Emanuele Marzetti

BIOMARKERS OF PHYSICAL FRAILTY (AND SARCOPENIA)

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

Conflict of Interest Disclosure

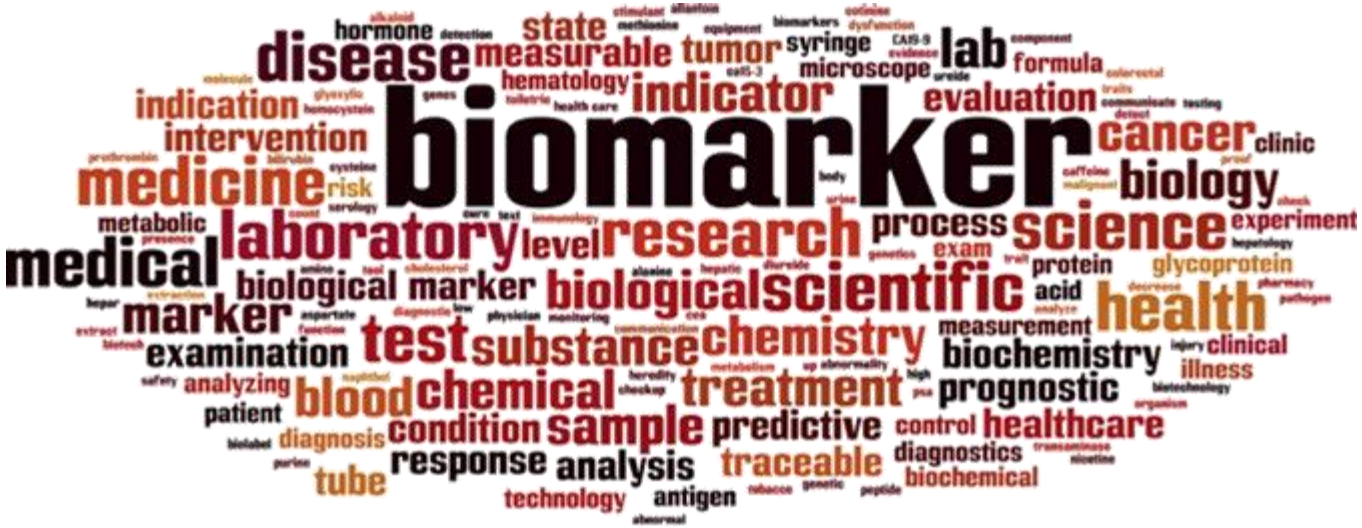
Consultant for

- Abbott
- Cepton
- Nutricia
- Pfizer

BIOMARKER

A defined **characteristic** that is **measured** as an indicator of **normal** biological processes, **pathogenic** processes, or **responses** to an exposure or intervention, including therapeutic interventions.

FDA-NIH Biomarker Working Group



Category	Definition/aim	Example
Susceptibility/Risk biomarker	Potential for **developing** a disease or medical condition in apparently healthy individual	Breast Cancer genes 1 and 2 (**BRCA1/2**) mutations in breast cancers
Diagnostic biomarker	**Detect** or confirm the presence of a disease	Blood sugar or hemoglobin A1c (**HbA1c**) for diabetes
Monitoring biomarker	**Assessing** the status of a disease or the **effect** of interventions	Prostate-specific antigen (**PSA**) in patient with prostate cancer
Prognostic biomarker	**Identify** the likelihood of a clinical event, disease recurrence, or **progressio**n	Prostate-specific antigen (**PSA**) in patient with prostate cancer
Predictive biomarker	**Identify** individuals who are more likely to experience a favorable or unfavorable **effect** from a specific **intervention** or exposure	Epidermal Growth Factor Receptor (**EGFR**) mutations in NSCLC patients to select patients for anti-EGFR drug therapy
Pharmaco-dynamic/ Response biomarker	Show that a **biological response** has occurred in an individual who has received an **intervention** or exposure	**Blood pressure** for antihypertensive agent or sodium restriction

FDA-NIH Biomarker Working Group

Category	Definition/aim	Frailty and sarcopenia biomarkers
Susceptibility/Risk biomarker	Potential for **developing** a disease or medical condition in apparently healthy individual	
Diagnostic biomarker	**Detect** or confirm the presence of a disease	
Monitoring biomarker	**Assessing** the status of a disease or the **effect** of interventions	
Prognostic biomarker	**Identify** the likelihood of a clinical event, disease recurrence, or **progressio**n	
Predictive biomarker	**Identify** individuals who are more likely to experience a favorable or unfavorable **effect** from a specific **intervention** or exposure	
Pharmaco-dynamic/ Response biomarker	Show that a **biological response** has occurred in an individual who has received an **intervention** or exposure	

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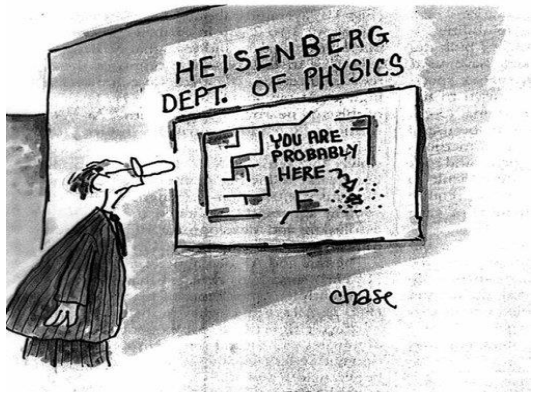
MAJOR OBSTACLES TO THE DEVELOPMENT OF BIOMARKERS FOR FRAILTY AND SARCOPENIA

- Multiple and only partly overlapping operational definitions.
- Complex, multifactorial conditions.
- Incomplete knowledge of pathogenesis.
- Multiple mechanisms are likely to be simultaneously involved in development of frailty and sarcopenia → *multiple biomarkers may be needed to fully frame the conditions*.
- Frailty and sarcopenia (usually) develop over years and pathogenic processes may not necessarily be the same during their whole course → *different biomarkers may be needed depending on the stage*.



JOURNAL OF THE AMERICAN GERIATRICS SOCIETY AGS

Operationalization of Frailty Using Eight Commonly Used Scales and Comparison of Their Ability to Predict All-Cause Mortality

Olga Theou, PhD, Thomas D. Brothers, BA,* Arnold Mitnitski, PhD,* and Kenneth Rockwood, MD*†*

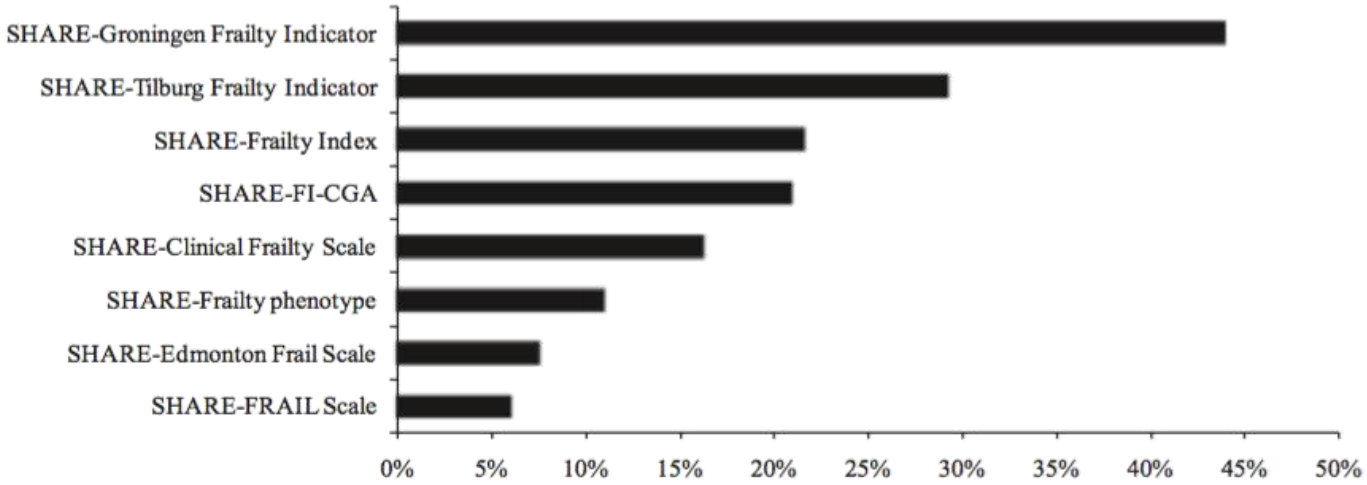
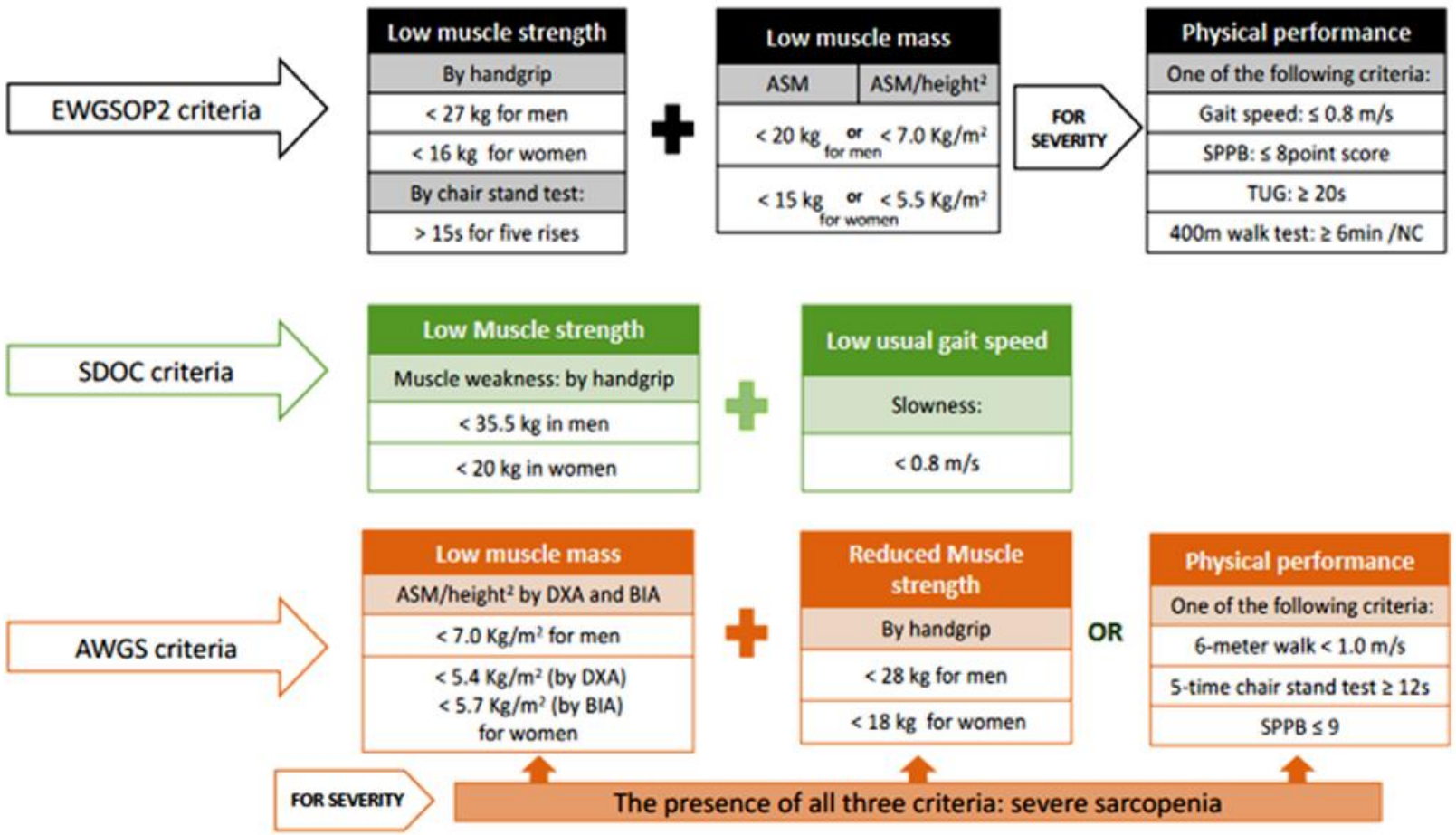


Figure 1. Prevalence of frailty. SHARE = Survey of Health, Ageing and Retirement in Europe; FI-CGA = Frailty Index based on a Comprehensive Geriatric Assessment.

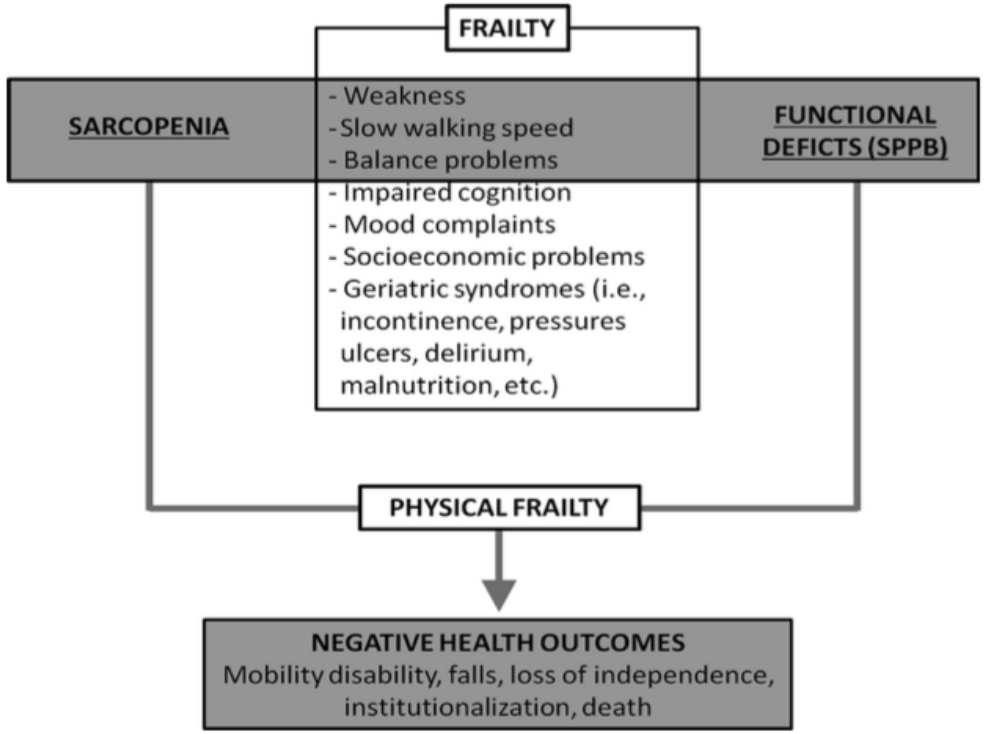


Meza-Valderrama et al., Nutrients 2021

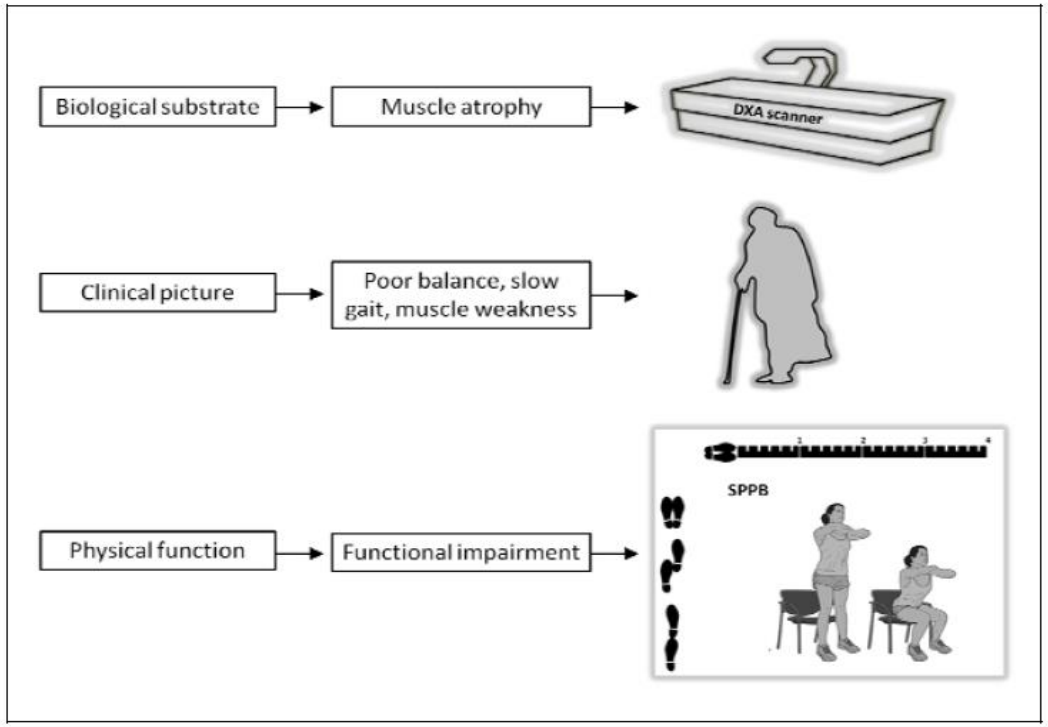
Biosphere

BIOmarkers associated with Sarcopenia and PHysical frailty in ElderRly pErsons

PHYSICAL FRAILTY & SARCOPENIA: THE NEW KID ON THE BLOCK



Landi et al., Clin Geriatr Med 2015



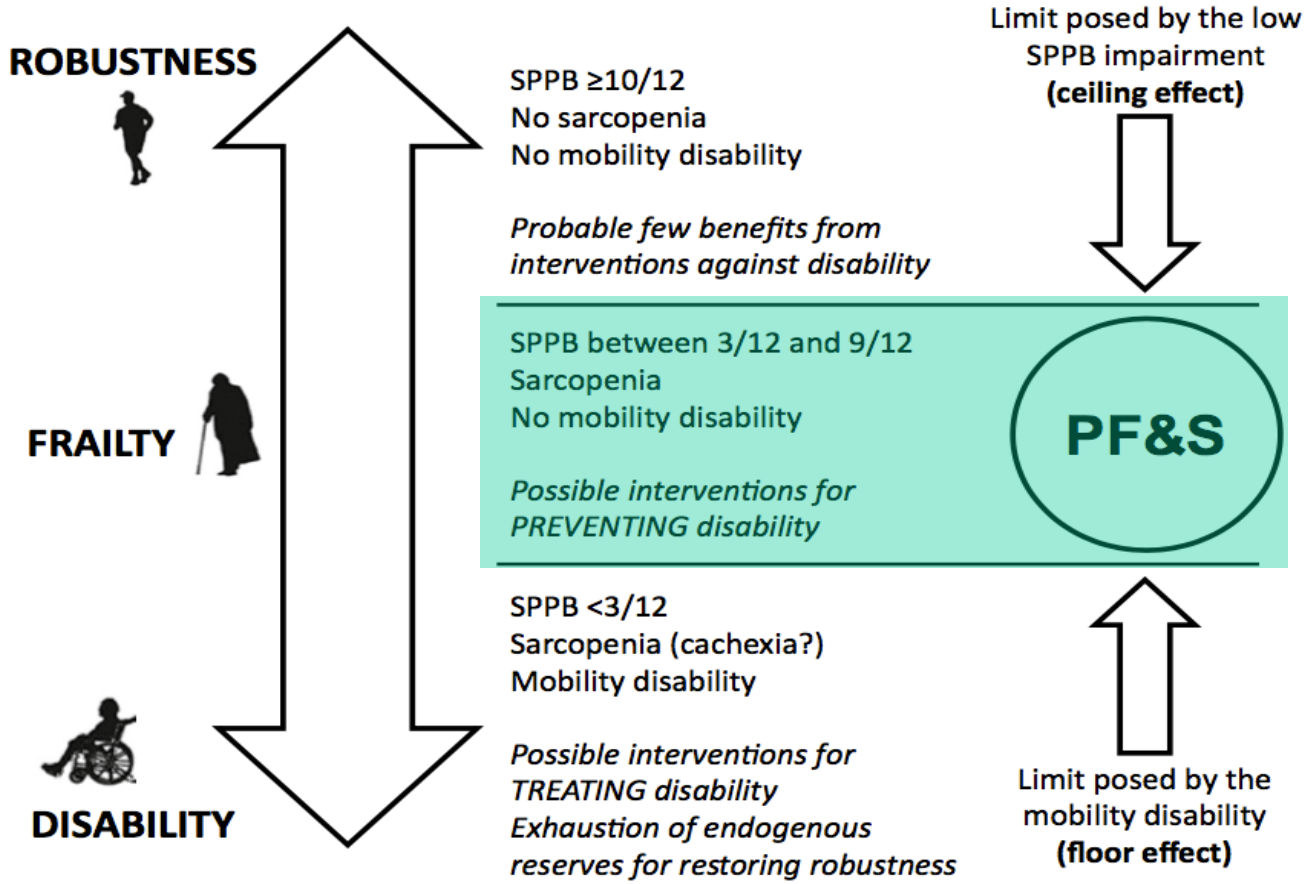
Marzetti et al., Transl Med UniSa 2016

Aging Clin Exp Res (2017) 29:81–88
DOI 10.1007/s40520-016-0716-1

ORIGINAL ARTICLE

Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial

Matteo Cesari[1,2] · Francesco Landi[3] · Riccardo Calvani[3] · Antonio Cherubini[4] · Mauro Di Bari[5,6] · Patrick Kortebein[7,8,9] · Susanna Del Signore[10] · Regis Le Lain[11] · Bruno Vellas[1,2] · Marco Pahor[12] · Ronenn Roubenoff[13] · Roberto Bernabei[3] · Emanuele Marzetti[3] · For the SPRINTT Consortium



European Journal of Internal Medicine 56 (2018) 19–25

Contents lists available at ScienceDirect

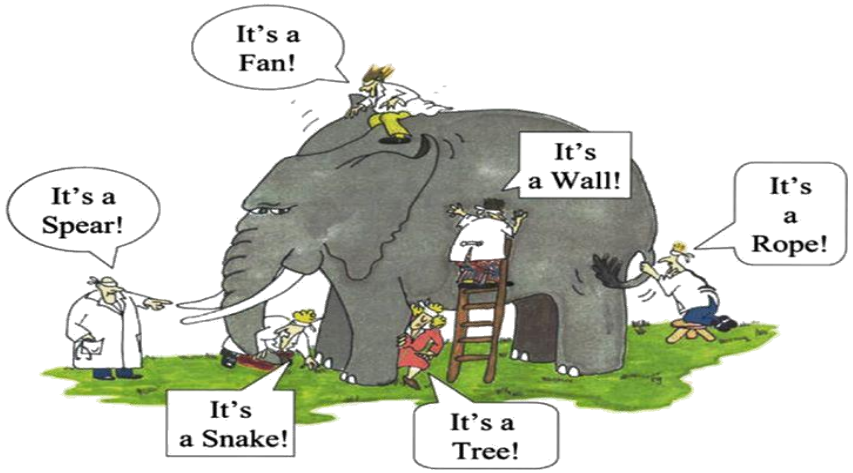
European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

The "BIOmarkers associated with Sarcopenia and PHysical frailty in ElderRly pErsons" (BIOSPHERE) study: Rationale, design and methods

Riccardo Calvani[a,1], Anna Picca[a,*], Federico Marini[b], Alessandra Biancolillo[b], Matteo Cesari[c,d], Vito Pesce[e], Angela Maria Serena Lezza[e], Maurizio Bossola[f], Christiaan Leeuwenburgh[g], Roberto Bernabei[a], Francesco Landi[a], Emanuele Marzetti[a]

BIOSPHERE was designed to develop a biomarker discovery procedure for PF&S, using multivariate methodologies as an alternative approach to traditional single-marker strategies



Fit-for-purpose Statistics

- Statistics were mostly borrowed from chemometrics and were chosen to handle correlated, multi-platform variables.
- Tests were selected to identify biomarker patterns within a large number of analytes collected in a relatively small participant sample.
- Robust cross-validation procedures were applied to ensure findings were not attributable to chance correlations.

"Data don't make any sense,
we will have to resort to statistics."

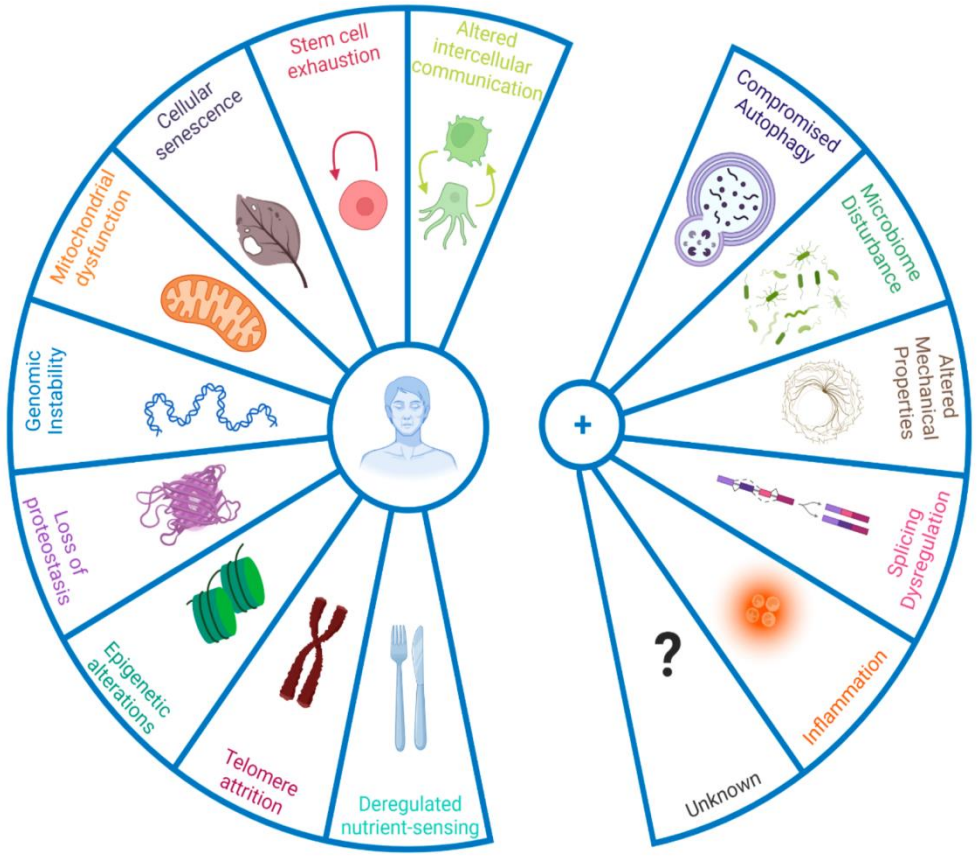
The Hallmarks of Aging

Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

Cell

Cell *153*, June 6, 2013

New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary



GeroScience (2018) 40:419–436
https://doi.org/10.1007/s11357-018-0042-y

CrossMark

REVIEW ARTICLE

A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup

Jamie N. Justice · Luigi Ferrucci · Anne B. Newman · Vanita R. Aroda · Judy L. Bahnson · Jasmin Divers · Mark A. Espeland · Santica Marcovina · Michael N. Pollak · Stephen B. Kritchevsky · Nir Barzilai · George A. Kuchel

Blood-based biomarkers for geroscience-guided trials

Biomarker	Underlying Biologic Process & Role
IL-6, CRP TNFRII	**Inflammation & Intercellular Signaling** Interleukin 6 (IL-6) is a proinflammatory cytokine and Tumor Necrosis Factor-α RII is a TNF -α receptor involved in acute-phase response. C-Reactive Protein (CRP) is an acute phase protein produced in response to inflammation. Cytokine dysregulation is a driver of pathophysiologic processes leading to disease, functional decline, frailty, and death.
GDF15	**Stress Response & Mitochondria** Growth Differentiating Factor 15 (GDF15) is a member of the TGF-β superfamily robustly associated with mortality, cardiovascular events, cognitive decline and dementia. GDF15 is increasingly recognized in mitochondrial dysfunction, and as a biomarker of aging.
IGF-1 Insulin	**Nutrient Signaling** Disruption of the insulin/ insulin-like growth factor (IGF-1) signaling pathway is implicated in longevity in animal models. In humans, IGF-1 and fasting insulin are responsive to caloric restriction, and low IGF-1 in growth hormone receptor deficiency conveys disease protection.
Cystatin-C	**Kidney Aging** Cystatin C, an extracellular inhibitor of cysteine proteases, is a marker of renal disease and aging. It is an independent risk factor for all cause and CVD-related mortality, and multi-morbidity, and higher levels are consistently associated with poor physical function and cognition.
NT-proBNP	**Cardiovascular Health** B-type natriuretic peptides (BNP, NT-proBNP) are secreted in response to cardiomyocyte stretching to decrease vascular resistance. NT-proBNP has a greater-half life and accuracy compared with BNP and is used to diagnose and establish prognosis for heart failure.
HGBA1c	**Metabolic Aging** Glycated hemoglobin (hemoglobin A1c, HGBA1c) is formed in a non-enzymatic glycation pathway and is a marker for 3-mo average plasma glucose. High HGBA1c reflects poor glucose control, and in older nondiabetics is strongly associated with death, chronic disease, and functional decline.
Molecular Signature	**Epigenetic, Interdependent, Multi-Omic** Data intensive molecular platforms can explore global changes in epigenetic, transcriptomic, proteomic and proteostasis, and small metabolite signatures. These approaches may better capture complex and multifactorial processes underlying aging.

PHYSICAL FRAILTY & SARCOPENIA: A PROTOTYPICAL GEROSCIENCE CONDITION

Muscle-specific processes

- Mitochondrial dysfunction
- Redox imbalance
- Alterations in protein homeostasis
- Acceleration of myonuclear apoptosis
- Dysregulation of autophagy
- Neuromuscular junction aberrant remodeling
- Iron dyshomeostasis

Non-muscle-specific processes

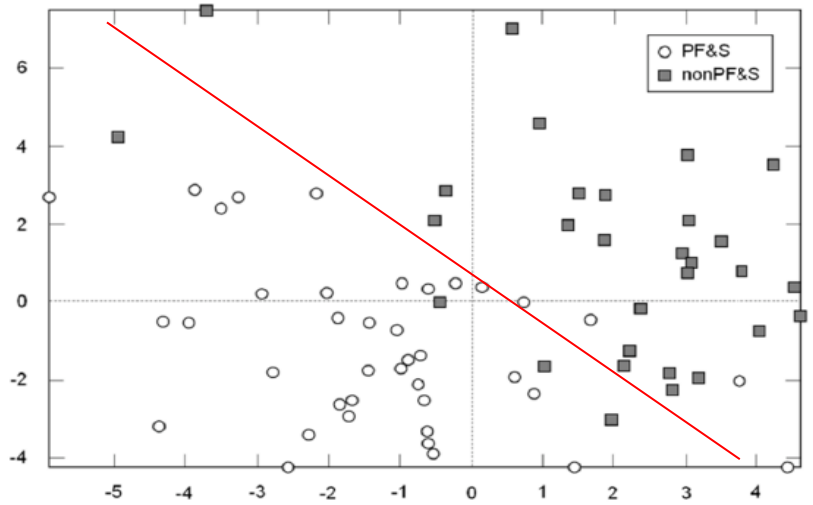
- Systemic inflammation
- Hormonal changes
- Telomere shortening (senescence)
- Malnutrition
- Gut dysbiosis

Nutrients 2018, *10*, 1691; doi:10.3390/nu10111691

A Distinct Pattern of Circulating Amino Acids Characterizes Older Persons with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study

Riccardo Calvani [1,2], Anna Picca [1,2,*], Federico Marini [3], Alessandra Biancolillo [3], Jacopo Gervasoni [1,2], Silvia Persichilli [1,2], Aniello Primiano [2], Hélio José Coelho-Junior [2,4], Maurizio Bossola [1,2], Andrea Urbani [1,2], Francesco Landi [1,2], Roberto Bernabei [1,2] and Emanuele Marzetti [1]

Controls:	78.5 ±6.0%
PF&S:	75.1 ±4.6%
Total:	75.6 ±3.9%



	PF&S (n = 38)	nonPF&S (n = 30)	VIP	RP
α-aminobutyric acid (μmol/L)	20.0 ± 4.9	22.3 ± 5.7	2.2	8.0
Asparagine (μmol/L)	91.0 ± 12.6	77.8 ± 13.4	3.4	2.0
Aspartic Acid (μmol/L)	24.6 ± 5.4	17.0 ± 4.0	5.8	2.6
Citrulline (μmol/L)	44.8 ± 12.1	36.8 ± 11.5	2.1	2.8
Ethanolamine (μmol/L)	10.3 ± 1.7	9.0 ± 2.2	1.7	9.9
Glutamic acid (μmol/L)	71.7 ± 16.6	54.3 ± 21.2	2.3	8.5
Methionine (μmol/L)	22.6 ± 2.8	23.4 ± 5.7	1.3	6.3
Sarcosine (μmol/L)	1.9 ± 0.6	1.5 ± 0.5	1.4	8.0
Taurine (μmol/L)	220.1 ± 36.5	189.5 ± 47.2	1.8	6.7

Experimental Gerontology 122 (2019) 129–138

Contents lists available at ScienceDirect

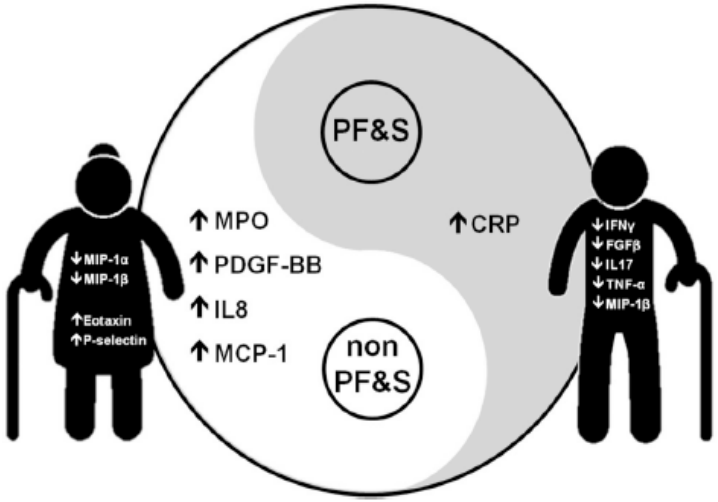
Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Inflammatory signatures in older persons with physical frailty and sarcopenia: The frailty "cytokinome" at its core

Emanuele Marzetti[a], Anna Picca[a,b,*], Federico Marini[c], Alessandra Biancolillo[c], Hélio José Coelho-Junior[b,d], Jacopo Gervasoni[a,b], Maurizio Bossola[a,b], Matteo Cesari[e,f], Graziano Onder[a,b], Francesco Landi[a,b], Roberto Bernabei[a,b,*], Riccardo Calvani[a,b]

Controls: 68.7 ± 2.5%
PF&S: 82.3 ± 1.6%
Total: 75.6 ± 1.3%



	Women (n=125)		Men (n=75)	
	PF&S (n=75)	NonPF&S (n=50)	PF&S (n=25)	NonPF&S (n=50)
MPO (ng/mL)	227.5 (182.3)	667.3 (593.4)	313.0 (263.5)	558.0 (490.3)
PDGF-BB (ng/mL)	3.1 (1.8)	3.9 (2.5)	2.8 (1.2)	3.6 (1.8)
IL8 (pg/mL)	9.85 (6.5)	13.6 (10.2)	9.3 (5.4)	15.8 (12.9)
MCP-1 (pg/mL)	31.8 (10.1)	34.6 (14.0)	30.3 (16.4)	43.3 (25.5)
CRP (mg/L)	2.8 (4.1)	1.8 (2.1)	3.2 (7.3)	1.8 (2.1)
MIP-1β (pg/mL)	175.6 (72.4)	176.2 (76.7)	144.0 (88.0)	189.4 (58.4)
MIP-1α (pg/mL)	3.3 (10.5)	4.2 (10.6)	4.3 (10.4)	5.9 (9.8)
P-selectin (ng/mL)	108.8 (39.5)	95.7 (47.3)	99.1 (47.0)	108.0 (39.7)
Eotaxin (pg/mL)	158.8 (167.3)	133.6 (182.1)	183.0 (175.4)	169.0 (137.9)
IL17 (pg/mL)	17.0 (7.0)	18.7 (7.0)	14.6 (7.4)	20.5 (10.5)
IFNγ (pg/mL)	2.5 (0.7)	3.0 (1.2)	2.5 (0.7)	3.2 (2.3)
FGF b (pg/mL)	44.9 (20.1)	51.2 (24.0)	39.4 (19.9)	53.9 (24.4)
TNF-α (pg/mL)	37.5 (23.9)	44.1 (26.3)	32.7 (19.2)	48.3 (35.6)

GeroScience
https://doi.org/10.1007/s11357-020-00197-x

ORIGINAL ARTICLE

Identification of biomarkers for physical frailty and sarcopenia through a new multi-marker approach: results from the BIOSPHERE study

Riccardo Calvani · Anna Picca · Federico Marini · Alessandra Biancolillo · Jacopo Gervasoni · Silvia Persichilli · Aniello Primiano · Hélio J. Coelho-Junior · Matteo Cesari · Maurizio Bossola · Andrea Urbani · Graziano Onder · Francesco Landi · Roberto Bernabei · Emanuele Marzetti

Table 2 Composition of matrices used for sequential and orthogonalized covariance selection (SO-CovSel) analysis

Data block	Number of variables	Variables
Matrix 1	27	IL1-β, IL1-ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, FGF basic, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1α, MIP-1β, CCL5, CCL11, IP-10, PDGF-BB, TNF-α
Matrix 2	4	CRP, MPO, FGF-21, BDNF
Matrix 3	6	CAF, P-Selectin, HtrA1, Hsp72, P3NP, IGF-1
Matrix 4	37	1-methylhistidine, 3-methylhistidine, 4-hydroxyproline, α-aminobutyric acid, β-alanine, β-aminobutyric acid, γ-aminobutyric acid, alanine, aminoadipic acid, anserine, arginine, asparagine, aspartic acid, carnosine, citrulline, cystathionine, cystine, ethanolamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, phosphoethanolamine, phosphoserine, proline, sarcosine, serine, taurine, threonine, tryptophan, tyrosine, valine

GeroScience
https://doi.org/10.1007/s11357-020-00197-x

ORIGINAL ARTICLE

Check for updates

Identification of biomarkers for physical frailty and sarcopenia through a new multi-marker approach: results from the BIOSPHERE study

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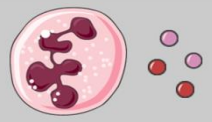
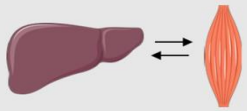
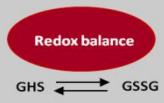
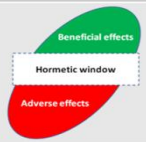
Controls:	79.9 ± 5.1%
PF&S:	80.6 ± 5.3%
Total:	80.3 ± 3.8%

Candidate biomarkers	Biological actions and putative roles in PF&S pathophysiology	
MPO PDGF-BB		**Inflammation, immunosenescence, and "hormetic" regenerative signals** MPO is a pro-inflammatory cytokine mainly secreted by neutrophils at sites of inflammation. PDGF-BB is a growth factor involved in platelet-mediated regeneration of skeletal muscle. Reduced levels of MPO and PDGF may be indicative of immunosenescence and decreased muscle regenerative capacity.
Asparagine Aspartic acid Citrulline		**Nitrogen and glutamine metabolism** Citrulline is synthesised from glutamine and is involved in nitrogen homeostasis. Asparagine and aspartic acid are metabolised in resting muscles and provide metabolic intermediates for glutamine synthesis. High levels of asparagine, aspartic acid, and citrulline in PF&S may suggest perturbations in nitrogen and glutamine metabolism.
α-aminobutyric acid		**Oxidative stress** α-aminobutyric acid is a non-essential amino acid involved in glutathione metabolism. Reduced levels of α-aminobutyric acid in older people with PF&S may suggest perturbations in glutathione biosynthesis and redox balance.
Hsp72		**Stress response** Hsp72 is produced in response to a variety of stressors. Hsp72 exhibits potent immunomodulatory effects. Low Hsp72 levels in older people with PF&S may suggest perturbations in hormetic stress signals.

nutrients

MDPI

Article

Gut Microbial, Inflammatory and Metabolic Signatures in Older People with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study

Anna Picca [1,2], Francesca Romana Ponziani [2], Riccardo Calvani [1,2,*], Federico Marini [3], Alessandra Biancolillo [3,4], Hélio José Coelho-Júnior [5], Jacopo Gervasoni [1,2], Aniello Primiano [1,2], Lorenza Putignani [6], Federica Del Chierico [7], Sofia Reddel [7], Antonio Gasbarrini [1,2], Francesco Landi [1,2], Roberto Bernabei [1,2,*] and Emanuele Marzetti [1,2]

Table 2. Composition of the multi-block dataset used for Sequential and Orthogonalized Covariance Selection (SO-CovSel) analysis.

Data Block	Biological Pathway	Variables
Matrix 1	Inflammation	CCL5, CCL11, IFN-γ, FGF-β, G-CSF, GM-CSF, IL1β, IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, TNF-α
Matrix 2	Protein/amino acid metabolism	1-methylhistidine, 3-methylhistidine, 4-hydroxyproline, α-aminobutyric acid, β-alanine, β-aminobutyric acid, γ-aminobutyric acid, alanine, aminoadipic acid, anserine, arginine, asparagine, aspartic acid, carnosine, citrulline, cystathionine, cystine, ethanolamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, phosphoethanolamine, phosphoserine, proline, sarcosine, serine, taurine, threonine, tryptophan, tyrosine, valine
Matrix 3	Gut microbiota	*Actinobacteria, Adlercreutzia, Aerostipes, Aerotruncus, Akkermansia, Alcaligenaceae, Atopobium, Bacteroidaceae, Bacteroides, Bacteroidetes, Barnesiellaceae, Bifidobacteriaceae, Bifidobacterium, Bilophila, Blautia, Carnobacteriaceae, Christensenella, Christensenellaceae, Clostridiaceae, Collinsella, Coprococcus, Coriobacteriaceae, Cyanobacteria, Dehalobacteriaceae, Dehalobacterium, Desulfovibrionaceae, Dethiosulfovibrionaceae, Dialister, Dorea, Eggerthella, Enterobacteriaceae, Enterococcaceae, Enterococcus, Erysipelotrichaceae, EtOH8, Eubacterium, Euryarchaeota, Faecalibacterium, Firmicutes, Granulicatella, Haemophilus, Lachnobacterium, Lachnospira, Lachnospiraceae, Lactobacillaceae, Lactobacillus, Methanobacteriaceae, Methanobrevibacter, Mogibacteriacea, Oscillospira, Parabacteroides, Paraprevotella, Paraprevotellaceae, Pasteurellaceae, Peptostreptococcaceae, Phascolarctobacterium, Porphyromonadaceae, Prevotella, Prevotellaceae, Proteobacteria, Pyramidobacter, Rikenellaceae, Roseburia, Ruminococcaceae, Ruminococcus, Ruminococcus, S24-7, Slackia, Streptococcaceae, Streptococcus, Sutterella, Synergistetes, Tenericutes, TM7, Veillonella, Veillonellaceae, Verrucomicrobia, Verrucomicrobiaceae*

nutrients

MDPI

Article

Gut Microbial, Inflammatory and Metabolic Signatures in Older People with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study

Anna Picca [1,2], Francesca Romana Ponziani [2], Riccardo Calvani [1,2,*], Federico Marini [3], Alessandra Biancolillo [3,4], Hélio José Coelho-Júnior [5], Jacopo Gervasoni [1,2], Aniello Primiano [1,2], Lorenza Putignani [6], Federica Del Chierico [7], Sofia Reddel [7], Antonio Gasbarrini [1,2], Francesco Landi [1,2], Roberto Bernabei [1,2,*] and Emanuele Marzetti [1,2]

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Data Block	Biological Pathway	Variables
Matrix 1		CCL5, CCL11, IFN-γ, FGF-β, G-CSF, GM-CSF, IL1β, IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, TNF-α
Matrix 2	Protein/amino acid metabolism	1-methylhistidine, 3-methylhistidine, 4-hydroxyproline, α-aminobutyric acid, β-alanine, β-aminobutyric acid, γ-aminobutyric acid, alanine, aminoadipic acid, anserine, arginine, asparagine, aspartic acid, carnosine, citrulline, cystathionine, cystine, ethanolamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, phosphoethanolamine, phosphoserine, proline, sarcosine, serine, taurine, threonine, tryptophan, tyrosine, valine

Controls: 91.7%
PF&S: 87.5%
Total: 90.0%

Table 4. Levels of relevant analytes as resulted from SO-CovSel analysis.

	PF&S (n = 18)	nonPF&S (n = 17)
MIP-1α (pg/mL)	2.98 (11.04)	10.64 (11.15)
Aspartic acid (μmol/L)	26.95 (9.33)	16.10 (9.28)
Threonine (μmol/L)	109.90 (33.60)	125.80 (55.60)
Barnesiellaceae (log2FC)	0.0010 (0.007)	0.0030 (0.003)
Christensenellaceae (log2FC)	0.0004 (0.005)	0.0023 (0.004)
Oscillospira (log2FC)	0.0147 (0.227)	0.0109 (0.009)
Ruminococcus (log2FC)	0.0674 (0.091)	0.0620 (0.058)

Data are shown as median and interquartile range.

...pes, Aerotruncus, ...um, Bacteroidaceae, ...e, Bifidobacteriaceae, ...arnobacteriaceae, ..., Clostridiaceae, ...eae, Cyanobacteria, Desulfovibrionaceae, ...orea, Eggerthella, ..., Enterococcus, ...um, Euryarchaeota, ...ntella, Haemophilus, ...chnospiraceae, ...anobacteriaceae, ...ea, Oscillospira, ...raprevotellaceae, ...hascolarctobacterium, Prevotellaceae, ...ellaceae, Roseburia, ...inococcus, S24-7, ...ccus, Sutterella, Synergistetes, Tenericutes, TM7, Veillonella, Veillonellaceae, Verrucomicrobia, Verrucomicrobiaceae

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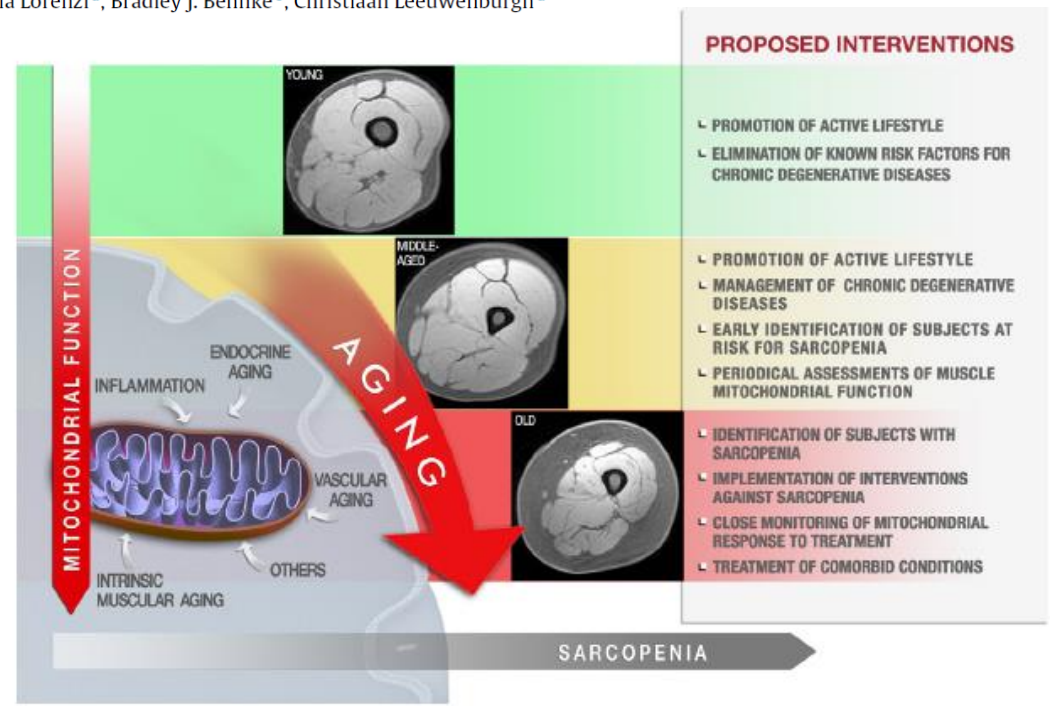
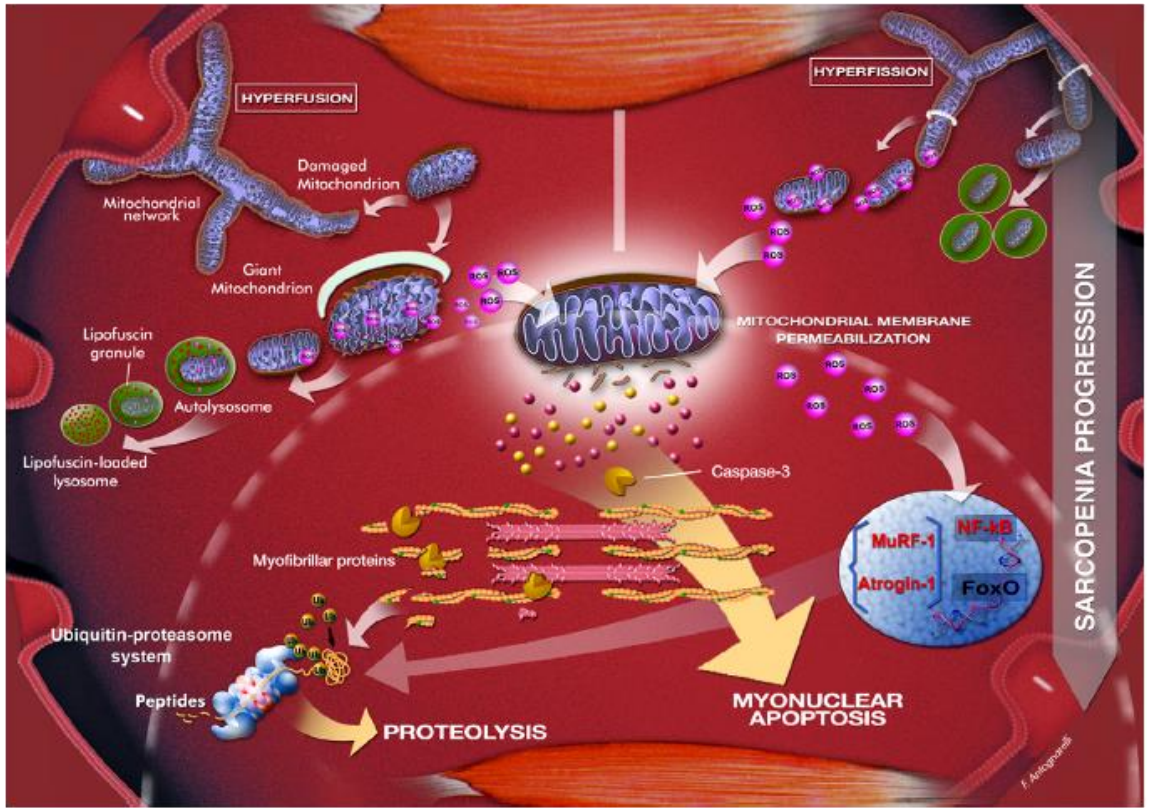
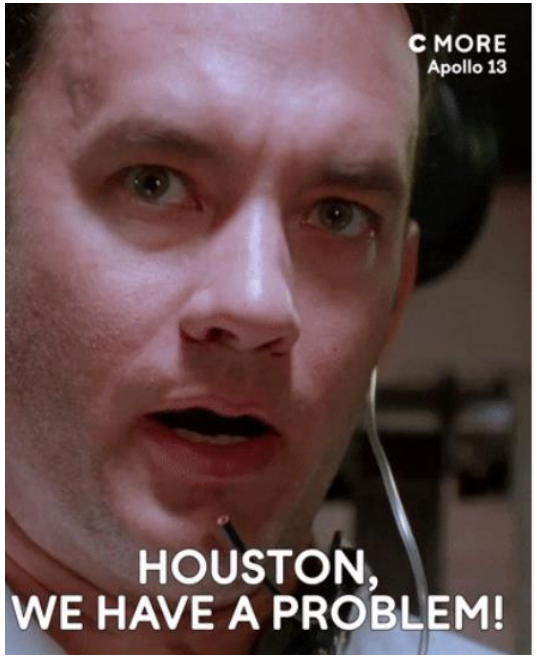
Review

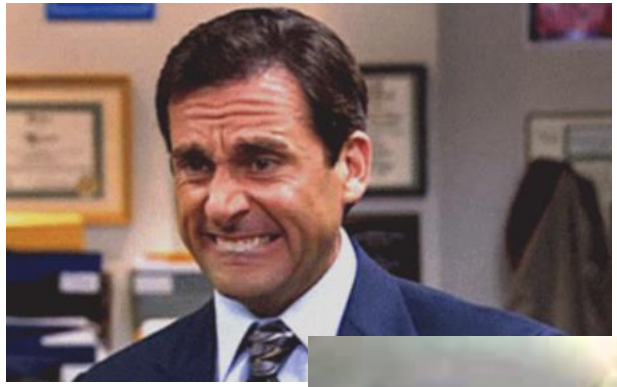
Mitochondrial dysfunction and sarcopenia of aging: From signaling pathways to clinical trials☆

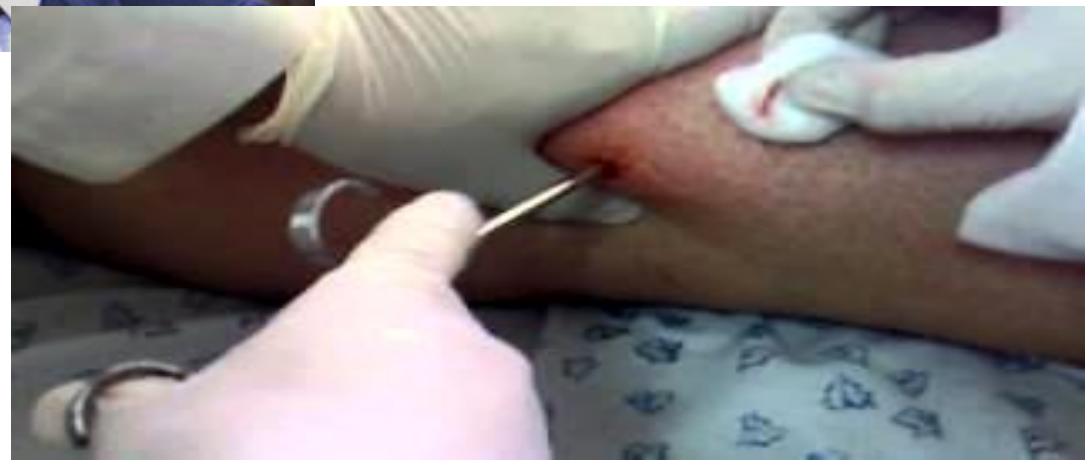
Emanuele Marzetti[a,*,1], Riccardo Calvani[b,1], Matteo Cesari[c], Thomas W. Buford[d,e], Maria Lorenzi[a], Bradley J. Behnke[e], Christiaan Leeuwenburgh[d]






C MORE
Apollo 13
HOUSTON,
WE HAVE A PROBLEM!





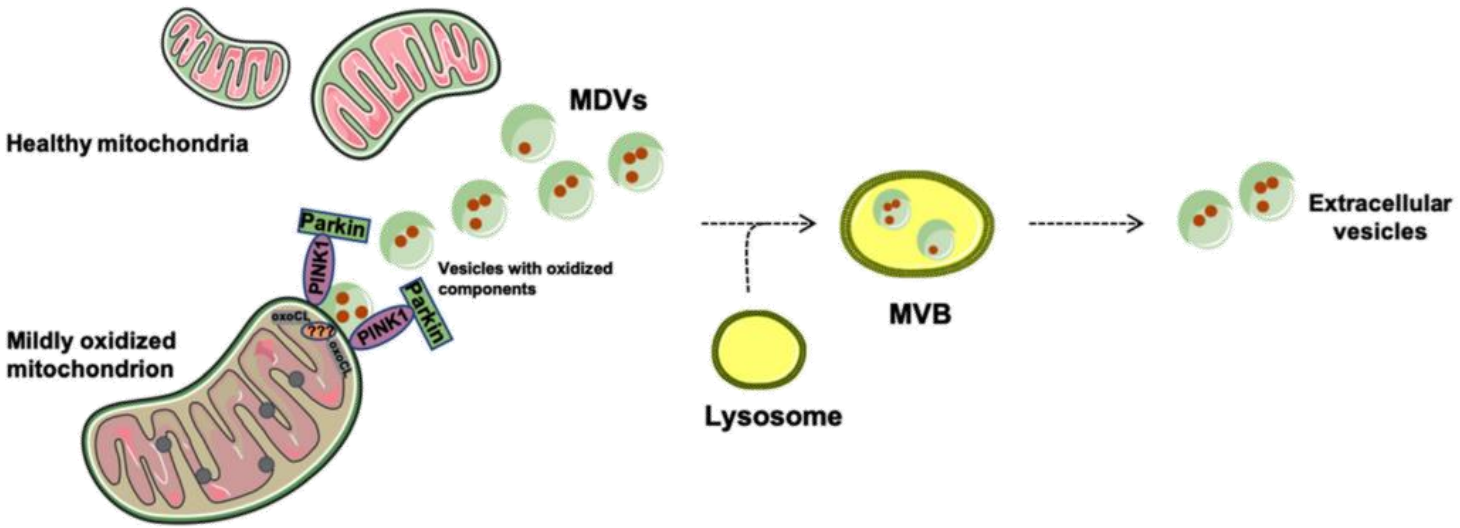
Journal of *Clinical Medicine*

MDPI

Review

Generation and Release of Mitochondrial-Derived Vesicles in Health, Aging and Disease

Anna Picca [1,†], Flora Guerra [2,†], Riccardo Calvani [1,*], Hélio José Coelho-Junior [3], Maurizio Bossola [1,3], Francesco Landi [1,3], Roberto Bernabei [1,3], Cecilia Bucci [2,*] and Emanuele Marzetti [1,3]



Mildly oxidized mitochondria are targeted by phosphatase and tensin homolog-induced kinase 1 (PINK1) and Parkin. This priming process, in conjunction with oxidized cardiolipin (oxoCL)-driven membrane curvatures and other unknown proteins, assists in the generation of MDVs. MDVs reach out to the endolysosomal system and form multivesicular bodies (MVBs) that are extruded from cells as extracellular vesicles.

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
67° CONGRESSO NAZIONALE SIGG
LA LONGEVITÀ DECLINATA AL FEMMINILE

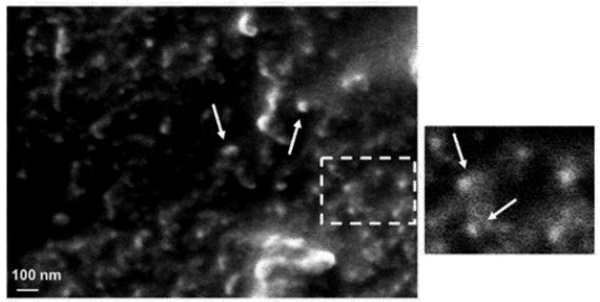
cells

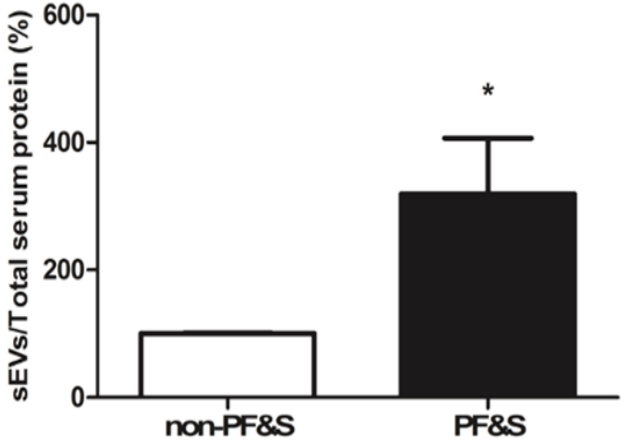
MDPI

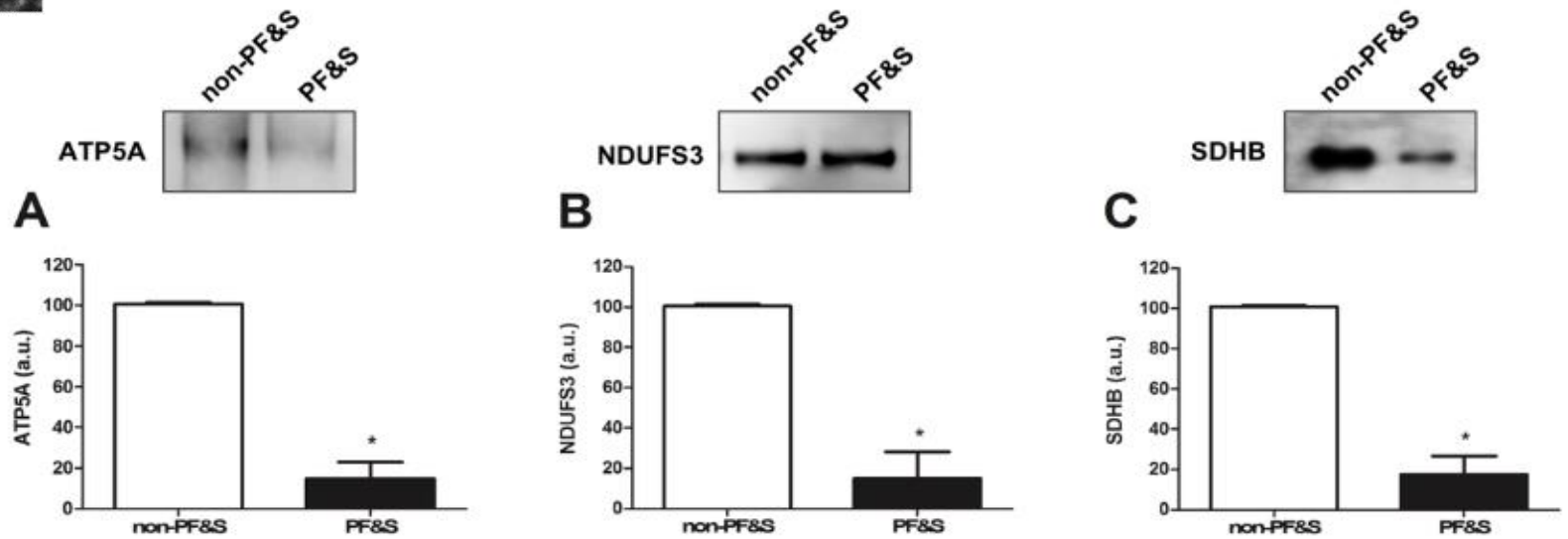
Article

Older Adults with Physical Frailty and Sarcopenia Show Increased Levels of Circulating Small Extracellular Vesicles with a Specific Mitochondrial Signature

Anna Picca [1,†], Raffaella Beli [2,†], Riccardo Calvani [1,*], Hélio José Coelho-Júnior [3], Francesco Landi [1,3], Roberto Bernabei [1,3], Cecilia Bucci [2], Flora Guerra [2,*] and Emanuele Marzetti [1,3]







frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH
published: 22 September 2020
doi: 10.3389/fcell.2020.564417

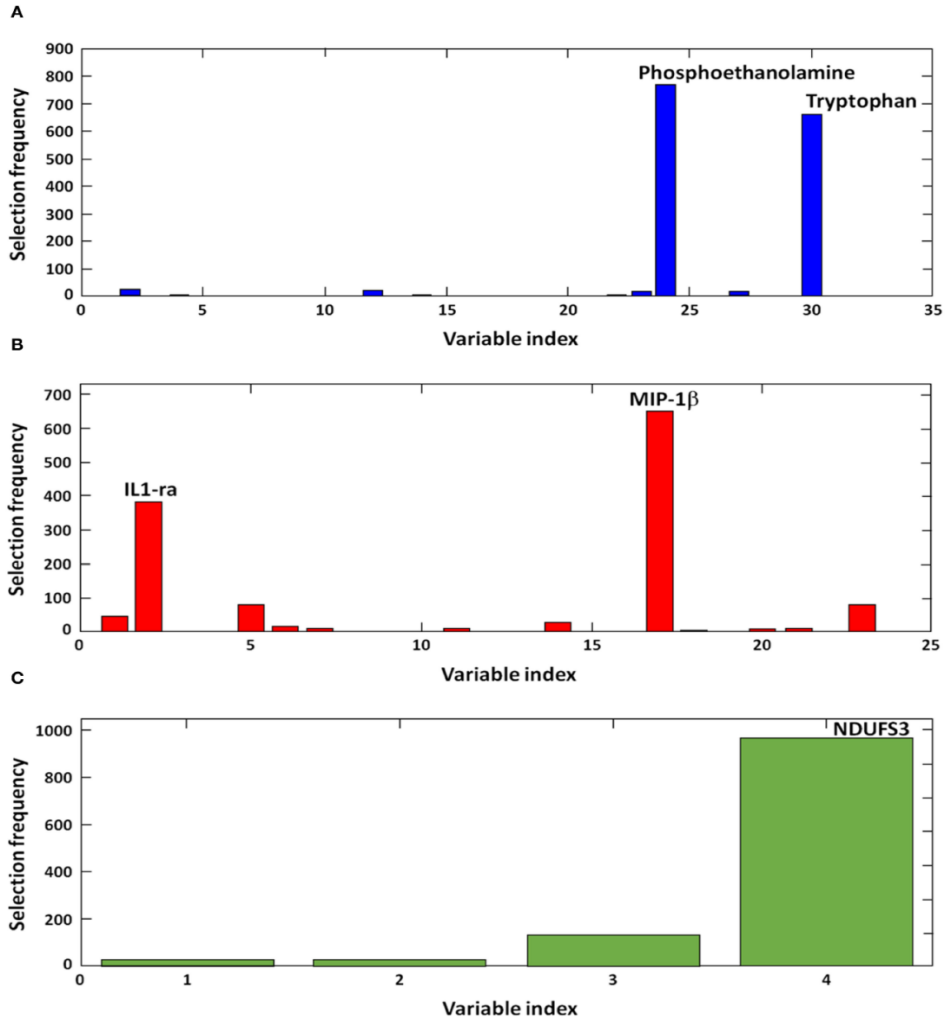
Circulating Mitochondrial-Derived Vesicles, Inflammatory Biomarkers and Amino Acids in Older Adults With Physical Frailty and Sarcopenia: A Preliminary BIOSPHERE Multi-Marker Study Using Sequential and Orthogonalized Covariance Selection – Linear Discriminant Analysis

Emanuele Marzetti[1,2], Flora Guerra[3], Riccardo Calvani[1], Federico Marini[4], Alessandra Biancolillo[5], Jacopo Gervasoni[1,2], Aniello Primiano[2], Hélio José Coelho-Júnior[2], Francesco Landi[1,2], Roberto Bernabei[1,2], Cecilia Bucci[3] and Anna Picca[1]*

TABLE 1 | Composition of the biomarker panel.

Biological pathways	Biomolecules
Inflammation	BDNF, CRP, IL1-β, IL1-ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, FGF basic, FGF21, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1α, MIP-1β, CCL5, CCL11, IP-10, MPO, PDGF-BB, TNF-α, VEGF
Amino acid metabolism	1-methylhistidine, 3-methylhistidine, 4-hydroxyproline, α-aminobutyric acid, β-alanine, β-aminobutyric acid, γ-aminobutyric acid, alanine, aminoadipic acid, anserine, arginine, asparagine, aspartic acid, carnosine, citrulline, cystathionine, cystine, ethanolamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, phosphoethanolamine, phosphoserine, proline, sarcosine, serine, taurine, threonine, tryptophan, tyrosine, valine
MDVs	ATP5A, CD63, MTCOI, NDUFB8, NDUFS3, SDHB, UQCRC2

Controls: 83.6 ± 9.2%
PF&S: 80.6 ± 5.3%
Total: 80.3 ± 3.8%



International Journal of *Molecular Sciences*
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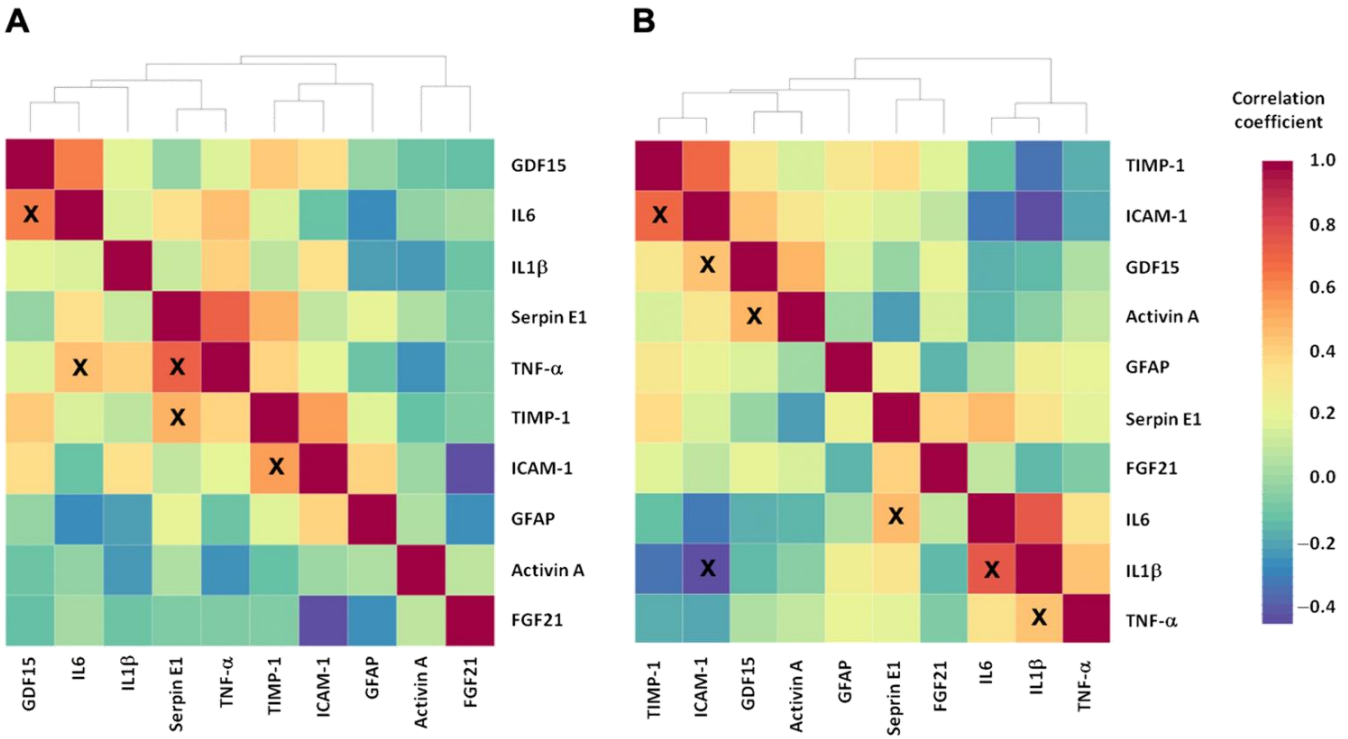
Article

Circulating Inflammatory, Mitochondrial Dysfunction, and Senescence-Related Markers in Older Adults with Physical Frailty and Sarcopenia: A BIOSPHERE Exploratory Study

Anna Picca [1,2], Riccardo Calvani [1,*], Hélio José Coelho-Júnior [3], Federico Marini [4], Francesco Landi [1,3] and Emanuele Marzetti [1,3]



IL1-β
IL6
TNF-α
Activin A
ICAM-1
Serpin E1
TIMP-1
GFAP
GDF15
FGF21

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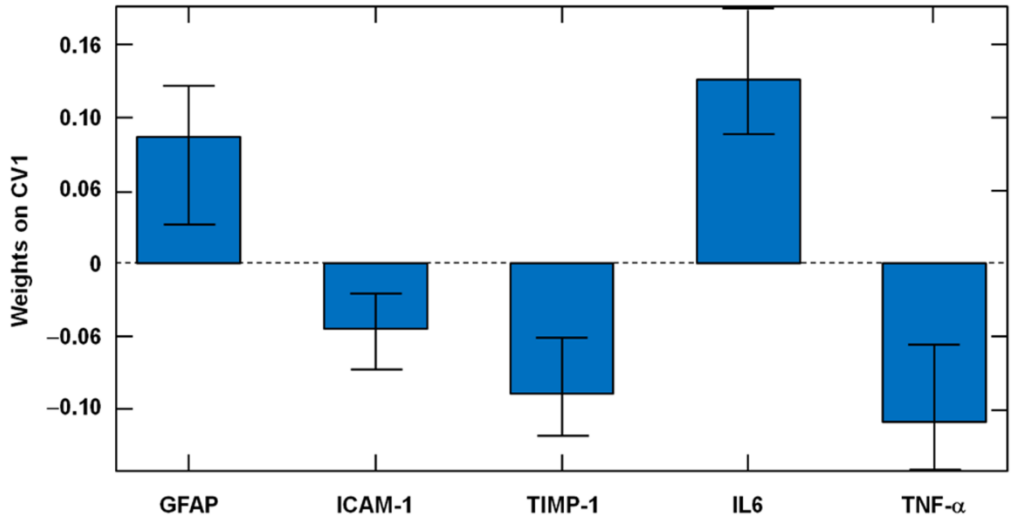
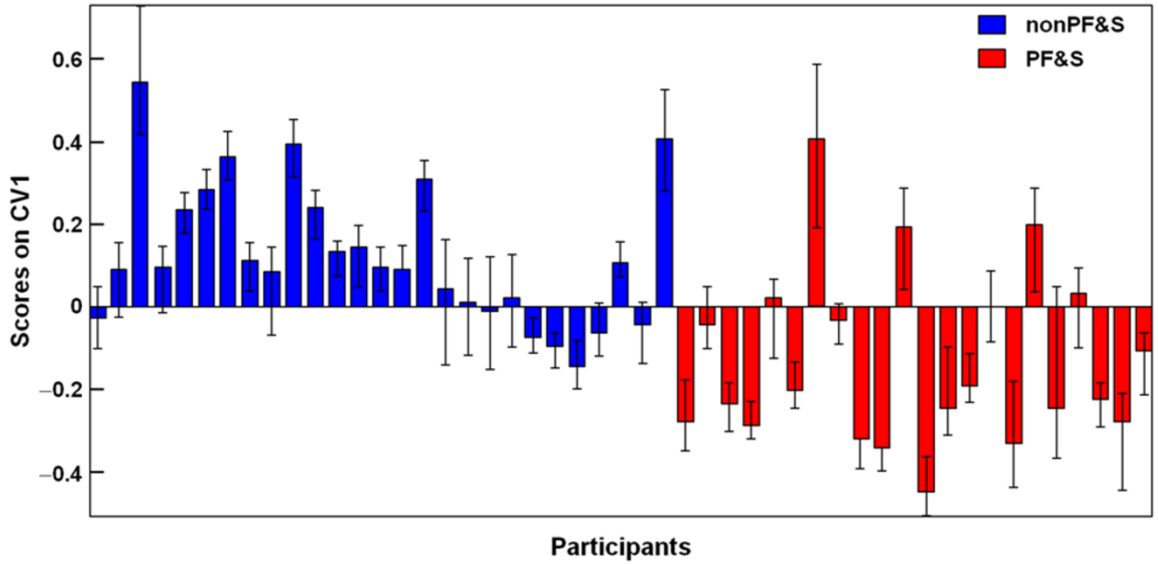
Article

Circulating Inflammatory, Mitochondrial Dysfunction, and Senescence-Related Markers in Older Adults with Physical Frailty and Sarcopenia: A BIOSPHERE Exploratory Study

Anna Picca [1,2], Riccardo Calvani [1,*], Hélio José Coelho-Júnior [3], Federico Marini [4], Francesco Landi [1,3] and Emanuele Marzetti [1,3]





Controls:	**72.8**	**± 4.7%**
PF&S:	**75.0**	**± 4.9%**
Total:	**74.0**	**± 3.4%**

CONCLUSION

- Multivariate/multidimensional modeling of complementary biomarkers is a suitable strategy for capturing the complexity of physical frailty & sarcopenia.
- The analytical approach applied in BIOSPHERE allowed identifying specific patterns of (biologically plausible) candidate biomarkers pertaining to complementary physiologic domains.
- Findings obtained in BIOSPHERE are preliminary and need to be validated longitudinally and in larger-scale studies.

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Innovative Medicines Initiative – Joint Undertaking (IMI–JU 115621)

Fondazione Roma (NCDs call 2013)

Centro Studi “Achille e Linda Lorenzon”

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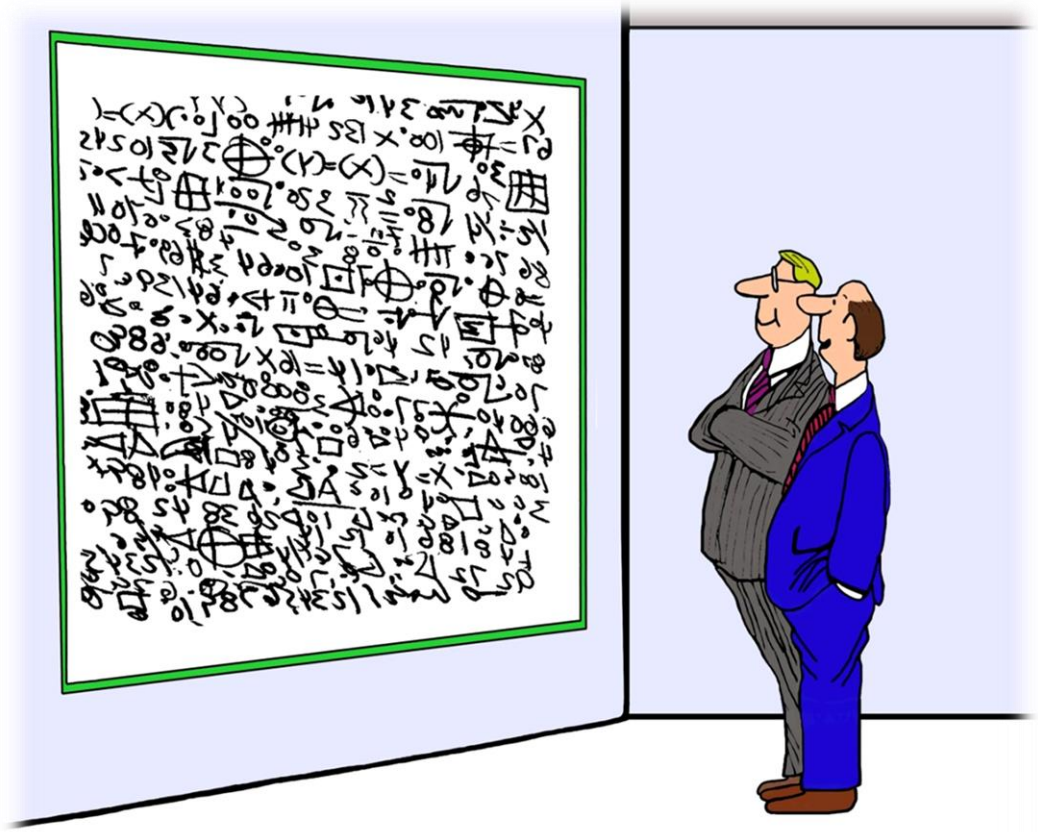

"When you put it like that, it makes complete sense."

emanuele.marzetti@policlinicogemelli.it