REVIEW ARTICLE

A Comparative Review of Frailty Models and a description of the European-wide FRAILOMIC Initiative: designed to promote Healthy Aging

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ABSTRACT

Background

Frailty in aging populations is associated with increasing evidence of ill health, functional loss, increasing dependency and premature death. The FRAILOMIC Initiative was designed to define, predict and prevent frailty by means of identifying omic markers associated with the diagnosis, risk, and prognosis of frailty. The project hopes to build the foundations for a consensus towards a single operative, clinical definition of frailty to guide the development of ready-to-use kits measuring biomarkers to facilitate frailty risk prediction and improve diagnostic accuracy of frailty in clinical practice.

Aims

We review current models of frailty, describe the design of the FRAILOMIC study, and discuss the advent of the concept of intrinsic capacity as influencing the science of frailty and how this can be clinically interpreted.

Methods

Two main frailty models (Fried Phenotype model; Cumulative Deficit Model) are described and evaluated by detailed literature review. A description of the exploratory phase of the FRAILOMIC initiative is given which resulted in the identification of 13 omic markers related to frailty: these are currently being validated in a validation phase. We then discuss how combining the characteristics of frailty with omic-based biomarkers will enable the development of predictive, diagnostic and prognostic models.

Conclusions

Relating biomarkers associated with frailty to a continuous measure of intrinsic capacity will help in identifying and monitoring at-risk populations. The FRAILOMIC Initiative will provide key insights into the prevention, early detection, and treatment of frailty to reduce the impact of disability in our aging populations.

Key Words: Frailty, biomarkers, FRAILOMIC, aging, epidemiology

1. Introduction and the Rise of Frailty

The global population of older people is increasing rapidly. From 2013 to 2060 the proportion of the population aged ≥65 years is projected to increase from 18% to 28% and the proportion of those aged ≥80 years from 5% to 12%.[1] An aging population raises social and economic challenges and as the number of older people increases, so too will the number of people with age-related disability and dependence.

Aging is generally associated with functional decline of the neurological, muscular and cardiovascular systems,[2-6] resulting in impaired capacity to perform daily activities.[7] The transition from a robust status to one of age-related disability is usually preceded by a physiological condition termed frailty.[5,8] Age-related frailty is associated with a decline in immunity and an increase in inflammation .[9] Increased biomarkers such as interleukin (IL)-6 and C-reactive protein (CRP) have been demonstrated in older adults with frailty.[10,11] Declines in plasma concentrations of growth and sex hormones and production of the steroid precursor

dehydroepiandrosterone are also typically associated with aging and frailty.[11-17] The aging process may also involve the development of insulin resistance and coupled with unregulated inflammation, can lead to the onset of diabetes and chronic inflammation ultimately contributing to the chronic development of frailty.[5,18]

2. Biomarkers as tools of enquiry

While some older adults retain robust physical health for many years, others develop frailty and the reasons for this are often unknown. Increasing our understanding of biomarker patterns in aging is crucial to apply effective steps towards delaying the onset of frailty, late-life disability and its adverse consequences,[19] and to promote an active approach in the management of frailty in home-based and clinical settings.[20,21]

The FRAILOMIC Initiative (www.frailomic.org) is an ongoing, international, large scale research project run by a consortium of four universities, eight small and medium sized enterprises, three leading research centers and four hospital-based research groups that collaborate to identify biomarker patterns in aging. The project is attempting to identify 'omics-based' biomarkers that may be useful (i) for the evaluation of the risk of developing frailty (ii) in contributing towards to a better definition and diagnosis of frailty and (iii) to provide improved predictive measures of the prognosis of frailty when used in combination with current clinical criteria and laboratory biomarkers (Figure 1). In this narrative review, we evaluate the extent to which the FRAILOMIC initiative will extend our current understanding of frailty and provide the tools to help prevent frailty and promote healthy aging.

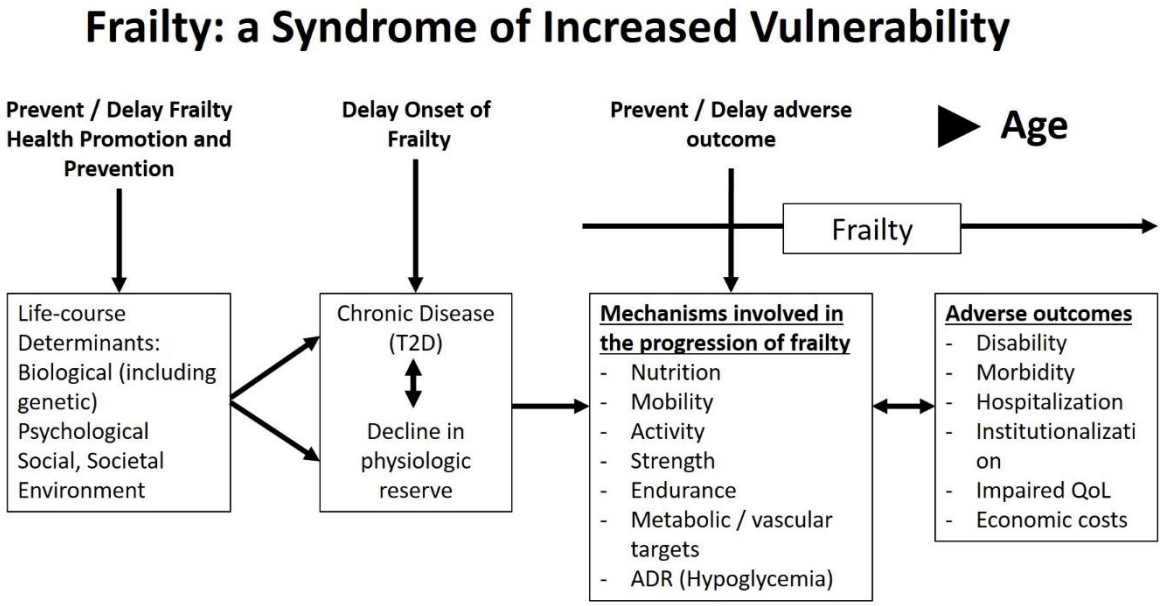

Figure 1: Frailty: a syndrome of Increased Vulnerability. TSHA=Toledo Study of Healthy Ageing; 3C-B=Three-City-Bordeaux cohort.

2.1. Defining and Measuring Frailty

Although frailty can be characterised using classical clinical phenotypes and laboratory-based biomarkers, a universally accepted definition of frailty remains to be agreed upon.[22,23] The most widely accepted definition is 'an age-associated biological syndrome characterised by a decrease of the biological reserve and resistance to stress, due to a decline in several physiological systems, putting the individual in a special risk category when facing minor stressors and associated to poor outcomes (disability, hospitalisation and death)' (Figure 2).[16,19] Two widely used approaches to assess frailty are Fried's Frailty Criteria and the Cumulative Deficit Model Frailty Index (FI).

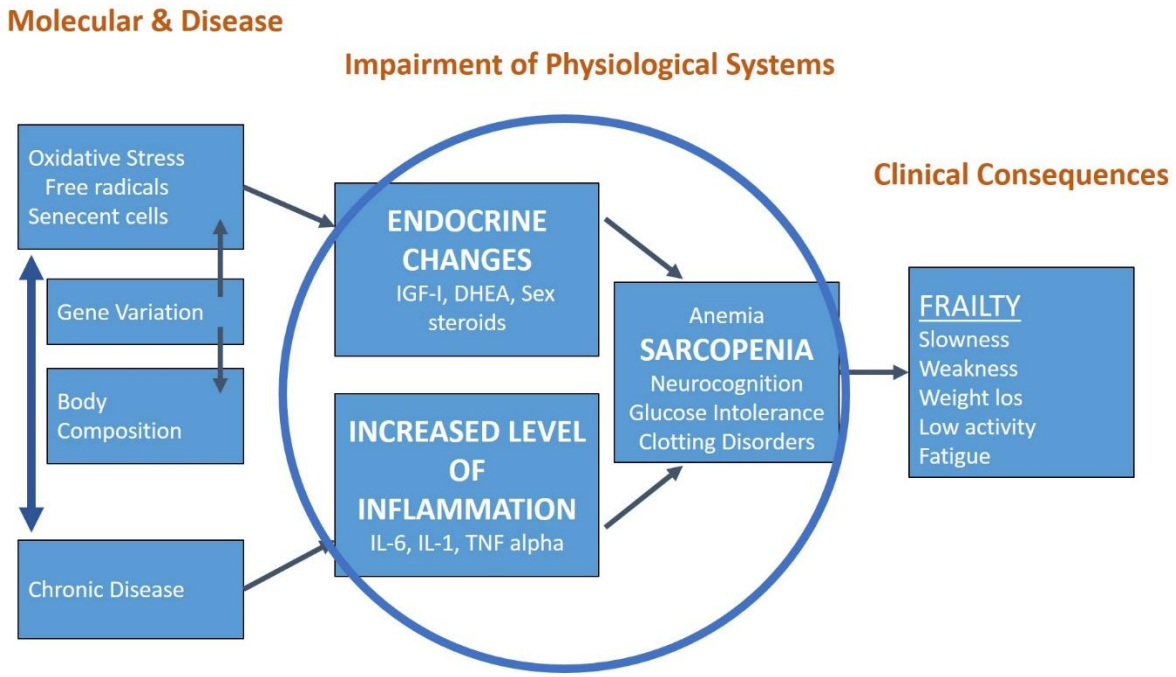

Figure 2: Molecular and clinical pathways underlying frailty. IGF-1=insulin-like growth factor 1; DHEA=Dehydroepiandrosterone; IL=interleukin; TNF=tumour necrosis factor

2.1.1. Fried's Frailty Criteria

Fried's Frailty Criteria were developed based on findings from 5,317 participants in the Cardiovascular Health Study (CHS) and use five characteristics to establish the frailty phenotype model.[24] In this model, frailty is diagnosed based on the presence of at least three of the five physical attributes and capabilities of an individual. These include: weight loss (unintentional weight loss of 4.5 kg or more in the last year), exhaustion (self-reported), physical inactivity, slow walking speed, and weakness (low grip strength).[8,24] Studies using Fried's Frailty Criteria estimate the prevalence of frailty at between 3.8–16.3%, depending on the population studied.[14,25-29]

2.1.2. Cumulative Deficit Model Frailty Index

The Cumulative Deficit Model Frailty Index (FI) incorporates additional characteristics and includes abnormal laboratory values, disease and disability states. Developed as part of the Canadian Study on Health & Ageing (CSHA), the FI

consists of 92 parameters,[16,30-32] and has been reduced to 36 variables, without loss of predictive power.[33] The FI model has strong predictive capacity for adverse outcomes and mortality.[32,33] In a sample of 2,740 community-dwelling Canadian subjects, aged 65–102 years, the FI estimated 622 participants (22.7%; 95% confidence interval [CI]: 21.0–24.4%) were frail.[33] However, there are disadvantages to the FI model, including its impracticality in clinical settings due to the assessment of a large number of variables. More importantly, the FI does not appear to differentiate between frailty and disability.[34,35]

2.2. Comparisons of the Frailty Models

Comparisons of Fried's Frailty Criteria (which gives rise to the frailty phenotype) and the FI model showed discrepancies between derived estimations for frailty prevalence and risk prediction.[36-38] For example, estimates of frailty prevalence in the United States National Health and Nutrition Examination Survey (NHANES) were 3.6% with the frailty phenotype and 34% with the FI .[36] Furthermore, some participants who were categorised as robust with Fried's Frailty Criteria, were categorised as vulnerable or frail with the FI. Although clinicians often favor one of the two models, Cesari et al. suggested that the phenotype and the FI models should be utilised as complementary tools.[39] Combining Fried's Frailty Criteria and the FI using a weighted mean for each phenotype, based on the magnitude of phenotypic associations with frailty, demonstrated that slow gait speed was the most informative component and weight loss was the least informative factor.[40]

2.3. THE FRAILOMIC INITIATIVE: A MULTIPHASE STUDY

The FRAILOMIC Initiative is a large-scale research project funded under the European FP7 framework. FRAILOMIC aims to identify the risk factors that cause incipient frailty to progress to overt disability. Its strategy consists of analysing a range of putative biomarkers based on medical literature review and data from exploratory studies with low sample sizes related to aging, frailty and disability.[41] After selection, a panel of candidate biomarkers of frailty will be tested and validated in other populations.

The project consists of four phases. The initial exploratory phase, which has been completed, investigated candidate biomarkers of frailty in small groups. As expected for a highly heterogeneous phenotype such as frailty, omic markers were identified in various domains and pathways. Of the candidates selected a priori because of their association with inflammation, regulation of cell proliferation, regulation of gene expression, muscle dysfunction, insulin pathway, stress response, and cardiovascular homeostasis, 13 showed promising associations with the diagnosis of frailty, improving diagnostic accuracy between 2-10% when compared with using clinical measures only. The results of phase one will be published later in 2018. The second phase, validating these candidates from the phase one, is due to finish mid-2018. The third phase will investigate the best fitted models, which will be developed as clinical toolkits in the fourth phase [Figure 3].

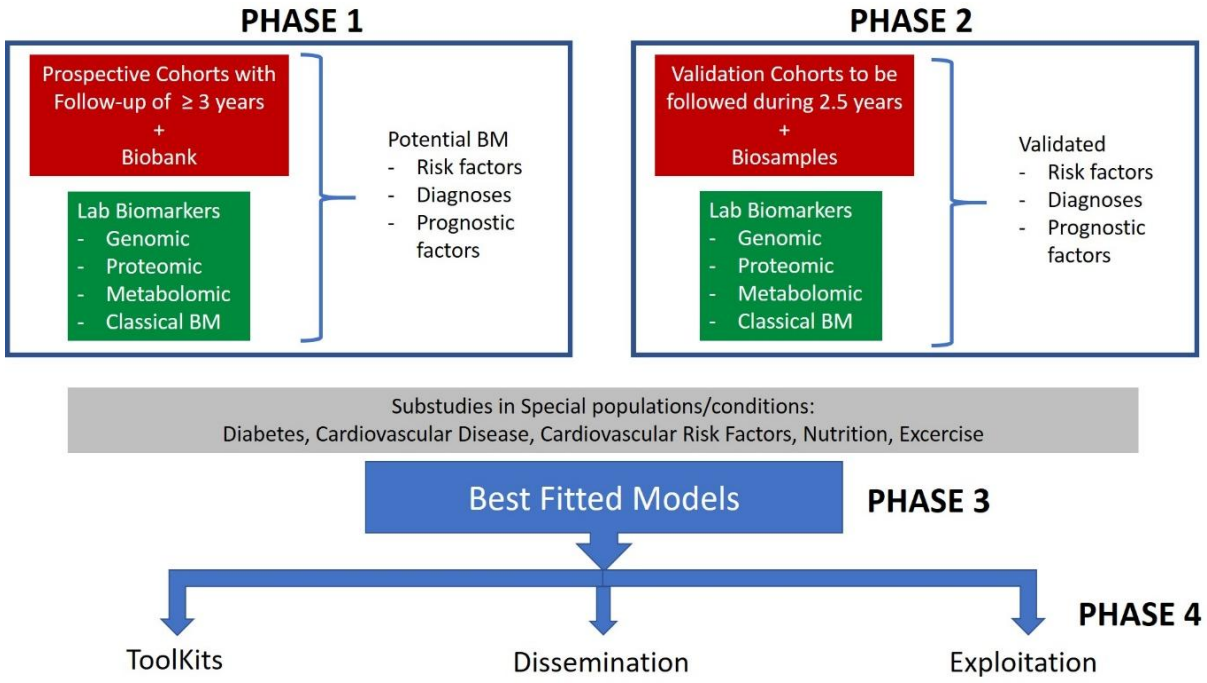

Figure 3: Frailomic Study Design. BM=biomarker; CVD=cardiovascular disease; CVRF=Cardiovascular risk factor

2.3.1. Characteristics of the Cohorts

The FRAILOMIC project has access to samples from over 75,000 participants; 51,860 of whom are older than 65 years. There are nine established population-based cohorts participating in the study [Table 1].

Table 1: Clinical data and classical laboratory biomarkers for the assessment of frailty

Type	Variable Name	Definition	Values/Units
Demographics	Age	Age at point of inclusion	Years
	Gender	Gender	Male / Female
	Education	Level of education	Low / Intermediate / High
	Death[a]	Alive or deceased	Alive / Deceased
Frailty	Fragility[a]	Frailty defined by Fried's frailty criteria: frail ≥ 3 criteria; prefrail= 2 criteria; robust =0–1 criteria	Robust / Pre-frail / Frail
Mini-Mental State Examination (MMSE)	MMSE	MMSE Score	0–30

Depression Status	Depression	Centre for Epidemiological Studies Depression Scale (CES-D) and Geriatric Depression Scale (GDS)	Normal, Mild-moderate, Severe
Activity Status	Daily Activity List (DAL)[a]	DAL score: Disabled if unable to perform at least one of the 5 ADLs without help (incontinence excluded)	Yes/No
Lifestyle	Wine	Wine glasses per day	Number
	Beer	Beer glasses per day	Number
	Spirit	Spirit glasses per day	Number
	Smoking current	Current smoker	Yes/ No
	Smoking former	Former smoker	Yes/ No
	Quantification Smoking	Cigarettes per day	Number
Drugs	Drugs	Yes / No for each drug	Yes/ No
Physical examination	Weight	Weight of the individual	kg
	Height	Height of the individual	cm
	ECG	ECG and heart rate	Bts/min
	BP	Systolic and Diastolic blood pressure	mm Hg
	Waist size	Waist circumference	cm
	BMI	Body mass index	0–100
	Obesity	Severely underweight less, underweight, Normal, Overweight,Obese I, Obese II, Obese III	Severely underweight less, underweight, Normal, Overweight,Obese I, Obese II, Obese III
Comorbidities	Cardiovascular disease	Hypertension	Yes/ No
	Angina pectoris	Angina pectoris	Yes/ No

	Myocardial Infarction	Myocardial Infarction	Yes/ No
	Congestive heart failure	Congestive heart failure	Yes/ No
	Stroke	Stroke	Yes/ No
	Diabetes mellitus	Diabetes mellitus	Yes/ No
	Cancer	Cancer	Yes/ No
Cardiovascular risk factors	Cardiovascular risk	Cardiovascular risk	Yes/ No
Biological data	Eosi	Eosinophils	n in K/uL
	Baso	Basophils	n in K/uL
	Lympho	Lymphocytes	%
	Mono	Monocytes	%
	Eosi2	Eosinophils	%
	Baso2	Basophils	%
	RedBlood	Red blood cells	n in millions/µL
	Hemo	Hemoglobin	g/dL
	Hema	Hematocrit	%
	MCV	Mean corpuscular volume	fL
	MCH	Mean corpuscular hemoglobin	Pg
	MCHC	MCH concentration	g/dL
	Redcelldist	Red cell distribution width	g/dL
	Plat	Platelets	n in K/uL
	MPV	Mean platelet volume	fL
	CRP	C-reactive protein high sensitivity	µg/mL
	TTest	Total testosterone	ng/mL
	ADMA	Assymetric dimethyl Arginine	µmol/L
	Glucose	Blood glucose	mg/dL
	Creati	Serum creatinine	mg/dL
	Choles	Total cholesterol	mg/dL
	HDL	HDLcholesterol	mg/dL
	LDL	LDL cholesterol	mg/dL

Trigly	Triglycerides	mg/dL
HbA1c	Glycated hemoglobin	%

[a]= assessment also conducted at follow-up. Abbreviations: HDL= high-density lipoprotein; LDL= low-density lipoprotein

The basis of this project has already been reported and will be summarized here.[22] Four cohorts are involved in the exploratory phase: InChianti, the Health and Aging in elderly farmers cohort (AMI), the Three-City (3C) Bordeaux cohort and the Toledo Study of Healthy Ageing (TSHA). Four cohorts are participating exclusively in the validation phase: the study of elderly people in Sardinia island (SardiNIA), the Study of Nutrition and Cardiovascular Risk in Spain (ENRICA), the Study of Global Ageing and Adult Health (SAGE) and the MultiDomain Alzheimer Preventive Trial (MAPT) and Network of Research into Physical Exercise and Health for Special Populations (EXERNET) and TSHA [Table 2]. The latter cohort will be participating in both exploratory and validation phases.

Table 2::Additional data available from participating cohorts

Cohort/ Study Name	**InChianti**	**SardiNIA**	**3C**	**AMI**	**TSHA**	**ENRICA**	**SAGE**	**MAPT**	**Exernet**
Presence of diabetes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Presence of ischaemic heart disease	Only MI	Yes	Yes	Yes	Yes	Yes [a]	Yes	Yes	Yes
Presence of stroke	Yes	Yes	Yes	Yes	Yes	Yes [a]	Yes	Yes	Yes
Presence of peripheral artery disease	Yes	Yes	Yes	Yes	Yes	Yes [a]	Yes	Yes	Yes
Presence of hypertension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes
Prospective information on hospitalisation periods available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes
Days in nursing home	Yes	Yes	Status only[b]	Status only[b]	Not Yet	Yes	Yes	–	Yes
Permanent Institutionalisation	Yes	Yes	Yes	Yes	Not Yet	Yes	Yes	–	In process
Death	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a=self reported; b= status for living in nursing home only (not duration)
Abbreviations: AMI= Health and Ageing in elderly farmers cohort; ENRICA= Study of Nutrition and Cardiovascular Risk in Spain;MAPT= MultiDomain Alzheimer Preventive Trial;MI= myocardial infarction; SAGE= Study of Global Ageing and Adult Health; TSHA= Toledo study for healthy ageing; 3C=Three-City-Bordeaux cohort

2.3.2. The Study Design and Investigated Outcomes

The first phase of the FRAILOMIC Initiative, the exploratory phase, has focused on identifying biomarkers associated with frailty using samples from the population-based cohorts. Inclusion in these cohorts required participants to be age 65 years or older, biological samples (serum/plasma and urine) from the point of cohort inclusion had been stored and were available for shipment to laboratories, and the case report forms (CRFs) had follow up data for 2.5 years or more. The case report forms (CRFs) included data on diet, physical activity and had sufficient information to establish cardiovascular risk factor (CVRF) profiles, history of cardiovascular disease (CVD) and to assess frailty status using Fried's Frailty criteria. Individuals with incomplete CRFs or with no biological samples collected were judged not suitable for the study. To ensure adequate numbers of participants for statistical analysis, selection was performed to a 1:3 ratio of frail to non-frail individuals.

The exploratory phase was designed in three parts according to the project objectives [Table 3]: a case-control study to predict the risk of frailty, a cross-sectional study to improve the diagnostic accuracy of frailty, and a prospective study to evaluate the prognosis of adverse outcomes. The power obtained in the exploratory phase was generally greater than most existing exploratory studies using omic approaches for cardiovascular disease and other chronic conditions.[42-44]

The ongoing validation phase ongoing aims to validate omic signatures from the exploratory phase in five independent populations using the methodology and research outcomes detailed below:

Table 3: Study design components of the exploratory phase

#	Aim	Design	Study Subjects	Outcome
1	Identify omic markers associated with the **risk** of frailty	Prospective nested case-control studies	Non-frail (robust) older people	Differences in omic biomarker levels between groups (those who became frail vs. those who remained non-frail)
2	Improve the **diagnosis** of frailty by using omic markers	Cross-sectional studies	Frail and non-frail (robust) older people	Differences in omic biomarker levels between groups
3	Characterise **prognosis** of frailty by using omic markers	Prospective cohort studies	Frail older people	Incidence of disability, hospitalisation or death according to omic biomarkers

Outcome 1: The Identification of Biomarkers that Predict the Incidence/Risk of Frailty

A nested case-control study was carried out to identify candidate biomarkers that predict the incidence of frailty. Biological samples from individuals who were categorized as robust at baseline and became frail (incident case group) and from individuals that remained robust (control group) were evaluated.

Outcome 2: Identification of Diagnostic Biomarkers of Frailty

Biomarkers were evaluated for efficient diagnosis of frailty and their ability to improve on the diagnostic ability of Fried's criteria. In this case, a cross-sectional study was carried out using baseline data from all the participants.

Outcome 3: Identification of Candidate Biomarkers Useful for Predicting Adverse Outcomes in Frail Individuals

A prospective study was conducted for the identification of biomarkers involved in characterising the prognosis of frailty. For this study, individuals who were considered frail but free of disability at baseline were followed over 2.5 years to assess the incidence of disability, hospitalization, and death.

3. Analyses, Confounders and False Positive Associations

Biomarker levels may increase progressively with increasing risk of developing a condition and most have wide ranging values in individuals with and without disease. Therefore, a variety of cut-off points should be evaluated for the ability of each biomarker to predict the disease risk. Ideally, the identification of biomarkers and their cut-off points should have high specificity to avoid false positives and high sensitivity to reduce false negatives. The sensitivity and specificity of the biomarkers under evaluation will be assessed with receiver operating characteristic curves (ROCs), with the general principle that those biomarkers demonstrating larger area under the ROC curves (AUC) will yield the most useful results in clinical tests.[45] Statistical analyses for case-control, diagnostic and prognostic/survival studies included logistic regressions adjusted for age and sex, receiver operating characteristics (ROC) curve analyses and Cox proportional hazard models.

3.1. Strengths and Limitations

A particular strength of this project lies in the suitability of the participating cohorts to assess the contribution of omics, morbidity, and lifestyle, including nutrition, to the natural progression of frailty. All cohorts have data on cardiovascular risk profiles and cognitive phenotypes. Data collection on adverse outcomes is ongoing and will be periodically updated. To maximize the data from the contributing cohorts, a significant effort has been placed on data harmonization allowing not only for meta-analysis but also data pooling. In addition, every study has specific strengths to analyze putative pathways between omic factors and frailty. For example, participants of the 3C-Bordeaux and the ENRICA cohorts, which together comprise over 5,000 individuals, have undergone detailed phenotyping of nutritional aspects; the AMI and EXERNET cohorts are well suited for exercise data[46,47]; the TSHA cohort has measure of intrinsic capacity and several frailty scales[37]; and by including a study from South Africa (SAGE), it is possible to externally validate the biomarkers in a population of very different socio-demographic and ethnic background.

Another important strength of FRAILOMIC is the extent of omic markers

measured (over 35000). While it is common to see single omic groups evaluated against their association with frailty, they are rarely evaluated together. The ability to identify cross-omic risk profiles and also to follow up on interesting hits by evaluating the correlation with other marker related pathways is a major step forward for omic research in general and for frailty research in particular.

One limitation includes the likelihood of false positive associations when considering the large array of omic markers tested and the number of associations. Minimising error rates is more important than the power to detect differences/associations. A false discovery rate (FDR) algorithmic tool was developed and applied by the FRAILOMIC consortium to control for false positive associations.[48-50] The exploratory phase was the first time FDR was used for the discovery of molecular signatures involving several data types. To further minimize the risk of false positive associations, the statistical significance threshold was set at $p<0.0000001$ for omic-based analyses and at $p<0.001$ for candidate markers. Only markers that passed these stringent thresholds were forwarded to the validation phase to ensure true positive signals.

4. Frailty, multimorbidity and Intrinsic Capacity: *how the FRAILOMIC project takes us further forward*

In the dominant paradigm of healthcare and research, cardiovascular disease, obesity and diabetes, cognitive impairment and dementia, and arthritis and mobility loss are each interpreted, managed and treated as separate entities. However, frail older subjects frequently present with comorbidities and recent studies suggest arterial aging, indexed as arterial stiffness, might represent a common underlying pathophysiological mechanism with different organ-based clinical manifestations .[2,51,52] Recently it has been argued that it is important to differentiate between multimorbidity and frailty and that although it might be possible that specific co-morbid conditions exacerbate the risk of suffering adverse health outcome when being frail, the focus of research into frailty should be into resilience factors that allow the individual to cope with stressors .[53] This concept has been called “intrinsic capacity” by the World Health Organisation (WHO) and goes beyond the classification of high and low risk by describing a continuous capacity gradient that supports the analysis of trajectories over the lifecourse and facilitates the evaluation of interventions.[54]

Accordingly, the FRAILOMIC initiative will evaluate the interaction between common chronic diseases and diagnostic and prognostic markers of frailty on frailty, intrinsic capacity, and adverse health outcomes [Table 3].

5. Conclusions

With life expectancy increasing, the focus on longevity has been replaced with a greater emphasis on healthy active life expectancy. A reduction of the prevalence of frailty by preventing or delaying the condition may provide a platform for healthy aging and is likely to bring great benefits for individuals, healthcare and society.[8,55-57] However, to enable interventions to take place an agreement for a universal definition of frailty is imperative. In particular, further research is required to advance our understanding of what determines the onset of frailty and its relation to chronic disease with aging.

The FRAILOMIC Initiative aims to develop clinical instruments by combining clinical, classical laboratory, and omics-based biomarkers of frailty. By identifying molecular signatures of frailty, the project

will make a significant contribution to its universal definition. This will assist clinicians to both accurately diagnose frailty and to screen individuals at risk of becoming frail while also providing insights on how to improve the prognosis of frail individuals in terms of preventing progression and reducing adverse outcomes. By using rationally designed toolkits, clinicians will be provided with the opportunity to plan the optimal intervention for at-risk individuals in order to prevent, or at least delay, the onset of this frailty. This project will also help towards an improved quality of life and a reduction of the burden of disability in patients with common age-related chronic conditions.

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CONFLICT OF INTEREST

No conflicts of interest of any kind are present among the authorship.

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