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advantAGE
MANAGING FRAILTY

Title:	Extending and Expanding the Knowledge on Frailty to Foster Innovative Policy on Frailty: A Systematic Review
WP Leader:	MUG
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EXECUTIVE SUMMARY

Background:

The ADVANTAGE Joint Action (JA) "Managing Frailty'' aims to build a shared understanding among policy makers and stakeholders in order to develop a common European approach to the prevention of frailty. Work package 8.2 (WP8) aims to gather evidence of research gaps in the prevention and management of frailty across the European member states.

Methods:

Systematic reviews were conducted to identify scientific papers regarding gaps in the evidence of knowledge of frailty. Furthermore, a review of evidence arising from European Union (EU) funded projects and inputs from the other WPs of the present JA were included.

Recommendations for ADVANTAGE:

We identified seven domains of gaps in research and explored these as 17 topics, providing 12 recommendations which will help to extend evidence-based knowledge on the processes involved in the development of frailty and its consequences such as progression to disability, therefore modelling the impact of frailty on society.

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ACRONYMS

COPD = Chronic Obstructive Pulmonary Disease.

CRP = C-reactive protein.

DNA = Deoxyribose Nucleic Acid.

EC = European Commission.

eFI = Electronic Frailty Index.EU = European Union.

EHRs = Electronic Health Records.

HGS = Hand-grip Strength.

ICD = International Classification of Diseases.

IL = Interleukin.

JA = Joint Action.

MS = Member State.

NHS = National Health Service.

PACE = Program of All-inclusive Care for the Elderly.

SHARE = Survey of Health, Ageing, and Retirement in Europe.

SIPA = System of Integrated Care.

WP = Work package.

WP8 = Work Package 8.

INTRODUCTION

Despite the large number of research programs funded by public and private agencies, thousands of publications and a myriad of articles in lay press, many relevant issues are still unsolved in the field of frailty. WP8.2 identifies what are the relevant issues in which research may contribute to generate advances. This document summarizes those identified in a systematic review of the literature, European Union (EU)-funded research projects and inputs from the different WPs.

METHODS

A search was conducted in:

A) The EU-2020 Program, with review of projects funded in the last two calls of Horizon 2020 contained in the CRODIS EU portal.

B) Relevant documents identified through engine-driven repertories (Google).

C) Literature review with the general descriptors (Annex 1).

The search included PubMed, EMBASE, SCOPUS, COCHRANE from January 1st, 2015 until 30th May, 2017.

RESULTS

Figure 1 (Annex 2) shows the flowchart of the systematic review. The result of number of papers reviewed and cited in this document are presented for seven domains in Table 1. Key issues and recommendations are summarized at the end of the document in Table 2.

Table 1. Results of the active search of recent papers and documents on research gaps in frailty

Domain	Documents reviewed	Documents cited
Identification and assessment	8	4
Human Models of Disease	10	3
Mechanisms and markers	23	12
Health Care Models	8	6
Clinical mangement	36	7
Environmental issues	11	6
Ethnicity and Migration	10	3

1. Identification and assessment

Electronic frailty index: New ways to recognise frailty easily and rapidly in the community must be devised (Rockwood, 2016). One potential solution is to leverage the power of electronic health records (EHRs) which are now widely used in primary care. Unfortunately, the condition of frailty is not included in the International Classification of Diseases (ICD)-9 or ICD-10 and consequently, it is not recorded in the EHRs. However, a recent European Commission (EC) report (Gesundheit Österreich, 2016) describes how frailty equivalents can be identified in EHRs, and so they coined the term 'electronic frailty index' (eFI). Indeed, there is evidence for the successful development and use of the eFI (Schoufour et al., 2017), and while it is currently considered a screening tool, it has a wide range of potential future uses in clinical, public health, and research settings.

Handgrip strength (HGS) reference values: The evaluation of frailty must include the assessment of muscle strength and so, HGS is a key parameter and is one of the five classic frailty phenotype's criteria. HGS is of prognostic value for all-cause mortality, fatal and non-fatal cardiovascular morbidity, and vulnerability to disease and frailty. Several studies have described differences in HGS between countries and races (Leong et al., 2015; the reasons for these differences are not well established, although regional and ethnic differences in socio-economic status and protein intake seem to be the most relevant factors. Therefore, individual HGS measurements should be interpreted using regional/ethnic-specific reference ranges.

2. Human models of disease

Physiological dysregulation: Monothematic models for explaining the natural history of frailty, such as oxidative stress, immunodeficiency, low-grade inflammation, or telomere shortening, have not proved useful in understanding the roots of the process. Therefore, holistic models should provide a more homeostatic view of the problem. Physiological dysregulation is the age-related breakdown of the capacity of complex regulatory networks to maintain organismal homeostasis because of alterations in these networks (Li et al., 2015). The concept is based on the simultaneous dysregulation of multiple mechanisms during aging and places relevance on how the dynamics of these systems affects the process of deterioration. Likewise, dysregulation is not only a set of accumulated problems or dysfunctions, it is a breakdown in the function of this complex system (Cohen et al., 2015). Several studies have tried to study this phenomenon by selecting biomarkers or defining dysregulation scores to assess the uniformity among populations of potentially frail individuals as a statistical distance (Li et al., 2015; Cohen et al., 2015). The resulting calculated allostatic load could thus help to identify patterns of dysfunction in longitudinal studies which can then be used as early markers of frailty.

A concept that is linked with allostatic load, but which takes into account the bidirectional nature of aging and age-related diseases, is that of *Geroscience* (Kohanski et al., 2016). According to this paradigm, early exposure to a chronic disease and/or its treatments results in the acceleration of aging phenotypes, including loss of functional capacity and the appearance of clinical symptoms of aging-related diseases which are not obviously related to the earlier event. Geroscience links the biology of aging and disease and the physiology of frailty, three fields in which there has been enormous progress in the past few decades.

3. Mechanisms and markers

Many recent studies have focused on the search for biomarkers that fulfil two roles:
i) disease markers valid for early detection, diagnosis, and/or treatment monitoring, and
ii) markers that can give clues into the mechanisms of frailty development.

Many groups have focused on oxidative stress, low-degree inflammation, immunity deregulation, and cellular damage pathways, using new laboratory tools such as genomics, epigenetics, proteomics, and metabolomics.

A recent cross-sectional systematic review associated frailty and pre-frailty with reduced antioxidant parameters and oxidative stress, but could not pinpoint it as a causal mechanism of frailty because of the study design. Likewise, frailty and pre-frailty were associated with high levels of inflammation, especially C-reactive protein (CRP) and Interleukin (IL)-6, in cross-sectional studies but not in longitudinal studies (Lu et al., 2016). Single nucleotide polymorphisms have been identified in the frailty-associated genes tumor necrosis factor, protein tyrosine phosphatase receptor type J, and interleukin-18 (Mekli et al., 2015). Similarly, immune-endocrine biomarkers have also been considered, but no causal role was established (Baylis et al., 2013).

It is also worth mentioning the emerging role of microbiota and their associated metabolites in healthy aging (Lynch et al., 2015). Age-related microbial changes result in increased proteolytic and decreased saccharolytic bacteria. Studies in older adults have demonstrated that the gut microbiota is related to diet, location of residence, and basal inflammation, and is linked to clinical problems including frailty (Jackson et al., 2016). Probiotics can modify the gut environment, reducing low-level inflammation and even improving exhaustion and handgrip strength parameters (Buigues et al., 2016).

Biomarkers of many types from several different sources have been linked with pre-frailty and frailty states, although their reproducibility and prognostic value is limited. Genetic polymorphisms in genes involved in different pathways and systems, telomere length, and Deoxyribose Nucleic Acid (DNA) methylation have all been linked to frailty. Moreover, a pattern characterised as increased angiotensinogen, kininogen-1, and

antithrombin III protein levels has been identified in frail individuals (Lin et al., 2017). Likewise, low levels of sirtuin—as a by-product of longevity-associated genes—is associated with frailty (Viña et al., 2016). Moreover, European studies like FRAILOMICS are also shedding light onto the complex world of frailty biomarkers (Lippi et al., 2015).

4. Health care models

Strategies designed to manage chronic diseases tend to focus on single conditions, whereas most people over 75 have a number of conditions and want to be treated as individuals who need holistic, coordinated, personalised care, rather than as a collection of diseases. In order to improve care models for frail individuals, professionals must first recognise the barriers to such care. In addition, it is important that future research studies are designed with the aim of obtaining appropriate outcomes, thus helping physicians to maximise the benefits to patients and reducing health care system costs.

According to the Deloitte Centre for Health Solutions (Deloitte, 2016), the main barriers to the provision of holistic care are:

i) the fact that health and social care are funded separately even though the complex needs of frail patients mean that these two elements are completely interdependent;
ii) the fragmented care-delivery model;
iii) the complexity and high workload, requiring coordination with different medical specialists, of the personnel providing care to the frail; also, the staff who spend the most time caring for frail individuals receive the least training and lowest salary of all the personnel involved;
iv) the impact of poor housing conditions on disease and the development of frailty, and in exacerbating the effects of isolation and loneliness.

Until recently, many countries and regions across Europe have lacked appropriate care models for frailty. However, the experience of the few cases where such models have been implemented, the National Health Service (NHS) (NHS England, 2014), the King's Fund (Oliver et al., 2014), the Program of all-inclusive care for the elderly (PACE) (Eng et al., 1997), the System of Integrated Care (SIPA) (Bergman et al., 2003), and PRISMA (Hébert et al., 2003), have provided invaluable insights for the execution of similar future policies and for improving their cost-effectiveness (Baillie et al., 2014).

The Deloitte report also provides several recommendations for improving the care of frail individuals (Deloitte, 2016) including:

i) adopting a population health management policy requiring the search for and registry of frail older people;
ii) implementing targeted and early intervention strategies;
iii) designating a single point of access to care and appointed care-coordinators;

iv) annual frailty checks and priority access to services in order to provide rapid assessment and diagnosis to everyone aged over 75 years;
v) promoting the return to home with continuity care following hospitalisations;
vi) patient empowerment;
vii) improving living conditions;
viii) inspecting, registering, and accrediting nursing and care homes;
ix) implementing a frailty care pathway in hospitals.

5. Clinical management

Many different approaches have been taken to treat frailty but very few have combined these treatments. Interventions include different drugs, melatonin, vitamin D metabolites, testosterone, nutritional components, probiotics, physical exercise, and cognitive treatments, as well as complex lifestyle changes. A comparative study of these interventions, demonstrated that the physical, nutritional, and cognitive interventional approach showed some benefits. However, older people tend to accumulate multiple medications, often from different specialist physicians, and these sometimes have subtle secondary effects that can interfere with daily life. Thus, while the careful selection of drugs for treating frailty is imperative, it is arguably more important to consider streamlining or reducing such polypharmacy.

When frailty is identified, it can be managed by identifying and addressing conditions that might underlie the condition and by mitigating stressors that might precipitate adverse outcomes. In addition, the presence of frailty can affect the potential risks and benefits of other medical interventions, diagnostic and therapeutic processes, and the provision of appropriate treatment for chronic diseases and comorbid conditions including cancer, cardiovascular disease, Chronic Obstructive Pulmonary Disease (COPD), rheumatic disorders, depression, diabetes, hypertension, dyslipidemia, and obesity. Thus, it is essential to develop recommendations which are specifically tailored to frail individuals.

The pursuit of more clinical trials regarding frailty is important because they provide fact-based knowledge which can serve as a guide for the better management of frail patients. Considering the multidimensional nature of frailty, assessment of therapeutic measures requires careful design because the outcomes of different interventions can impact the diverse components of frailty in varying ways (Niedernhofer et al., 2017). Besides mortality or hospitalisation risk, such secondary outcomes include: healthcare use and costs, self-rated health and quality of life, disability, institutionalisation, mental health, social relationships, sarcopenia, and safety parameters.

6. Environment

Investigation into the relationship between environmental pollution and frailty has produced discordant results. Even if pollution does not increase the direct risk of developing frailty, its impact on certain chronic diseases, especially COPD, is well established and so, logically, pollution is also likely to negatively affect the pulmonary capacity of frail subjects (Cohen et al., 2017, García-Esquinas et al., 2017).

Until recently, the impact of indoor air quality on frail individuals has received little attention. However, an association between high carbon dioxide levels, breathlessness, and coughs, as well as an inverse relationship between relative humidity and wheezing has been shown (Bentayeb et al., 2015). Likewise, exposure to second hand tobacco smoke has received attention, with one study showing that the presence of two or more smokers at home is associated with frailty (García-Esquinas et al., 2015).

Some studies have also reported the relevance of places of residence on the development of frailty; the socio-economic level of neighborhoods, and the presence or absence of green spaces (Mantovani et al., 2015) and transportation facilities (Jones et al., 2013) can positively or negatively impact the development and progression of frailty.

7. Migration and ethnicity

There are significant differences between different countries and regions in terms of the prevalence and incidence of frailty; these variations are relevant both in terms of health care and to better understand the natural history of frailty and the factors that influence it. In this context, very few studies on frailty have specifically considered immigrant populations. According to data from the Survey of Health, Ageing, and Retirement in Europe (SHARE), the socio-economic levels of both the country of residency and of origin influenced not only the risk of frailty but also the level of cognitive and motor performance at older ages (Brothers et al., 2014). Factors related to the differences include biological, economical, and educational considerations, as well as perceived discrimination (Siordia et al., 2016).

The risk of developing frailty has been considered in different biological and race backgrounds, although confounding factors such as socio-economic and geographic factors operate in the majority of these studies. Differences in HGS (an essential element in the detection of frailty) between countries and races have been mentioned above (Leong et al., 2015).

CONCLUSION

The intersection of the research needs detected in this report and those selected by other ADVANTAGE JA WPs allows to prioritize some research topics. Table 2 includes the specific recommendations with the stakeholders to be involved and the deliverables needed.

Table 2. Key issues and recommendations to cover research gaps in frailty, with the stakeholders to be involved and the deliverables needed. WP_ indicate that the proposal comes from the corresponding work package (WP) of the ADVANTAGE Joint Action. (WP_) indicates that the proposal was shared with the corresponding WP. EHR: Electronic Health Record. eFI: Electronic Frailty Index. ICD: International Classification of Diseases.

RECOMMENDATION	STAKEHOLDER	DELIVERABLES
Increase the identification in Primary Care	Stakeholders with EHR	Code (descriptor) for frailty in the next update of the ICD. Development and use of the eFI as screening tool.
Differences in parameters to assess frailty among regions and ethnic groups (for example hand-grip)	Epidemiologists and clinicians	Reference values tailored to ethnic and/or regional differences
Identify physiological dysregulation as early markers of the frail phenotype	Epidemiologists, clinicians and researchers	Identify subtle systemic dysfunctions prone to develop frailty
The intersection between aging biology and chronic diseases and conditions must be analysed in more detail	Epidemiologists, clinicians and researchers	Identify accelerators of frailty in chronic diseases Projects' funders should ask for the inclusion of baseline frailty measurements, instead of the measurement of frailty from existing data Identify treatments of chronic diseases with impact on frailty
Development of reliable biomarkers of frailty risk	Epidemiologists, clinicians and researchers	Testing in longitudinal studies as predictor of becoming frail

		Define patterns of risk combining -omics
Evaluation of new care tools and models	Stakeholders, health care authorities and clinicians	WP7: Evaluate the most effective types of enablement programmes, to identify those that are most likely to benefit, the most effective timing, duration and frequency of restorative interventions. WP7: Identify the most effective combinations of community health and social care interventions Outcomes to be tested: Care cost, hospitalisation rate, transition to long-term care facilities, onset of disabilities and quality of life
Searching for elements of success common to the frailty-care programmes	Stakeholders, health care authorities and clinicians	
Impact of frailty in the evolution of chronic diseases	Epidemiologists, clinicians and researchers	Disease specific outcomes (WP4)
Impact of diagnostic and therapeutic procedures of chronic diseases on frailty	Scientific societies guideline experts epidemiologists, clinicians and researchers	Disease-specific algorithms for frail subjects to choose and evaluate elective treatments for chronic comorbidities (WP4)
Optimize the design of clinical trials in frailty subjects	Epidemiologists, clinicians and researchers	Unify criteria on: subject selection, assessment methods, study duration, outcomes
Research for on the quality of indoor air	Industry, administration	Regulatory standards in indoor climate-control equipment for nursing homes
Environment and risk of frailty	Urban planners, administrations	Increase green spaces Improve transportation facilities

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ANNEX 1

Literature review with the general descriptors

["Elderly" "Aged", Older adult", "Older person", "Geriatric"; "Frailty", "Frail", "Vulnerable", "Functional decline"; combined with the "OR" Boolean term] AND specific descriptors ["Cancer", "COPD", "cardiovascular disease", "cirrhosis", "arthritis", "depression", "inappropriate drug use", "diabetes", "hypertension", "cognitive dysfunction", "Alzheimer", "vascular dementia", "anxiety", "social deprivation", "loneliness", "health perception", "natural history", "biomarkers", human models", "electronic health records", "big-data", "climate", "pollution", "living cities", "codification" "CIE 10", "drug", "treatment", "experimental models", "human models"; combined with the "OR" Boolean term].

ANNEX 2

Figure 1. Flowchart of the selection of research papers