient deficiencies (7). These physiological impairments result in the five clinical characteristics of frailty: weakness, low energy, slow walking speed, low physical activity, and weight loss (8). The presence of any three of these phenotypes indicates that a person is "frail"; one or two phenotypes indicates "prefrail"; and none of these characteristics indicates the person is "robust". Fried and colleagues went on to validate this concept in two large datasets from the Cardiovascular Health Study (CHS) (8) and the Women's Health and Aging Studies (WHAS) (9). In both data sets, among women between the ages of 70 and 79, the prevalence of frailty was approximately 11% and the presence of frailty was associated with an increased risk of mortality as well as with a dose-dependent (based on the number of frailty criteria) increased risk of developing dependence in activities of daily living (10).

While the Fried and colleagues' quantifies frailty using five measures, Rockwood and colleagues have developed a frailty index (FI) based on the Comprehensive Geriatric Assessment (CGA), which counts up to 70 items. The FI-CGA thus characterizes frailty across multiple dimensions by including measures of mood, cognition, and social vulnerability (11). In a study of community-dwelling older adults in Canada, the FI- CGA estimated a frailty prevalence of 22.7%, with higher scores predicting an increased risk of death (12).

FROM FRAILTY TO DISABILITY

Frailty develops progressively, with the early phase likely most responsive to intervention and the later, non-reversible stages most costly. In a study of 754 community-dwelling, non- disabled older adults, Gill and colleagues showed that frailty is a dynamic process with frequent transitions. While the overall trend was towards worsening of frailty status, and the likelihood of transitioning from being frail to non-frail was very low, about 10% of prefrail subjects transitioned to non-frail during each 18 month follow-up period (13). Frailty is not synonymous with disability, although frailty is a strong predictor of disability. Both conditions are characterized by functional impairment, however, many disabled people are not frail and the underlying biology of frailty distinguishes it from disability (14). Nor is frailty synonymous with sarcopenia, although sarcopenia is clearly a major contributing factor to frailty (15).

Frailty has been linked to longer hospital stays and increased mortality in hospitalized patients (16). Moreover, in their study of disability trajectories of community-dwelling older persons during the last year of life, Gill and colleagues found that frailty was the most common condition leading to death, followed by organ failure, cancer, other causes, advanced dementia, and sudden death (17). Yet despite evidence linking frailty to poor outcomes, frailty is not implemented clinically in most countries. Since many people are not identified as frail, they frequently are treated inappropriately in health care settings. For example, regardless of age, a frail person may be unable to withstand aggressive medical treatment that could benefit a non-frail person.

IMPLEMENTING FRAILTY INTO CLINICAL PRACTICE

The identification of frailty in its early stages, i.e., the "prefrail" stage, is important because of the potential to address treatable conditions such as fatigue and weakness, and slow or reverse functional decline. Intervention studies have also demonstrated the potential for improving frailty status, particularly with exercise-based interventions (18). Nutritional supplementation to address weight loss and muscle dysfunction (19-21), and drugs for conditions such as sarcopenia (22, 23), may also represent feasible approaches to treating the underlying conditions of frailty. Multidomain interventions are also under investigation (24).

Polypharmacy is also thought to be a major risk factor for frailty (25). Thus, identifying frailty in an older person may motivate physicians to reevaluate the drugs they are prescribing. Another possible risk factor is vitamin D deficiency (26), although the evidence is contradictory.

In order for frailty to be incorporated into the routine practice of primary care physicians, a simple screening test is needed. Several different methods of screening for frailty have been developed and validated. The Fried criteria were operationalized into a screening algorithm for use in the Cardiovascular Healthy Study (CHS). The FI-CGA was validated in the Canadian Study of Health and Aging (27). Other frailty measures have also been proposed, including

the Study of Osteoporotic Fractures (SOF) Index (28). All of these measures count deficits, and all of them quantify the degree of frailty and thus, the degree of vulnerability to adverse outcomes. Moreover, all of them reflect an aging-associated failure of physiological systems.

The IANA FRAIL scale, based on both the Fried (CHS) and Rockwood (FI-CGA) scales, is a six-question self-report measure that takes less than 30 seconds to administer and has been shown to predict mortality and disability in older Australians (29) and correlates IADLs and strength and mobility outcomes in middle-aged African-Americans (29, 30).

Informant interviews, for example, the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale, can also be used as a rapid and reliable screen for frailty. This scale asks the physician to assign a score ranging from 1 (very fit) to 7 (severely frail) based on clinical impression of co-morbidity, cognitive impairment, and disability. It has been shown to correlate with the CGA-FI (31).

Another frailty screening tool that relies on the clinical opinion of the general practitioner has been developed in France. In response to the French government's policy for preventing disability in older persons, a day hospital was established in 2011 at the Gérontopôle of Toulouse (i.e., the geriatric center of Toulouse) for the evaluation of frailty and prevention of disability (32). Geriatric patients are referred to the center by general practitioners who detect signs of symptoms of frailty and are screened using a simple, quick frailty questionnaire as well as an assessment of gait speed. The Gérontopôle Frailty Screening Tool asks six questions regarding living alone, weight loss, fatigue, mobility, memory, and slow gait speed. If the physician identifies one of these areas as an area of concern, he/she is asked, "In your own clinical opinion, do you feel that your patient is frail and at an increased risk for further disabilities?" It is this last question that is used to identify patients who are frail.

The goal of the Gérontopôle Center is to identify frailty in the early stages through a multidisciplinary evaluation, attempt to identify the cause or causes (i.e., underlying diseases or risk factors), and implement multidisciplinary interventions adapted to each patient's individual needs. These interventions may include nutrition, physical exercise and/or physical therapy, social support, and education. Patients are followed up principally by their general practitioner as well as through phone contact and a structured interview with a nurse from the center to assess the efficacy of the interventional plan.

PSYCHOSOCIAL AND COGNITIVE CONTRIBUTIONS TO FRAILTY

Research from the CSHA has also shown that social vulnerability, distinct but related to frailty, is also associated with higher mortality in the elderly, and that social factors such socio-economic status, social support, and social engagement can be quantified using a social vulnerability index (11). Using this tool, they found that even among healthy and fit elders, social vulnerability was associated with a 22% increased risk of mortality (33). Other frailty models incorporate psychosocial and cognitive components to varying degrees (34), acknowledging that these factors play important roles in the development of frailty.

RECOMMENDATIONS

Participants in the Consensus Conference used a modified Delphi process to reach consensus on major points related to frailty (6). In addition, through their discussions, participants emphasized the importance of raising awareness about frailty among geriatricians, general practitioners, and other primary care providers in order to implement frailty in clinical practice. The following recommendations were agreed upon:

- Prioritize the identification of frail older persons in community settings, hospitals, and specialty clinics in order to ensure that people with frailty are treated appropriately and have access to interventional studies.
- Build frailty clinics such as the one built at the Gérontopôle of Toulouse as a means of providing optimal management of frail elders.
- Develop intervention programs incorporating physical and cognitive exercise, social support, and nutrition for people in the earliest stages of frailty in order to slow or reverse frailty.
- Build stronger basic and clinical research programs in order to better understand the underlying causes of frailty, identify therapeutic targets, and develop new treatment strategies.

APPENDIX

The Orlando frailty conference group include six major International (International Association of Gerontology and Geriatrics, Society of Sarcopenia, Cachexia and Wasting Diseases, and the International Association of Nutrition and Aging), European (European Union Geriatric Medical Society) and United States of America societies (American Medical Directors Association and American Federation of Aging Research) were asked to provide delegates to attend the consensus meeting.

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REFERENCES

1. UNDESA: World Population Aging 2011. 2011.
2. Seeman TE, Merkin SS, Crimmins EM, Karlamangla AS. Disability trends among older Americans: National Health And Nutrition Examination Surveys, 1988-1994 and 1999-2004. Am J Public Health 2010;100:100- 107.
3. Vellas B, Cestac P, Moley JE. Implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging 2012;16:599-600.
4. Adams K, Corrigan JM (Eds.). Priority Areas for National Action: Transforming Health Care Quality. Washington, D.C.: National Academies Press 2003.
5. Rodriguez-Manas L, Feart C, Mann G, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci 2013;68:62-67.
6. Morley JE, Vellas B, Abellan van Kan G, et al. Frailty Consensus: A Call to Action. J Am Med Dir Assoc 2013;14(6):392-7.
7. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006;54:991-1001.
8. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-156.
9. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006;61:262-266.
10. Boyd CM, Xue QL, Simpson CF, Guralnik JM, Fried LP. Frailty, hospitalization, and progression of disability in a cohort of disabled older women. Am J Med 2005;118:1225-1231.
11. Andrew MK, Mitnitski AB, Rockwood K. Social vulnerability, frailty and mortality in elderly people. PLoS One 2008;3:e2232.
12. Rockwood K, Rockwood MR, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. J Am Geriatr Soc 2010;58:318-323.
13. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med 2006;166:418-423.
14. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and co- morbidity in relation to frailty: how much do they overlap? Arch Gerontol Geriatr 2012;55:e1-8.
15. Cooper C, Dere W, Evans W et al. Frailty and sarcopenia: definitions and outcome parameters. Osteoporos Int 2012;23:1839-1848.
16. Khandelwal D, Goel A, Kumar U, Gulati V, Narang R, Dey AB. Frailty is associated with longer hospital stay and increased mortality in hospitalized older patients. J Nutr Health Aging 2012;16:732-735.
17. Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. N Engl J Med 2010;362:1173-1180.
18. Lee P-H, Lee Y-S, Chan D-C. Interventions targeting geriatric frailty: A systemic review. J Clin Geront Geriat 2012;3:47-52.
19. Ferrando AA, Paddon-Jones D, Hays NP, et al. EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. Clin Nutr 2010;29:18-23.
20. Fitschen PJ, Wilson GJ, Wilson JM, Wilund KR. Efficacy of beta- hydroxy-beta-methylbutyrate supplementation in elderly and clinical populations. Nutrition 2013;29:29-36.
21. Chale A, Cloutier GJ, Hau C, Phillips EM, Dallal GE, Fielding RA. Efficacy of Whey Protein Supplementation on Resistance Exercise-Induced Changes in Lean Mass, Muscle Strength, and Physical Function in Mobility-Limited Older Adults. J Gerontol A Biol Sci Med Sci 2013;68(6):682-90

22. Cadilla R, Turnbull P. Selective androgen receptor modulators in drug discovery: medicinal chemistry and therapeutic potential. Curr Top Med Chem 2006;6:245-270.
23. Kovacheva EL, Hikim AP, Shen R, Sinha I, Sinha-Hikim I. Testosterone supplementation reverses sarcopenia in aging through regulation of myostatin, c-Jun NH2-terminal kinase, Notch, and Akt signaling pathways. Endocrinology 2010;151:628-638.
24. Singh NA, Quine S, Clemson LM, et al. Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized controlled trial. J Am Med Dir Assoc 2012;13:24-30.
25. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol 2013;69(3):319-26.
26. Shardell M, D'Adamo C, Alley DE, et al. Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: the Invecchiare in Chianti Study. J Am Geriatr Soc 2012;60:256-264.
27. Jones D, Song X, Mitnitski A, Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. Aging Clin Exp Res 2005;17:465-471.
28. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med 2008;168:382-389.
29. Lopez D, Flicker L, Dobson A. Validation of the frail scale in a cohort of older Australian women. J Am Geriatr Soc 2012;60:171-173.
30. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601-608.
31. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.
32. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B. The integration of frailty into clinical practice: preliminary results from the Gerontopole. J Nutr Health Aging 2012;16:714-720.
33. Andrew MK, Mitnitski A, Kirkland SA, Rockwood K. The impact of social vulnerability on the survival of the fittest older adults. Age Ageing 2012;41:161-165.
34. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. J Am Geriatr Soc 2009;57:830- 839.

INCORPORATING FRAILTY INTO CLINICAL PRACTICE AND CLINICAL RESEARCH

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While frailty is a common syndrome in older persons that is associated with very significant morbidity and mortality, the often subtle and varied clinical manifestations have fostered disagreement regarding its definition, causes, and natural history. Recently consensus has begun to emerge on the acceptance of the following definition for physical frailty "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (1). Based on this emerging consensus and the development of several rapid, validated screening tests, our understanding of the epidemiology of this syndrome is rapidly advancing.

There is now widespread recognition that frailty should be distinguished from disability, and that it exerts its major clinical relevance as a risk factor for the development or aggravation of disability and dependence and risk for mortality and vulnerability to stressors (2). Frailty has several distinct stages in its clinical evolution (Figure 1) with different potential for prevention on and treatment at different stages (3). Substantial progress is being made in describing the epidemiology and etiology, and at least four treatment approaches have been identified as very promising, including exercise, protein-calorie supplementation, vitamin D administration and reduction of polypharmacy.

In the context of this rapidly growing interest in frailty, we identify several valuable strategies for inclusion of special attention to the syndrome in the clinical care of older persons as well as a number of specific clinical research opportunities (Table 1).

Figure 1
Continuum of resilience/frailty in older adults

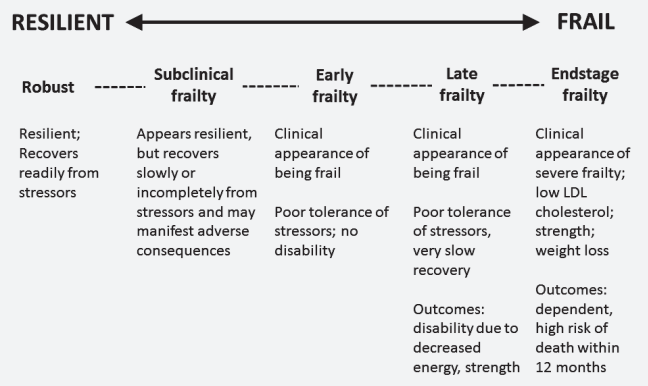

Table 1
Clinical research opportunities in frailty

Record frailty status of all clinical research subjects
Identify patient selection criteria for treatments
Determine dose-response for effective treatments
Elucidate natural history of frailty
Evaluate impact of frailty on drug effects
Determine recovery time after stress in frail patients
Study value of volunteering in frail elders

CLINICAL PRACTICE

Recognition of the importance and prevalence of frailty, and its various stages, is crucial to the effective management of geriatric patients. Just as geriatric care routinely includes screening for cognitive impairment, screening for frailty should be incorporated into patients' regular evaluations. This screening, using standardized measures, can be accomplished quickly and a low cost by nurses or other health care providers and need not be conducted by physicians. It's is Important to identify and target both pre-frail and to identify the frail, especially those who do not yet show disability/dependence, since frailty can be often be seen as a milestone on the pathway to disability.

In addition to screening, the presence or absence of frailty, and its severity should be noted as a major diagnosis as a routine component of the patient's medical record, with specific indication of the treatment that has been employed. This 'red flag' can be especially helpful in prospectively identifying patients who may be at special risk of complication or prolongation of hospital stay after surgery or acute illness.

CLINICAL RESEARCH

In clinical studies involving elderly, including interventions of specific treatments or new models of care or observational studies that follow patients over time, individuals should be routinely characterized as to their frailty status, again using a validated scale, as this may be an important determinant of their response to the various interventions.

Regarding research that specifically targets frailty, we need studies of:

– the best patient selection and 'dose' of currently recommended treatments (exercise, nutritional supplementation, Vitamin D) and optimal treatment combinations- and how to titrate to clinical status and stage of frailty.
– the natural history, with a focus on identification of factors that may initiate the pathway to frailty.
– recognition of the late stage of frailty which is not responsive to treatment, and is a pre-death phase during which the patients should be eligible for hospice.
– the impact of frailty on the metabolism, distribution, effectiveness and toxicity of medications.
– the impact of frailty on recovery from stress, such as hip fracture, major surgery and the like. Such research will inform many guidelines as to how soon and how intense rehabilitation efforts should be, and timing and duration, as it may take frail individuals much longer to recover from the acute effects of the stress and be prepared to benefit from the rehabilitation therapy.
– design of hospital and other treatment settings to optimize recovery from illness for those who are frail.

Regarding the identification of new effective treatments, we believe a strong case can be made for the potential value of social engagement, such as through volunteering, in preventing or mitigating frailty (4, 5). Volunteering has clear beneficial health effects, including delaying the onset of some physical impairments, and seems to especially be effective in enhancing health status in individuals with low socio-economic status or fair health status, who are at enhanced risk of frailty. Given its prevalence and clinical importance, frailty is a public health issue; broad-based volunteer programs can be seen as a public health intervention. Such studies, in addition to a focus on physical frailty, should also include so called "psychological frailty" which often includes isolation and an enhanced realistic, possible sense of vulnerability. We hypothesize that dimension of the volunteer experience, may be if well organized to enhance social connectedness, particularly effective in mitigating these symptoms. Advancement of research into the role of volunteering will be greatly facilitated by inclusion of formal screening for frailty in all ongoing private and government-sponsored volunteer programs.

We are entering an era of great promise in our understanding of frailty. Scrupulous attention to the special needs and risks patients will improve the quality and cost-effectiveness of care. And there is a growing sense that as research in the area accelerates, interventions that prevent the initiation or progression of the frailty pathway may soon be within our grasp.

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REFERENCES

1. Morley J E et al, Frailty Consensus: A Call to Action. JAMDA 2013; 392- 397
2. Fried LP, Walston JD, Ferrucci L. Frailty (Chapter 52). In: Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP Asthana S and Hazzard WR, (editors) Hazzard's Geriatric Medicine and Gerontology. 6th edn. 2009. McGraw Hill, New York, pp 631-645
3. Yang Y and Lee, LC. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the U.S. older adult population. J Gerontol B Psychol Sci Soc Sci. 2010; 65B (2) : 246-255
4. Cutler SJ, Hendricks J, O'Neill G. Civic Engagement and Aging. In: Binstock RH and George LK, (eds) Handbook of Aging and the Social Sciences. 7th edn. 2011. Academic Press, London, pp 221-233
5. Lum TY and Lightfoot E. The effects of volunteering on the physical and mental health of older people. Research on Aging 2005; 27(1): 31-55

FRAILTY IS A COMPLEX GERIATRIC SYNDROME WITH MULTIPLE FUNCTIONAL NEEDS: A COMPREHENSIVE APPROACH IS NEEDED

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ABSTRACT

Objective: To evaluate the prevalence and associated functional needs for frailty among otherwise healthy community-dwelling middle-aged and elderly people in Taiwan. Design: a cross-sectional study. Setting: communities in I-Lan County of Taiwan. Participants: 1839 otherwise healthy community-dwelling people aged 50 years and older. Intervention: None Measurements: Frailty defined by Fried's criteria, Charlson's comorbidity index (CCI), Functional Autonomy Measurement System (SMAF), Center for Epidemiologic Studies Depression Scale (CES-D), Mini-Nutrition Assessment (MNA), Mini–Mental State Examination (MMSE), and Short Form-12 quality of life questionnaire. Results: Overall, 1839 subjects (mean age: 63.9±9.3 years, 47.5% males) participated in this study and men were more likely to have more education year, smoking and alcohol drinking habit. The prevalence of frailty was 6.8%, pre-frailty was 40.5% and 53.7% of all subjects were robust. Compared to subjects with different frailty status, age, education year, alcohol drinking habit, hypertension, diabetes mellitus, hyperlipidemia, CCI, walking speed, handgrip strength, score of SMAF, CES-D, MNA, MMSE, quality of life were significantly different between groups (P all < 0.05). Older age, poorer physical function, poorer cognitive function, poorer nutritional status, more depressive symptoms, higher CCI and poorer quality of life were all independent associative factors for frailty. Conclusions: Frailty was not merely a geriatric syndrome, but the combination of multiple geriatric syndromes. Further study is needed to evaluate the clinical benefits of integrated health promotion activities in the communities to reverse frailty and associated functional care needs.

Key words: Frailty, Geriatric Syndrome, Comprehensive Geriatric Assessment.

INTRODUCTION

Frailty, a well-known geriatric syndrome, is featured by the vulnerable state of older people with reduced physiological reserve and increased susceptibility to adverse health outcomes1. Various adverse health outcomes have been reported to be associated with frailty, such as falls, disability, hospitalizations, reduced health-related quality of life, nursing home admissions and mortality (1,2). In Taiwan, the prevalence of frailty differed from study to study according to

the different healthcare settings (3,4), but it was not greatly different from the literature. More importantly, frailty usually was not present as an independent condition, and it frequently interacted with multimorbidity and disabilities (4). A great body of evidences disclosed that the presence of frailty may complicate the management for individual clinical conditions (5-8). Therefore, managing elderly patients with frailty usually needed a comprehensive approach in clinical practice. Nevertheless, frailty-related functional impairments of otherwise healthy people with frailty were less commonly reported.

I-Lan Longitudinal Aging Study (ILAS) recruited otherwise healthy community-dwelling middle-aged and elderly population for study. ILAS excluded subjects with communication difficulty, dementia, nursing home residents, subjects with limited life expectancy, as well as physical disability (9). Despite the relatively better health conditions of ILAS participants, results of ILAS have shown associations of frailty with cardiometabolic risk (10), cognitive decline (11), falls, fractures, low bone mineral density and sarcopenia, as well as hospitalizations (12). These associations were not different from that of the literature, which confirmed the similar health characteristics of frailty defined in ILAS to other studies. The main aim of this study was to explore the associated functional care needs for frailty among otherwise healthy community-dwelling middle-aged and elderly people to for the further comprehensive intervention programs to promote overall health in the communities.

MATERIALS AND METHODS

Study subjects

The I-Lan Longitudinal Aging Study (ILAS) is a community-based aging cohort study in I-Lan County of Taiwan, which randomly selected community-dwelling people aged 50 years and older to evaluate the complex interrelationship between aging, frailty, sarcopenia and cognitive decline (9). All participants were invited via mail or telephone to participate by the research team, and were enrolled when they signed the consent forms. The inclusion criteria for ILAS were: (1) residents aged 50 years and older, and (2) inhabitants who presently live in Yushan Township without a plan to move to other places. Subjects with the following conditions were excluded for study: (1) unable to communicate with the research nurses, (2) unable to complete all evaluation tests, (3) with a limited life expectancy due to major illnesses, (4) unable to complete functional assessments within a reasonable time, and (5) current residents in long-term care facilities. Overall, 1,839 subjects participated in the study. The whole study and the consent procedure had been approved by the Institutional Review Board of Taipei Veterans General Hospital and National Yang Ming University.

Demography and functional assessments

A questionnaire consisting of demographic information, socioeconomic condition, medical history and quality of life was performed for the subjects by research nurses. The burden of multimorbidity was evaluated by using Charlson's Comorbidity Index (13). Tobacco use was categorized as follows: non-smoker, ex-smoker (quit in past 6 months) and current smoker. Alcohol drinking status was categorized as drinkers and non-drinkers. A comprehensive functional assessment was performed for all participants, including the Functional Autonomy Measurement System for physical function test (14), the Center for Epidemiologic Studies Depression Scale (CES-D) for measuring the mood status (15), the Mini-Nutrition Assessment (MNA) for nutritional status measurement (16), and the Mini-Mental State Examination (MMSE) for cognitive function measurement (17).

Quality of life measurement

In this study, quality of life was measured by the Short Form-12 (SF-12) for quality of life, which consisted of physical component summary (PCS) and mental component summary (MCS) (18). Higher score in PCS and MCS was considered having higher quality of life. In this study, subjects with the higher than the mean of total score of PCS and MCS were categorized as having good quality of life.

Muscle strength and physical performance

For all participants, handgrip strength was measured using digital dynamometers (Smedlay's Dynamo Meter; TTM, Tokyo, Japan), with participants standing in an upright position with both arms down on their sides. The best result for three tests of the dominant hand was used for further analysis (19). Moreover, participants performed a timed 6-meter walk with static start without deceleration for each participant to evaluate their physical performance (20).

Definition of frailty

In this study, frailty was defined by using Fried's criteria, including exhaustion, weakness, slowness, physical inactivity and weight loss (1). Exhaustion was defined using the 2 statements by the CES-D. Weakness was defined by low handgrip strength, and slowness was defined by slow gait speed. Physical inactivity was evaluated by using Taiwanese version of International Physical Activity Questionnaire (IPAQ) (21). The cutoff for weakness, slowness and physical inactivity was determined by the gender-specific lowest quintile of the study subjects of the corresponding tests. Weight loss was defined as having involuntary weight loss of >5% in the past year or 3kgs within past 3 months. Frailty status (robust, pre-frail and frail) was determined based on the Fried's criteria.

Statistical analysis

In this study, continuous variables were expressed as the mean ± standard deviation, and the categorical data was expressed by percentages. Comparisons of continuous data were done by Student's t test and comparisons of categorical data were done by Chi square test when appropriate. Comparisons between groups of different frailty statuses were performed by using one-way ANOVA. To determine the independent associative factors for frailty, logistic regression model was used by inputting variables with P<0.10 in the univariate analysis. Five items of frailty definition were not entered for regression model to avoid over-adjustment. All statistical analysis was performed by the commercial software (SPSS 18.0, SPSS Inc, Chicago, IL, USA). For all tests, the two-tailed P value<0.05 was considered statistical significant.

RESULTS

Demography

Overall, 1839 subjects (mean age: 63.9±9.3 years, 47.5% males) participated in this study. Table 1 summarized the demographic characteristics of all study subjects and the comparisons between men and women in this study. In this study, men were older than women (65.1±9.7 vs 62.9±8.7 years, P<0.001) and having more education years (7.1±5.0 vs 5.4±4.8 years, P<0.001). Besides, men were more likely to smoke and to carry current habit of alcohol consumption than women. In the comparisons of multimorbidity, men were similar to women except that women had a higher percentage of hyperlipidemia. Despite men were having faster gait speed (1.6±0.5 vs 1.4±0.4 m/s, P<0.001) and handgrip strength (35.1±8.3 vs 21.8±5.4 kg, P<0.001) than women, the frailty status of men were similar to women. In functional assessment, women were poorer in nutritional status (26.9±1.9 vs 27.4±1.7 in MNA, P<0.001), depressive symptoms (2.8±5.2 vs 2.0±3.7 in CES-D, P<0.001) and cognitive status (25.1±4.4 vs 26.2±3.5, P<0.001) than men. In the comparisons of quality of life, women were poorer in both PCS (49.5±5.7 vs 50.8±5.6, P<0.001) and in MCS (53.6±5.5 vs 54.2±4.4, P<0.001) than men.

Epidemiology of frailty

In this study, the prevalence of frailty was 6.8%, pre-frailty was 40.5% and 53.7% of all subjects were robust. The prevalence of frailty status between men and women was similar. Table 2 summarized the comparisons between subjects with different frailty status, which showed that age significantly increased when the subjects became frailer. Similar trends were identified in education year, alcohol drinking habit, hypertension, diabetes mellitus, hyperlipidemia, CCI, walking speed, handgrip strength, score of SMAF, CES-D, MNA, MMSE, PCS and MCS (P all< 0.05).

Associative factors for frailty

Table 3 summarized independent associated factors for frailty in this study. Older age, poorer physical function, poorer cognitive function, poorer nutritional status, more depressive symptoms, higher CCI and poorer quality of life were all independent associative factors for frailty. Education year, alcohol drinking habit and multimorbidity were not statistically significantly associated with frailty in the regression model.

DISCUSSION

In this study, the prevalence of frailty was somewhat lower than that in the Cardiovascular Health Study, which may be related to the inclusion and exclusion criteria. Independent associative factors for frailty in this study included older age, poorer physical function, poorer cognitive function, poorer nutritional status, more depressive symptoms, more complex multimorbidity, and poorer quality of life. From results of this study, frailty was not merely a geriatric syndrome, but frailty per se was the combination of multiple geriatric syndromes. Therefore, frailty may pose a very high risk of health for older people, even among otherwise healthy community-dwelling middle-aged and older people.

A number of frailty intervention programs have been developed with inconsistent results. The mainstream of frailty intervention programs was exercises and nutrition, either alone or in combinations (22). Different combinations of exercise programs have been reported and the combined aerobic and resistance exercise was considered the most effective approach (23). However, not every intervention program was effective and the newly developed programs were through multifactorial intervention, which was compatible to our study results. Associations between frailty, depression and cognitive decline have been reported as before, but rarely did the frailty intervention programs include these components. Our previous study in the post-acute settings showed that improvement of physical functional could also improve the depressive symptoms of older people without use of antidepressants (24).

From this study, we may consider frailty was not just a geriatric syndrome like others but a complex geriatric syndrome that was of much greater health risk for older people. The associated conditions of frailty may lessen the benefits of frailty intervention programs if these conditions were not taken as a whole. To apply the concepts of comprehensive geriatric assessment (CGA) may play an active role in frailty intervention programs (25). Patients in the post-acute care settings may be the best scenario to demonstrate the potential benefits because these patients were frail and free from acute illnesses. It has been shown that CGA-based inter-

vention successfully promoted physical functional recovery for post-acute care patients and the improvements were shown in depressive moods, cognitive function, as well as nutritional status (26). Moreover, these improvements significantly reduced 1-year mortality following post-acute care services (27). Although the subjects in the communities were not as frail as patients in the post-acute care settings, they eventually shared similar challenges and deserve a comprehensive approach. A recent study demonstrated the success of an integrated intervention in the reversal of frailty (28).

Despite all the efforts went into this study, there were still some limitations. First, the cross-sectional study design limited the possibilities to explore how frailty interacts with other functional deficits in the long term. However, ILAS per se was a longitudinal study design, we would be able to evaluate the interaction between frailty and other functional deficits in the future. Second, this is an observational study that limited the possibilities to know how other functional deficits improved when frailty was improved. Third, results of this study may underestimate the complex care needs for frailty since the study subjects were considered healthier than the general population. In conclusion, frailty was not merely a geriatric syndrome, but the combination of multiple geriatric syndromes. Early identification of other accompanying functional care needs of frailty was of great importance to design a comprehensive intervention program. Further study is needed to evaluate the clinical benefits of integrated health promotion activities in the communities to reverse frailty and associated functional care needs.

REFERENCES

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-156
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
3. Lin CC, Li CI, Meng NH, Lin WY, Liu CS, Lin CH, et al. Frailty and its associated factors in an elderly Taiwanese metropolitan population. J Am Geriatr Soc 2013;61:292-4.
4. Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr 2010;50 Suppl 1:S43-7.
5. Wilhelm-Leen ER, Hall YN, K Tamura M, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. Am J Med 2009;122:664-71
6. Krumholz HM, Chen J, Chen YT, Wang Y, Radford MJ. Predicting one-year mortality among elderly survivors of hospitalization for an acute myocardial infarction: results from the Cooperative Cardiovascular Project. J Am Coll Cardiol 2001;38:453-9
7. Lichtman JH, Krumholz HM, Wang Y, Radford MJ, Brass LM. Risk and predictors of stroke after myocardial infarction among the elderly: results from the Cooperative Cardiovascular Project. Circulation 2002;105:1082-7
8. Singh M, Rihal CS, Lenno RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside estimation of risk from percutaneous coronary intervention: the new mayo clinic risk scores. Mayo Clin Proc 2007;82:701-8
9. Lee WJ, Liu LK, Peng LN, Lin MH, Chen LK; ILAS Research Group. Comparisons of sarcopenia defined by IWGS and EWGSOP criteria among older people: Results from the I-Lan Longitudinal Aging Study. J Am Med Dir Assoc 2013;14:528.e1-7
10. Hwang AC, Liu LK, Lee WJ, Chen LY, Peng LN, Lin MH, Chen LK. Association of frailty and cardiometabolic risk among community-dwelling middle-aged and elderly people: Results from I-Lan Longitudinal Aging Study. Rejuvenation Res 2015 (in press)
11. Wu YH, Liu LK, Chen WT, Lee WJ, Peng LN, Wang PN, Chen LK. Cognitive function in individuals with physical frailty but without dementia or cognitive complaints: Results from I-Lan Longitudinal Aging Study. J Am Med Dir Assoc 2015 Aug 25. Pii: S1525-8610(15)0049292. Doi: 10.1016/j.jamda.2015.07.013 Epub ahead of print
12. Liu LK, Lee WJ, Chen LY, Hwang AC, Lin MH, Peng LN, Chen LK Association between frailty, osteoporosis, falls and hip fractures among community-dwelling people aged 50 years and older in Taiwan: Results from I-Lan Longitudinal Aging Study. Plos One 2015;10:e0136968
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-83.
14. Hebert R, Carrier R, Bilodeau A. The Functional Autonomy Measurement System (SMAF): description and validation of an instrument for the measurement of handicaps. Age Ageing 1988;17: 293-302.
15. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1: 385–401
16. Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature--What does it tell us? J Nutr Health Aging 2006;10: 466-485
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189-198.
18. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1) Lincoln, RI: QualityMetric Incorporated; 2002.
19. Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 2008;63:984-90.
20. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.
21. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exer 2003;35:1381-95.
22. Lee PH, Lee YS, Chan DC. Interventions targeting geriatric frailty: a systemic review. J Clin Gerontol Geriatr 2012;3:47-52
23. Yamada M, Arai H, Sonoda T, Aoyama T. Community-based exercise program is cost-effective by preventing care and disability in Japanese frail older adults. J Am Med Dir Assoc 2012;13:507-11

24. Liu ME, Chou MY, Liang CK, Ho CA, Lin YT, Lo YK, Peng LN, Chen LK. No adverse impact of depressive symptoms on the effectiveness of postacute are service: a multicenter male-predominant prospective cohort study. J Chin Med Assoc 2014;77:38-43
25. Nykanen I, Rissanen TH, Sulkava R, Hartikainen S. Effects of individual dietary counseling as part of a comprehensive geriatric assessment (CGA) on frailty status: a population-based intervention study. J Clin Gerontol Geriatr 2012;3:89-93.
26. Lee WJ, Peng LN, Cheng YY, Liu CY, Chen LK, Yu HC. Effectiveness of short-term interdisciplinary intervention on postacute patients in Taiwan. J Am Med Dir Assoc 2011;12:29-32
27. Chen LK, Chen YM, Hwang SJ, Peng LN, Lin MH, Lee WJ, Lee CH; Longitudinal Older Veterans Study Group. Effectiveness of community hospital-based post-acute care on functional recovery and 12-month mortality in older patients: a prospective cohort study. Ann Med 2010;42:630-6.
28. Ng TP, Feng L, Nyunt MS, Niti M, Tan BY, Chan G, Khoo SA, Chan SM, Yap P, Yap KB. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015 Jul 6. pii: S0002-9343(15)00567-7. Doi: 10.1016/j.amjmed. 2015.06.017 [Epub ahead of print]

Table 1.

Baseline demographic characteristics and comparisons between men and women of I-Lan Longitudinal Aging Study

	Total (N=1839)	Men (N=873)	Women (N=966)	P value
Age (years)	63.9±9.3	65.1±9.7	62.9±8.7	<0.001
Body mass index (Kg/m2)	24.9±3.6	24.9±3.3	24.8±3.8	0.433
Education year	6.2±5.0	7.1±5.0	5.4±4.8	<0.001
Cigarette Smoking (%)				
Never smoker	69.5	40.2	96.0	<0.001
Ex-smoker	12.2	24.7	0.9	
Current smoker	18.3	35.1	3.1	
Current alcohol drinking (%)	33.0	49.8	17.8	<0.001
Multimorbidity				
Hypertension (%)	41.4	42.2	40.8	0.570
Diabetes mellitus (%)	16.8	16.4	17.2	0.662
Coronary heart disease (%)	5.2	4.4	5.9	0.141
Hyperlipidemia (%)	7.8	6.1	9.3	0.011
CCI	1.0±1.3	1.0±1.2	1.0±1.3	0.959
Physical performance				
Walking speed (m/s)	1.5±0.5	1.6±0.5	1.4±0.4	<0.001
Handgrip strength (Kg)	28.1±9.6	35.1±8.3	21.8±5.4	<0.001
Frailty status (%)				
Robust	52.7	50.9	54.5	0.289
Pre-frail	40.5	42.3	38.8	
Frail	6.8	6.9	6.7	
Functional assessment				
SMAF	-0.18±1.63	-0.20±1.79	-0.16±1.47	0.575
CES-D	2.4±4.6	2.0±3.7	2.8±5.2	<0.001
Mini-Nutritional Assessment	27.2±1.8	27.4±1.7	26.9±1.9	<0.001
MMSE	25.6±4.0	26.2±3.5	25.1±4.4	<0.001
Quality of life				
PCS	50.1±5.7	50.8±5.6	49.5±5.7	<0.001
MCS	53.9±5.0	54.2±4.4	53.6±5.5	0.007

CCI = Charlson's Comorbidity Index; SMAF = the Functional Autonomy Measurement System; CES-D = the Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; PCS = Physical Component Summary; MCS = Mental Component Summary

Table 2.
Comparisons of clinical characteristics among subjects with different frailty status

	Total (N=1839)	Robust (N=970, 52.7%)	Pre-frail (N=744, 40.5%)	Frail (N=125, 6.8%)	P value
Age (year)	63.9±9.3	60.7±7.5	66.3±9.3	74.6±9.2	<0.001
Sex (M%)	47.5	45.8	49.6	48.0	0.289
BMI (Kg/m²)	24.9±3.6	24.8±3.5	24.9±3.6	24.7±4.0	0.655
Education year	6.2±5.0	7.5±4.8	5.2±4.8	2.6±3.5	<0.001
Cigarette smoking (%)					0.359
Never smoker	67.4	69.3	65.4	60.9	
Ex-smoker	19.7	18.5	21.4	20.3	
Current smoker	12.9	12.2	13.2	18.8	
Current alcohol drinking (%)	35.0	38.7	32.1	15.4	<0.001
Multimorbidity					
Hypertension (%)	41.4	34.6	47.6	57.6	<0.001
Diabetes mellitus (%)	16.8	13.4	18.7	32.0	<0.001
Coronary heart disease (%)	5.2	4.4	5.8	7.2	0.260
Hyperlipidemia (%)	7.8	6.2	9.4	10.4	0.025
CCI	1.0±1.3	0.7±1.1	1.2±1.3	2.1±1.4	<0.001
Physical performance					
Walking speed (m/s)	1.5±0.5	1.7±0.4	1.4±0.4	0.9±0.3	<0.001
Handgrip strength (Kg)	28.1±9.6	30.9±9.0	26.0±9.2	18.8±7.1	<0.001
Functional assessment					
SMAF	-0.2±1.6	-0.0±0.2	-0.1±0.5	-2.0±5.8	<0.001
CES-D	2.4±4.6	1.5±2.6	2.7±4.4	8.2±10.0	<0.001
Mini-Nutritional Assessment	27.2±1.8	27.5±1.6	27.1±1.8	25.3±2.6	<0.001
MMSE	25.6±4.0	26.8±3.0	25.0±4.0	20.8±5.8	<0.001
Quality of life					
PCS	50.1±5.7	50.9±4.5	50.0±5.8	44.1±9.1	<0.001
MCS	53.9±5.0	54.6±3.6	53.7±5.0	49.1±9.9	<0.001

CCI = Charlson's Comorbidity Index; SMAF = the Functional Autonomy Measurement System; CES-D = the Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; PCS = Physical Component Summary; MCS = Mental Component Summary

Table 3. Independent associative factors for frailty

	Odds ratio	95% Confidence Interval	P value
Age (years)	1.105	1.069-1.143	<0.001
Education year	1.026	0.958-1.100	0.460
Current alcohol drinking (%)	0.934	0.733-1.189	0.578
Multimorbidity			
Hypertension (%)	0.905	0.552-1.484	0.693
Diabetes mellitus (%)	1.703	0.952-3.046	0.073
Hyperlipidemia	0.877	0.413-1.861	0.877
CCI	0.978	0.802-1.193	0.825
Functional assessment			
SMAF	0.761	0.635-0.913	0.003
CES-D	1.096	1.059-1.135	<0.001
Mini-Nutritional Assessment	0.799	0.713-0.895	<0.001
MMSE	0.883	0.832-0.937	<0.001
Poor quality of life	2.328	1.408-3.939	0.001

CCI = Charlson's Comorbidity Index; SMAF = the Functional Autonomy Measurement System; CES-D = the Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; PCS = Physical Component Summary; MCS = Mental Component Summary

HOW STUDIES SHOW THE BENEFITS OF A MULTIDISCIPLINARY APPROACH OF CARE APPLIED TO FRAIL OLD ADULTS

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Demographic trends show absolute and relative increases of older persons in our societies. Such scenario endangers the sustainability of our healthcare systems. In fact, it is well established that age-related conditions and, in particular, disabilities are particularly burdening for the person but also for the public health system. For this reason, in this last decade, a relevant body of scientific literature has focused the need of implementing preventive actions against disability in the elders.

The concept of "frailty syndrome" has been defined and increasingly studied. Frailty is defined as the extreme vulnerability of the organism to endogenous and exogenous stressors, exposing the individual at higher risk of negative health-related outcomes (1). Too many and too heterogeneous are today the older persons in our societies for describing them only according to a pure chronological criterion (i.e., number of years lived). Frailty may indeed represent a way for replacing the obsolete concept of "chronological age" with a more accurate and person-tailored parameter of "biological age" (2).

Although the theoretical concept of frailty is agreed, its practical translation still presents some limitations due to the existence of multiple (and largely non-overlapping) operational definitions. It is noteworthy, for example, how some authors have tended to consider frailty as a pre-disability phenomenon, whereas others have promoted the detection of the syndrome even in patients with severe disability conditions. It is likely that such heterogeneous translation of frailty is due to the need of measuring the "biological age" of the elder in the presence of different clinical substrata and/or settings. In other words, a gradient of risk for negative events can always be generated by assessment instruments. Moreover, it should also be acknowledged that frailty is not (yet) a specific disease, but a syndrome requiring a multidomain and multidisciplinary approach. That is, after frailty is detected (whatever is the adopted instrument to measure it), a comprehensive geriatric assessment should follow.

Scientific literature about the importance of conducting a comprehensive geriatric assessment in vulnerable elders is vast. The multidimensional and multidisciplinary approach to geriatric syndrome has documented beneficial effects when applied in multiple clinical settings and conditions. Several trials have demonstrated that person-tailored interventions based on results of a comprehensive geriatric assessment are able to prevent major negative health-related outcomes in the older persons living in the community (3), home care (4), and hospital (5). It could be too long and not within the scopes of the present summary to go in the details of the available evidence. Nevertheless, it might be sufficient to simply cite the most relevant meta-analysis conducted (already) in 1993 by Stuck and colleagues (6). In this study, Authors examined results of 28 randomized controlled trials (more than 9,000 participants) testing the effects of comprehensive geriatric assessment-based in-

terventions versus controls. Findings clearly demonstrated that comprehensive geriatric assessment programs linking geriatric evaluation with strong long-term management are effective for improving survival and function in older persons.

Probably, orthopaedic surgery represents the first discipline which has successfully implemented a close collaboration with geriatricians for the assessment and management of older persons (i.e., hip fracture patients). For example, Antonelli Incalzi and colleagues (7) demonstrated that assigning a geriatrician to assist with the medical care of (hip fracture) older patients in orthopaedic wards was associated with increased operation rate, decreased mortality, and shortened length of stay. More recently, oncologists (8) and cardio-surgeons (9) have started more frequently looking for the comprehensive geriatric assessment as the mean for conducting a higher number of their old patients to their specific interventions. The search of such collaborations is easily explained by the common presence of "geriatric" patients (with all their complexities and peculiarities) in almost every hospital ward and service. In fact, several medical specialities are today facing the effects of the global aging on their patients' characteristics. Geriatric patients require adaptations of care, personalization of interventions, and modifications of standard protocols that can be reached only through the implementation of the comprehensive geriatric assessment.

The positive results obtained in specific clinical settings have recently fostered geriatric research at trying to extend the use of the multidimensional and multidisciplinary approach in primary care and as part of preventive strategies dedicated to community-dwelling older persons. For example, since October 2011, the Gérontopôle of the Centre Hospitalier Universitaire de Toulouse has been conducting an innovative day hospital unit exclusively devoted to frailty in the community (the so-called Frailty Clinic) (10, 11). In collaboration with the general practitioners of the area, the Gérontopôle has been receiving non-disabled frail elders for assessing their overall health status through a comprehensive geriatric assessment, identifying the causes of their frailty condition using a multidisciplinary approach, and then proposing a person-tailored plan of preventive intervention. It is noteworthy that almost half of the frail older persons assessed at our Frailty Clinic were found to have at least one undiagnosed condition. This means that the presence of the general practitioner (who refers the individual to our service) may not be sufficient to comprehensively assess the older person's clinical complexity. A coordinated and multidisciplinary evaluation is indeed required to identify the inner causes of the frailty condition. The detection of a previously unknown clinical condition will surely conduct to the need of a specific treatment. On the other hand, the early intervention may signify 1) preventing more serious consequences in the future, and 2) potentially solve (part of) the individual's complaints. This infrastructure does not only play a major role at detecting early signs of diseases (thus anticipating the treatment/intervention to the preliminary phases of the pathological process), but it is also important to diffuse knowledge and awareness about the importance of preventing disability at older age.

In conclusion, the frailty condition (and related literature) should always be considered together with the large amount of evidence supporting the adoption of the comprehensive geriatric assessment in older persons. More studies are required to demonstrate that such multidimensional and multidisciplinary approach is beneficial also when applied among community-dwelling older persons in the prevention of disability. Such evaluation should be particularly focused at limiting the risk of "overdiagnosis" in order to assure an ethical and cost-effective conduction of the intervention.

REFERENCES

1. Morley JE, Vellas B, Abellan van Kan G et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392-397.
2. Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing 2014;43:10-12.
3. Stuck AE, Minder CE, Peter-Wüest I et al. A randomized trial of in-home visits for disability prevention in community-dwelling older people at low and high risk for nursing home admission. Arch Intern Med 2000;160:977-986.
4. Landi F, Onder G, Tua E et al. Impact of a new assessment system, the MDS-HC, on function and hospitalization of homebound older people: a controlled clinical trial. J Am Geriatr Soc 2001;49:1288-1293.
5. Baztán JJ, Suárez-García FM, López-Arrieta J, Rodríguez-Mañas L, Rodríguez-Artalejo F. Effectiveness of acute geriatric units on functional decline, living at home, and case fatality among older patients admitted to hospital for acute medical disorders: meta-analysis. BMJ 2009;338:b50.
6. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 1993;342:1032-1036.
7. Antonelli Incalzi R, Gemma A, Capparella O, Bernabei R, Sanguinetti C, Carbonin PU. Continuous geriatric care in orthopedic wards: a valuable alternative to orthogeriatric units. Aging (Milano) 1993;5:207-216.

8. Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. Surgical Oncology 2010;19:117-123.
9. Lilamand M, Dumonteil N, Nourhashemi F et al. Gait speed and comprehensive geriatric assessment: Two keys to improve the management of older persons with aortic stenosis. Int J Cardiol 2014
10. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B. The integration of frailty into clinical practice: preliminary results from the gérontopôle. J Nutr Health Aging 2012;16:714-720.
11. Tavassoli N, Guyonnet S, Abellan Van Kan G et al. Description of 1,108 older patients referred by their physician to the "Geriatric Frailty Clinic (G.F.C) for assessment of frailty and prevention of disability" at the Gérontopôle. J Nutr Health Aging 2014;18:457-464.

FRAILTY IN GENERAL PRACTICE

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Key words: Prevention, aging, elderly, assessment, intervention.

CONTEXT

Western countries are currently undergoing a period of demographic and epidemiologic transition. The prevalence of chronic comorbidities and dependency rises with life expectancy (1). It is possible to identify persons at increased risk of fall, hospitalization, dependency, or death (2). The "frailty" of these persons reflects their physiological age. Frailty prevention concerns all adults and mainly relies on nutritional education, including physical activity and diet (3).

DEFINITIONS

The Société Française de Gériatrie et Gérontologie defines the frailty of the elderly as a clinical syndrome corresponding to a reduction of a person's stress adaptation capacities, modulated by physical, psychological and social factors. Its evaluation must involve clinical criteria predictive of the risk of functional decline and adverse outcomes (2).
The Fried model, developed in the USA in the early 2000s, is considered to be a reference model for frailty (4). It is based on the assessment of five physiological criteria: unintentional weight loss, slow walking speed, feelings of exhaustion, low physical activity and self-perceived muscle weakness. The presence of three criteria is enough to define the frailty status, with the presence of one or two defining pre-frailty. The frailty clinical criteria are dynamic and potentially reversible, particularly through pluriprofessional intervention. While the Fried model is simple and robust, it does not include any cognitive, psychological or social criteria (5), dimensions which may alter the expression of the somatic factors.

CONCEPT

In clinical practice, frailty can be considered a risk factor for health status deterioration, beyond the effect of chronological age. It is actually more a risk marker than a causal factor for health status deterioration, as can be a disease (6). Like metabolic syndrome, the frailty syndrome is not recognized in the International Classification of Primary Care (ICPC-2, WONCA) or in the International Classification of Diseases (ICD-10, WHO).

Frailty better predicts mortality risk than chronological age. It also predicts the risk of complications arising from disease a little better than the diseases themselves. A patient's polypathological state incompletely covers the frailty status (7). The ability to recognize the syndrome and to intervene appropriately represents an issue for general practitioners/family physicians (8), as frailty situations are at the heart of general practice (9).

FREQUENCY

Frailty prevalence, measured according to the Fried model, has been estimated at 15% of the French population over 65 years of age, and the prevalence of pre-frailty at 44% (10). Frailty prevalence increases with age, is higher in women than in men, and decreases with education level. Since consultations of patients over 65 years of age account for 28% of consultations, frail patients may represent around 4% of those attending general practice (11).

EVALUATION

The aims of frailty evaluation are to improve the quality of life and limit the management costs (12). It can also aid to orientate the management of elderly patients, in particular when facing high risk interventions (cancer treatment, surgery, etc.) or when the ranking of priorities is required (e.g. in case of multiple chronic conditions).

Initial and follow-up frailty evaluation can benefit patients living at home or retirement home. It can be integrated within the framework of mass screening or of an early diagnosis. The latter can be initiated based on warning signs, such as non-specific signs (fatigue, unexplained weight loss, repeated infections), falls, acute delirium or fluctuating functional disabilities. Frailty evaluation can be complemented by a simplified comprehensive geriatric assessment. Screening for frailty raises ethical issues, because it is applied to asymptomatic patients and could generate constraints and hazards (6). Pre-frailty detection looks useless in clinical practice, owing to its very high frequency in the population and the lack of specific intervention.

TOOLS

Various frailty indexes have been developed, which include up to 70 variables. Several have a good statistical validity, in particular an instrument derived from the Fried criteria to distinguish between frail, pre-frail and non-frail patients (13), and the "frailty index" to measure the frailty level (14). These available tools show acceptable negative predictive values but low positive predictive values. The "frailty index" can eventually be used within a two-step strategy. In general practice, any test may be administered across several consultations.

Frailty evaluation by general practitioners implies the availability of a tool adapted to their practice, which is easy and quick to use. The clinical utility and user-friendliness of the available tools in primary care remain to be demonstrated. To comply with the biopsychosocial approach, which is characteristic of general practice (15), the criteria should encompass the psychological and social dimensions, beyond the mere biological dimension highlighted in the Fried's model. They should identify elements on which the general practitioner can design a dashboard and a care plan.

INTERVENTIONS

A program of home visits to elderly persons, including clinical examination, may reduce functional disabilities in moderately aged individuals. The global evaluation of elderly patients in the ambulatory setting improves the quality of care and, likely, patients' quality of life and autonomy. Some multidimentional interventions can decrease the risk of referring elderly patients to retirement homes or hospitals, especially for those under 65 years of age.

The management of frail elderly patients consists of initially treating the problems that may favor their frailty, going on to correct reversible frailty elements (16). In moderately frail patients, prolonged and intensive programs of physical re-education can prevent dependency. On the other hand, evidence is still lacking regarding the effectiveness of interventions targeting diet (17).

Practically, the management of frail elderly patients usually includes care and support, within an approach that can be coordinated by the general practitioner, in collaboration with other primary care professionals. Effective management, particularly for patients living at home, implies the availability of the different professionals involved (physiotherapist, occupational therapist, ophthalmologist, dietician, etc.), which may vary with the patient's location.

ON-GOING INVESTIGATIONS

An interesting investigation involving French general practitioners is currently being conducted by the Gérontopole in Toulouse (18). It is based on patients' screening using a simple tool based on the Fried criteria and including the notion of patient isolation, a cognitive dimension, and the physician's clinical sense. Patients identified as frail are then referred to a hospital platform for multidisciplinary evaluation.

At a national level, a project concerning the management of elderly persons at risk of losing their autonomy (PAERPA) is being conducted in eight French regions, with the aim of optimizing elderly care pathways involving professionals from the health and social care fields. This project consists of "opportunistically" detecting elderly persons at risk of dependency (frail or having a chronic disease), performing a standardized geriatric assessment and then providing a personalized care plan.

PENDING ISSUES

Before any generalization, it is advisable to assess the reversibility of the different frailty elements and the risk- benefit and cost-benefit ratios of various evaluation and intervention strategies. The main points to compare are targets (mass screening vs. early diagnosis), evaluation features (tools, sequences), evaluation operator (general practitioners, other primary care professionals, geriatricians), intervention features (physical, psychological, social, etc.). These strategies also need to be compared to traditional diagnostic and therapeutic management approaches, which target symptoms and diseases. Ideally, current and future research should enable the development of a decision algorithm that will support pluriprofessional primary care. It is essential

that the models investigated take into account patients' adherence and preferences, because their priorities can differ from those of the health professionals (19).

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REFERENCES

1. Meslé F. Progrès récents de l'espérance de vie en France: Les hommes comblent une partie de leur retard. Population 2006;61:437–62.
2. Rolland Y, Benetos A, Gentric A, et al. La fragilité de la personne âgée : un consensus bref de la Société française de gériatrie et gérontologie. Geriatr Psychol Neuropsychiatr Vieil 2011;9:387–90.
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people Lancet 2013;381:752–62.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:146–56.
5. Fortun MP, Krolak-Salmon P, Bonnefoy M. Analyse descriptive et comparative des différents modèles de fragilité. Cah Année Gérontol 2008;22:12–27.
6. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. J Gerontol A Biol Sci Med Sci 2007;62:731–7.
7. Boeckxstaens P, Vaes B, Legrand D, Dalleur O, De Sutter A, Degryse J-M. The relationship of multimorbidity with disability and frailty in the oldest patients: A cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. Eur J Gen Pract 2015;21:39-44.
8. Rougé Bugat M-E, Cestac P, Oustric S, Vellas B, Nourhashemi F. Detecting frailty in primary care: a major challenge for primary care physicians. J Am Med Dir Assoc 2012;13:669–72.
9. Mission Evaluation des compétences professionnelles des métiers de la santé du Ministère de la santé et des sports, Collège national des généralistes enseignants. Référentiel métier et compétences des médecins généralistes, 2009.
10. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009;64:675–81.
11. Letrilliart L, Supper I, Schuers M, et al. ECOGEN: étude des Eléments de la COnsultation en médecine GENérale. exercer 2014;114:148–57.
12. Lacas A, Rockwood K. Frailty in primary care: a review of its conceptualization and implications for practice. BMC Med 2012;10:4.
13. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC Geriatr 2010;10:57.
14. Drubbel I, Numans ME, Kranenburg G, Bleijenberg N, de Wit NJ, Schuurmans MJ. Screening for frailty in primary care: a systematic review of the psychometric properties of the frailty index in community-dwelling older people. BMC Geriatr 2014;14:27.
15. Wonca Europe. The European definition of general practice/family medicine. 2011 edition. http://www.woncaeurope.org/sites/default/files/documents/Definition%203rd%20ed%202011%20with%20revised%20 wonca%20tree.pdf.
16. De Lepeleire J, Iliffe S, Mann E, Degryse JM. Frailty: an emerging concept for general practice. Br J Gen Pract 2009;59:e177–82.
17. Daniels R, van Rossum E, de Witte L, Kempen GIJM, van den Heuvel W. Interventions to prevent disability in frail community-dwelling elderly: a systematic review. BMC Health Serv Res 2008;8:278.
18. Oustric S, Renard V. Cibler et dépister la fragilité en médecine générale : c'est maintenant... (Edit.). Cah Année Gérontol 2012;1–2.
19. Junius-Walker U, Wrede J, Schleef T, et al. What is important, what needs treating? How GPs perceive older patients' multiple health problems: a mixed method research study. BMC Res Notes 2012;5:443.

FRAILTY AND DRUG USE

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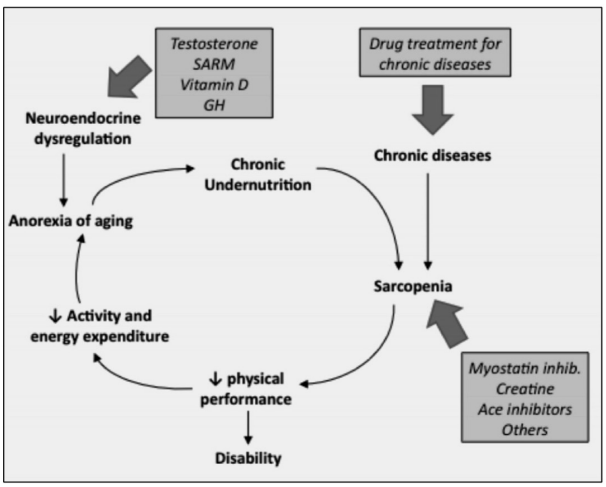
Key words: Prevention, multimorbidity, polypharmacy, elderly.

Older adults often have co-occurring multiple chronic and acute diseases, which progressively and steadily increase in prevalence with age (1, 2). The treatment of these diseases usually requires multiple drugs (polypharmacy); it has been estimated that more than 50% of persons aged 65 years or older receive five or more drugs concomitantly (3, 4). Drug use in the older population might raise several concerns related to an increased risk of drug-drug and drug-disease interactions, poor adherence to treatment, and increased risk of adverse drug reactions (5-7). In this chapter we will discuss what role drugs and polypharmacy play in the development, management and treatment of frailty.



Frailty is a complex condition and there may be multiple factors associated with its onset and development. The Figure illustrates potential targets for drug treatment of frailty: chronic somatic conditions, sarcopenia, and hormonal deficits. Hormonal deficits in testosterone, Vitamin D, or growth hormone may lead to neuroendocrine dysregulation, contributing to decreased muscle mass and 'anorexia of aging' (8). Chronic conditions can lead to frailty via numerous pathways, including the onset of sarcopenia, or by causing disability or reduced physical functioning. Sarcopenia itself is associated with reduced physical functioning and the onset of disability (9-12). All three pathways, contribute both separately and together to an overall syndrome of frailty in the elderly. Therefore, the role of drugs on the development, management and treatment of frailty should take all three factors into account.

DRUGS TO TREAT CHRONIC CONDITIONS

Frailty is associated with numerous chronic somatic conditions, including cerebrovascular disease, diabetes, coronary disease, and hypertension, among others. Given the association between chronic conditions and frailty, one angle to take when considering the treatment of frailty is whether drugs used to treat the chronic conditions associated with frailty may in turn lead to improvements in frailty and related functional outcomes. Currently, data concerning this issue are poor. One reason for this is that large drug trials

are often not designed to assess the impact of the respective treatment on outcomes other than the primary disease. Thus, they may not adequately assess outcomes such as frailty or improvements in functional outcomes. For example, Di Bari et al (13) looked at data from a randomized control trial of antihypertensive medication in older adults, where the primary and secondary endpoints were clinical outcomes such as stroke, myocardial infarction, coronary disease, cardiovascular morbidity, and mortality. Using this data they subsequently examined whether the treatment also had an effect on frailty-related outcomes such as functional factors. Their study identified a number of limitations in examining these endpoints in such as study. In particular, there was a differential loss of data for participants in the treatment and placebo group, which led to a bias in the results concerning the functional and cognitive outcomes. Older and more impaired elderly were more likely to be lost to follow-up, and this selective drop out made it difficult to draw any firm conclusions about the effect of the treatment on these frailty-related outcomes. This raises the issue that there is a great need for well-conducted randomized control trials that examine 'real world' outcomes of drug treatments for chronic diseases, including frailty-related factors such as improvements in physical functioning, hospitalization, dependency in activities of daily living, among others.

DRUGS TO TREAT SARCOPENIA

Sarcopenia, a clinical syndrome characterized by loss of muscle mass accompanied by functional deterioration such as walking speed, walking distance, or grip strength (14), has been proposed as a biological substrate of physical frailty (9). Sarcopenia predicts frailty, as well as other poor outcomes including hip fracture, disability, and mortality (10-12). Evidence suggests that treating sarcopenia may lead to clinically beneficial outcomes in older person with frailty (15, 16).

There are numerous potential causes and associated factors related to the development of sarcopenia, including genetic factors, vascular factors, mitochondrial defects, insulin resistance, poor blood flow, and decreasing levels of testosterone, vitamin D, and growth hormone among others (for a recent review see (17)). Consequently, given the range of factors involved in the pathophysiology of sarcopenia, there might be numerous approaches for treating the disorder, including non-pharmacological interventions such as resistance exercise (18), and pharmacological approaches such as Creatine Selective Androgen Receptor Modulators (SARMS) to increase muscle mass and physical functioning (19), myostatin antibodies to increase muscle volume, and angiotensin converting enzyme inhibitors to improve physical functioning (20, 21), among others. In addition to the current drug treatments, there is a wide range of pharmacological options that can potentially be considered for developing future treatments for sarcopenia, such as growth differentiation factor, myokines activators and inhibitors, nitric oxide, and biguanides, among others (17). Results of trials focused on the use of these drugs to specifically treat sarcopenia and prevent frailty have, so far, not providing any convincing evidence.

HORMONAL TREATMENTS

Testosterone has been shown to increase muscle strength and mass in older persons (22-24), as well as improving functional outcomes such as strength and walking distance in patients with frailty (25, 26), and decreasing hospitalization in frail older persons (27). Testosterone is currently considered to be the most effective and safest treatment for sarcopenia (17), although there are numerous potential side effects. Current trials are ongoing, with particular emphasis on comparing testosterone treatment with SARMs, which may potentially be safer. There is currently little evidence concerning the effect of SARMS on sarcopenia, as the only clinical trial on the subject was halted, but initial evidence from this study showed an improvement in functional abilities such as stair climbing and gait speed (19). Other SARMs trials on patients with other chronic diseases such as COPD, osteoporosis, chronic kidney disease, and cancer reported improvements in functional abilities such as stair climbing (28), and increased muscle mass (29-31). More studies on the effect of SARMs on clinical and functional outcomes in patients with sarcopenia are needed, as well as studies directly comparing the treatment effect of SARMs versus testosterone in patients with sarcopenia and frailty.

Vitamin D is an established treatment for sarcaponia (32); it increases muscle strength (33, 34) and has positive effects on frailty-related outcomes in older persons such as decreasing the incidence of falls (33), hip fractures (35), and mortality (36). Other hormonal treatments such as growth hormone are currently not considered as effective treatments for sarcopenia. Although growth hormone has been shown to increase muscle mass and mean body mass in older persons (37, 38) it does not appear to improve muscle strength, and is associated with numerous side effects (38-40).

DRUGS AS A CAUSE OF FRAILTY

In addition to the discussion of how to treat frailty, consideration also needs to be taken into the role that drugs may have on the development of frailty. Numerous specific medications have been shown to be associated with frailty and frailty-related factors. In particular, the use of anticholinergic drugs is associated with frailty and related factors such as falls, hip fractures, and reduced activities of

daily living functions (41-44). Inappropriate drug prescribing is also another pathway through which drugs might cause frailty. For example, improper use of diuretics in certain patients could inadvertently lead to increased frailty and frailty-related factors by causing dehydration (45-47). Another such example is the overuse and inappropriate use of proton pump inhibitors in the elderly, which can cause vitamin B12 deficiency, reduce calcium absorption, increase fracture risk, and are associated with increased mortality (48-50). Further, poor management of drug regimes can lead to frailty. For example, the overtreatment of diabetes in older persons is associated with frailty (51, 52), and diabetes treatment in frail older individuals needs to be carefully managed, especially in nursing home patients (52). Finally, polypharmacy is related to an increase in frailty in older adults (53-55). This relationship may be bidirectional. On one hand, an increase in the number of chronic conditions that are associated with frailty can increase polypharmacy. For example, diabetes is associated with frailty, as well as comorbidity and polypharmacy in geriatric patients (2, 51, 56, 57). On the other hand, there is also evidence to suggest that polypharmacy itself may be involved in the development of frailty (58-60). Polypharmacy was shown to be associated with more than a twofold increased incidence of developing frailty over two years in men (58). The authors suggested that the high-risk prescribing may have directly aggravated the clinical features of frailty. Thus, a reduction of polypharmacy is advised for both the prevention and management of frailty (61).

FRAILTY AS AN EFFECT MODIFIER

Finally, it is necessary to discuss how frailty could act as an effect modifier in the treatment of chronic diseases. The concept of "reverse epidemiology" has been demonstrated in conditions such as chronic heart failure and chronic kidney failure (62, 63), where certain risk factors, such as hypertension, lose their importance and may actually become protective factors. This theory could apply similarly to frailty. The pharmacological treatment of older adults might differ based on their frailty status and, in particular, the benefits of a given pharmacological treatment might be reduced in the presence of frailty. For example, although antihypertensive treatment in robust older persons with hypertension is beneficial, the association between hypertension and mortality in older persons is mediated by frailty factors such as slower walking speed (64). Treating hypertension in frail older persons might have no benefits and could lead to negative outcomes (65, 66). Similarly, the treatment of diabetes to achieve tight glycemic control might be unrewarding in frail people and the overtreatment of diabetes is associated with frailty (51, 52, 67). If future studies can further support the theory of reverse epidemiology in frailty, it might be questionable whether pharmacological treatment in frailty is appropriate, given that the use of many medications leads to negative side effects.

In conclusion, the role of drugs on the onset, development and management of frailty is complex, and current evidence is sparse. Specifically, more data are needed from randomized control trials examining 'real world' outcomes of drug treatments for chronic diseases, as well as evidence concerning the treatment of sarcopenia and effects on frailty and frailty- related outcomes. Current research supports the need for good drug management and reduction of polypharmacy to reduce frailty.

Conflict of Interest: None

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REFERENCES

1. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev. 2011;10:430-9.
2. Onder G, Palmer K, Navickas R, et al. Time to face the challenge of multimorbidity. A European perspective from the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). Eur J Intern Med. 2015;26:157-9.
3. Onder G, Bonassi S, Abbatecola AM, et al. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). J Gerontol A Biol Sci Med Sci. 2014;69:430-7.
4. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA. 2002;287:337-44.
5. Marengoni A, Pasina L, Concoreggi C, et al. Understanding adverse drug reactions in older adults through drug-drug interactions. Eur J Intern Med. 2014;25:843-6.
6. Dumbreck S, Flynn A, Nairn M, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ. 2015:350;h949.
7. Nobili A, Pasina L, Tettamanti M, et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J Clin Pharm Ther. 2009;34:377-86.
8. Visvanathan R. Anorexia of Aging. Clin Geriatr Med. 2015;31:417-27.
9. Landi F, Calvani R, Cesari M, et al. Sarcopenia as the Biological Substrate of Physical Frailty. Clin Geriatr Med. 2015;31:367-74.

10. Landi F, Cruz-Jentoft AJ, Liperoti R, et al. Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from iISIRENTE study. Age Ageing. 2013;42:203-9.
11. Oliveira A, Vaz C. The role of sarcopenia in the risk of osteoporotic hip fracture. Clin Rheumatol. 2015 Apr 26. [Epub ahead of print]
12. Hirani V, Blyth F, Naganathan V, et al. Sarcopenia Is Associated With Incident Disability, Institutionalization, and Mortality in Community- Dwelling Older Men: The Concord Health and Ageing in Men Project. J Am Med Dir Assoc. 2015;16:607-13.
13. Di Bari M, Pahor M, Franse LV, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol. 2001;153:72-8.
14. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
15. Rolland Y, Onder G, Morley JE, et al. Current and future pharmacologic treatment of sarcopenia. Clin Geriatr Med. 2011;27:423-47.
16. Sukuma K, Yamaguchi A. Molecular mechanisms in aging and current strategies to counteract sarcopenia. Curr Aging Sci. 2010;3:90-101.
17. Morley JE. Pharmacologic Options for the Treatment of Sarcopenia. Calcif Tissue Int. 2015 Jun 23. [Epub ahead of print]
18. Michel JP, Cruz-Jentoft AJ, Cederholm T. Frailty, Exercise and Nutrition. Clin Geriatr Med. 2015;31:375-87.
19. Papanicolaou DA, Ather SN, Zhu H, et al. A phase IIA randomized, placebocontrolled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013;17:533-43.
20. Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ. 2007;177:867-74.
21. Onder G, Penninx BW, Balkrishnan R, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet. 2002;359(9310):926-30.
22. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increses physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005;90:1502-10.
23. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: A 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82:1661-7.
24. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. J Gerontol A. 2003;58:618-25.
25. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;95:639-50.
26. Kenny AM, Kleppinger A, Annis K, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58:1134-43.
27. Chapman IM, Visvanathan R, Hammond AJ, et al. Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. Am J Clin Nutr. 2009;89:880-9.
28. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle. 2011;2:153-61.
29. Sharma S, Arneja A, McLean L, et al. Anabolic steroids in COPD: a review and preliminary results of a randomized trial. Chron Respir Dis. 2008;5:169-76.
30. Macdonald JH, Marcora SM, Jibani MM, Kumwenda MJ, Ahmed W, Lemmey AB. Nandrolone decanoate as anabolic therapy in chronic kidney disease: a randomized phase II dose-finding study. Nephron Clin Pract. 2007;106:125–35.
31. Frisoli A Jr, Chaves PH, Pinheiro MM, Vl Szejnfeld. The effect of nandrolone decanoate on bone mineral density, muscle mass, and hemoglobin levels in elderly women with osteoporosis: a double-blind, randomized, placebo-controlled clinical trial. J Gerontol A. 2005;60:648– 53.
32. Rizzoli R. Nutrition and Sarcopenia. J Clin Densitom. 2015 Jun 6. [Epub ahead of print]
33. Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96:2997-3006.
34. Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014;99:4336-45
35. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012;367:40-9.
36. Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab. 2012;97:2670-81.
37. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med. 1990;323:1-6.
38. Kim MJ, Morley JE. The hormonal fountains of youth: myth or reality? J Endocrinol Invest. 2005;28:5-14.
39. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-1 concentrations. Clin Endocrniol (Oxf). 1993;39:417-25.
40. Liu H, Bravata DM, Olkin I, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med. 2007;146:104-15
41. Moulis F, Moulis G, Balardy L, et al. Exposure to atropinic drugs and frailty status. J Am Med Dir Assoc. 2015:16:253-7.
42. Landi F, Dell'Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. J Am Med Dir Assoc. 2014;15:825-9.
43. Lowry E, Woodman RJ, Soiza RL, Mangoni AA. Associations between the anticholinergic risk scale score and physical function: Potential implications for adverse outcomes in older hospitalized patients. J Am Med Dir Assoc. 2011;12:565-72.
44. Moga DC, Carnahan RM, Lund BC, et al. Risks and benefits of bladder antimuscarinics among elderly residents of Veterans Affairs Community Living Centers. J Am Med Dir Assoc. 2013;14:749-60.
45. Thomas DR, Cote TR, Lawhorne L, et al. Understanding clinical dehydration and its treatment. J Am Med Dir Assoc. 2008;9:292-301.
46. Wilson MM. The management of dehydration in the nursing home. J Nutr Health Aging 1999;3:53-61.

47. Schols JM, De Groot CP, van der Cammen Tj, Olde Rikkert MG. Preventing and treating dehydration in the elderly during periods of illness and warm weather. J Nutr Health Aging. 2009;13:150-7.
48. de Souto Barreto P, Lapeyre-Mestre M, Mathieu C, et al. Prevalence and associations of the use of proton-pump inhibitors in nursing homes: a cross-sectional study. J Am Med Dir Assoc. 2013;14:265-9.
49. Maggio M, Corsonello A, Ceda GP, et al. Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals. JAMA Intern Med. 2013;173:518-23.
50. Ngamruengphong S, G.I. Leontiadis, S. Radhi, et al. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2011;106:1209-18.
51. Sinclair A, Morley JE, Rodriguez-Mañas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc. 2012;13:497-502.
52. Sinclair A, Morley JE. How to manage diabetes mellitus in older persons in the 21st century: applying these principles to long term diabetes care. J Am Med Dir Assoc. 2013;14:777-80.
53. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community- dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012;65:989-95.
54. Bennett A, Gnjidic D, Gillett M, et al. Prevalence and impact of fall-risk- increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. Drugs Aging. 2014;31:225-32.
55. Moulis F, Moulis G, Balardy L, et al. Searching for a polypharmacy threshold associated with frailty. J Am Med Dir Assoc. 2015;16:259-61.
56. Chen LK, Chen YM, Lin MH, Peng LN, Hwang SJ. Care of elderly patients with diabetes mellitus: a focus on frailty. Ageing Res Rev. 2010;9 Suppl 1:S18-22.
57. Araki A, Ito H. Diabetes mellitus and geriatric syndromes. Geriatr Gerontol Int. 2009;9:105-14.
58. Gnjidic D1, Hilmer SN, Blyth FM, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther. 2012;91:521-8.
59. Bronskill SE, Gill SS, Paterson JM, et al. Exploring variation in rates of polypharmacy across long term care homes. J Am Med Dir Assoc. 2012;13:309e15-21.
60. Gokce Kutsal Y, Barak A, Atalay A, et al. Polypharmacy in the elderly: A multicenter study. J Am Med Dir Assoc. 2009;10:486-90.
61. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392-7.
62. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol. 2004;43:1439-44.
63. Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. Am J Clin Nutr. 2005;81:1257-66.
64. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012;172:1162-8.
65. Goodwin JS. Embracing complexity: A consideration of hypertension in the very old. J Gerontol A Biol Sci Med Sci. 2003;58:653-8.
66. Gueyffier F, Bulpitt C, Boissel JP, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. Lancet. 1999;353:793-6.
67. Benetos A, Novella JL, Guerci B, et al. Pragmatic diabetes management in nursing homes: individual care plan. J Am Med Dir Assoc. 2013;14:791- 800.

EXERCISE: AN IMPORTANT KEY TO PREVENT PHYSICAL AND COGNITIVE FRAILTY

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INTRODUCTION

The life expectancy of older individuals continues to increase with persons aged 70 years and more representing the fastest growing proportion of the western population (1). At the same time, this extended life should involve the preservation of autonomy through the maintenance of physical and cognitive function. However, with normal aging, people will develop frailty. Thus, identifying cost-effective interventions, which prevent frailty, is one of the most important challenges of health care systems. The difficulty in developing specific interventions to prevent or delay frailty is due to the complexity of the phenomenon, which involves many different physiological, cognitive, and psychological systems. Because no single manifestation of frailty can encompass the whole of the symptoms or signs present, consensual exercise training guidelines remain paradoxically difficult. Therefore, the aim of this review is to address an overview of the literature regarding the effect of exercise/physical activity in the prevention of physical and cognitive frailty.

EXERCISE AND PHYSICAL FRAILTY

Although there is not a universally accepted operational definition of frailty, the most commonly used definition of a physical phenotype of frailty comes from the Fried Frailty Index (FFI). Fried proposed identifying frailty in the individual by observing the presence of at least three of the five following symptoms: shrinking (nutritional/metabolic component assessed by unintentional weight loss), weakness (indicated by muscle strength), poor endurance and energy (per self-reported exhaustion), slowness (demonstrated by slow walking speed) and low amounts of physical activity (2).

There is evidence to suggest that history of leisure time physical activity (LTPA) is related to frailty. In fact; Savela et al. showed that people with high LTPA had up to 80% lower risk of frailty compared to sedentary subjects (3). This conclusion has been confirmed by others who observed that regularly engaged exercise activities in elderly individuals were less likely to develop frailty through a 5 year period than those who were sedentary (4, 5).

The benefits of exercise in improving functional capacities which include daily living activities, falls and quality of life of frail older adults has been considerably reported through reviews or meta-analyses (6-9). Regarding the literature, low intensity resistance training (10, 11), power resistance training (12), multimodal (13, 14); could be recommended to older frail individuals but not flexibility home programs or chair based exercises alone (10, 15, 16). In addition, aerobic exercise could also counteract physical frailty through the improvement of the maximal oxygen uptake (Vo2max) (17) and increased muscle mass (18, 19).

EXERCISE AND COGNITIVE FRAILTY

It is not satisfactory to define frailty in the physical domain alone since there are other factors that have not yet been examined, but are recognized as part of the frailty syndrome such as cognition. While physical frailty is a widely recognized problem in the elderly, cognitive frailty has only recently become the focus of inquiry. Recently, the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) summarized cognitive frailty as a heterogeneous clinical manifestation characterized by the simultaneous presence of physical frailty and cognitive impairment, in the absence of dementia (20).

It is well establish that aerobic exercises such as walking may prevent the decline in cognitive function in non-frail older adults (21-23). However, few studies have examined the effect of other types of exercises (tai-chi, body and mind, resistance training) on cognitive function. For example, it has been observed that resistance training contributes positively and significantly in the improvement of brain functional plasticity, executive function and response inhibition (24, 25). There is also evidence to suggest that home based exercises may improve executive function, specifically response inhibition, after 6 months (26). Moreover, studies have shown that Tai Chi could positively affect cognitive performance in older adults (27). It should also be noted that combining aerobic training to resistance training is more efficient in improving cognitive function in older adults than aerobic or resistance training alone (28, 29). However, current evidence is limited, and research is needed on the role of exercise parameters (e.g. volume, types, and intensity) on specific cognitive functions. Indeed, it has been reported that the volume, intensity and variation of physical activities as well as the history of practice was positively associated with processing speed, memory, mental flexibility, executive function and overall cognitive function (30, 31). Finally it has been proposed that exercise could prevent cognitive frailty through an improvement on brain plasticity, structural brain reserves and cerebral blood flow (32-34).

Thus, even if exercise is promising to improve cognitive decline with age in non-frail individuals, to our knowledge only one study has been conducted to improve cognitive function using exercise alone in frail older adults (35). This study concluded that aerobic training combined to resistance training is efficient to improve executive functions, processing speed and working memory. Thus, RCT using exercise training to counteract cognitive frailty are needed in frail elderly because this population is poorly studied.

PRACTICAL GUIDELINES

Overall, it is important to propose an exercise program reproducible at home including gradual increases in the volume, intensity, complexity and type of all of the exercises through resistance, aerobic, as well as body and mind training. Since 64 % of older people are considered as sedentary, increasing the long-term adherence is important in order to create a specific training program that includes regular changes in the intensity and type of exercises and is feasible at home (counteract the transportation).

More specifically, resistance-training programs should be performed two to three times per week, with two sets of 8-12 repetitions at an intensity that starts at 20%-30% and progresses to 80% of 1RM. In addition, progressively, we could increase the tempo to turn on power training, which is more efficient to improve or maintain muscle quality. All these exercises should be realized in exercise rooms under supervision or at home using for example Swissball; free-weight, elastic band, chair and others with occasional supervision. To optimize the functional capacity of individuals, resistance/power training programs should be combined with exercises in which daily activities are simulated, such as the sit- to- stand, tandem foot standing, heel–toe walking, line walking, stepping practice, standing on one leg, weight transfers (from one leg to the other). These exercises are often offered through body and mind activities such as tai chi and pilates. Aerobic training should include walking with changes in pace and direction, treadmill walking, step-ups, stair climbing, and stationary cycling. Aerobic exercise may start at 5-10 min during the first weeks of training and progress to 15-30 min for the remainder of the program. The Rate of Perceived Exertion scale should be used for prescribing the exercise intensity, and an intensity of 12–14 on the Borg scale appears to be well tolerated.

CONCLUSION

In General, to prevent physical and cognitive frailty adverse effects, frail older adults could practice multimodal physical activity programs (resistance/power, aerobic and body and mind exercise) at least twice a week during 30-45 min per session at moderate to high intensity. In addition, to optimize the physical training prescription and meet these goals in subjects with physical and/or cognitive frailty, the most effective type of exercise program should be identified by considering the optimal combination of intensity, volume, and frequency training that would promote neuromuscular, muscular and cardiovascular adaptations and thus result in improved functional and cognitive capacity in the frail elderly.

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REFERENCES

1. Manton KG, Vaupel J. Survival after the Age of 80 in the United States, Sweden, France, England, and Japan. N Engl J Med 1995;333:1232-5.
2. Fried LP, Tangen CM, Walston J et al. Frailty in Older Adults: Evidence for a Phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
3. Savela SL, Koistinen P, Stenholm S, et al. Leisure-Time Physical Activity in Midlife Is Related to Old Age Frailty. J Gerontol A Biol Sci Med Sci 2013;68:1433-8.
4. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB. The Association between Physical Function and Lifestyle Activity and Exercise in the Health, Aging and Body Composition Study. J Am Geriatr Soc 2004;52:502-9.
5. Peterson MJ, Giuliani C, Morey MC, et al. Physical Activity as a Preventative Factor for Frailty: The Health, Aging, and Body Composition Study. J Gerontol A Biol Sci Med Sci 2009;64:61-68.
6. Cadore EL, Moneo AB, Mensat MM, et al. Positive Effects of Resistance Training in Frail Elderly Patients with Dementia after Long-Term Physical Restraint. Age (Dordr) 2014;36:801-11.
7. Chou CH, Hwang CL, Wu YT. Effect of Exercise on Physical Function, Daily Living Activities, and Quality of Life in the Frail Older Adults: A Meta-Analysis. Arch Phys Med Rehab 2012;93: 237-44.
8. Gine-Garriga M, Roque-Figuls M, Coll-Planas L, Sitja-Rabert M, Salva A. Physical Exercise Interventions for Improving Performance-Based Measures of Physical Function in Community-Dwelling, Frail Older Adults: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 2014;95:753-69 e3.
9. Weening-Dijksterhuis E, de Greef MHG, Scherder EJA, Slaets JPJ, van der Schans CP. Frail Institutionalized Older Persons: A Comprehensive Review on Physical Exercise, Physical Fitness, Activities of Daily Living, and Quality-of-Life. Am J Phys Med Rehab 2011;90:156-68.
10. Brown M, Sinacore DR, Ehsani AA, Binder F, O Holloszy J, Kohrt WM. Low-Intensity Exercise as a Modifier of Physical Frailty in Older Adults. Arch Phys Med Rehab 2000;81:960-65.
11. Chandler JM, Duncan PW, Kochersberger G, Studenski S. Is Lower Extremity Strength Gain Associated with Improvement in Physical Performance and Disability in Frail, Community-Dwelling Elders? Arch Phys Med Rehab 1998;79:24-30.
12. Izquierdo M, Lusa Cadore E. Muscle Power Training in the Institutionalized Frail: A New Approach to Counteracting Functional Declines and Very Late-Life Disability. Curr Med Res Opin 2014;30:1385-90.
13. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, ByersA. A Program to Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home. New Engl J Med 2002;347:1068-74.
14. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults: The Life Study Randomized Clinical Trial. JAMA 2014;311:2387-96.
15. Anthony K, Robinson K, Logan P, Gordon AL, Harwood RH, Masud T. Chair-Based Exercises for Frail Older People: A Systematic Review. BioMed Res Int 2013 (2013).
16. Binder EF, Schechtman KB, Ehsani AA, et al. Effects of Exercise Training on Frailty in Community-Dwelling Older Adults: Results of a Randomized, Controlled Trial. J Am Geriatr Soc 2002;50:1921-28.
17. Ehsani AA, Spina RJ, Peterson LR et al. Attenuation of Cardiovascular Adaptations to Exercise in Frail Octogenarians. J Appl Phys 2003;95:1781-88.
18. Harber MP, Konopka AR, Douglass MD, et al. Aerobic Exercise Training Improves Whole Muscle and Single Myofiber Size and Function in Older Women. Am J Physiol Regul Integr Compar Physiol 2009;297:R1452-R59.
19. Sugawara J, Miyachi M, Moreau KL, Dinenno FA, DeSouza CA, Tanaka H. Age-Related Reductions in Appendicular Skeletal Muscle Mass: Association with Habitual Aerobic Exercise Status. Clin Physiol Functional Imaging 2002;22:169-72.
20. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive Frailty: Rational and Definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. J Nutr Health Aging 2013;17:726-34.
21. Hindin SB, Zelinski EM. Extended Practice and Aerobic Exercise Interventions Benefit Untrained Cognitive Outcomes in Older Adults: A Meta-Analysis. J Am Geriatr Soc 2012;60: 136-41.
22. Landi F, Onder G, Carpenter I, Cesari M, Soldato M, Bernabei R. Physical Activity Prevented Functional Decline among Frail Community-Living Elderly Subjects in an International Observational Study. J Clin Epidemiol 2007;60:518-24.
23. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic Exercise and Neurocognitive Performance: A Meta-Analytic Review of Randomized Controlled Trials. Psychosomatic Med 2010;72:239.
24. Cassilhas RC, Viana VAR, Grassmann V, et al. The Impact of Resistance Exercise on the Cognitive Function of the Elderly. Med Sci Sports Exer 2007;39:1401.
25. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance Training and Executive Functions: A 12-Month Randomized Controlled Trial. Arch Intern Med 2010;170:170-78.
26. Liu-Ambrose T, Donaldson MG, Ahamed Y, et al. Otago Home-Based Strength and Balance Retraining Improves Executive Functioning in Older Fallers: A Randomized Controlled Trial. J Am Geriatr Soc 2008;56:1821- 30.
27. Chang YK, Nien YH, Tsai CL, Etnier JL. Physical Activity and Cognition in Older Adults: The Potential of Tai Chi Chuan. J Aging Phys Act 2010;18:451-72.
28. Bherer L, Erickson KI, Liu-Ambrose T. A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults. J Aging Res 2013;657508.
29. Rolland Y, Abellan van Kan G, Vellas B. Physical Activity and Alzheimer's Disease: From Prevention to Therapeutic Perspectives. J Am Med Dir Assoc 2008:9:390-405.
30. Arab L, Sabbagh MN. Are Certain Life Style Habits Associated with Lower Alzheimer Disease Risk? J Alzheimer Dis 2010;20:785.
31. Voelcker-Rehage C, Niemann C. Structural and Functional Brain Changes Related to Different Types of Physical Activity across the Life Span. Neurosci Biobehavioral Rev 2013;37:2268-95.
32. Angevaren M, Vanhees L, Wendel-Vos W et al. Intensity, but Not Duration, of Physical Activities Is Related to Cognitive Function. Eur J Cardiovasc Prev Rehab 2007;14:825-30.
33. Cotman CW, Berchtold NC. Exercise: A Behavioral Intervention to Enhance Brain Health and Plasticity. Trends Neurosci 2002;25:295-301.
34. Ide K, Secher NH. Cerebral Blood Flow and Metabolism During Exercise. Progr Neurobiol 2000;61:397-414.
35. Langlois F, Minh Vu TT, Kergoat MJ, Chassé K, Dupuis G, Bherer L. The Multiple Dimensions of Frailty: Physical Capacity, Cognition, and Quality of Life. Int Psychogeriatr 2012;24:1429-36.

THE ROLE OF NUTRITION FOR THE PREVENTION AND TREATMENT OF FRAILTY

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INTRODUCTION

While definitions of frailty still vary, it is generally agreed upon that frailty is characterized by decreased reserve and robustness, causing extreme vulnerability to stressors (1) that is mainly observable as diminished physical strength and endurance (2-4). Nutrition is a crucial contributing factor in the complex etiology of frailty and its key component sarcopenia (5), as it provides the energy and essential nutrients needed for the maintenance and performance of all organs and bodily functions, including muscle. However, nutritional intake in general decreases with ageing (among the reasons is the so-called anorexia of ageing) (6-8), and moreover, older individuals with anorexia seem to exhibit altered eating patterns characterized by lower consumption of nutrient-rich foods (9). This may be aggravated by functional problems impairing food access (10) and/or by following restrictive diets (i.e. low-cholesterol, low-salt, diabetes) (11). Monotonous diets result, and it is often challenging for older adults to meet their needs for energy and protein (12-15), but in particular for micronutrients (16-19). A chronic lack of energy, macro- and/or micronutrients, however, not only limits bodily functions, but over time promotes atrophy and subsequent loss of body tissues, including muscle (20-22). Thereby, chronic malnutrition is disturbing metabolic balance, decreasing the reserves of the body and diminishing its abilities to cope with stressors (4,21), i.e. promoting frailty.

This article aims to give a short overview on current knowledge concerning the role of nutrition for the prevention and treatment of frailty, while providing readers with references giving an overview for further reading.

OBSERVATIONAL DATA

Epidemiological studies examining the association between dietary intake or nutritional status and frailty have indeed supported a putative role for nutrition in the development of frailty (17,23) and its key components sarcopenia and functional decline (10,18,21,24-26). In these studies, malnutrition, the risk of malnutrition, the presence of weight loss and/or low body weight/BMI were shown to be closely associated with frailty (17,27,28). Older adults that were frail (17,28,29) (or, in some studies, had less lean/muscle mass and/or worse physical performance, which may be regarded as signs for sarcopenia and frailty) (18,24,26,30-32) were found to have lower intakes of energy, protein and/or of several micronutrients, as well as lower plasma concentrations of various nutrients when compared with non-frail older individuals (or better performing persons, respectively). Semba et al. (33) observed in their study that each additional nutrient deficiency raised the risk of frailty in older women by almost 10%. This emphasises the importance of ensuring a high quality of older persons' diets in addition to sufficient quantity as an essential component in the prevention and treatment of frailty.

Although weight loss often is the most visible sign of chronic malnutrition (and one of the defining characteristics of physical frailty according to Fried et al.) (34), the absence of weight loss as well as a normal or even elevated body weight does not necessarily signify an adequate nutritional intake, especially with regard to micronutrients (35). Moreover, a stable or even increasing body weight may mask an "internal" gradual reduction in lean body mass (skeletal muscle and bone mass) that is accompanied by gains in (visceral) fat mass (20,36). In recent years, epidemiological research has come to notice that also the presence of obesity (beginning from BMI>30 kg/m^2, but certainly at BMI>35 kg/m^2) and/or of excessive (visceral) fat mass heavily aggravates the risk of mobility limitations and frailty (27,28,36-39), especially when it occurs in combination with sarcopenia (sarcopenic obesity)(36). Putting the focus on weight loss or body weight alone may thus inadvertently lead to overlook frailty and/or nutritional deficits in overweight and obese older adults or those with no obvious weight loss.

INTERVENTION STUDIES

Supplementation with protein or specific amino acids

Given their important role in (muscle) metabolism, the nutrients most extensively studied for the treatment or prevention of frailty, and especially of sarcopenia, are proteins and (essential) amino acids (AA). Current evidence indicates that older persons may have reduced ability to use ingested protein for muscle protein synthesis, and it is suggested to increase the recommendations for protein intake in this age group to at least 1,0-1,2 g/kg body weight/day in order to maintain, or help regain, muscle mass (for an extensive review of these topics see (10,12–15,17,20,21,24,25,30-32,40-44). Under debate is also whether the source of ingested protein, specific AA or the timing of protein ingestion are relevant factors affecting the anabolic effect of protein intake in older adults.

To date, reliable evidence from RCTs including frail older individuals is scarce (28,45), and most studies in this area focus on sarcopenia and/or include healthy older persons. Moreover, interventional studies using protein supplements (mainly whey/casein protein or mixed/individual AA), and in rare cases protein rich foods such as meat or dairy products (31,42,46), mostly focus on the gain of body weight and/or lean/muscle mass or on metabolic outcomes. Studies reporting functional outcomes so far provide heterogeneous results: supplementation has been shown to increase lean mass and to improve (or at least to reduce the decline in) physical function in some studies (13,14,28,41-43,46-49) and was able to attenuate frailty in one small RCT(50). In other trials, however, such interventions failed to show beneficial effects on strength and performance, although sometimes achieving an increase in body weight and/or lean mass (15,31,32,51,52).

Supplementation with other substances

Other nutritional supplements that have been tested in older adults, although again mostly in healthy and not frail persons, and mainly in relation to sarcopenia, are vitamin D, creatine, beta-hydroxy-beta-methylbutyrate (ß-HMB), arginine, beta-alanine and citrulline, omega 3 fatty acids and antioxidants including carotenoids, selenium, vitamin E and C and isoflavones (reviewed in (10,13,15,17,24,25,28,32,40-43,47,53).). However, to date the number of studies is too small and their designs and results are too heterogeneous to draw reliable conclusions regarding relevant effects of supplementation of these substances to help maintain or restore robustness in the older population.

Combination of nutrition and exercise interventions

As described before, based on the currently available evidence it remains unclear if nutritional supplementation of protein and/or any other substance in itself may have sufficient effects to attenuate frailty (28). As in some studies the combination with exercise and/or physical activity was most effective to reinforce lean/muscle mass and physical performance (28,31,45-47,54,55) and to decrease frailty (50), it is currently recommended to combine both approaches (21,44).

This is especially important in the case of frail but excessively obese older persons: future treatment strategies for these individuals might need to include the consideration of potential functional benefits of weight loss (39), however, any weight loss (whether intentional or not) in older persons may have potentially harmful effects by promoting sarcopenia, bone loss, nutritional deficiencies, disability and even excess mortality (36,37,56,57). It is therefore of utmost importance for these individuals to achieve a gain (or as a minimal requirement, avoiding a loss) of muscle mass while losing excess fat mass. This implies that it is advisable to judge the benefits of any intervention in such obese (but also in in non-obese) frail participants not according to (change of) body weight, but instead to focus on changes in body composition and, most importantly, on functional outcome parameters.

The goal of maintaining muscle is most effectively achieved by adding physical activity and/or exercise components (58). Indeed, in the few studies with older adults conducted in this field, any intervention including nutritional changes with the goal of losing weight provided the best functional results when combined with exercise as a supporting factor (36,39,59-61). However, taking into consideration the

"obesity paradox" (57) (several meta-analyses indicate that being overweight up to a BMI of 30 kg/m² or even more may protect older persons against mortality and morbidity), and that the harmful effects of obesity only increase at a BMI >30 kg/m² or more, for every frail obese individual the necessity of weight loss has to be really thoroughly reflected (57).

WHOLE DIET APPROACH

A major problem regarding the use of single nutrients in frailty prevention and therapy is that people do not eat single nutrients, but foods and meals containing a whole range of interacting constituents. Therefore it may be more appropriate to consider the influence of the whole diet on frailty, and also on its key components sarcopenia and functional decline (10,18,62). Indeed, some epidemiological studies have indicated that high adherence to "healthy" dietary patterns such as the currently best-investigated Mediterranean diet (characterised by high consumption of nutrient-dense foods such as fruits and vegetables, wholemeal cereals and oily fish, but low intake of saturated fats (18,62,63) in older adults is associated with a lower risk of frailty (17,28,64), or with greater muscle strength and/or better functional performance (10,64,65). However, research in this field has only started recently (63), and there is still a paucity of data regarding the effects of certain food groups and/or dietary intake patterns on the risk of frailty in older age.

CONCLUSIONS

Inadequate nutritional intake is an important modifiable risk factor for frailty. Existing evidence supports the importance of adequate dietary quantity and especially quality to ensure sufficient intakes of energy, protein and micronutrients (21). However, to date no nutritional intervention or supplementation concept has emerged as being effective for the prevention or treatment of frailty (17). Further research, including specifically the group of frail older persons and those at risk of frailty, and focussing on functional benefits as an outcome, is needed to allow definite recommendations for optimal diet, i.e. food and nutrient intakes, for this population.

Consequently, current best practice for frail older persons remains to recommend the intake of high-quality, nutrient-dense foods in order to achieve adequate provision of energy, protein and micronutrients, and to avoid weight loss, together with the promotion of physical activity (21). For severely obese frail older adults, if the benefits of weight loss are clearly established, the most appropriate therapeutic approach might consist of a very moderate energy restriction of 200-500 kcal/day, targeted at a moderate weight loss of 0,5-1 kg/week (or 8-10% of initial body weight after 6 months), while assuring a protein intake of at least 1 g/kg body weight/day and appropriate intake of micronutrients, and always combined with physical activity and/or exercise (36,57,59).

REFERENCES

1. Rodríguez-Mañas, L., Féart, C., Mann, G. et al. (2013) Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 68, 1, 62-67.
2. Clegg, A., Young, J., Iliffe, S. et al. (2013) Frailty in elderly people. The Lancet 381, 9868, 752-762.
3. Morley, J. E., Vellas, B., Abellan van Kan, G. et al. (2013) Frailty consensus: a call to action. Journal of the American Medical Directors Association 14, 6, 392-397.
4. Cooper, C., Dere, W., Evans, W. et al. (2012) Frailty and sarcopenia: definitions and outcome parameters. Osteoporosis International 23, 7, 1839-1848.
5. Landi, F., Calvani, R., Cesari, M. et al. (2015) Sarcopenia as the biological substrate of physical frailty. Clinics in Geriatric Medicine 31, 3, 367-374.
6. Morley, J.E. (2013) Pathophysiology of the anorexia of aging. Current Opinion in Clinical Nutrition and Metabolic Care 16, 1, 27-32.
7. Martone, A.M., Onder, G., Vetrano, D.L. et al. (2013) Anorexia of aging: a modifiable risk factor for frailty. Nutrients 5, 10, 4126-4133.
8. Porter Starr, K.N., McDonald, S.R., Bales, C.W. (2015) Nutritional vulnerability in older adults: a continuum of concerns. Current Nutrition Reports 4, 2, 176-184.
9. Donini, L.M., Poggiogalle, E., Piredda, M. et al. (2013) Anorexia and eating patterns in the elderly. PloS one 8, 5, e63539.
10. Robinson, S., Cooper, C., Sayer, A.A. (2012) Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. Journal of Aging Research 2012, 510801.
11. Zeanandin, G., Molato, O., Le Duff, F. et al. (2012) Impact of restrictive diets on the risk of undernutrition in a free-living elderly population. Clinical Nutrition 31, 1, 69-73.
12. Paddon-Jones, D. & Leidy, H. (2014) Dietary protein and muscle in older persons. Current Opinion in Clinical Nutrition and Metabolic Care 17, 1, 5-11.
13. Deutz, N.E.P., Bauer, J.M., Barazzoni, R. et al. (2014) Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN expert group. Clinical Nutrition 33, 6, 929–936.
14. Beasley, J.M., Shikany, J.M., Thomson, C.A. (2013) The role of dietary protein intake in the prevention of sarcopenia of aging. Nutrition in Clinical Practice 28, 6, 684-690.
15. Millward, D.J. (2012) Nutrition and sarcopenia: evidence for an interaction. The Proceedings of the Nutrition Society 71, 4, 566-575.
16. Ter Borg, S., Verlaan, S., Mijnarends, D.M. et al. (2015) Macronutrient Intake and Inadequacies of Community-Dwelling Older Adults, a Systematic Review. Annals of Nutrition & Metabolism 66, 4, 242-255.
17. Bonnefoy, M., Berrut, G., Lesourd, B. et al. (2015) Frailty and nutrition: searching for evidence. The Journal of Nutrition, Health & Aging 19, 3, 250-257.

18. Inzitari, M., Doets, E., Bartali, B. et al. (2011) Nutrition in the age-related disablement process. The Journal of Nutrition, Health & Aging 15, 8, 599-604.
19. Zujko, M.E., Witkowska, A.M., Waskiewics, A. et al. (2015) Dietary antioxidant and Flavonoid intakes are reduced in the elderly. Oxidative Medicine and Cellular Longevity, Article ID 843173, 1-8.
20. Boirie, Y., Morio, B., Caumon, E. et al. (2014) Nutrition and protein energy homeostasis in elderly. Mechanisms of Ageing and Development 136-137, 76-84.
21. Volkert, D. (2011) The role of nutrition in the prevention of sarcopenia. Wiener Medizinische Wochenschrift 161, 17-18, 409-415.
22. Schneider, S.M., Al-Jaouni, R., Pivot, X. et al. (2002) Lack of adaptation to severe malnutrition in elderly patients. Clinical Nutrition 21, 6, 499-504.
23. Kaiser, M., Bandinelli, S., Lunenfeld, B. (2010) Frailty and the role of nutrition in older people. A review of the current literature. Acta Biomedica Atenei Parmensis 81 Suppl 1, 37-45.
24. Rondanelli, M., Faliva, M., Monteferrario, F. et al. (2015) Novel insights on nutrient management of sarcopenia in elderly. BioMed Research International 2015, 524948.
25. Calvani, R., Miccheli, A., Landi, F. et al. (2013) Current nutritional recommendations and novel dietary strategies to manage sarcopenia. The Journal of Frailty & Aging 2, 1, 38-53.
26. Milaneschi, Y., Tanaka, T., Ferrucci, L. (2010) Nutritional determinants of mobility. Current Opinion in Clinical Nutrition and Metabolic Care 13, 6, 625-629.
27. Hubbard, R.E., Lang, I.A., Llewellyn, D.J. et al. (2010) Frailty, Body Mass Index, and abdominal obesity in older people. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 65A, 4, 377-381.
28. Secher, M., Guyonnet, S., Ghisolfi, A. et al. (2014) Nutrition, Frailty and prevention of disabilities with ageing. Clinical Nutrition Highlights 9, 1, 1-26.
29. Kobayashi, S., Asakura, K., Suga, H. et al. (2014) Inverse association between dietary habits with high total antioxidant capacity and prevalence of frailty among elderly Japanese women: a multicenter cross-sectional study. The Journal of Nutrition, Health & Aging 18, 9, 827-839.
30. Deer, R.R. & Volpi, E. (2015) Protein intake and muscle function in older adults. Current Opinion in Clinical Nutrition and Metabolic Care 18, 3, 248-253.
31. Nowson, C. & O'Connell, S. (2015) Protein requirements and recommendations for older people: a review. Nutrients, 7, 6874-6899.
32. Welch, A.A. (2014) Nutritional influences on age-related skeletal muscle loss. The Proceedings of the Nutrition Society 73, 01, 16-33.
33. Semba, R.D., Bartali, B., Zhou, J. et al. (2006) Low serum micronutrient concentrations predict frailty among older women living in the community. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 61, 6, 594-599.
34. Fried, L.P., Tangen, C.M., Walston, J. et al. (2001) Frailty in older adults: evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 56, 3, M146-56.
35. Agarwal, S., Reider, C., Brooks, J.R. et al. (2015) Comparison of prevalence of inadequate nutrient intake based on body weight status of adults in the United States: an analysis of NHANES 2001-2008. Journal of the American College of Nutrition 34, 2, 126-134.
36. Normandin, E., Houston, D.K., Nicklas, B.J. (2015) Caloric restriction for treatment of geriatric obesity: Do the benefits outweigh the risks? Current Nutrition Reports 4, 2, 143-155.
37. Porter Starr, K.N. & Bales, C.W. (2015) Excessive body weight in older adults. Clinics in Geriatric Medicine 31, 3, 311-326.
38. García-Esquinas, E., José García-García, F., León-Muñoz, L.M. et al. (2015) Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. Obesity 23, 4, 847-855.
39. Anton, S.D., Karabetian, C., Naugle, K. et al. (2013) Obesity and diabetes as accelerators of functional decline: can lifestyle interventions maintain functional status in high risk older adults? Experimental Gerontology 48, 9, 888-897.
40. Bauer, J.M. & Diekmann, R. (2015) Protein supplementation with aging. Current Opinion in Clinical Nutrition and Metabolic Care 18, 1, 24-31.
41. Cruz-Jentoft, A.J., Landi, F., Schneider, S.M. et al. (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age and Ageing 43, 6, 748-759.
42. Fukagawa, N.K. (2013) Protein and amino acid supplementation in older humans. Amino acids 44, 6, 1493-1509.
43. Bauer, J.M., Biolo, G., Cederholm, T. et al. (2013) Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group. Journal of the American Medical Directors Association 14, 8, 542-559.
44. Morley, J.E., Argiles, J.M., Evans, W.J. et al. (2010) Nutritional recommendations for the management of sarcopenia. Journal of the American Medical Directors Association 11, 6, 391-396.
45. Bendayan, M., Bibas, L., Levi, M. et al. (2014) Therapeutic interventions for frail elderly patients: part II. Ongoing and unpublished randomized trials. Progress in Cardiovascular Diseases 57, 2, 144-151.
46. Bibas, L., Levi, M., Bendayan, M. et al. (2014) Therapeutic interventions for frail elderly patients: part I. Published randomized trials. Progress in Cardiovascular Diseases 57, 2, 134-143.
47. Malafarina, V., Uriz-Otano, F., Iniesta, R. et al. (2013) Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. Journal of the American Medical Directors Association 14, 1, 10-17.
48. Cawood, A.L., Elia, M., Stratton, R.J. (2012) Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Research Reviews 11, 2, 278-296.
49. Bauer, J.M., Verlaan, S., Bautmans, I. et al. (2015) Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. Journal of the American Medical Directors Association.
50. Ng, T.P., Feng, L., Nyunt, M.S.Z. et al. (2015) Nutritional, physical, cognitive, and combination Interventions and frailty reversal among older adults: a randomized controlled trial. The American Journal of Medicine, 1-12.
51. Milne, A.C., Potter, J., Vivanti, A. et al. (2009) Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Systematic Review, 2, Cd003288.
52. Komar, B., Schwingshackl, L., Hoffmann, G. (2015) Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. The Journal of Nutrition, Health & Aging 19, 4, 437-446.
53. Halfon, M., Phan, O., Teta, D. (2015) Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. BioMed Research International 2015, 953241.
54. Denison, H.J., Cooper, C., Sayer, A.A. et al. (2015) Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. Clinical Interventions in Aging 10, 859-869.

55. Cermak, N.M., Res, P.T., de Groot, L.C. et al. (2012) Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. The American Journal of Clinical Nutrition 96, 6, 1454-1464.
56. Murphy, R.A., Reinders, I., Register, T.C. et al. (2014) Associations of BMI and adipose tissue area and density with incident mobility limitation and poor performance in older adults. The American Journal of Clinical Nutrition 99, 5, 1059-1065.
57. Mathus-Vliegen, E.M.H. (2012) Prevalence, pathophysiology, health consequences and treatment options of obesity in the elderly: a guideline. Obesity facts 5, 3, 460-483.
58. Weinheimer, E.M., Sands, L.P., Campbell, W.W. (2010) A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutrition Reviews 68, 7, 375-388.
59. Freiberger, E., Goisser, S., Porzel, S. et al. (2015) Sarcopenic obesity and complex interventions with nutrition and exercise in community-dwelling older persons - a narrative review. Clinical Interventions in Aging, 1267.
60. Porter Starr, K.N., McDonald, S.R., Bales, C.W. (2014) Obesity and physical frailty in older adults: a scoping review of lifestyle intervention trials. Journal of the American Medical Directors Association 15, 4, 240-250.
61. Poggiogalle, E., Migliaccio, S., Lenzi, A. et al. (2014) Treatment of body composition changes in obese and overweight older adults: insight into the phenotype of sarcopenic obesity. Endocrine 47, 3, 699-716.
62. Wirfält, E., Drake, I., Wallström, P. (2013) What do review papers conclude about food and dietary patterns? Food & Nutrition Research 57.
63. Kiefte-de Jong, J.C., Mathers, J.C., Franco, O.H. (2014) Nutrition and healthy ageing: the key ingredients. The Proceedings of the Nutrition Society 73, 249-259.
64. León-Muñoz, L.M., García-Esquinas, E., López-García, E. et al. (2015) Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Medicine 13, 11.
65. Panza, F., Solfrizzi, V., Giannini, M. et al. (2014) Nutrition, frailty, and Alzheimer's disease. Frontiers in Aging Neuroscience 6, 221.

HOW TO INCLUDE THE SOCIAL FACTOR FOR DETERMINING FRAILTY?

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Abstract: Traditionally, frailty has been understood as a biological syndrome associated with bad health-related outcomes. However, nowadays there are no universally accepted diagnostic criteria for this syndrome, much less studies approaching it from a non-biological framework. Some previous work has been able to highlight social factors as important features implicated in the development of this entity, and are now recognized as relevant to understand frailty. However, research in this field is still limited. It seems clear that social factors, often ignored in the medical context, might represent risk factors for the development of this geriatric syndrome. To identify these factors, as well as their role in the physiopathology of frailty, could be of great importance in order to establish potential multidimensional models to treat frailty. A life course approach to determine the correlates and trajectories of frailty seems to be necessary. The allostatic load through life and chronic inflammation in the elderly are potential mediators of this relationship. Therefore, social profile should be systematically assessed and taken into account when evaluating an elderly person. So, the present review proposes how to include social factors as another determinant of frailty.

Key words: Frailty, social factors, allostatic load,immunosenescence, disability.

SOCIAL FACTORS AS DETERMINANTS OF FRAILTY STATUS

Social determinants of health

Nowadays, it is clear that health inequities arising from the societal conditions in which people are born, grow, live, work and age, are all social determinants of health. These include early years' experiences, education, economic status, employment and work conditions, housing and environment, and access to effective systems of preventing and treating ill health. In addition, research on the determinants of adult and old-adult health recognizes the need to incorporate earlier life circumstances. The scarcity of longitudinal and nationally representative studies with extensive information on socioeconomic status and health status gives us an opportunity to understanding how early, middle, and late life factors influence the life cycle trajectory of health and thus of frailty (1).

Life course perspective

Since the seminal paper by Ben Shlomo and Kuh (2), a number of studies have reported associations between socioeconomic status (SES) and health in adulthood with consistent evidence that the socioeconomically disadvantaged have higher prevalence of chronic disease and rates of mortality than the more advantaged. Evidence also in-

dicates that socioeconomic disadvantage in childhood is associated with a range of adverse health-related outcomes in adulthood often independent of adult SES. Childhood SES, through its association with a range of factors, including growth and early life nutrition, may influence the peak level of physical capability attained in early adulthood, thereby affecting levels later in life. Adverse effects of SES may also accumulate across the life course. Poor adult SES is associated with worse objectively measured physical performance levels, and it has been recently shown that this effect is also seen with childhood SES independently of adult SES (3). Such an association has important implications for the development of interventions programs targeting frail persons and the prevention and improving the physical capability levels of elderly.

The specific aging experience of some populations, characterized by poverty and poor social conditions along with high comorbidity, disability and a scarcity of health and social services, has only recently been recognized. Research among Latin American older persons arising from the SABE (Salud Bienestar y Envejecimiento; Spanish for Health, Well-being and Aging) survey, a multicentric cross-sectional study involving 10,661 men and women 60 years and older in seven large Latin American cities (4), indicates that a poor material environment during childhood is associated with poor physical functioning and mental health. In the same vein, they have shown that a differential exposure and vulnerability to social and biological factors among men and women are associated with gender differences in physical function and mental health. In addition, social and health conditions of the life course were associated with the phenotype of frailty, and that differential exposure and/or vulnerability to social and health conditions of life course may account for gender differences in frail persons. This association between life course factors and frailty increases our understanding about the social origins of frailty.

Disadvantages existing in early life and reproduced along the life course may then account for the syndrome of physical frailty. New theoretical models aiming to explain gender and social differences in frailty status should emphasize the use of a life course perspective.

Social and life-style correlates of frailty

Thus, social factors are now recognized as relevant to understand frailty. However, research into the prevalence of frailty and its correlates, particularly social influences, is still limited. A group in Hertfordshire, at the United Kingdom, using data from the Hertfordshire Cohort Study, has shown that frailty (defined by the Fried et al. criteria) is partly determined by social inequalities across levels of education, home ownership, and car availability. These results seem to be mediated by co-morbidities that occur more frequently among socially disadvantaged individuals (5). On the other hand, previous research in Latin American elderly has also found that social factors such as poorer socio-economic conditions, little education, non-white-collar occupation, or insufficient income are more frequently present in frail subjects. Recent findings in a Mexican cohort partially replicate those previously reported. A cross-sectional analysis of the Mexican Study of Nutritional and Psychological Markers of Frailty (the Coyoacán cohort) (6), has shown that not having a partner, not participating in important decisions, and having a poor self-perceived economic situation were all correlates of prevalent frailty. In addition, those receiving a pension were protected against frailty, which may be a reflection of having better life conditions and access to health-care of these participants. The sum of these factors might traduce a socially adverse environment increasing the odds for elderly to be frail. However, a longitudinal approach is needed in order to better understand this association.

It seems clear that social factors, often ignored in the medical context, might represent risk factors for the development of frailty. Therefore, social profile should be systematically assessed and taken into account when evaluating an elderly person for the development and implementation of multidimensional prevention and treatment programs.

Trajectories of frailty as a function of social vulnerability

This longitudinal approach has been thoroughly explored in the Health and Retirement Survey (7), where the frailty index (FI) for cohorts born before 1942 exhibit quadratic increases with age and accelerated increases in the accumulation of health deficits. At any age, females, non-white individuals, and those with lower education and income exhibit greater degrees of deterioration than their male, white, and higher SES counterparts. Patterns of sex, race, and SES differentials in rates of aging vary across cohorts. The authors report that adjusting for social behavioral factors, the analysis provides evidence for physiological differences in the aging process among older adults. Their results allow concluding that the expression of biological aging and the accumulation of general system damage do not follow the same path, under different circumstances, within a human population. In fact, individuals' slopes of change with age are sensitive to the social conditions in which they are embedded.

MECHANISMS AND MEDIATORS

Allostatic load

There is a growing interest in understanding how the experience of SES adversity across the life course may accumulate to negatively affect the functioning of biological regulatory systems, which are important to functioning and health in late adulthood. In this vein, allostatic load (AL) is conceptualized as a cumulative index of wear and tear across multiple physiological systems involved in the body's effort to adapt to internal and external stressors over time. AL has been examined as a preclinical physiological marker of risk for adverse health-related outcomes. Recent analyses indicate higher AL as a function of greater SES adversity at each phase of, and cumulatively across, the life course. This association is only modestly attenuated when accounting for a wide array of health status, behavioral, and psychosocial factors (8). So, SES adversity experience may cumulate across the life course to have a negative impact on multiple biological systems in adulthood. Then, AL could be related to an indicator of decreased reserves such as frailty. In fact, higher baseline value for the AL score has been associated with greater likelihood of frailty in two recent surveys. In the MacArthur Successful Aging Study (9), higher levels of AL were associated with greater probability of development of frailty over a 3-year follow-up in a sample of initially high-functioning older adults. This association remains even after adjustments by for co- occurring physical disability and co-morbidity, which may be associated with alterations in biomarker levels. In the Women's Health and Aging studies, regression models showed that by one unit of increase in the AL score was associated with increasing strata of frailty (OR = 1.16; 95% CI = 1.04 to 1.28) adjusting by race, age, education, smoking status, and co- morbidities (10).

Inflammation

Disturbances in many interacting physiological systems may contribute to decrease resilience face to adverse stressors, and will need systems biological approaches to analysis. Inflammation contributes to these alterations, which are determined and feeding back by alterations in the immune system with aging.

Being as the potential ill effect of a lower SES can be observed across such a wide range of such conditions, it suggests a common biological mechanism through which SES adversity is related to health. The underlying hypothesis of this general conceptual model is that those with a lower SES are subject to environmental, psychological and behavioral characteristics, and experiences that more often put demands on these biological systems, leading to greater system wear and tear over time, and subsequently enhancing risk for poor health and functioning. Evidence for SES gradients in biomarkers of these potential physiological pathways to disease is increasing. Lower SES, assessed by several indicators (e.g.: education, income, occupational status, financial strain, etc.), has been associated with more "risky" patterns of biological functioning, including higher levels of hormones, which have been hypothesized to be elevated under conditions of stress. Sympathetic nervous system and hypothalamic-pituitary- adrenal hormones axis, poorer metabolic profiles or higher circulating levels of C-reactive protein, fibrinogen, and other indicators of inflammatory burden have also been found to be increased among those with lower SES. This effect is further complicated by the higher occurrence of chronic diseases associated with, or driven by, chronic inflammation. There is likely a final common pathway for interactions of these many factors altering the immune response to infections and leading to the increased prevalence and incidence of chronic inflammatory diseases. The clinical burden most likely resulting from such immune dysregulation could be overwhelming. Thus, understanding the pathophysiological basis of frailty would be of great importance as a handle for manipulation and, eventually, prevention.

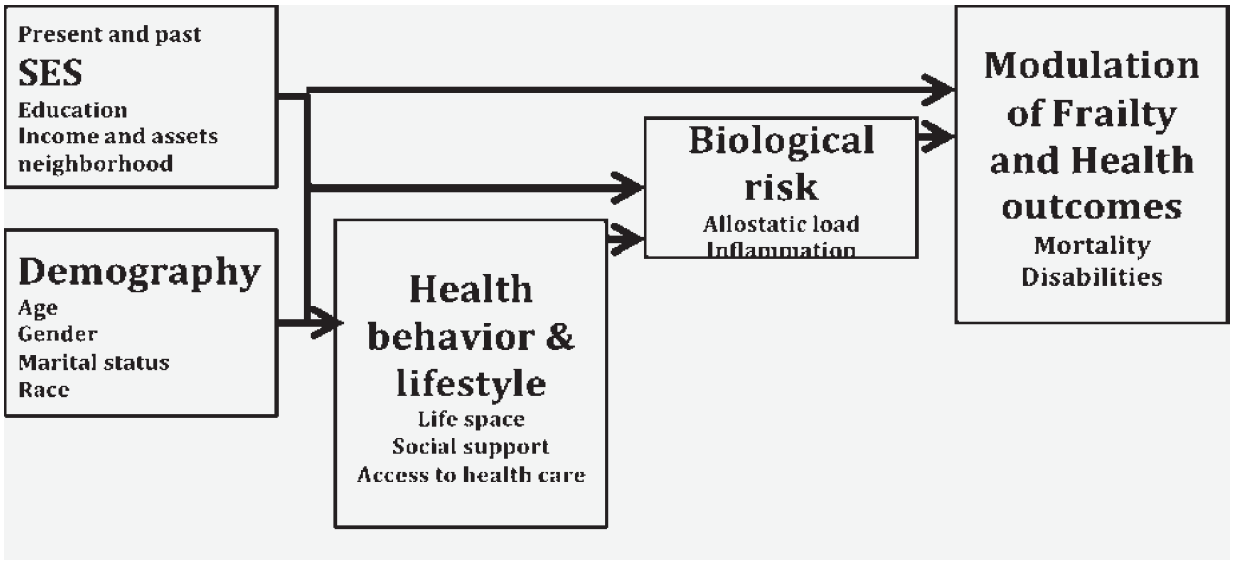
Although it is currently very difficult to assign a definitive and unique biological pathway to frailty, inflammation could eventually take this role. This means that inflammation should already be considered an important target for prevention and intervention to investigate whether this would decrease the incidence of frailty in the elderly population. Despite these reservations, it is still worthwhile to try to intervene. In the meantime, our research efforts should continue to elucidate the pathophysiological basis of frailty in order to design better interventions to improve the quality of life of the elderly in the rapidly increasing aging populations of the developed, and even developing countries.

SOCIAL FACTORS AS MODULATORS OF FRAILTY OUTCOMES

Social vulnerability is related to the health of elderly people, but its measurement and relationship with frailty is controversial. In order to compare social vulnerability and frailty, and to study social vulnerability related to mortality, Andrew et al (11) have tried to operationalize social vulnerability according to a deficit accumulation approach. They have shown how it increases with age, women having higher index values than men. It also tends to be higher amongst people who are frail, and it is associated with higher mortality, independent of frailty. Nevertheless, social vulnerability was shown to be only weakly to moderately associated with frailty. The authors consider that both frailty and social vulnerability may be related, they seem to be distinct, particularly since each contributes independently to mortality.

Figure 1

Levels of influence of socioeconomic status (SES) on frailty and its outcomes. Modified from: (18)



In the Dutch experience (12), social vulnerability has been approached as "social frailty", and it has been measured through the Tilburg Frailty Indicator on the basis of three criteria: living alone, lack of contacts, and lack of support. If someone meets at least two of these three criteria, they are considered as socially frail. Those individuals in this category will not necessarily become physically frail, or be admitted to a care or nursing home or will die. The observed relationship between social and physical frailty could strengthen if other indicators of social frailty were used. Research has shown that health problems can lead to shrinkage of personal networks and withdrawal from social contacts (13). In the English Longitudinal Aging Study (14), neighborhood deprivation and individual socioeconomic status were independently associated with frailty in community-dwelling older people. FI scores were higher in those with low individual socioeconomic resources who also lived in deprived neighborhoods. In a survey in several Hispanic communities in the southern United States (15), respondents at risk of increasing frailty lived in a less ethnically dense Mexican-American neighborhood, were older, do not have private insurance or Medicare, had higher levels of medical conditions, had lower levels of cognitive performances, and reported less positive affect. In this population, personal as well as neighborhood characteristics confer protective effects on individuals' health. Besides a protective environment, engagement in productive activities is also positively associated with physical and psychological health as well as survival of older adults. It has also been shown that high-functioning older adults who participate in productive activities are less likely to become frail, even after adjusting for age, disability, and cognitive function. Activities such as volunteering, but not childcare or paid works, have been independently associated with a lower cumulative odd of frailty (16). Another seemingly useful dimension of social functioning is "life space" defined upon the distance a person routinely travels to perform activities. Determining how far and how often the person leaves his or her place of residence and the degree of independence has been shown useful to predict frailty (17). Multivariate survival models showed that, in comparison to women who left the neighborhood four or more times per week, those who left the neighborhood less frequently were 1.7 times (95% CI: 1.1 to 2.4; $p<0.05$) more likely to become frail, and those who never left their homes experienced a threefold increase in frailty-free mortality (95% CI: 1.4 to 7.7; $p<0.01$), after adjustment for chronic disease, physical disability, and psychosocial factors. Together, these results suggest that a slightly constricted life space may be a marker and/or risk factor for the development of frailty that may prove useful as a screening tool or a target of intervention. The Life Space Assessment scale measures mobility in terms of the spatial extent of a person's life and has been shown to be useful for this purpose.

Based on this evidence, the relationship between physical and social frailty may thus be stronger; further research on the different indicators of objective and subjective social frailty could provide more clarity. The implication for measuring frailty is that social frailty items should be included in the measure, but perhaps should not be given the greatest weight in assessing frailty. Consideration could even be given to starting from a minimum criterion for physical frailty when determining the frailty of an individual, supplement-

ed by social frailty. Although much work remains to be done to characterize social vulnerability among the elderly, we need to recognize that it plays a role in modulating the adverse health-related outcomes of frailty.

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REFERENCES

1. Johnson RC, Schoeni RF, Rogowski JA. Health disparities in mid-to-late life: The role of earlier life family and neighborhood socioeconomic conditions. Soc Sci Med 2011;doi: 10.1016/j.socscimed.2011.10.021.
2. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002;31:285-293.
3. Birnie K, Cooper R, Martin RM, Kuh D, Sayer AA, Alvarado BE, et al. Childhood socioeconomic position and objectively measured physical capability levels in adulthood: A systematic review and meta-analysis. PLoS One 2011;6:e15564.
4. Alvarado BE, Zunzunegui MV, Béland F, Bamvita JM. Life course social and health conditions linked to frailty in Latin American older men and women. J Gerontol A Biol Sci Med Sci 2008;63:1399-1406.
5. Syddall H, Roberts HC, Evandrou M, Cooper C, Bergman, H, Aihie Sayer
A. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. Age ageing 2010;39:197-203.
6. Casale-Martínez RI, Navarrete-Reyes AP, Avila-Funes JA. Social determinants of frailty among Mexican community-dwelling elderly J Am Geriatr Soc 2012;60:In press.
7. Yang Y, Lee LC. Dynamics and heterogeneity in the process of human frailty and aging: evidence from the US older adult population. J Gerontol B Psychol Sci Soc Sci 2010;65B:246-245.
8. Gruenewald TL, Karlamangla AS, Hu P, Stein-Merkin S, Crandall C, Koretz B, et al. History of socioeconomic disadvantage and allostatic load in later life. Soc Sci Med 2012;74:75-83.
9. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. J Am Geriatr Soc 2009;57:1525-1531.
10. Szanton S, Allen J, Seplaki C, Bandeen-Roche K, Fried L. Allostatic load and frailty in the women's health and aging studies. Biol Res Nurs 2009;10:248–256.
11. Andrew MK, Mitnitski AB, Rockwood K Social vulnerability, frailty and mortality in elderly people. PLoS One 2008;3: e2232.
12. van Campen C. Frail older persons in the Netherlands. The Netherlands Institute for Social Research The Hague. 2011. www.scp.nl/english/ dsresource? objectid=29060&type=org. Accessed 31 January 2012.
13. Ertel KA, Glymour MM, Berkman LF. Social networks and health: A life course perspective integrating observational and experimental evidence. JSPR 2009;26:73-92.
14. Lang, IA, Hubbard RE, Andrew MK, Llewellyn DJ, Melzer D, Rockwood
K. Neighborhood deprivation, individual socioeconomic status, and frailty in older adults. J Am Geriatr Soc 2009; 57:1776-1780.
15. Aranda MP, Ray LA, Snih SA, Ottenbacher KJ, Markides KS. The protective effect of neighborhood composition on increasing frailty among older Mexican Americans: a barrio advantage? J Aging Health 2011;23:1189-1217.
16. Jung Y, Gruenewald TL, Seeman TE, Sarkisian CA. Productive activities and development of frailty in older adults. J Gerontol B Psychol Sci Soc Sci 2010;65:256-261.
17. Xue QL, Fried LP, Glass TA, Laffan A, Chaves PH. Life-space constriction, development of frailty, and the competing risk of mortality: the Women's Health And Aging Study I. Am J Epidemiol 2008;167:240–248.
18. Rosero-Bixby L, Dow WH. Surprising SES gradients in mortality, health, and biomarkers in a Latin American Population of adults. J Gerontol B Psychol Sci Soc Sci 2009;64B:105-117.

IMPLEMENTING FRAILTY SCREENING, ASSESSMENT, AND SUSTAINED INTERVENTION: THE EXPERIENCE OF THE GÉRONTOPÔLE

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Abstract: Despite its interest, frailty is not yet adequately implemented in the everyday clinical practice. Frailty is characterized by an initial functional loss which 1) still allows the individual to be independent in the daily life (although with some difficulties), and 2) may be reversed by targeted interventions. In the present article, we discuss: Why frailty is clinically relevant? Why frailty has not yet been implemented in daily clinical practice? How to implement frailty into clinical practice following the Gérontopôle experience? Intervention to be effective must be targeted, strong, and maintained.

Key words: Frailty, intervention, clinical practice, sarcopenia.

INTRODUCTION

One of the challenges for our society is the prevention of age-related disabilities and dependency. The number of severely dependent older adults is projected to rise from 350 million in 2010, to 488 and 614 in 2030 and 2050, respectively (1). Geriatric medicine has consequently to modify itself and adapt its practice in order to adequately counteract such dramatic scenario.

Geriatric medicine started to be systematically developed approximately 40 years ago when the increasing number of older adults with disability and dementia admitted to hospital emergency units threatened the sustainability of the healthcare organizations. Today, almost 95% of the geriatric medicine forces are devoted to the care of age-related disabilities. The epidemiological scenario and the high healthcare costs required for the management of dependent individuals require the adoption of strategies aimed at preventing the loss of physical function and anticipate the take in charge of older persons at risk of negative outcomes. For these reasons, more and more medical specialties (e.g., oncology, cardiology, neurology…) has started looking with greater interest at the geriatric experience simply because they have found themselves at treating geriatric conditions and geriatric patients in their daily routine practice.

In order to objectively define the condition of risk preceding disability and representing the ideal target for ad hoc preventive interventions, the scientific community has developed and described the so-call frailty syndrome. Such early stage of the disabling cascade is characterized by an initial functional loss which 1) still allows the individual to be independent in the daily life (although with some difficulties), and 2) may be reversed by targeted interventions (2-14). In theory, older persons might be classified in three groups, each one with specific necessities and peculiarities to consider in the clinical practice:

a. Older adults in overall healthy conditions (i.e., robust). These individuals may present diseases and clinical con-

ditions (e.g., hypertension, diabetes, history of treated malignancies, vascular diseases…), but these are not affecting their physical function and quality of life. Roughly, older persons represent between 50 and 60% of older adults (7).

b. On the other hand, we have older persons presenting disabilities. These individuals (dependent for the performance of basic activities of daily living, such as eating, walking, dressing, bathing, toileting, personal hygiene) are confined to their houses or reside in nursing homes. At old age, the condition of disability is hard to be reversed, especially if it is due to chronic and degenerative disorders. Disabled elders represent approximately 10% of the population aged 65 years and older, but are the vast majority of patients usually seen in geriatric departments. The maintenance of an efficient healthcare system necessarily passes through the prevention of such catastrophic condition. After all, primary aim of geriatrics is indeed the extension of disability-free life expectancy.
c. The third group is composed by frail older adults (approximately 30 to 40% of older persons aged 65 years and older). The frailty condition has often been operationalized using the criteria proposed and validated by Fried and colleagues, the so-called « frailty phenotype » (4). It is assessed by considering five signs/symptoms: unintentional weight loss, muscular weakness, exhaustion, slow gait speed, and sedentary behavior. The individual is considered as « frail » if presenting three or more of these criteria, and « pre-frail » in the presence of one or two. Studies indicate that non-disabled pre-frail and frail older persons represent about 30% and 10% of the community- dwelling older population, respectively. It is noteworthy that frail elders are a group of individuals with major unmet medical needs, mainly because not frequently referring to clinical services. Nevertheless, this is indeed an optimal target population for developing effective programs aimed at preventing disability in the elderly. In fact, these individuals are not disabled, but present an extreme vulnerability to stressors and a high risk for major negative health-related outcomes (8, 15).

In the present article, we will discuss:
– Why frailty is clinically relevant
– Why frailty has not yet been implemented in daily clinical practice
– How to implement frailty into clinical practice following the experience of the Gérontopôle?

WHY FRAILTY IS CLINICALLY RELEVANT

Using the previously mentioned frailty phenotype, a study conducted in a large cohort study including a population representative of several European countries found that pre- frail and frail elders are highly prevalent in our societies (about 40% and 10%, respectively) (16). These findings have been confirmed by a more recent systematic review taking into account studies also from other continents (17). The frailty syndrome is strongly related to an increase risk of major health- related outcomes, including severe disability, hospitalization, institutionalization, and mortality (4, 17-23). Frail older persons are not exposed to negative outcomes, but (if left untreated) will generate a relevant consumption of healthcare resources in the next future (3). Moreover, evidence exists that effective and multidimensional interventions (largely based on the comprehensive geriatric assessment) in frail individuals may prevent functional decline, institutionalization, and mortality (24-26).

The role of geriatric medicine is indeed to much more focus on the preservation of the older person's physical function. It is not surprisingly, for example, that the concept of «dismobility» (parallel to that of frailty) was recently proposed by Cummings and colleagues (and operationalized as a gait speed slower than 0.6 m/sec) (27). The loss of capacity in mobility increases with age in both men (from 1.2% between 50 to 54 years up to 31% after 85 years of age) and women (from 0.4% between 50 to 54 years up to 52% after 85 years of age). Such relevant burden (for the person as well as for the society) implicitly indicate the need of developing services and practices for «novel» clinical conditions, peculiar of the still not sufficiently studied growing older population.

WHY FRAILTY HAS NOT YET BEEN IMPLEMENTED IN DAILY CLINICAL PRACTICE

Despite its interest, frailty is not yet adequately implemented in the everyday clinical practice. We may identify three main reasons:

- Up to few years ago, geriatric medicine was not sufficiently strong from an academic viewpoint. This has been changing in these last years and geriatrics has assumed a more relevant position in many countries.
- Public policies have not adequately considered the costs of aging population. Today, a restructuring of healthcare systems is becoming urgent in order to face the increasing (absolute and relative) number of elders seeking for care.
- In parallel, the interest of pharmaceutical industries has started to become attracted by the geriatric syndromes. Age-related conditions (e.g., frailty) may not be so clear and straightforward as traditional diseases (e.g., diabetes, hypertension…), but are largely prevalent suggesting interesting marketing perspectives.

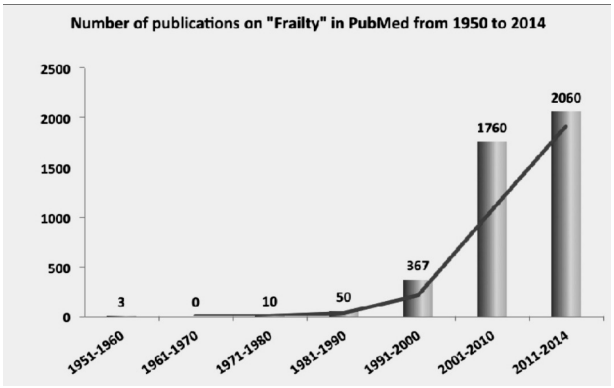
It means that some barriers (or red lights) have being passed (and lights are becoming green)!

The number of publications indexed in PubMed about frailty is exponentially increasing (Figure 1). International

meetings such as the International Conference on Frailty and Sarcopenia Research (ICFSR) attract a growing number of participants with a parallel improvement of quantity and quality of scientific data in the field (28). New drugs are under development in the domain of sarcopenia (i.e., the age-related skeletal muscle decline, a cornerstone of the frailty syndrome). Frailty is today becoming one of the priorities for international institutions, including the European Commission and the World Health Organization. Major scientific projects have been recently funded from European Agencies such as the Innovative Medicines Initiative (IMI), for example the SPRINT-T study (29). The Journal of Frailty & Aging is becoming widely diffused (30) and some web sites (e.g., "Implementing Frailty into Clinical Practice" (31) or the French site "Ensemble prévenons la dépendance" (32) help the diffusion of knowledge and awareness on the theme.

Figure 1

The evolution of number of publications on Frailty from 1950 to 2014



HOW TO IMPLEMENT FRAILTY INTO CLINICAL PRACTICE FOLLOWING THE EXPERIENCE OF THE GÉRONTOPÔLE?

The Gérontopôle has been missioned twice by the French Ministry of Health. The first mandate was received under the Nicholas Sarkoz's presidency, the second (few months later) from François Hollande. In both documents, the Gérontopôle is asked to:

a. Implement screening procedures for identifying frail elders in order to target preventive strategies against disability
b. Design and develop frailty clinics aimed at proposing person-tailored and multidomain interventions against disability
c. Designing models of long-term preventive interventions against disability
d. Promote the prevention of iatrogenic disability in hospitalized frail elders.

Every intervention in medicine (and especially in geriatrics) will be effective only if optimally targeted, powered, and maintained.

THE SCREENING OF FRAILTY FOR IDENTIFYING THE TARGET POPULATION

As mentioned, frail elders represent an optimal target for interventions against disability because 1) not yet experiencing the outcome of interest, and 2) expressing a potential for risk reversibility. It is likely that the cost-effectiveness of targeting this population may also be convenient (3, 8). To facilitate the screening of frail elders in the clinical practice, multiple instruments have been developed. Of particular interest, the FRAIL instrument by Morley and colleagues (33) and the Gérontopôle Frailty Screening Tool (GFST) (34-36) (Figure 2). The GFST is specifically designed to be used by general practitioners (GPs). It first supports the GP in the evaluation of the main frailty criteria (according to the frailty phenotype). In the case one or more frailty signs/symptoms are presents, the GP is then invited at expressing his/her clinical judgment about the vulnerability of the subject. It is only then that the GP (according to his/her clinical judgment) is invited at referring the patient to a frailty clinic. Such design of the instrument prioritizes the subjective impression of frailty provided by the clinician. Moreover, it will directly involve the GP in the future care of the frail person after the frailty clinic will release the person-tailored recommendations (thus guaranteeing adherence to them). We found that almost 95% of the patients referred to our frailty clinic by the mean of the GFST were indeed frail and at risk for disability (37, 38), implying the efficacy of the instrument for its task. The GFST was also recently approved by the French National Authority for Health [Haute Autorité de Santé (HAS)] as the national tool for the detection of frailty in older persons aged 65 years and older (39). The instrument has also been translated in several languages and validated (versus standard assessment tools of frailty and disability) by a recent European initiative (31, 40) (Figure 2). A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability (i.e., the FiND questionnaire) has also been recently validated by our group (41). The questionnaire can be sent by mail or completed over a phone interview. This tool is specifically designed for large-scale campaigns in the population. It enables the individual to auto-detect his/her health profile, raising awareness about the possible need of medical attention. In other words, positive results at the FiND questionnaire should encourage the individual at looking for a medical evaluation. The GP (possibly with the GFST) will then judge whether the condition of risk for disability indeed exists or not, taking the proper countermeasures if necessary. The FiND questionnaire is validated and has also been translated in several languages (31) (Figure 3).

Figure 2
The Gérontopôle Frailty Screening Tool (GFST) for the detection of frail older patients (Vellas et al. J Nutr Health Aging 2013;17:629-631)

Toulouse GÉRONTOPÔLE

Patients aged 65 years and older without both functional disability (Activities of Daily Living score ≥ 5/6) and current acute disease

	YES	NO	DON'T KNOW
Does your patient live alone?	☐	☐	☐
Has your patient involuntarily lost weight in the last 3 months?	☐	☐	☐
Has your patient been more fatigued in the last 3 months?	☐	☐	☐
Has your patient experienced increased mobility difficulties in the last 3 months?	☐	☐	☐
Has your patient complained of memory problems?	☐	☐	☐
Does your patient present slow gait speed (i.e., >4 seconds to walk 4 meters)?	☐	☐	☐

If you have answered YES to one or more of these questions:

Do you think your patient is frail? ☐ YES ☐ NO

If YES, is your patient willing to be assessed for his/her frailty status at the Frailty Clinic? ☐ YES ☐ NO

Figure 3
The self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability (The FiND Questionnaire) - English version (Cesari et al. PLoS One 2014;9:e101745)

Domain	Questions	Answers	Score
Disability	**A.** Have you any difficulties at walking 400 meters?	a. No or some difficulties	0
		b. A lot of difficulties or unable	1
	B. Have you any difficulties at climbing up a flight of stairs?	a. No or some difficulties	0
		b. A lot of difficulties or unable	1
Frailty	**C.** During the last year, have you involuntarily lost more than 4.5 kg?	a. No	0
		b. Yes	1
	D. How often in the last week did you feel than everything you did was an effort or that you could not get going?	a. Rarely or sometimes (twice or less/week)	0
		b. Often or almost always (3 or more times per week)	1
	E. Which is your level of physical activity?	a. Regular physical activity (at least 2–4 hours per week)	0
		b. None or mainly sedentary	1

If A+B≥1, the individual is considered as "disabled".
If A+B = 0 and C+D+E≥1, the individual is considered as "frail".
If A+B+C+D+E = 0, the individual is considered as "robust".
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Table 1

Settings, target population, persons involved, and possible tools for the evaluation of frailty

Setting	Population	Persons involved	Possible Tool
Community Health Promotion Program	Older persons living in the community	Responsible for the screening campaigns (e.g., municipalities, health insurance, public health authorities...), researchers involved in large-scale studies	FiND Questionnaire
Outpatients' Clinic for Frailty	Pre-frail and frail older persons	Responsible for the referral to the clinic: GP, healthcare professional, Geriatrician, individual or his/her proxies Responsible for the assessment at the clinic: GP (specifically trained), Geriatrician	GFST
Day Hospital for Frailty	Pre-frail and frail older persons (usually more complex cases)	Responsible for the referral to the day hospital: GP, Geriatrician Responsible for the assessment at the day hospital: GP (specifically trained), Geriatrician	GFST (for referral only) Frailty phenotype, comprehensive geriatric assessment

DEVELOPMENT OF FRAILTY CLINICS FOR AN ADEQUATELY POWERED INTERVENTION

In the presence of frailty, the first action to take is the identification of the underlying causes. This will allow the definition of the most effective and tailored intervention.

Outpatients' clinics for frailty

A first access to the frailty evaluation is possible at the so-called « outpatients' clinic for frailty ». In this setting, the older person is referred by his/her proxies as well as healthcare professionals. The older person him/herself may independently look for an evaluation in this setting.

In this setting, the physician assesses physical and cognitive domains, social status, and clinical conditions. He/she then provides his/her recommendations for preventing disability. A geriatrician or a specifically trained GP can conduct such frailty outpatient's clinics. However, other health professionals (e.g., nurses, dieticians, physical therapists, neuropsychologists) should be available in the case of a single and specific recommendations might be needed.

If the older person is found to present a light-mild stage of frailty in the absence of complex comorbidities, the frailty assessment and intervention will be conducted and concluded during such ad hoc outpatient consultation.

If the problem appears to be more complicated (e.g., objective cognitive impairment, malnutrition, depression…) and requiring a multidisciplinary intervention, the patient will then be referred to the frailty day hospital (38).

Day hospital for frailty

Frail older persons admitted to the day hospital for frailty undergo a comprehensive geriatric assessment. The activities of the Gérontopôle day hospital for frailty have been described in previous papers (37, 38). The characteristics of persons admitted to this service are summarized in tables 2 and 3. Our population was found to be old (mean age 82.9 years), and composed in majority by women (69%). More than 40% of the evaluated persons lived alone; our sample presented mean number of comorbid conditions of 4.8. According to the frailty phenotype, 423 patients (39.1%) were pre-frail, and 590 (54.5%) frail. The mean score at the Activities of Daily Living (ADL) scale was 5.5/6. This shows that subjects were still autonomous for basic activities of daily living, although an initial functional decline was present (and highlighted by the reduced score at the Instrumental ADL, mean score 5.6/8). A relevant part of the sample (37.9%) presented history of falls. The mean usual gait speed was 0.78 m/sec, and 74.4% presented a score equal to or lower than 9 at the Short Physical Performance Battery (SPPB), indicating a moderate to high risk of disability. Early dementia was observed in 14.9% of the patients referred to our frailty day hospital, 51.5% had a Clinical Dementia Rating score of 0.5 reflecting mild cognitive impairment. Protein-energy malnutrition was reported in 8% of the evaluated subjects, and about 40% of the sample presented risk of malnutrition.

For what concerns the proposed Personalized Prevention Plan (PPP), it is noteworthy that in 54.6% of the subjects we identified at least one medical condition requiring medical attention, and in 32.8% substantial therapeutic changes were required. A nutritional, physical activity, and social interventions were proposed in 61.8%, 56.7%, and 25.7% of the cases.

It is thus evident that without our process of screening, assessment and intervention, this population would have remained exposed to uncontrolled medical conditions and/or difficulties, that is feeding the vicious cycle ending in the onset of negative health outcome. Since October 2011 (and up to August 2014), 1,841 frail older persons have been evaluated at the Gérontopôle Frailty day hospital.

Community health promotion program

Community health promotion programs should be developed under the initiative of health authorities, municipalities, and health insurances. We have developed such program in a rural area in Midi-Pyrénées region (the MINDED Program) with the support of the Agence Nationale de la Recherche (ANR) (40). The self-reported screening tool for detecting community-dwelling older persons with frailty (the FiND questionnaire) was specifically developed within the context of this study. We are now extending such programs in urban communities: in the suburbs of Toulouse (city of Cugnaux) as well as in some low-income districts characterized by high prevalence of elders (e.g., Empalot district). All these programs are done in collaboration with the GPs, pharmacists, and health professionals.

PROLONGED INTERVENTION

Frail subjects usually present comorbidities and require powered and prolonged interventions in order to meet criteria of effectiveness. For this reason, the support of GPs is particularly important. The intervention should be practical and feasible. At the end of frail person's assessment at the frailty day hospital, the proposed interventions are discussed with the subject and members of his/her family (if possible). The referent GP is also contacted on the same day. Two weeks after the assessment, a nurse calls the frail person to verify that the proposed recommendations have been put in place, and discuss about potential issues. After one month from the initial evaluation, the nurse carries out a second phone contact. In this case, she fills out a questionnaire assessing the impact of intervention on the subject's general health and function. An annual follow-up visit at frailty day hospital is also proposed to most of the frail persons. For those who present a particularly high risk of disability, a shorter delay between follow-up visit is adopted. The intervention is usually multi-domain (simultaneously including physical and cognitive exercises, nutrition intervention, social intervention, and/or control of comorbidities and risk factors). However, stronger action is usually foreseen for one (pivotal) domain according to priorities generated by the comprehensive geriatric assessment and the subject's needs/resources. Overall, the physical and cognitive interventions are similar to those we previously adopted in the MAPT study (42). The MAPT intervention proposed two sessions per week (for the first month), one session per week (for the second month), and then one session per month thereafter. We are planning to implement in the next future the use of novel technologies to support the monitoring of the subjects' physical and cognitive functions as well as their nutrition status and behaviors.

Table 2

Baseline socio-demographic characteristics of the G.F.C population (n=1,108) (Tavassoli et al. J Nutr Health Aging 2014; J Nutr Health Aging 2014;18:457-64)

Characteristic	G.F.C population (n=1,108) Mean ± SD or n (%)
Age (y), n=1,108	82.9±6.1
Gender (female), n=1,108	20 (69.0)
BMI (kg/m²), n=698	25.9±5.1
Living home alone, n=1,083	460 (42.5)
Mean number of comorbidities/person	4.8±3.0
Comorbidities (all types), n=560	487 (87.0)
Heart diseases	149 (26.6)
Vascular diseases	345 (61.6)
Endocrine or metabolic disorders	145 (25.9)
Chronic pulmonary diseases	88 (15.7)
Neurological diseases	86 (15.4)
Psychiatric disorders	96 (17.1)
Renal, urological or genital disorders	142 (25.4)
Gastrointestinal or liver diseases	135 (24.1)
Osteo-articular diseases	227 (40.5)
ORL or ophthalmology disorders	130 (23.2)
Cancer or malignant blood diseases/AIDS	165 (29.5)
Fall history in last 3 months, n=285	108 (37.9)
Having any kind of human help, n=1,105	767 (69.4)
Home maid	575 (52.0)
Old age allowance	190 (17.2)

BMI, Body Mass Index; G.F.C, Geriatric Frailty Clinic; ORL, Oto-Rhino-Laryngologist

Implementation at the regional level (Midi-Pyrénées region)

The Gérontopôle in collaboration with the Midi-Pyrénées Regional Health Authority [Agence Régionale de Santé (ARS)] has deployed the activity of frailty in all the eight departments (healthcare areas) of the Midi-Pyrénées region (South-West of France).

To make this possible, we created the "Regional team for aging and prevention of disabilities" [Equipe Régionale Viellissement et Prévention de la Dépendence (ERVPD)]. This team includes not only the chair and co-chair of the departments of geriatrics of the main hospitals of the region, but also more than 700 volunteers working in the field of geriatrics [i.e., 305 physicians, 110 directors of health facilities, 59 directors of social and medical facilities (nursing home, home care…), 57 nurses…]. We have conducted multiple actions with this team on the topic of frailty and

prevention of disability. For example, we have distributed more than 70,000 brochures throughout the Midi-Pyrénées region [published by the French Mutuality (Mutualité Française)] for raising awareness about frailty and possibility to intervene.

Table 3
Baseline characteristics of the G.F.C population (n=1,108) (Tavassoli et al. J Nutr Health Aging 2014; J Nutr Health Aging 2014;18:457-64)

Characteristic	G.F.C population (n=1,108) Mean ± SD or n (%)
Frailty status, n=1,082	
Not frail	69 (6.4)
Pre-frail (1-2 criteria)	423 (39.1)
Frail (≥3 criteria)	590 (54.5)
Frailty criteria, n=1,082	2.6±1.4
Unintentional weight loss, n=1,098	358 (32.6)
Feeling of exhaustion, n=1,083	353 (32.6)
Slow gait speed, n=1,065	547 (51.4)
Decreased muscle strength, n=1,084	722 (66.6)
Sedentariness, n=1,096	665 (60.7)
MMSE score (/30), n=1,071	24.6±4.9
CDR score (/3), n=1,039	
CDR=0	353 (34.0)
CDR=0.5	531 (51.1)
CDR=1	111 (10.7)
CDR≥2	44 (4.2)
MIS score (/8), n=1,038	6.6±1.9
MIS-D score (/8), n=1,036	6.0±2.3
ADL score (/6), n=1,102	5.5±1.0
IADL score (/8), n=1,094	5.6±2.4
SPPB score (/12), n=1,063	7.3±2.9
Good performance (SPPB=10-12),	272 (25.6)
Medium performance (SPPB=7-9),	388 (36.5)
Poor performance (SPPB=0-6),	403 (37.9)
Gait speed (m/s), n=1,065	0.78±0.27
Wrist strength (kg), n=1,083	20.6±8.2
MNA score (/30), n=1,048	23.2±4.1
Good nutritional status (MNA>23.5)	550 (52.5)
Risk of malnutrition (MNA=17-23.5)	414 (39.5)
Malnourished (MNA<17)	84 (8.0)
Vitamin D concentration (ng/ml), n=1,065	18.1±11.3
≤ 10 ng/ml	343 (32.2)
11-29 ng/ml	563 (52.9)
≥ 30 ng/ml	159 (14.9)
GDS score (/15), n=424	4.8±3.1
Presence of depressive symptoms (GDS>5)	155 (36.6)
Abnormal distance vision, n=1,019	840 (82.4)
Abnormal near vision, n=1,039	232 (22.3)
Abnormal Amsler grid, n=1,060	177 (16.7)
HHIE-S score (/40), n=1,055	9.5±9.8
Significant hearing impairment (HHIE-S>21)	330 (31.3)
Urinary incontinence score (/6), n=280	1.7±1.4
Urinary disorders causing discomfort for everyday life (score≥1)	215 (76.8)
OHAT score (/16), n=271	2.8±2.4
The mouth not considered healthy (OHAT>4)	44 (16.2)

ADL, Activities of Daily Living [0 = Low (patient very dependent), 6 = High (patient independent)]; CDR, Clinical Dementia Rating (0= no dementia, 0.5= very mild dementia, 1= mild dementia, 2= moderate dementia, 3= severe dementia); GDS, Geriatric Depression Scale; G.F.C, Geriatric Frailty Clinic; HHIE-S, Hearing Handicap Inventory for the Elderly - Screening; IADL, Instrumental Activities of Daily Living [0 = Low (patient very dependent), 8 = High (patient independent)]; MIS, Memory Impairment Screen free; MIS-D, Memory Impairment Screen delayed recall; MNA, Mini Nutritional Assessment; MMSE, Mini Mental State; OHAT, Oral Health Assessment Tool; SD, Standard Deviation; SPPB, Short Physical Performance Battery.

ACTIONS AGAINST IATROGENIC DISABILITY OCCURRING DURING THE HOSPITALIZATION OF THE FRAIL OLDER ADULT

It is very well known to both health professionals and general public that hospitalizations often represent a cause for further dependency in frail older adults. However, such risk is usually accepted as a fatality. The loss of autonomy occurring during the hospitalization to the frail elder is often due to the non-adaptation of our healthcare services and infrastructures to the needs of the aging population. It is indeed a matter of raising knowledge and improving the cultural background about aging and age-related conditions among the healthcare personnel.

We have recently conducted a study at the Gérontopôle with the objective to determine the frequency, causes, and the potential for preventing iatrogenic disability (43). We assessed 503 hospitalized older persons aged 75 years and more from 105 medical and surgical units of Toulouse University Hospital (the 4th largest hospital in France). The study was conducted between October 2011 and March 2012. All the participants with a hospital stay of two days or longer were included. Iatrogenic disability (i.e., determined by the hospitalization) was defined as the loss of 0.5 points or more on the ADL scale occurring between the time from the hospital admission and the discharge. The prevalence of this condition was 11.9%. Among the 60 cases of iatrogenic disability we identified, it was judged that 49 (81.7%) could have been potentially preventable. The main factors associated with iatrogenic disability were the overuse of diapers (49.0%), the transurethral urinary catheterization (30.6%), the poor mobilization or excessive bed rest (26.5%), and lack of encouragement in the mobility

(55.1%). Due to the fact that around 30% of older adults aged 75 years and older are hospitalized each year, actions aimed at limiting iatrogenic disability may represent an important and cost-effective strategy to consider. It is urgent to systematically act, as it has been doing for other conditions (e.g., nosocomial infections).

COMMENTS AND RESEARCH DIRECTIONS: TARGETING FRAILTY TO DEVELOP INNOVATION, CLINICAL RESEARCH AND THE « SILVER ECONOMY »

Two domains appear to be of high priority to maintain autonomous living with advancing age: mobility and memory. In the recent years (and likely more in the future), the age-related mobility loss has been studied in the framework of sarcopenia. It is noteworthy that the SPRINT-T program aims to operationalize a clinical condition simultaneously combining frailty and sarcopenia. This may lead to the identification of an objective and clinical target for non-pharmacological and pharmacological interventions (e.g., myostatin inhibitors currently under development) (44).

On the other hand, if we want to fight dementia we must again work in the prevention and at its earliest stages. It is interesting that more than 50% of the older adults seen at our frailty day hospital have some objective cognitive impairment. Thus, it becomes important understanding the relationship between frailty and neurodegenerative disorders (e.g., Alzheimer's disease). This may help us at better tuning the diagnostic procedures and interventions against disabling conditions. In fact, it is possible that not all of the subjects with cognitive impairment have or will develop a neurodegenerative disorder. It is likely that their cognitive loss might be explained by other causes (e.g., vascular disease, depression, earing and visual impairment…), implicitly indicating the need of differentiating the subsequent interventions. This might foster research in the amelioration of current biomarkers of risk (e.g., those capturing the pathological features of dementias). In the next years, it is likely that a primary role as matter of research will be played by the so-called cognitive frailty (or cognitive impairment due to frailty conditions) (45).

We need to move the geriatric practice from the standard services to the field of prevention. Frail older adults indeed represent an optimal target for implementing strategies aimed are counteracting the detrimental manifestations of the aging process.

Finally, it is important to mention how the accomplishment of our ambitious objective (i.e., prevention of disability) passes through a reformulation and creation of novel resources. In the war against age-related frailty, disability and dependency, we need ad hoc clinical and research infrastructures as well as promotion of international collaborations. We need to learn from our experiences with the aim of improving our messages and strategies in the view of clinically relevant and innovative results.

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REFERENCES

1. Alzheimer Disease International: World Alzheimer Report 2013, Journey of Caring. http://www.alz.co.uk/research/WorldAlzheimerReport2013.pdf (accessed August 19, 2014).
2. Katz S, Branch LG, Branson MH, Papsidero JA, Beck JC, Greer DS. Active life expectancy. N Engl J Med 1983; 309: 1218-1224.
3. Fried TR, Bradley EH, Williams CS, Tinetti ME. Functional disability and health care expenditures for older persons. Arch Intern Med 2001; 161: 2602-2607.
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-56.
5. Rodríguez-Mañas L, Féart C, Mann G et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci 2012; 68: 62-67.
6. Morley JE, Vellas B, Abellan van Kan G et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392-397.
7. Vellas B, Cestac P, Morley JE. Implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging 2012; 16: 599-600.
8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752-762.
9. Cesari M, Vellas B, Gambassi G. The stress of aging. Exp Gerontol 2013; 48: 451- 456.
10. Bernabei R, Landi F, Gambassi G et al. Randomised trial of impact of model of integrated care and case management for older people living in the community. BMJ 1998; 316: 1348-1351.
11. Stuck AE, Minder CE, Peter-Wüest I et al. A randomized trial of in-home visits for disability prevention in community-dwelling older people at low and high risk for nursing home admission. Arch Intern Med 2000; 160: 977-986.
12. Glasziou P, Moynihan R, Richards T, Godlee F. Too much medicine; too little care. BMJ 2013; 347: f4247.
13. Moreno-Aguilar M, Garcia-Lara JMA, Aguilar-Navarro S, Navarrete-Reyes AP, Amieva H, Avila-Funes JA. The phenotype of frailty and health-related quality of life. J Frailty Aging 2013; 2: 2-7.
14. O'Connell MDL, Tajar A, O' Neill TW et al. Frailty is associated with impaired quality of life and falls in middle-aged and older European men. J Frailty Aging 2013; 2: 77-83.

15. Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing 2014; 43: 10-12.
16. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle- aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009; 64: 675-681.
17. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012; 60: 1487–92.
18. Gutman GM, Stark A, Donald A, Beattie BL. Contribution of self-reported health ratings to predicting frailty, institutionalization, and death over a 5-year period. Int Psychogeriatr 2001; 13 Supp 1: 223-31.
19. Frisoli A Jr, Chaves PH, Ingham SJ, Fried LP. Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: results from the Women's Health and Aging Study (WHAS) II. Bone 2011; 48: 952-7.
20. Bandeen-Roche K, Xue QL, Ferrucci L, Walston J, Guralnik JM, Chaves P, Zeger SL, Fried LP. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci. 2006; 61: 262-6.
21. Rantanen T, Guralnik JM, Sakari-Rantala R, Leveille S, Simonsick EM, Ling S, Fried LP. Disability, physical activity, and muscle strength in older women: the Women's Health and Aging Study. Arch Phys Med Rehabil 1999; 80: 130-5.
22. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, Hillier TA, Cauley JA, Hochberg MC, Rodondi N, Tracy JK, Cummings SR. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med 2008; 168: 382-9.
23. Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA, Dam TT, Marshall LM, Orwoll ES, Cummings SR. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. Osteoporotic Fractures in Men Research Group. J Am Geriatr Soc 2009; 57: 492-8.
24. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. BMJ 2011; 343: d6553.
25. Beswick AD, Rees K, Dieppe P, Ayis S, Gooberman-Hill R, Horwood J, Ebrahim S. Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. Lancet 2008; 371: 725-735.
26. Stuck AE, Egger M, Hammer A, Minder CE, Beck JC. Home visits to prevent nursing home admission and functional decline in elderly people: systematic review and meta-regression analysis. JAMA 2002; 287: 1022-1028.
27. Cummings SR1, Studenski S2, Ferrucci L. A diagnosis of dismobility-giving mobility clinical visibility: a Mobility Working Group recommendation. JAMA 2014; 311: 2061-2062.
28. International Conference on Frailty and Sarcopenia Research. http://www.frailty- sarcopenia.com/ (accessed August 19, 2014).
29. The Innovative Medicines Initiative. http://www.imi.europa.eu/ (accessed August 19, 2014).
30. The Journal of Frailty and Aging. www.jfrailtyaging.com/ (accessed August 19, 2014).
31. Implementing Frailty into Clinical Practice. http://www.frailty.net/ (accessed August 19, 2014).
32. Ensemble prévenons la dépendence. http://www.ensembleprevenonsladependance.fr/ (accessed August 19, 2014).
33. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012; 16: 601-608.
34. Vellas B, Balardy L, Gillette-Guyonnet S, Abellan Van Kan G, Ghisolfi-Marque A, Subra J, Bismuth S, Oustric S, Cesari M. Looking for frailty in community-dwelling older persons: the Gérontopôle Frailty Screening Tool (GFST). J Nutr Health Aging 2013; 17: 629-631.
35. Xue QL, Varadhan R. What is missing in the validation of frailty instruments? J Am Med Dir Assoc 2014; 15(2): 141-142.
36. Cesari M, Vellas B. Response to the letter to the editor: "what is missing in the validation of frailty instruments?". J Am Med Dir Assoc 2014; 15(2): 143-144.
37. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B; Platform Team. The integration of frailty into clinical practice: preliminary results from the Gérontopôle. J Nutr Health Aging. 2012; 16: 714-720.
38. Tavassoli N, Guyonnet S, Abellan Van Kan G, Sourdet S, Krams T, Soto ME, Subra J, Chicoulaa B, Ghisolfi A, Balardy L, Cestac P, Rolland Y, Andrieu S, Nourhashemi F, Oustric S, Cesari M, Vellas B and the Geriatric Frailty Clinic (G.F.C) for Assessment of Frailty and Prevention of Disability Team. Description of 1,108 Older Patients Referred by their Physician to the "Geriatric Frailty Clinic (G.F.C) for Assessment of Frailty and Prevention of Disability" at the Gerontopole. J Nutr Health Aging 2014; 18: 457-464.
39. Fiche points clés et solutions, Haute Autorité de Santé (HAS). http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-06/fiche_parcours_fragilite_vf.pdf (accessed August 19, 2014).
40. Cesari M, Demougeot L, Boccalon H, Guyonnet S, Vellas B, Andrieu S. The Multidomain Intervention to preveNt disability in ElDers (MINDED) project: rationale and study design of a pilot study. Contemp Clin Trials 2014; 38: 145-154.
41. Cesari M, Demougeot L, Boccalon H, Guyonnet S, Abellan Van Kan G, Vellas B, Andrieu S. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. PLoS One 2014; 9: e101745.
42. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, Cuffi MN, Bordes S, Gasnier Y, Robert P, Bories L, Rouaud O, Desclaux F, Sudres K, Bonnefoy M, Pesce A, Dufouil C, Lehericy S, Chupin M, Mangin JF, Payoux P, Adel D, Legrand P, Catheline D, Kanony C, Zaim M, Molinier L, Costa N, Delrieu J, Voisin T, Faisant C, Lala F, Nourhashemi F, Rolland Y, Abellan Van Kan G, Dupuy C, Cantet C, Cestac P, Belleville S, Willis S, Cesari M, Weiner MW, Soto ME, Ousset PJ, Andrieu S. MAPT Study: A Multidomain Approach for Preventing Alzheimer's Disease: Design and Baseline Data. JPAD 2014; 1: 13-22.
43. Sourdet S, Lafont C, Rolland Y, Nourhashemi F, Andrieu S, Vellas B. Preventable Iatrogenic Disability in Elderly Patients during hospitalization. PLoS One 2014; in press.
44. White TA, LeBrasseur NK. Myostatin and sarcopenia: opportunities and challenges - a mini-review. Gerontology 2014; 60: 289-93.
45. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salvà A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B; IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging 2013; 17: 726-734.

LOOKING FOR FRAILTY IN COMMUNITY-DWELLING OLDER PERSONS: THE GERONTOPOLE FRAILTY SCREENING TOOL (GFST)

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Abstract: The frailty syndrome is a pre-disability condition suitable to be targeted by preventive interventions against disability. In order to identify frail older persons at risk of negative outcomes, general practitioners must be provided with an easy and quick screening tool for detecting frailty without special effort. In the present paper, we present the screening tool for frailty that the Gérontopôle of Toulouse (France) has developed and implemented in primary care in the region with the collaboration of the Department of Family Medicine of the University of Toulouse. The Gérontopôle Frailty Screening Tool (GFST) is designed to be administered to persons aged ≥65 years with no physical disability and acute clinical disease. It is composed by an initial questionnaire aimed at attracting the general practitioner's attention to very general signs and/or symptoms suggesting the presence of an underlying frailty status. Then, in a second section, the general practitioner expresses his/her own view about the frailty status of the individual. The clinical judgment of the general practitioner is finally retained for determining the eventual presence of frailty. Preliminary data document that almost everyone (95.2%) of the 442 patients referred to the Gérontopôle frailty clinic by general practitioners using the GFST indeed presents a condition of (pre-)frailty according to the criteria proposed by Fried and colleagues in the Cardiovascular Health Study. The use of the GFST may help at raising awareness about the importance of identifying frailty, training healthcare professionals at the detection of the syndrome, and developing preventive interventions against disabling conditions.

Key words: Preventive medicine, primary care, elderly; risk factors, frailty.

INTRODUCTION

Although a growing body of literature demonstrates the high prevalence and major clinical relevance of the frailty syndrome in older adults, its implementation in the daily practice is still lacking (1, 2). Geriatric medicine is very focused at taking care of older persons with disabilities, and the attempts to anticipate the disabling cascade are still preliminary and/or not sufficiently convinced. Nevertheless, in order to reduce the burdens posed by disabilities (to the

older person as well to the public health systems), it important to preventively act, when clinical conditions of risk can still be reversed or at least attenuated. The frailty syndrome is today largely recognized as the pre-disability condition more suitable to be targeted by preventive interventions against disability (3, 4).

One of the major challenges in implementing preventive interventions against disability resides in the need of re-designing part of the current clinical standards. In fact, the detection of frailty can be adequately conducted only by anticipating the "medicalization" of the older subject. Leaving undetected and/or untreated the frailty syndrome means delaying possible interventions, rendering potentially irreversible the process directed towards the spiral cascade of disability. For this reason, it is necessary to take adequate countermeasures as soon as the first signs/symptoms of frailty become manifest. In other words, it is needed to identify subjects at risk before their vulnerability is made evident by the onset of a major clinical event (e.g., falls, emergency room admissions, hospitalizations). In this context, a key role is played by general practitioners, primary referents for the individual's health as well as crucial for the implementation of every preventive action. Regrettably, the general practitioner's activity is often too busy to foresee the addition of new tasks or clinical duties to the daily routine. To efficiently and correctly identify frail older persons among his/her patients, the general practitioner must be supported, starting with the provision of an easy and quick screening tool for detecting the frailty status without special effort.

As previously described (5), since October 2011, we have developed in Toulouse (France) an innovative clinical setting specifically focused at targeting frailty with the aim of preventing incident disability in community-dwelling older persons. Such initiative, highly responsive to public health demands (6), has been designed and developed by the Gérontopôle and the Department of Family Medicine of the University of Toulouse. General practitioners in the Toulouse area have been first educated to the concept of frailty and the importance of detecting it in clinical practice. Then, they have been trained at the use of a specifically developed screening tool assisting their evaluation.

The Gérontopôle Frailty Screening Tool (GFST, Table 1) is designed to be applied to older persons (aged 65 years and older) with no physical disability (defined by complete preservation of the Activities of Daily Living (7)) and acute clinical disease. Two different parts compose the instrument. The first one appears as a questionnaire. Its main objective is to attract the general practitioner's attention to very general signs and/or symptoms potentially indicating the presence of an underlying frailty status. These questions largely mirror the criteria that are commonly used to operationalize the frailty status (8, 9). For example, they remind the general practitioner to pay attention to the gait speed and mobility of the individual, his/her weight stability, or the possible presence of exhaustion. This part also contains a specific question about eventual memory complaints of the subject (in agreement with current evidence linking the cognitive and physical domain in the determination and manifestation of frailty (10-13)) and another one about the social status of the person (a major component to consider in the design of preventive interventions against disability (14, 15)).

This preliminary, almost pedagogic, section is then followed by a second part in which the general practitioner expresses his/her own view about the frailty status of the individual. The clinical judgment of the general practitioner is here used to determine whether, after the evaluation of the previous criteria, he/she indeed believes the person is frail or not. Only if he/she agrees with the results of the first section identifying the possible presence of frailty, the intervention is proposed.

It might be argued that the design of the GFST may leave the detection of frailty to the subjective perception of the general practitioner. Such choice is mainly motivated by two reasons: 1) to avoid that a major clinical decision (i.e., referral of the individual to a clinical intervention) is solely left to a screening tool, and 2) to directly involve the general practitioner in the diagnosis and subsequent follow-up of the detected condition. Moreover, although the final decision is left to the clinical judgment of the general practitioner, it is still driven by the preliminary section listing the main defining criteria of the frailty syndrome.

In the context of Toulouse, taking action after the identification of frailty means explaining the subject the opportunity to undergo a multidisciplinary clinical assessment at the dedicated platform of the Gérontopôle (5). Here, the individual is comprehensively evaluated by a team of different healthcare professionals (i.e., geriatrician, nurse, neuropsychologist, physical therapist, dietician) with the objective of designing a personalized plan of intervention against disability.

The instrument provided by the Gérontopôle to the general practitioners of the Toulouse area is not yet validated. In particular, we do not know exactly how many false negatives were excluded from the preventive intervention at the platform. Current studies are ongoing to fill this gap. Nevertheless, the GFST has shown to adequately support the identification of frailty in community-dwelling older persons. In fact, data from the first 442 participants evaluated at the platform show that almost everyone (95.2%) resulted pre-frail (31.1%) or frail (64.1%) according to the criteria proposed by Fried et al. (8). Less than 5% was incorrectly referred to the platform as being robust or already disabled in the Activities of Daily Living. It is also noteworthy the high acceptance that the instrument had among

general practitioners, especially because not time- consuming or invasive of their clinical decisions and daily practice. All this implies that, after training the general practitioners at the detection of frailty, their clinical judgment may suffice at accurately estimating the risk profile of the older individual and seek for support. The use of the instrument we propose will likely become unnecessary once that the concept of frailty will be better established, the healthcare professionals will have familiarized with the detection of the syndrome, and specifically devoted clinical settings for its assessment/treatment will be available. At this time, we believe the GFST might optimally serve to diffuse knowledge about the detrimental syndrome of frailty, and render general practitioners more active in the promotion of preventive interventions against disability in older persons.

Table 1

The Gérontopôle Frailty Screening Tool (GFST)

Toulouse GÉRONTOPÔLE

Patients aged 65 years and older without both functional disability (Activities of Daily Living score ≥5/6) and current acute disease

	YES	NO	Do not know
Does your patient live alone?	❑	❑	❑
Has your patient involuntarily lost weight in the last 3 months?	❑	❑	❑
Has your patient been more fatigued in the last 3 months?	❑	❑	❑
Has your patient experienced increased mobility difficulties in the last 3 months?	❑	❑	❑
Has your patient complained of memory problems?	❑	❑	❑
Does your patient present slow gait speed (i.e., >4 seconds to walk 4 meters)?	❑	❑	❑

If you have answered YES to one or more of these questions:			
Do you think your patient is frail?	YES ❑	NO ❑	
If YES, is your patient willing to be assessed for his/her frailty status at the Frailty Clinic?	YES ❑	NO ❑	

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REFERENCES

1. Vellas B, Cestac P, Moley JE. Implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging 2012; 16: 599-600.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752-762.
3. Morley JE, Haren MT, Rolland Y, Kim MJ. Frailty. Med Clin North Am 2006; 90: 837-847.
4. Cesari M. Frailty and aging. J Frailty Aging 2012; 1: 3-5.
5. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B. The integration of frailty into clinical practice: preliminary results from the gérontopôle. J Nutr Health Aging 2012; 16: 714-720.
6. Ferrucci L, Guralnik JM, Studenski S et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. J Am Geriatr Soc 2004; 52: 625-634.
7. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963; 185: 914-919.
8. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-56.
9. Morley JE, Abbatecola AM, Argiles JM et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 2011; 12: 403-409.
10. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc 2010; 58: 248-255.
11. Avila-Funes JA, Pina-Escudero SD, Aguilar-Navarro S, Gutierrez-Robledo LM, Ruiz-Arregui L, Amieva H. Cognitive impairment and low physical activity are the components of frailty more strongly associated with disability. J Nutr Health Aging 2011; 15: 683-689.
12. Houles M, Canevelli M, Abellan Van Kan G, Ousset PJ, Cesari M, Vellas B. Frailty and cognition. J Frailty Aging 2012; 1: 56-63.
13. Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline - a four-year prospective study in 2737 cognitively normal older adults. J Nutr Health Aging 2011; 15: 690-694.
14. Barusch A, Waters DL. Social engagement of frail elders. J Frailty Aging 2012; 1: 189-194.
15. Gutierrez-Robledo LM, Avila-Funes JA. How to include the social factor for determining frailty? J Frailty Aging 2012; 1: 13-17.

THE INTEGRATION OF FRAILTY INTO CLINICAL PRACTICE: PRELIMINARY RESULTS FROM THE GÉRONTOPÔLE

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Abstract: Background: Disability is commonly considered as an irreversible condition of advanced age. Therefore, preventive actions need to be taken before the disabling cascade is fully established, that is in the pre- disability phase defined "frailty syndrome". The complexity and heterogeneity of frailty requires a clinical approach based on multidimensionality and multidisciplinary. In this paper, we present the main characteristics of the newborn Platform for Evaluation of Frailty and Prevention of Disability (Toulouse, France). Intervention: Persons aged 65 years and older screened for frailty by general practitioners in the Toulouse area are invited to undergo a multidisciplinary evaluation at the Platform. Here, the individual is multidimensionality assessed in order to preventively detect potential risk factors for disability. At the end of the comprehensive evaluation, the team members propose the patient (in agreement with the general practitioner) a preventive intervention program specifically tailored to the his/her needs and resources. Results: Mean age of our population is 82.7 years, with a large majority aged 75 years and older. Most patients are women (61.9%) Approximately two thirds of patients received any kind of regular help. Regarding level of frailty, 65 patients (41.4%) were pre-frail, and 83 (52.9%) frail. For what concerns the functional status, 83.9% of patients presented slow gait speed, 53.8% were sedentary, and 57.7% had poor muscle strength. Only 27.2% of patients had a SPPB score equal to or higher than 10. Autonomy in ADL was quite well preserved (mean ADL score 5.6 ± 0.8) as expected, suggesting that the patients of the platform have not yet developed disability. Consistently, IADL showed a marginal loss of autonomy reporting a mean score of 6.0 ± 2.3. About one third of patients (33.1%) presented a MMSE score lower than 25. Dementia (measured by the CDR scale) was observed in 11.6% of the platform population, whereas subjects with mild cognitive impairment (that is CDR equal to 0.5) were 65.8%. New diagnosed depressive disorders were relatively rare with only 3.2% of patients showing signs of depression but some people were already treated. Numerous patients presented vision problems with 10.4% having abnormal findings at the Amsler grid. Finally, it is noteworthy that 9% of the platform population presented an objective state of protein-energy malnutrition, 34% an early alteration of nutritional status, while almost everyone (94.9%) had a vitamin D deficiency (partially explained by the period of the year, that is winter-spring, of most of the measurements). Conclusion: The Platform clinically evaluates and intervenes on frailty for the first time at the general population-level. This

model may serve as preliminary step towards a wider identification of early signs of the disabling cascade in order to develop more effective preventive interventions.

Key words: Frailty, elderly, prevention, disability, evaluation.

INTRODUCTION

Since the beginning of the 20th century, when first Nascher proposed the birth of the novel medical discipline, geriatrics has been specifically focused at taking care of older persons experiencing the heavy burden of age-related diseases (1). Up to few years ago, the geriatrician was in charge of assisting (i.e., evaluating and treating) those patients which could not be adequately followed in any other specialty due to their comorbidities, polypharmacy, social issues, and functional impairment. In particular, the average geriatric patient has commonly been for a long time an older person at advanced age already presenting relevant disabling conditions, significantly impairing his/her capacity to conduct an autonomous life. In other words, geriatric patients frequently experienced those conditions and/or clinical outcomes for which they were automatically excluded from standard interventions proposed at younger ages. Moreover, the primary outcome of disability significantly differentiates geriatric medicine from other specialties. This end-point (also considering the characteristics of the subjects at risk of developing it) imposes the adoption of alternative approaches and choice of different interventions, often in contrast with the so-called "evidence-based medicine".

Disability is commonly considered an irreversible condition in older persons. It is a clinical issue representing a priority for public health systems of developed countries. In fact, besides of posing severe burdens to the patient's quality of life, disability is associated with high healthcare costs (2). The detrimental effects (at both person- and society-level) of disability should be considered in the wider scenario of our aging societies. In this way, it becomes clear why we cannot anymore wait for assessing the standard geriatric patient already disabled, but we should preventively act before the irreversible disabling cascade is in place.

For this reason, during the last two decades, a growing body of literature has been specifically focused at exploring the "frailty syndrome". Frailty is commonly defined as a geriatric syndrome characterized by the reduction of physiological reserves and capacities of an individual needed to adequately face exogenous and endogenous stressors. Such condition poses the subject at increased risk of negative health-related events, including hospitalization, institutionalization, and disability. In particular, frailty is usually considered as a pre-disability state which, differently from disability, is still amenable for interventions and reversible (3).

On the basis of this novel concept, the heterogeneous older population was subsequently categorized into three subgroups to better design and develop person-tailored interventions: Older persons were then considered "disabled" if needing assistance in the accomplishment of basic activities of daily living, "frail" if presenting limitations and impairments in the absence of disability, and "robust" if no frailty or disability were present.

To translate the theoretical concept of frailty into practice, Fried et al. (3) proposed a model combining the evaluation of the following five criteria: sedentariness, involuntary weight loss, fatigue, poor muscle strength, and slow gait speed. According to this instrument, an older person is considered "frail" if presenting three or more of these defining criteria.

The identification of a pre-disability state (i.e., frailty) allows the detection of older persons at risk of negative events that may still benefit from preventive interventions against disability. This new concept of frailty modifies the common geriatric approach by leading it towards the importance of prevention, a field that was not possible to adopt in the past when only irreversible conditions came to the geriatrician evaluation. At the same time, the definition of a biological age provides the basis for identifying persons who indeed need the evaluation of a geriatrician, redirecting to the different specialties those who can be followed and treated using standard protocols because only an graphically old.

The "gold standard" intervention adopted in geriatric medicine is surely represented by the comprehensive geriatric assessment (CGA). The CGA consists of a global evaluation of the older patient performed by a multidisciplinary team finally resulting in the design of a person-tailored preventive or therapeutical intervention. Since the CGA is conducted using standardized scales and instruments, there is the possibility to evaluate the efficacy of the proposed interventions over time and more efficiently follow-up the patient.

In 1984, Rubenstein et al (4) first showed that CGA had a beneficial impact on institutionalization and mortality of older persons. Few years later, the meta-analysis by Stuck et al. (5) on 28 clinical trials confirmed such positive results extending them on multiple outcomes, including mortality, hospital admissions, cognitive decline, and functional impairment. In 2004, a randomized trial studied the effects of CGA (and CGA- derived interventions) in individuals aged 74 years and older in primary care (6). Interestingly, the study confirmed the idea that frailty is a reversible con-

dition (27.9% of frail individuals were no longer frail after the intervention).

Despite the importance of preventing disability, the implementation of frailty in the clinical setting is still limited. Major difficulties at preventively act against disability reside in:

1-The need to design a different geriatric approach to the older patient. In fact, as above-mentioned, the geriatrician cannot anymore wait to visit the (already disabled) patient, but preventively evaluate the health status of the older subject. This implies the need of a close collaboration between family physicians and geriatrics facilities in order to promptly detect the early signs of the disabling cascade and preventively act at the general population-level (7). In other words, the frailty detection and treatment are directed towards community- dwelling older persons which are not yet "medicalized" and may even not feel the immediate need of a clinical assessment.

2-The still limited recognition of frailty as a valid clinical condition (thus, to detect, measure, and treat). The novelty of frailty has raised intense debates about its nature and operational definition. Nevertheless, its theoretical background is today sufficiently strong to recommend the assessment of frailty in the clinical practice (8, 9).

In these last years, the French government has defined a new policy for preventing disability in older persons. To address this national (but even wider) public health issue, the geriatric center of Toulouse (i.e., the Gérontopôle of the Centre Hospitalier Universitaire de Toulouse) in association with the university Department of General Medicine of Toulouse (DUMG) and the regional health authority (Agence Regionale de Santé -ARS- Midi-Pyrénées) designed and developed an innovative Platform for the Evaluation of Frailty and the Prevention of Disability. Such platform is specifically aimed at supporting the comprehensive and multidisciplinary assessment of frail older persons. The identification of the specific causes of the increased status of vulnerability allows the multidisciplinary team to design a patient-tailored preventive plan of intervention against disability. In the present paper, we describe the platform structure and organization, and provide the main characteristics of the first 160 patients evaluated during the first eight months of operation.

THE STRUCTURE OF THE PLATFORM

The Platform for the Evaluation of Frailty and the Prevention of Disability was started in October 2011 as a separate activity of the geriatric day hospital unit of the Gérontopôle of Toulouse. It is currently hosted in four rooms (two clinical offices for the evaluation of patients and blood drawn, a waiting room and an administrative office) located at the Hospital Garonne (Toulouse, France). The platform currently accommodates up to four patients per day, five days per week. However, starting from January 2013, the platform will be able to evaluate up to eight patients per day, five times per week, at the new site of the Hospital La Grave (Toulouse, France).

Each patient evaluated at the platform must be referred by a physician detecting signs or symptoms of frailty in him/her. This service is paid by the social security health system to the hospital. As we can see in the results sections, the frail older adults referred to the platform have already some underlying diseases witch really need to be diagnosed. The platform provides the patient's assessment, treatment, and follow-up in close connection with family physicians. After one and three months from the evaluation, the platform staff contacts the patient (or his/her proxies) to make sure that the proposed interventions have been adopted and to estimate possible modifications of his/her health status.

Identification of the frail elderly person

Numerous screening tools are currently available to detect frailty in older persons, most of them primarily used in clinical research (10). Although several operational definitions have been developed over the last decade to support clinicians and researchers at objectively screening older persons for frailty, a controversy exists about the optimal instrument to be adopted (11). The major reason for such difficulties at reaching an agreement probably resides in the multidimensional nature of the frailty syndrome (12). This has led to the proposal of multiple tools, each one constitued by specific sets of items or tasks providing different phenotypes of frailty. For example, a panel of experts proposed gait speed as a possible parameter to screen frailty in older persons. After all, its predictive value for adverse outcome is widely demonstrated (13, 14). The adoption of physical performance tests in the screening of older persons at risk of health-related events has been proposed as preliminary step towards a structural reorganization of healthcare provision (15).

In a previous study, we explored the feasibility of a questionnaire screening frailty among general practitioners. The instrument was based on the gait speed test and proposed by 50 physicians of the Midi-Pyrénées region (France). The instrument was largely well accepted. However, two difficulties were mainly reported in the implementation of the instrument: finding a 4-meter track in the physician's office to measure gait speed, and the addition of a novel screening tool in the already busy practice (due to the complexity of patients) (16).

Taking into account data from literature and results from such preliminary survey, we developed a questionnaire to be used by general practitioners for screening frailty. In particular, it takes into account the physician's subjective perception of the patient's frailty status together with functional, social, cognitive, nutritional factors (Table 1). The

questionnaire was design to highlight the importance of the general practitioner in the definition of the frailty status of the individual. This was done by rendering of primary importance the clinical subjective feeling of the physician in the definition of the questionnaire result.

Table 1
Questionnaire for the detection of frail older patients used by general practitioners

Patients aged 65 years and over, independent (ADL 6/6), with no current acute disease			
SCREENING			
	YES	NO	DON'T KNOW
Does your patient live alone?	❑	❑	❑
Has your patient lost weight in the last 3 months?	❑	❑	❑
Has your patient felt more tired in the last 3 months?	❑	❑	❑
Has your patient found it more difficult to go around in the last 3 months?	❑	❑	❑
Does your patient complain of memory problems?	❑	❑	❑
Does your patient have a slow gait speed (more than 4 seconds to walk 4 meters)?	❑	❑	❑
=> If you have answered YES to one of these questions:			
Do you think your patient is frail?:	❑ YES	❑ NO	
If YES, does your patient agree to evaluation of his/her frailty in day hospital?	❑ YES	❑ NO	

The definition of frailty

Consistently with its wide use, the primary instrument to measure frailty at the platform is the operational definition proposed by Fried and colleagues and validated in the Cardiovascular Health Study (1). In particular, we define its five constituting criteria as follows:

– Involuntary weight loss is detected by asking "Have you involuntarily lost weight during the past months?" Current weight and self-reported usual weight are also recorded.
– Fatigue is defined by the patient's answers "often" or "most of the time" to the following two items, part of the CES-D scale: "During the last two weeks I felt that everything I did was an effort", and "During the last two weeks I felt that I could not get going".
– Sedentariness is assessed by administering the following question to the patient: "What is your current level of physical activity?". The patient can answer: No physical activity (confined to bed); Rather sedentary, some short walks or other exercise of very light intensity; Light intensity exercise (walking, dancing, fishing or shooting, shopping on foot) at least 2 to 4 hours a week; Moderate intensity exercise (running, walking uphill, swimming, gardening, cycling) for 1 to 2 hours a week, or light intensity exercise (walking, dancing, fishing or shooting) for more than 4 hours a week; Moderate intensity exercise more than 3 hours a week; Vigorous exercise several times a week. By answering the question, the participant is instructed that light intensity exercise does not cause sweating and does not prevent conversation, moderate intensity exercise causes sweating and conversation is not possible, and vigorous exercise involves maximum effort. Although this specific question is not validated, it has previously been used in literature to define sedentariness and physical activity levels in older persons (17, 18).
– Slow usual gait speed is measured after testing the patient over a 4-meter long track. Slow gait speed is considered as present if the patient takes more than 4 seconds (i.e., gait speed slower than 1 meter/second) to complete the task.
– Poor muscle strength is measured by a hand-held dynamometer. The gender- and body mass index-specific cut-points originally provided by Fried and colleagues (3) are used to identify subjects presenting this criterion of frailty.

The patient is considered frail if he/she presents three or more of these criteria, pre-frail if only one or two criteria are present.

Causes of frailty

The evaluation of the patient at the platform is primarily conducted by the geriatrician (or a general practitioner specifically formed in geriatrics) and a nurse. Sociodemographic (including living environment), anthropometric, and clinical (medical and surgical history, current treatments and allergies) are recorded. Moreover, all patients undergo a blood drawn for standard laboratory assessment (including vitamin D concentrations, and special tests if required by the patient's clinical conditions) and an electrocardiogram.

The evaluation includes the administration of the following questionnaires/scales objectively measuring the specific capacities of the person:

– Cognition: Memory Impairment Screen (free and delayed recall), AD8 Dementia Screening Interview (19), Mini Mental State (MMSE) (20), Clinical Dementia Rating (CDR) (21);

– Physical function: scales of disability in basic Activities of Daily Living (ADL) (22) and Instrumental ADL (IADL) (23), measures of physical performance (Short Physical Performance Battery, SPPB (24), Pepper Assessment Tool for Disability, PAT-D (25);
– Nutritional status: Mini Nutritional Assessment (MNA) (26);
– Mood: the Covi and Raskin scales for anxiety and depression (27, 28);
– Vision and hearing: Parinaud's scale (near vision), Monoyer's scale (distant vision), Amsler grid (detection of age-related macular degeneration, AMD), and the Hearing Handicap Inventory for the Elderly - Screening version (HHIES) (29).

The platform will soon receive a retinal camera to allow a more accurate detection of AMD and to screen other vision conditions (such as glaucoma). Moreover, a last generation dual energy X-ray absorptiometry (DXA) device, an I-DXA for the study of body composition and bone mineral density will be shortly implemented in the daily practice of the platform.

According to the results of the screening questionnaires/scales and the geriatrician clinical visit, additional evaluations might be proposed. For example, according to the patient's needs, a neuropsychiatrist, an ophtalmologist, a nutritionist, a physical therapist, a dentist, or a social assistant may be directly and promptly involved to complete the assessment and improve the definition of the subsequent plan of intervention.

At the end of the multidisciplinary evaluation, the geriatrician of the platform summarizes the results of all the performed evaluations to prepare a personalized intervention plan for the patient. The family practitioner of the patient is also immediately informed about the results of the visits to share with him the visit conclusions. Moreover, in the attempt of increasing the patient's adherence to the intervention and facilitate the follow-up, an appointment is readily taken for the patient with his/her own general practitioner within the following 15 days.

Interventions proposed

The plan of intervention proposed by the platform are specifically designed and adapted to each patient's resources and needs according to the results of the multidisciplinary evaluation. The comprehensive evaluation of frailty leads to the identification of potential risk factors for negative health- related events in different domains of the older patient's health. In particular, the possible causes for the increased vulnerability may consist of undiagnosed diseases or risk factors (at least partially linked to the aging process). When an unknown disease is detected, the patient is directed towards the specialist's evaluation for further investigation (if needed) and/or a specific treatment proposed.

Differently, if a risk factor is found, it is discussed with the patient to make him/her aware about its possible consequences. Such education of the patient is parallel with the plan of intervention that will be proposed. In fact, it will include behavioural and therapeutical suggestions to correct the specific risk factor according to the clinical priorities given by the physician. For example, if a risk of malnutrition is detected by the MNA at the preliminary assessment (i.e., frailty in the nutritional domain), the nutritionist (also on the basis of the objective data collected during the preliminary visit) may provide the patient with specific recommendations to improve his/her dietary intake. Similarly, in case of issues in the physical domain of the patient (e.g., sedentariness), the physical therapist may simply suggest specific exercises that can easily increase the physical activity level of the patient as well as fitness centers in the patient's neighbourhood. In the same way, a person with social issues may find specific support and information to reduce the barriers at the basis of his/her frailty status. In this context, it is noteworthy that the close relationship established between the platform with the administrative and healthcare authorities has allowed the creation of multiple possible alternatives in order to offer preventive protocols against disability.

The approach of targeting the specific issues of the patients raised at the end of a comprehensive geriatric assessment performed by a multidisciplinary team mirrors what has been previously shown to be particularly beneficial in frail older persons (5, 30, 31). Nevertheless, this is the first time that this model is exported and officially implemented in the primary prevention of disability.

Patients' follow-up

To make sure that the proposed recommendations are followed and to also determine their efficacy, a close follow-up is organized for all the patients undergoing the platform assessment. First, a phone contact is made the same day of the evaluation with the general practitioner to briefly explain the proposed plan of intervention and discuss possible therapeutical modifications. The general physician will also receive a detailed letter with all the results of the platform evaluation. An appointment is also organized for the patient with his/her own general practitioner within two weeks. One month after the platform evaluation, a nurse phones the patient to verify the put in place of the recommendations and facilitate the solution of possible issues. This first phone contact is also important to boost the attitude of the patient at improving his/her health status through the adoption of the proposed healthier lifestyle habits. At three months from the initial evaluation, a specifically trained nurse carries out a second phone evaluation. This is specifically focus at administering the PAT-D scale (25). This is a 23-item validated instrument

measuring the physical function of older persons. It has already been adopted in several trials with special focus on disability prevention. The patient rates his/her ability on a six-point Likert scale, ranging from 'able to perform an activity without difficulty' to 'unable'. If the physical function of the patient is deteriorated compared to the baseline evaluation, specific actions are taken from a new contact with the general practitioner to discuss the case, to the reservation of a out-patient clinical visit for the re-revaluation of the patient. Throughout the follow-up, the patient will continue having the general practitioner as primary referent for his/her health status.

Clinical research

Elderly persons who are frail and pre-frail often present aging-related disorders that are still at an early stage. Thus, as mentioned above, they can still benefit from early, innovative interventions. In this context, the platform plays an important role for research. In fact, the standardized and objective assessment conducted in the platform patients makes possible the creation of a unique database of community-dwelling older persons to study the biological and clinical foundations of the frailty syndrome. Moreover, the structured follow-up of patients allows the evaluation over time of the efficacy of the innovative interventions (e.g., novel medications, biotechnologies, telemedicine…) that will be made available. The conduction of clinical studies is also facilitated because the cohort of patients evaluated at the platform will allow the creation of ancillary projects testing specific hypotheses in a very cost-effective fashion. Finally, the detailed database of patients will constitute an important resource to easily find and contact possible candidates to future clinical trials.

THE PLATFORM POPULATION

The description of the main characteristics of the first 160 patients recruited during the first months of activity of the platform are reported in Table 2 and Table 3. Mean age of our population is 82.7 years, with a large majority aged 75 years and older. Most patients are women (61.9%) Approximately two thirds of patients received any kind of regular help. Only 14.1% received old age allowance.

Table 2

Socio-demographics characteristics of the first 160 patients evaluated during the first 6 months of operation of the platform

Characteristics	Mean (SD) or n (%)
Gender, n=160	
Woman	99 (61.9)
Man	61 (38.1)
Age (years), n=160	82.7 ± 6.1
<75	14 (8.7)
75-84	92 (57.5)
>85	54 (33.7)
Education, n=158	
Higher education	44 (27.8)
Senior high school	30 (20.9)
Junior high school	13 (8.2)
Primary school	64 (40.5)
No school attendance	4 (2.5)
Marital status, n=160	
Single	15 (9.4)
Divorced	11 (6.9)
Married	67 (41.9)
Separated	2 (1.2)
Widowed	63 (39.4)
Living with partner	2 (1.2)
Living environment, n=160	
Assisted living facility	6 (3.8)
Nursing home for dependent elderly	5 (3.1)
At home (communal home)	61 (38.1)
At home (individual home)	88 (55.0)
Help at home, n=160	
Yes	106 (66.2)
Kind of help, n=106	
Home help	55 (51.9)
Visiting nurse	12 (11.3)
Physical therapist	7 (6.6)
Old age allowance	15 (14.1)
Other	17 (16.0)

Table 3
Clinical characteristics of the first 160 patients evaluated during the first 6 months of operation of the platform

Characteristics	Mean (SD) or n (%)
Frailty status (according to Fried criteria), n=158	
Not frail	9 (5.7)
Pre-frail (1-2 criteria)	65 (41.4)
Frail (≥3 criteria)	83 (52.9)
Frailty criteria (according to Fried criteria)	
Recent weight loss, n=158	52 (32.9)
Feeling of exhaustion, n=157	49 (31.2)
Decreased muscle strength, n=156	90 (57.7)
Slow gait speed, n=155	130 (83.9)
Sedentarity, n=158	85 (53.8)
MMSE score (/30), n=154	25.4 ± 4.2 (12-30)
<20	19 (12.3)
20-24	32 (20.8)
25-27	41 (26.6)
>=28	62 (40.2)
CDR score, n=155	
0	35 (22.6)
0.5	102 (65.8)
1	14 (9.0)
2	4 (2.6)
MIS score (/8), n=157	6.4 ± 1.9 (0-8)
MIS-D score (/8), n=155	5.5 ± 2.6 (0-8)
AD-8 score (/8), n=157	3.3 ± 2.3 (0-8)
ADL score (/6), n=159	5.6 ± 0.8 (1-6)
IADL score (/8), n=159	6.0 ± 2.3 (0-8)
SPPB score (/12), n=157	7.4 ± 2.9 (0-12)
Good (score 10-12)	43 (27.2)
Medium (score 7-9)	53 (33.7)
Poor (score 0-6)	61 (38.8)
Gait speed (m/sec), n=155	0.8 ± 0.2 (0.2-1.3)
<0.6 m/sec	38 (24.5)
0.6 to 0.79 m/sec	43 (27.7)
0.8 to 1.0 m/sec	49 (31.6)
> 1.0 m/sec	25 (16.1)
Abnormal distant vision, n=140	107 (76.4)
Abnormal near vision, n=129	42 (32.5)
Abnormal Amsler grid, n=153	16 (10.4)
HHIES score (/40), n=152	7.1 ± 10.1 (0-40)
No disability	106 (69.3)
Moderate disability	26 (17.0)
Severe disability	21 (13.7)
Raskin score (/12), n=155	7.4 ± 2.9 (0-11)
Signs of depression	5 (3.2)
Nutritional status (MNA), n=157	89 (56.9)
Good (MNA ≥24)	54 (34.2)
Risk of malnutrition (MNA 17 to 23.5)	14 (8.9)
Malnourished (MNA <17)	
Vitamin D status, n=157	14.8 ± 10.1 (4-59)
≤ 10 ng/ml	73 (46.5)
11-29 ng/ml	76 (48.4)
≥ 30 ng/ml	8 (5.1)

Regarding level of frailty, 65 patients (41.4%) were pre-frail, and 83 (52.9%) frail. The fact that 93.3% of the subjects addressed in the platform are frail or pre frail implies the capacity of the screening questionnaire of adequately detect true positives in the general population.

For what concerns the functional status, 83.9% of patients presented slow gait speed, 53.8% were sedentary, and 57.7% had poor muscle strength. Only 27.2% of patients had a SPPB score equal to or higher than 10. Autonomy in ADL was quite well preserved (mean ADL score 5.6 ± 0.8) as expected, suggesting that the patients of the platform have not yet developed disability. Consistently, IADL showed a marginal loss of autonomy reporting a mean score of 6.0 ± 2.3. About one third of patients (33.1%) presented a MMSE score lower than 25. Dementia (measured by the CDR scale) was observed in 11.6% of the platform population, whereas subjects with mild cognitive impairment (that is CDR equal to 0.5) were 65.8%. New diagnosed depressive disorders were relatively rare with only 3.2% of patients showing signs of depression but some people were already treated. Numerous patients presented vision problems with 10.4% having abnormal findings at the Amsler grid. Thirteen percent of patients had a hearing loss.

Finally, it is noteworthy that 9% of the platform population presented an objective state of protein-energy malnutrition, 34% an early alteration of nutritional status, while almost everyone (94.9%) had a vitamin D deficiency (partially explained by the period of the year, that is winter-spring, of most of the measurements).

CONCLUSION

To prevent disability, frail older patients need to be identified and specifically evaluated starting from the general population through a close collaboration between general practitioners and ad-hoc geriatric infrastructures. The platform we designed and developed at Toulouse proposes preventive and therapeutical interventions, supports families and caregivers, and interacts with the general practitioners in order to optimize the management of the frail older patient. Our next objective will be the evaluation of the cost-effectiveness analysis of the platform and the evaluation of its clinical effectiveness over the long-term, in

particular for the primary outcome of physical disability prevention.

Our preliminary results from the first 160 patients we assessed should encourage the promotion of frailty to the level of a clinically relevant condition. The identification and management of frail elderly is nowadays a clinical priority, which can no longer wait.

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REFERENCES

1. Clarfield AM (1990) Dr. Ignatz Nascher and the birth of geriatrics. CMAJ 143(9):944-948.
2. Fried TR, Bradley EH, Williams CS, Tinetti ME (2001) Functional disability and health care expenditures for older persons. Arch Intern Med 161(21):2602-2607.
3. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al (2011) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56(3):M146-156.
4. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL (1984) Effectiveness of a geriatric evaluation unit. A randomized clinical trial. N Engl J Med 311(26):1664-1670.
5. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ (1993) Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 342(8878):1032- 1036.
6. Monteserin R, Brotons C, Moral I, Altimir S, San José A, Santaeugenia S, et al (2010) Effectiveness of a geriatric intervention in primary care: a randomized clinical trial. Fam Pract 27(3):239-245.
7. Vellas B, Cestac P, Moley JE (2012) Editorial: implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging 16(7):599-600.
8. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. (2012) Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci.
9. Cesari M (2012) Frailty and Aging. J Frailty Aging. 3-6.
10. De Vries NM, Staal JB, van Ravensberg CD, Hobbelen JSM, Olde Rikkert MGM, Nijhuis-van der Sanden MWG (2011) Outcome instruments to measure frailty: a systematic review. Ageing Res Rev 10(1):104-114.
11. Pel-Littel RE, Schuurmans MJ, Emmelot-Vonk MH, Verhaar HJJ (2009) Frailty: defining and measuring of a concept. J Nutr Health Aging 13(4):390-394.
12. Cesari M (2011) The multidimentionality of frailty: many faces of one single dice. J Nutr Health Aging 15(8):663-664.
13. Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, et al (2009) Gait speed at usual pace as a predictor of adverse outcomes in community- dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 13(10):881-889.
14. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al (2011) Gait speed and survival in older adults. JAMA 305(1):50-58.
15. Lafont C, Gérard S, Voisin T, Pahor M, Vellas B (2011) Reducing « iatrogenic disability » in the hospitalized frail elderly. J Nutr Health Aging 15(8):645-660.
16. Subra J, Rougé-Bugat M-E (2012) Gait speed: a new « vital sign » for older persons in primary care. J Frailty Aging 1(2):50-58.
17. Patel KV, Coppin AK, Manini TM, Lauretani F, Bandinelli S, Ferrucci L, et al (2006) Midlife physical activity and mobility in older age: The InCHIANTI study. Am J Prev Med 31(3):217-224.
18. Cesari M, Leeuwenburgh C, Lauretani F, Onder G, Bandinelli S, Maraldi C, et al (2006) Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr 83(5):1142-1148.
19. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, et al (2005) The AD8: a brief informant interview to detect dementia. Neurology 65(4):559-564.
20. Folstein MF, Folstein SE, McHugh PR (1975) « Mini-mental state ». A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3):189-198.
21. Morris JC (1997) Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr Suppl 1:173-176; discussion 177-178.
22. Katz S, Ford AB, Moskovitz RW, Jackson BA, Jaffe MW (1963) Studies of Illness in the Aged. the Index of Adl: A Standardized Measure of Biological and Psychosocial Function. JAMA 185:914-919.
23. Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9(3):179-186.
24. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 49(2):M85-94.
25. Rejeski WJ, Ip EH, Marsh AP, Miller ME, Farmer DF (2008) Measuring disability in older adults: the International Classification System of Functioning, Disability and Health (ICF) framework. Geriatr Gerontol Int 8(1):48-54.
26. Guigoz Y, Vellas B (1999) The Mini Nutritional Assessment (MNA) for grading the nutritional state of elderly patients: presentation of the MNA, history and validation. Nestle Nutr Workshop Ser Clin Perform Programme 1:3-11; discussion 11-12.
27. Lipman RS, Covi L (1976) Outpatient treatment of neurotic depression: medication and group psychotherapy. Proc Annu Meet Am Psychopathol Assoc (64):178-218.
28. Raskin A, Schulterbrandt J, Reatig N, McKeon JJ (1969) Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. J Nerv Ment Dis 148(1):87-98.
29. Sindhusake D, Mitchell P, Smith W, Golding M, Newall P, Hartley D, et al (2001) Validation of self-reported hearing loss. The Blue Mountains Hearing Study. Int J Epidemiol 30(6):1371-1378.
30. Stuck AE, Aronow HU, Steiner A, Alessi CA, Büla CJ, Gold MN, et al (1995) A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. N Engl J Med 333(18):1184-1189.
31. Stuck AE, Minder CE, Peter-Wüest I, Gillmann G, Egli C, Kesselring A, et al (2000) A randomized trial of in-home visits for disability prevention in community-dwelling older people at low and high risk for nursing home admission. Arch Intern Med 160(7):977-986.

FRAILTY AND NOVEL TECHNOLOGIES – A STEP AHEAD

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Abstract: Dependence and disability are almost inevitable consequences of population aging. As these conditions are considered irreversible, a growing interest has been directed towards the identification of related conditions that are still amenable to preventive interventions. In this context, frailty has attracted an increasing scientific interest. Frailty is characterized by decreased homeostatic reserves and diminished resistance to stressors. The frail elderly constitutes a complex population in terms of assessment, monitoring, adherence to recommendations, and follow-up. The use of novel technologies may be considerably helpful for both clinical and research purposes. In particular, technologies may support interventions preventing disability, improving the quality of life, and enhancing the wellbeing of frail people. Traditional assessment instruments can be complemented or replaced by mobile devices measuring and monitoring frailty domains (e.g., physical performance, cognitive function, physical activity, nutritional status). Novel technologies have indeed the potential to benefit, assess, monitor, and support frail older people to live independently and improve their quality of life.

Key words: Aging, prevention, information and communication technologies, assessment, screening.

Population aging is leading to a considerable increase in age-related pathological conditions, including dependence and disability. In 2010, more than 3 hundred million persons were disabled worldwide, and such estimate is projected to almost double by 2050, with considerable increases in costs for the healthcare system (1, 2). As dependence and disability are considered as almost irreversible conditions, a growing interest has been pointed to the identification of those health profiles that, although characterized by increased risk of negative events, may still be amenable to preventive interventions against disability. In this context, frailty has attracted a significantly increasing scientific interest (3).

Frailty is a multidimensional condition characterized by decreased homeostatic reserves and diminished resistance to stressors (4). It is also a consequence of cumulative decline in multiple physiological systems, and is associated with a greater risk of adverse health outcomes, such as falls, hospitalization, institutionalization and mortality (5). This concept is frequently adopted to indicate a status of pre-disability, characterized by potential reversibility.

Frail elders constitute a complex population in terms of screening, assessment, monitoring, and follow-up. It is likely that technologies may indeed play a role in supporting healthcare professionals and researchers in this context. In other words, the questionnaires, scales, and assessment tools usually completed by healthcare professionals may be complemented and supported by the implementation of novel technologies. An overview with few examples of novel technologies that can be used for the screening, assessment and follow-up of frail older persons is presented in this brief report. The list of examples is not exhaustive but indicative, just an example for indicating the high potentialities of this innovative and promising field.

The identification of frail older people in the routine clinical care and research is a difficult but important task. For example, electronic screening may be supported by technologies using large healthcare databases and sources to identify frail older persons in primary care (6).

Current literature on the use of novel technologies for the assessment and follow-up of older people is exponentially growing. For example, a mobile device characterized by a wide range of features (accelerometer sensors, wireless communication capabilities, and processing capacities among others) has recently been developed in order to support the frailty assessment (7). It provides information on anthropometric characteristics, nutritional, functional and cognitive status of the individual, potentially supporting the assessment of the healthcare professional. Its objective results are indeed shown to be consistent with results of the standard clinical evaluation. Another example of technologies used to measure physical performance may be represented by electronic walk-ways (e.g., www.protokinetics.com), which provide objective measures of movement patterns (i.e., gait analysis) and facilitate the identification of age-related abnormalities. A development of traditional instruments capturing some frailty criteria/domains (e.g., dynamometers for the measurement of muscle strength) are also evolving into more informative devices (8).

The use of technologies has also been proposed during the clinical interview of the older person for better understanding some specific features of his/her health status. For example, Marsh and colleagues (9) have validated the use of animation videos as examples for improving the assessment of mobility and activities of daily living. This approach uses a computer- based program displaying video clips constructed from computer animations. After viewing each video clip of the animated task, participants are asked a question about their ability to perform the same task. This method appeared to have a significant impact at improving the accuracy in the reporting of older adults' self-reporting of ability related to mobility.

In relation to the assessment of physical activity, commercial mobile applications currently available to promote physical activity among adults are numerous (10). These applications are able to monitor physical activity on a daily basis and even provide person-specific recommendations for maintaining a good health status and a healthy body weight (11).

Assessment and monitoring of nutritional intake and status is also very important for the frail elderly. In this case, long food frequency questionnaires could be replaced by mobile devices using applications that take a picture of the consumed meals. Then, through a dedicated online-based service, an analysis of the food can be conducted by specific software, and images converted into nutritional data (i.e., macro- and micro- nutrients composition). This information can be made directly accessible to dietitians, which may then provide personalized recommendations (12).

Furthermore, the improvement of domains other than physical function and nutrition may also positively affect the health status of frail older persons. In other words, multiple domains may generate and significantly enhance the frailty condition (e.g., vision impairment, hearing loss). In this context, visually impaired individuals could benefit from mobile applications designed to read out the text in a document or an image (e.g., https://itunes.apple.com/us/app/ saytext/id376337999?mt=8). Telephone devices including a monitor, which "reads" the voice of the caller and translates it to text, may reduce the isolation of individuals with hearing impairment (e.g., www.CaptionCall.com).

Once screening and assessment are complete, a main issue with frailty is the follow-up and the identification and evaluation of adherence to recommendations of the frail elderly. New technologies could be particularly helpful in this direction. An example of the use of novel technologies in improving the adherence to recommendations during the follow-up of patients is the use of a pedometer-based behavioral change program, which appeared to increase physical activity and performance of frail elders (13). Another example of how much technologies may help in this field, may be the use of mobile applications supporting the monitoring of compliance of older frail people to medications (e.g., http://seniornet.org/blog/). In addition, identification of adherence to recommendations with the use of technologies might be evaluated by the electronic check of renewal of drug prescriptions of pharmacies.

As a future perspective, the concept of a "smart home" (for example, equipped with sensors, actuators, and/or biomedical monitors) could be a promising way for improving the assistance at home of frail and disabled elders, potentially allowing greater functional independence, maintaining good health, and preventing negative adverse outcomes (including social isolation). In fact, these types of infrastructures usually operate in a network connected to a remote data center, which may promote the early diagnoses and anticipate healthcare procedures (14).

The use of novel technologies for preventing disability in frail people is yet limited and challenging. Indeed, while a lot of applications are targeted to younger populations, less are specific to older persons, especially if frail. Nevertheless, the aging population may represent an ideal target group of persons, which may greatly benefit from scientific advancements in this field. By stating this, we are not underestimating the costs and efforts of the extension of technologies to advanced age individuals. For example, randomized-controlled trials using technologies are particularly challenging due to the complexity of the population, the reduced willingness of consider technological devices as part of their daily life, lack of consensus on technology

definitions, and the poor standardization of the assessment tools. However, despite of such evident barriers, it is noteworthy that the number of people aged 65 years and older using the Internet is rapidly rising (15). And, of course, the large scale implementation of technologies in the field of frailty is subject to still-to-come positive results (especially for what concerns cost-effectiveness) from clinical trials.

In conclusion, frailty is a clinical condition determining an increased risk of adverse health-related events and requiring a complex, multidimensional evaluation. Novel technologies present interesting potentialities to support the complex research and clinical activities around this syndrome. We are just at the very beginning of an exciting new field of development for geriatrics and gerontology.

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REFERENCES

1. World Alzheimer Report 2013. ADI 2013.
2. Fried TR, Bradley EH, Williams CS, Tinetti ME. Functional disability and health care expenditures for older persons. Arch Intern Med 2001;161(21):2602-7.
3. Cesari M, Abellan Van Kan G, Ariogul S, et al. The European Union Geriatric Medicine Society (EUGMS) working group on "Frailty in older persons". J Frailty Aging 2013;2(3):118-120.
4. Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci 2013;68(1):62-7.
5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-62.
6. Drubbel I, Numans ME, Kranenburg G, et al. Screening for frailty in primary care: a systematic review of the psychometric properties of the frailty index in community-dwelling older people. BMC Geriatr 2014;14:27. doi: 10.1186/1471-2318-14-27.
7. Fontecha J, Hervás R, Bravo J, Navarro FJ. Mobile and Ubiquitous Approach for Supporting Frailty Assessment in Elderly People. J Med Internet Res 2013;15(9):e197.
8. Matsui Y, Fujita R, Harada T, et al. A new grip strength measuring device for detailed evaluation of muscle contraction among the elderly. J Frailty Aging 2014;3(3):142-147.
9. Marsh AP, Ip EH, Barnard RT, Wong YL, Rejeski WJ. Using video animation to assess mobility in older adults. J Gerontol A Biol Sci Med Sci 2011;66(2):217-27.
10. Middelweerd A, Mollee JS, van der Wal C, Brug J, Te Velde SJ. Apps to promote physical activity among adults: a review and content analysis. Int J Behav Nutr Phys Act 2014;11(1):97.
11. Hebden L, Cook A, van der Ploeg HP, Allman-Farinelli M. Development of smartphone applications for nutrition and physical activity behavior change. JMIR Res Protoc 2012;1(2):e9.
12. Zhu F, Bosch M, Woo I, et al. The Use of Mobile Devices in Aiding Dietary Assessment and Evaluation. IEEE J Sel Top Signal Process 2010;4(4):756-766.
13. Yamada M, Mori S, Nishiguchi S, et al. Pedometer-based behavioral change program can improve dependency in sedentary older adults: A randomized controlled trial. J Frailty Aging 2012;1(1):39-44.
14. Chan M, Campo E, Estève D, Fourniols JY. Smart homes - current features and future perspectives. Maturitas 2009;64(2):90-7.
15. Macfarlane H, Kinirons MT, Bultitude MF. WWW. Do not forget older people. Age Ageing 2012;41(6):807-10.

INNOVATIVE MEDICINES INITIATIVE: THE SPRINTT PROJECT

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Key words: Frailty, sarcopenia, disability, prevention.

The current healthcare systems are built around the traditional paradigm of patients suffering from a single acute illness. They are therefore largely unprepared to face the increasing demands for health services arising from the expansion of an older population with specific medical needs related to multiple chronic disorders. As a consequence, the medical conditions of a large and growing segment of the older European population are not efficiently managed by the available healthcare services (1). Among these conditions, the geriatric syndrome of frailty has emerged as a significant public health priority. It is defined as a multidimensional condition characterised by decreased reserve and diminished resistance to stressors (2). Such extreme vulnerability exposes the older individual to an increased risk of morbidity, disability, inappropriate healthcare use, institutionalization, poor quality of life, and death. Early detection and prevention of frailty are thus crucial to impede its progression and the development of its detrimental clinical consequences, while ensuring sustainability of healthcare systems of the Member States (3). Unfortunately, to date, no healthcare programmes or pharmacological treatments are available for frail older people. This is largely due to the lack of a precise, universal definition of frailty, linked in turn to the multidimensional nature of the condition. Eventually, the existing gaps in knowledge are reflected by the absence of effective interventions. Such a barrier may be overcome by developing and validating a robust conceptual framework to achieve a practical operationalisation of frailty. This should precisely define its pathophysiological and clinical foundations, to assist in the design and implementation of specific interventions aimed at restoring robustness and delaying the onset of adverse outcomes. The « Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies » (SPRINTT) project is specifically designed to overcome the existing barriers for an efficient public health intervention against frailty, and promote the implementation of successful aging strategies across Europe. To reach such an ambitious goal, the actions of the SPRINTT Consortium are directed towards the achievement of a consensus among academia, regulators, industry (pharmaceutical and medical devices), and patients' representatives over:

1. clear operationalisation of the presently vague concept of frailty;

2. identification of a target population with unmet medical needs;
3. evaluation and validation of methodologies for implementing preventive and therapeutic strategies among frail elders at risk of disability in the European Union;
4. definition of an experimental setting as a template for regulatory purposes and pharmaceutical investigations;
5. identification of biomarkers and health technology solutions to be implemented in clinical practice.

The SPRINTT project proposes a novel operationalisation of physical frailty recognising sarcopenia as its central biological substrate. This approach is based on the fact that the physical frailty phenotype overlaps substantially with sarcopenia (4). Indeed, many of the adverse outcomes of frailty are probably mediated by sarcopenia, which may therefore represent both the biological substrate for the development of physical frailty and the pathway through which the negative health outcomes of frailty ensue. Although physical frailty encompasses only a part of the frailty spectrum, the identification of a definite biological basis (i.e., skeletal muscle decline and loss of mobility function) opens new venues for the development of interventions to slow or reverse the progression of this condition. It is noteworthy that all of the components describing the Physical Frailty and Sarcopenia (PF&S) model are measurable and quantifiable. It is thus anticipated that the implementation of such a model will allow the identification of a precise subset of frail elderly citizens whose medical needs are presently unmet.
The ad hoc randomised clinical trial (RCT) resulting from the SPRINTT project will translate the PF&S model into a multi-component intervention [combining physical activity, nutritional assessment/counseling and implementation of Information & Communication Technology (ICT) solutions] aimed at preventing incident mobility disability and major negative health-related events.
The multi-component intervention proposed is original (such an intervention against the outcome of mobility disability has never been previously tested on a large scale, although built upon solid scientific background and data), relevant (it targets conditions of high prevalence in European community- living older persons), pertinent (it is focused on function, a primary component of quality of life and the one of the most important outcomes in the elderly), feasible (it will be carried out by internationally recognised researchers with outstanding experience in the field of PF&S), easily applicable at a population level (thus facilitating the future clinical implementation of the project findings), and scalable (it will validate health technology services and an ICT infrastructure that will enable optimal data acquisition/analysis and clinical decision-making, as well as ensure accessibility to the interventions from the user's home).

The RCT, based on a priori power calculation, plans to recruit 1,500 participants aged 70 years and older (750 per treatment arm), distributed across seven regional coordinating site across Europe and involving nine European Countries. The target population will be comprised of "real life", non-disabled older persons exposed to increased vulnerability to stressors.
The identification of such a population will rely on the three key elements that are at basis of the PF&S operationalisation:

- target organ deterioration (i.e., low muscle mass, measured by dual energy X-ray absorptiometry),
- clinical manifestation of physical frailty (i.e., weakness, slow walking speed, and poor balance),
- functional impairment [assessed using the Short Physical Performance Battery (SPPB].

The main exclusion criterion will be the presence of mobility disability, that is the first step of the disabling cascade, at baseline.
Participants will be randomised to either a multi-component intervention or an educational control group. Both interventions will be administered for up to three years.
The primary outcome will be the incidence of mobility disability, operationalised as incident inability to walk 400 metres. Secondary outcomes will include: changes in physical performance; ability of selected biomarkers to predict the rate of change in muscle mass & functional capacity; changes in frailty status; changes in sarcopenia parameters; incidence of falls and injurious falls; changes in nutritional status; changes in physical function, cognitive function and mood; changes in utilisation of healthcare services; changes in drug consumption and polypharmpacy; changes in quality of life; incident cognitive impairment; mortality rate.
To ensure the successful accomplishment of all SPRINTT goals, a unique and robust Consortium has been established that convenes internationally recognised leading experts in the field of PF&S. The Consortium is organised in multiple interacting work-package teams, reassembling academia, members of the European Federation of Pharmaceutical Industries and Associations (EFPIA), and two Small and Medium Enterprises (SMEs). Each participant supports with its own specific expertise the conduction of the SPRINTT work-packages. Each leader/co-leader "tandem" will coordinate a group of experts in specific domains. The expertise of each partner will thus be valorised, and the Consortium activities conducted in the most informed, shared, and appropriate way.

Conflict of interest: All the authors are investigators of the SPRINTT project, an Innovative Medicines Initiative (IMI)- funded project (including partners from the European Federation of Pharmaceutical Industries and Aasso-

ciations [EFPIA]). Matteo Cesari has received honoraria for presentations at scientific meetings and/or research fundings from Nestlé, Pfizer, Novartis. Bruno Vellas has served as consultant/advisor for Biogen, GSK, Lilly, Lundbeck, Medivation, MSD, Nestlé, Nutricia, Pfizer, Roche, Sanofi, Servier, TauRx Therapeutics, Novartis. The other authors have no conflict of interest to disclose.

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REFERENCES

1. Vellas B, Cestac P, Morley JE. Implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging 2012;16:599-600.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-762.
3. Morley JE, Vellas B, Abellan van Kan G et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392-397.
4. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci 2014; 6:192.

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