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STIAMO  
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# Sarcopenia e nutrizione: nuove evidenze

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Università Cattolica del Sacro Cuore

Gemelli



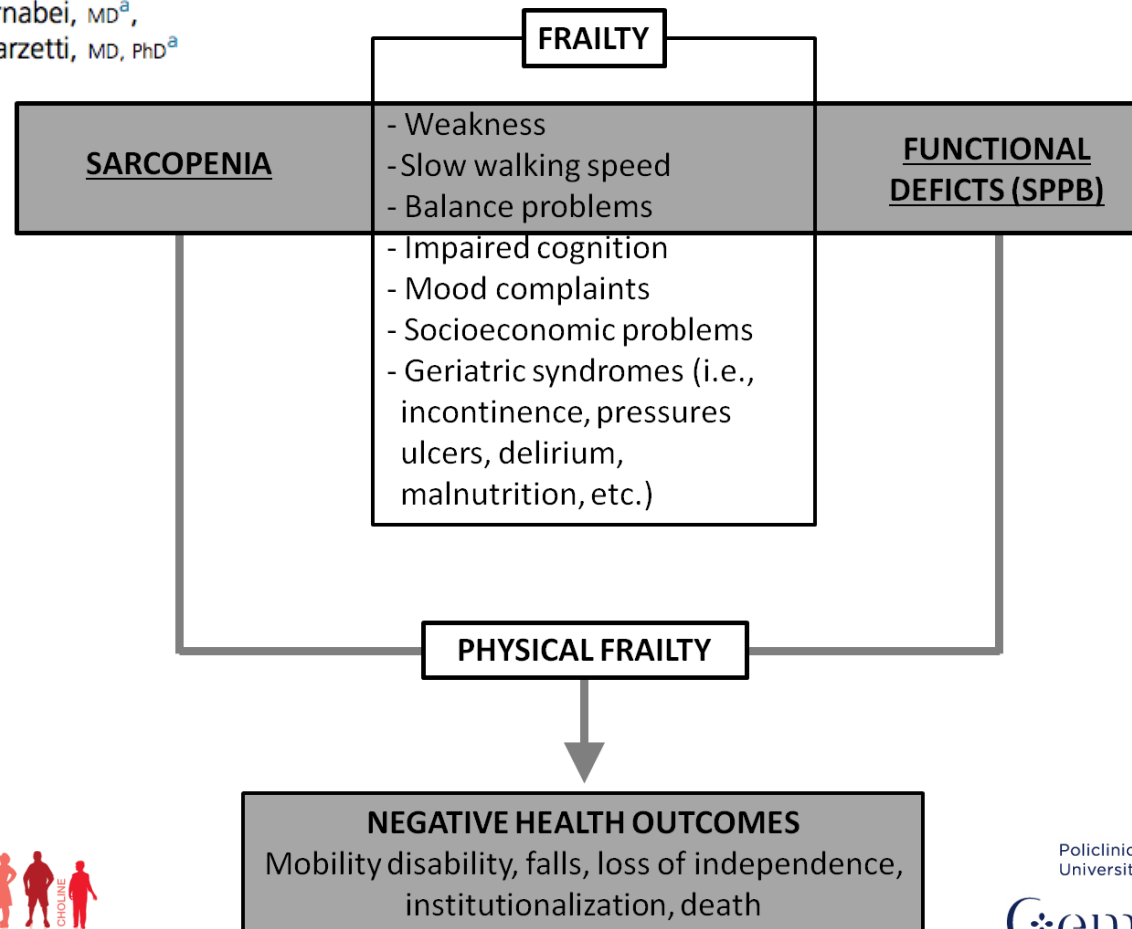
# Sarcopenia as substrate of frailty

## Sarcopenia as the Biological Substrate of Physical Frailty

Clin Geriatr Med (2015)

<http://dx.doi.org/10.1016/j.cger.2015.04.005>

Francesco Landi, MD, PhD<sup>a,\*</sup>, Riccardo Calvani, PhD<sup>a,1</sup>,  
Matteo Cesari, MD, PhD<sup>b,1</sup>, Matteo Tosato, MD, PhD<sup>a</sup>,  
Anna Maria Martone, MD<sup>a</sup>, Roberto Bernabei, MD<sup>a</sup>,  
Graziano Onder, MD, PhD<sup>a</sup>, Emanuele Marzetti, MD, PhD<sup>a</sup>





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Graziano Onder, MD, PhD<sup>a</sup>, Emanuele Marzetti, MD, PhD<sup>a</sup>

**Table 1**

**Conceptual framework of physical therapy and sarcopenia—resemblance to common conditions of advanced age**

Condition	Measurable Biological Substrate	Measurable Clinical Manifestations	Measurable Function
CHF	Myocardial dysfunction (echocardiography)	<ul style="list-style-type: none"> <li>• Shortness of breath</li> <li>• Fatigue</li> </ul>	6-min walking test
COPD	Airways destructive changes (spirometry)	<ul style="list-style-type: none"> <li>• Dyspnoea</li> <li>• Cough</li> <li>• Sputum</li> </ul>	6-min walking test
PAD	Arterial stenosis (Doppler echocardiography)	<ul style="list-style-type: none"> <li>• Intermittent claudication</li> <li>• Numbness</li> <li>• Ulcers</li> </ul>	Treadmill walking distance
PF&S	Reduced muscle mass (DXA)	<ul style="list-style-type: none"> <li>• Slow walking speed</li> <li>• Poor balance</li> <li>• Weakness</li> </ul>	SPPB

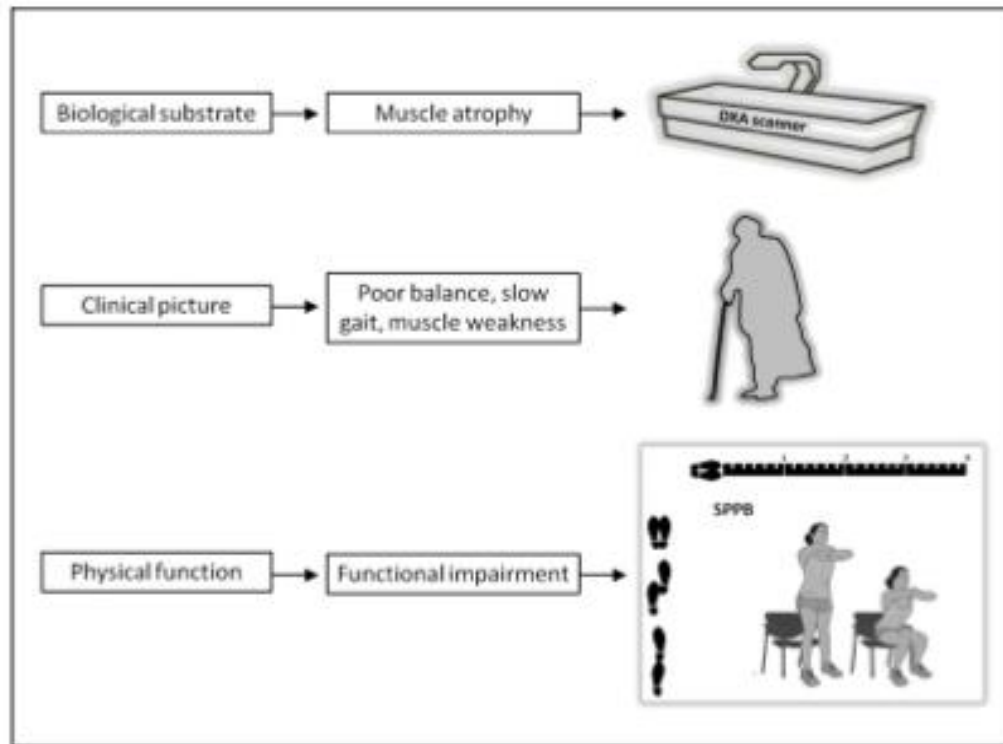




# Sarcopenia as substrate of frailty

## Operationalization of the physical frailty & sarcopenia syndrome: rationale and clinical implementation

Marzetti E,<sup>1\*§</sup> Calvani R,<sup>2\*</sup> Cesari M,<sup>3,4</sup> Tosato M,<sup>2</sup> Cherubini A,<sup>5</sup> Di Bari M,<sup>6</sup> Pahor M,<sup>7</sup> Saveria G,<sup>2</sup> Collamati A,<sup>2</sup> D'Angelo E,<sup>2</sup> Bernabei R,<sup>2</sup> Landi F;<sup>2</sup> on behalf of the SPRINTT Consortium





# Sarcopenia as substrate of frailty



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JAMDA

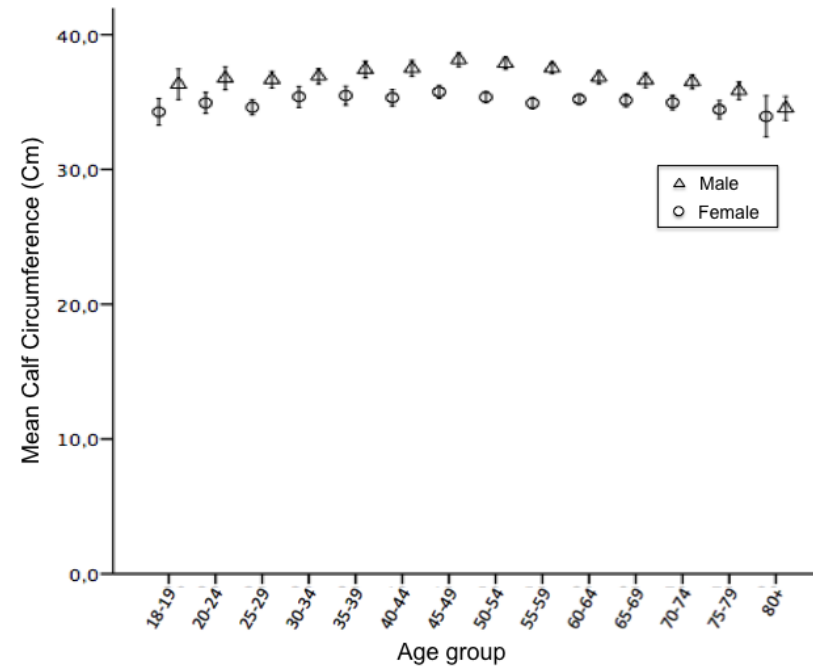
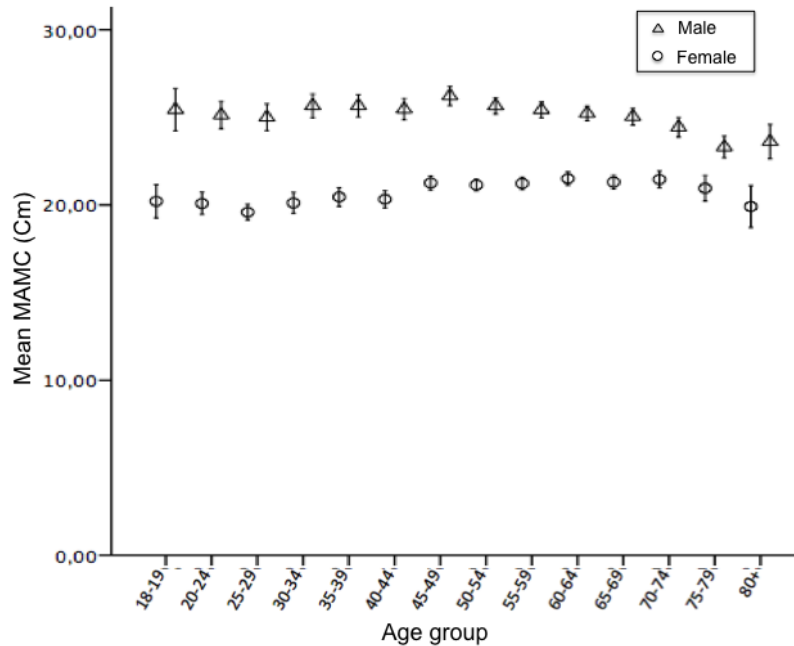
journal homepage: [www.jamda.com](http://www.jamda.com)



Original Study

## Age-Related Variations of Muscle Mass, Strength, and Physical Performance in Community-Dwellers: Results From the Milan EXPO Survey

Francesco Landi MD, PhD\*, Riccardo Calvani PhD, Matteo Tosato MD, PhD, Anna Maria Martone, Domenico Fusco MD, PhD, MD, Alex Sisto BA, Elena Ortolani MD, Giulia Saveria BS, Sara Salini MD, Emanuele Marzetti MD, PhD



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VERY IMPORTANT  
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# Sarcopenia as substrate of frailty



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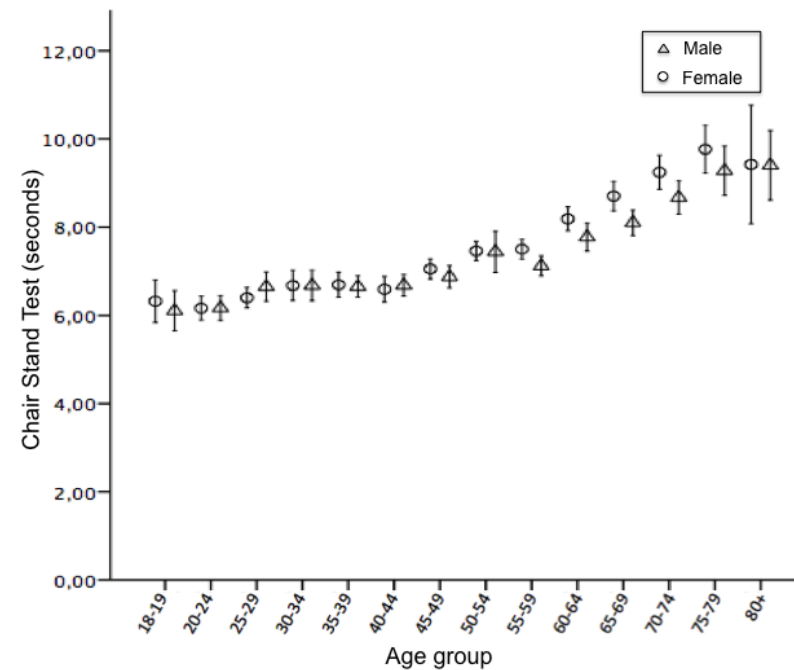
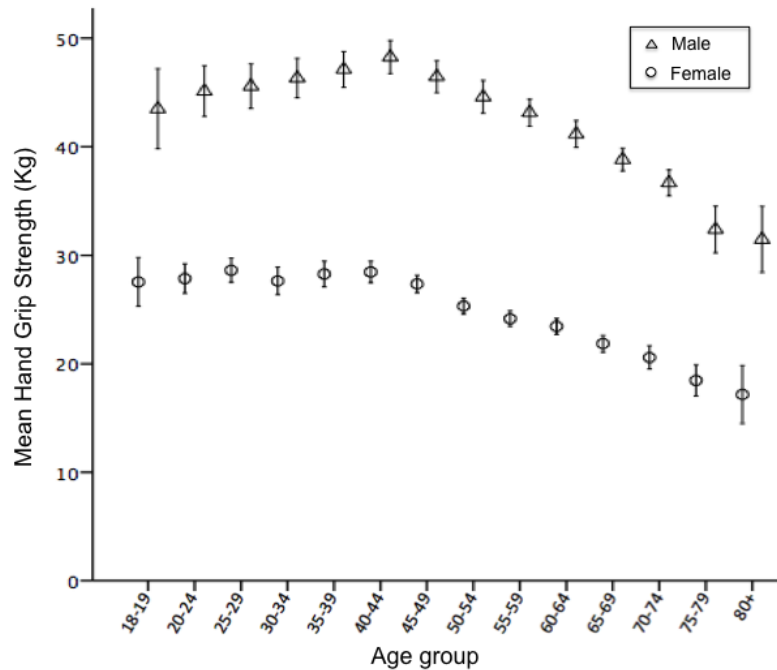
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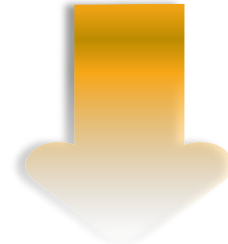
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% Loss of LBM	Associated complications <sup>1</sup>
10%	<ul style="list-style-type: none"><li>• Decreased immunity</li><li>• Increased risk of infection</li></ul>
20%	<ul style="list-style-type: none"><li>• Decreased wound healing</li><li>• Increased muscle weakness</li><li>• Increased risk of infection</li></ul>
30%	<ul style="list-style-type: none"><li>• Too weak to sit</li><li>• Pressure ulcers</li><li>• Pneumonia</li><li>• Lack of healing</li></ul>
40%	<ul style="list-style-type: none"><li>• Increased risk of death, usually from pneumonia</li></ul>



Limited activities  
of daily living

Lowered quality of life





# Aging and muscle

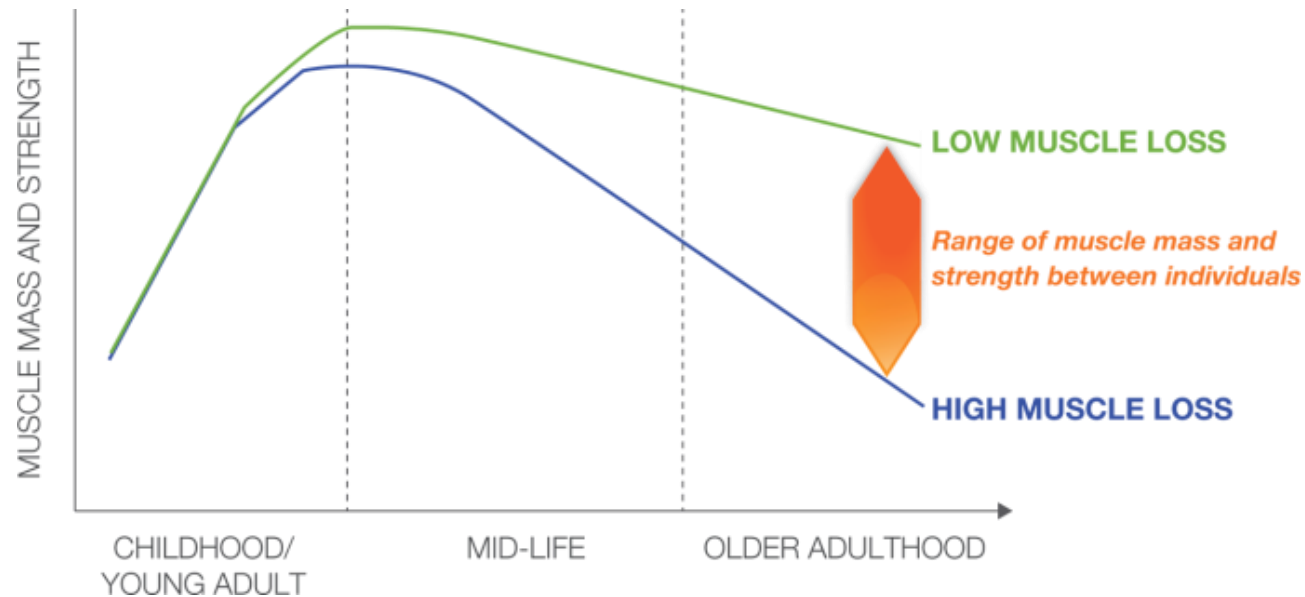
## Optimal LBM over a lifetime

For optimal maintenance with aging, it is important to build muscle when young, maintain it in mid-life, and minimize loss in older adulthood

Build

Maintain

Minimize Loss



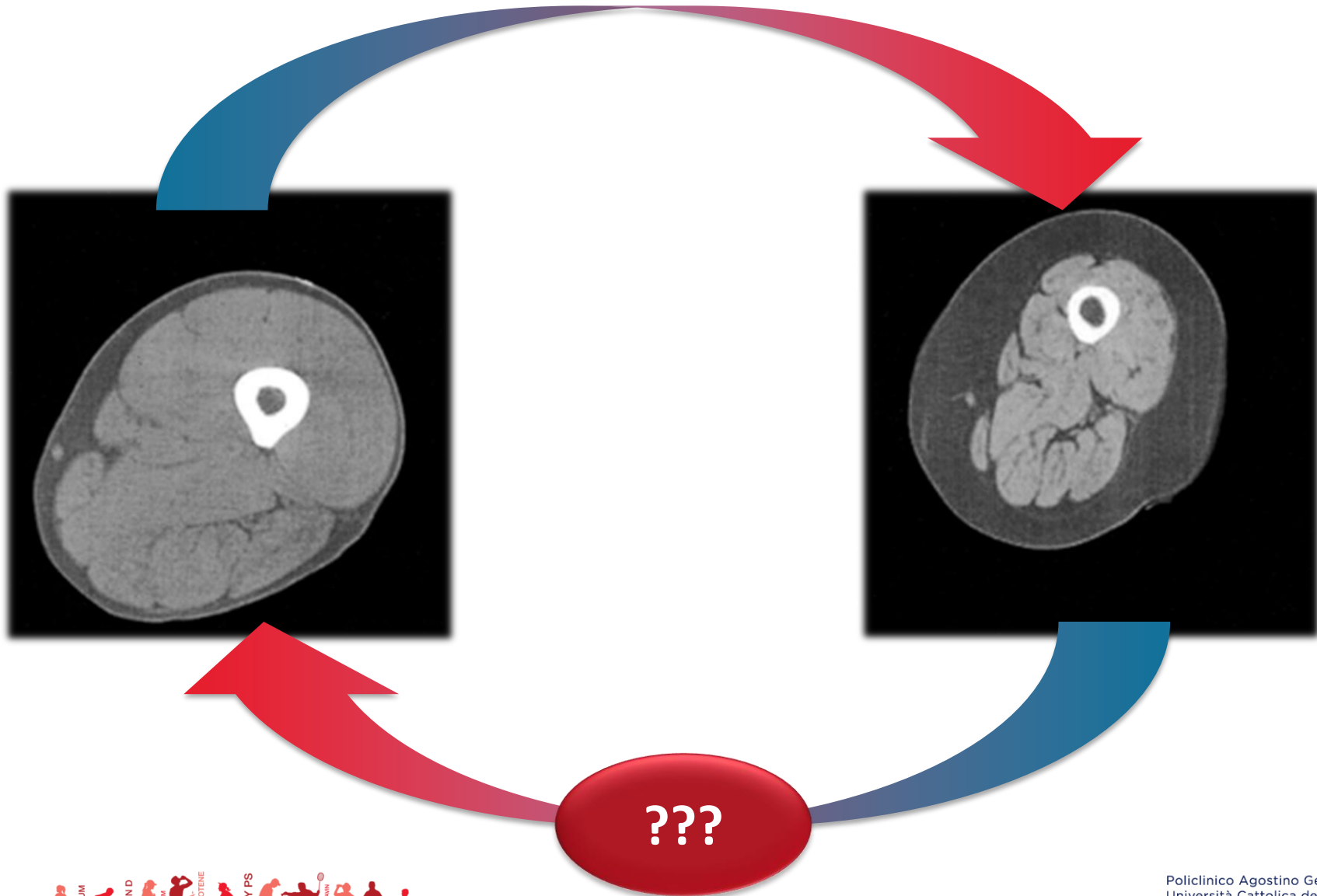
1. Sayer AA, et al. *J Nutr Health Aging*. 2008;12:427–432.



# Can sarcopenia be prevented and/or treated?



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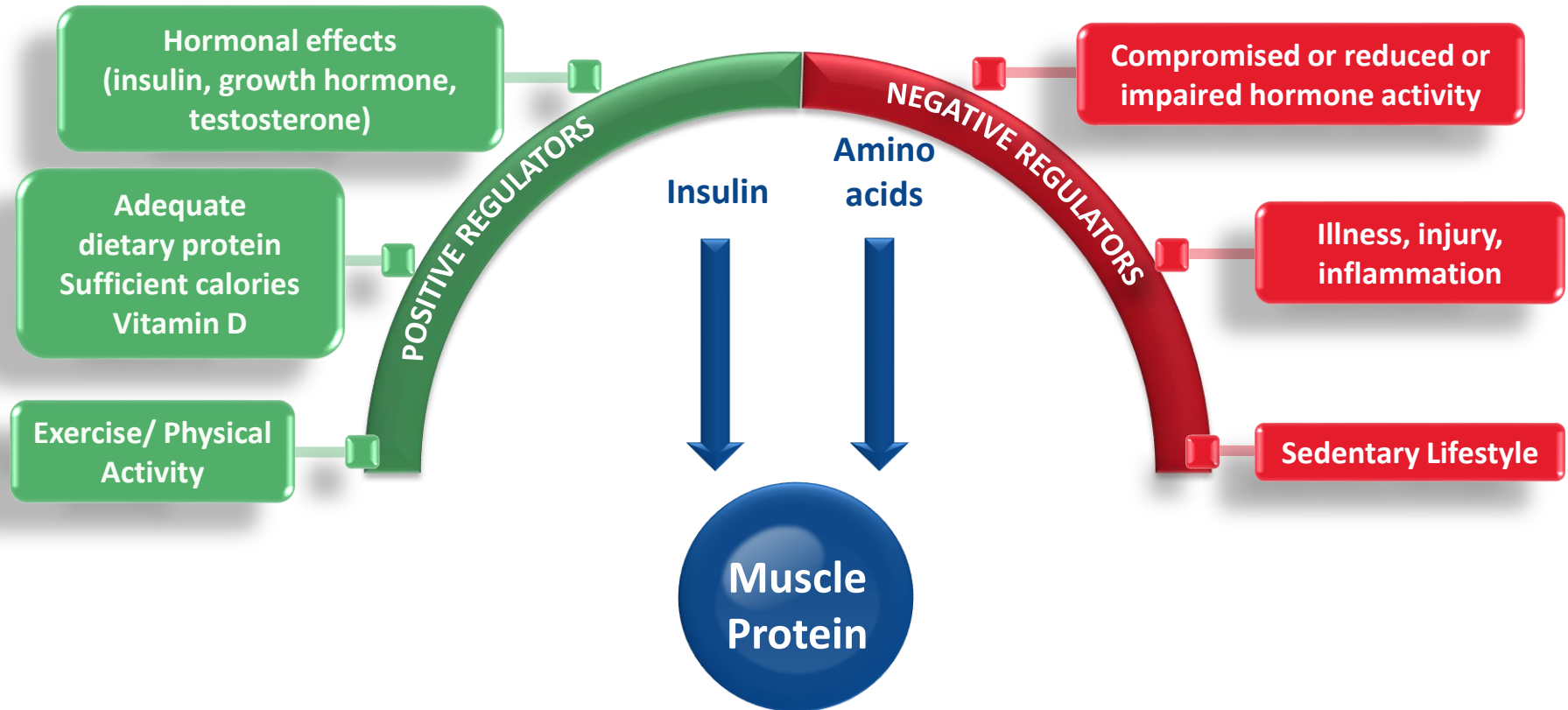
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# Aging and muscle

## Factors that affect muscle mass



Robinson S, et al. *J Aging Res.* 2012; 2012: 510801.





*Review*

## Protein Intake and Muscle Health in Old Age: From Biological Plausibility to Clinical Evidence



***nutrients***

Francesco Landi \*, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Elena Ortolani, Giulia Saveria, Emanuela D'Angelo, Alex Sisto and Emanuele Marzetti

- Protein: The principal component of all muscles
- Dietary intake required for muscle maintenance
- High quality protein to help support adults' protein needs; most aging adults do not consume enough protein<sup>4</sup>
- Inadequate levels reduce muscle reserves and immune function; increase skin fragility



*Nutrients 2016 May 14;8(5).*



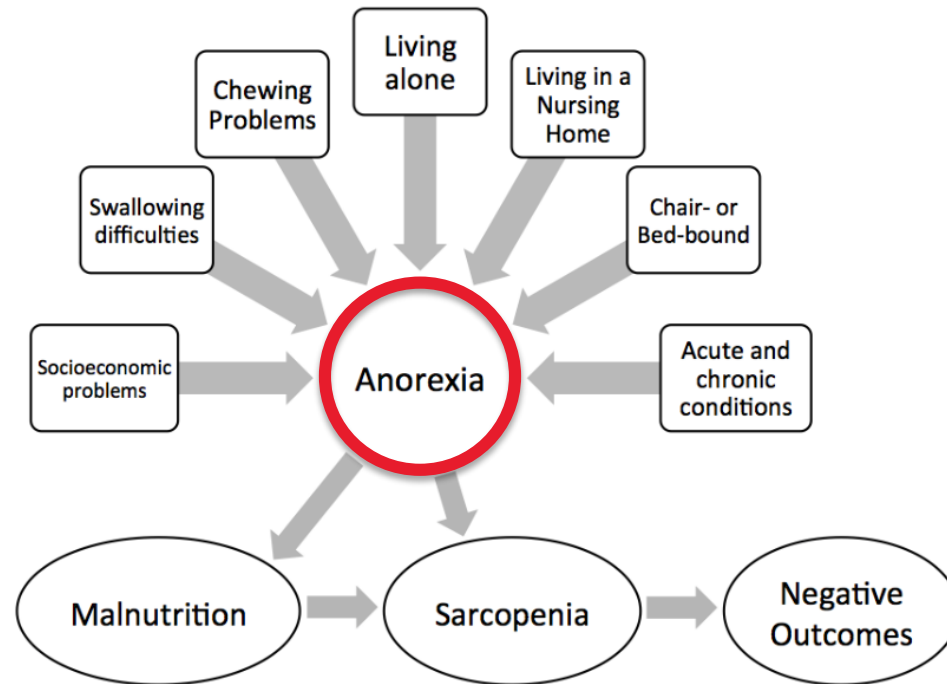
# 1.0 BACKGROUND



*Review*

## Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments

Francesco Landi \*, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Elena Ortolani, Giulia Saveria, Alex Sisto and Emanuele Marzetti



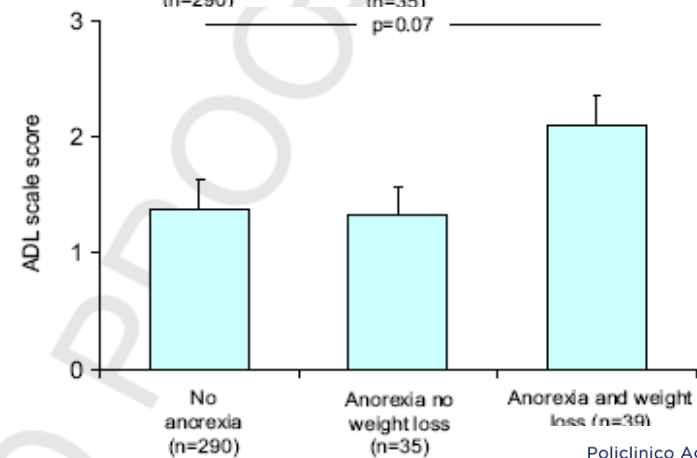
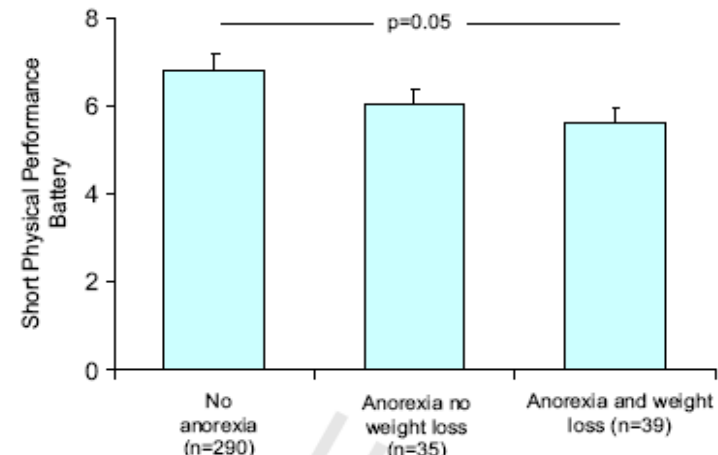
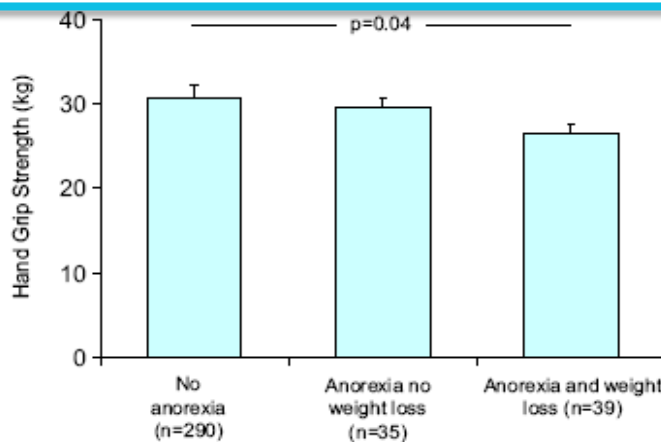
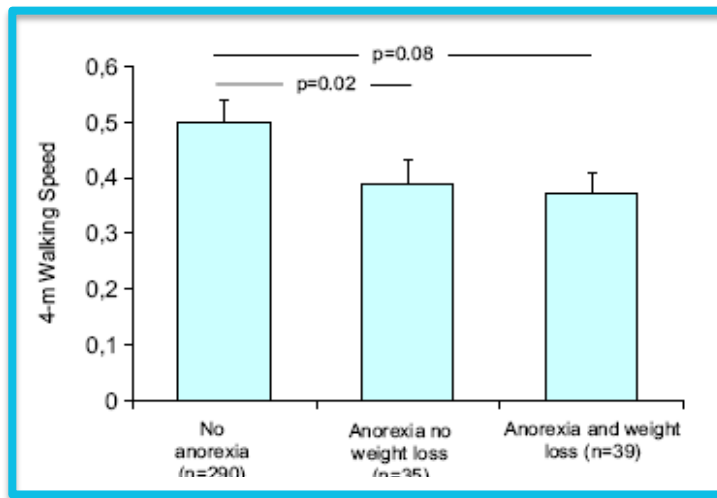
**Figure 3.** Risk factors for anorexia of aging and negative outcomes.





# 1.0 BACKGROUND

## Anorexia, physical function, and incident disability among the frail elderly population: Results from the iLSIRENTE Study





# 1.0 BACKGROUND



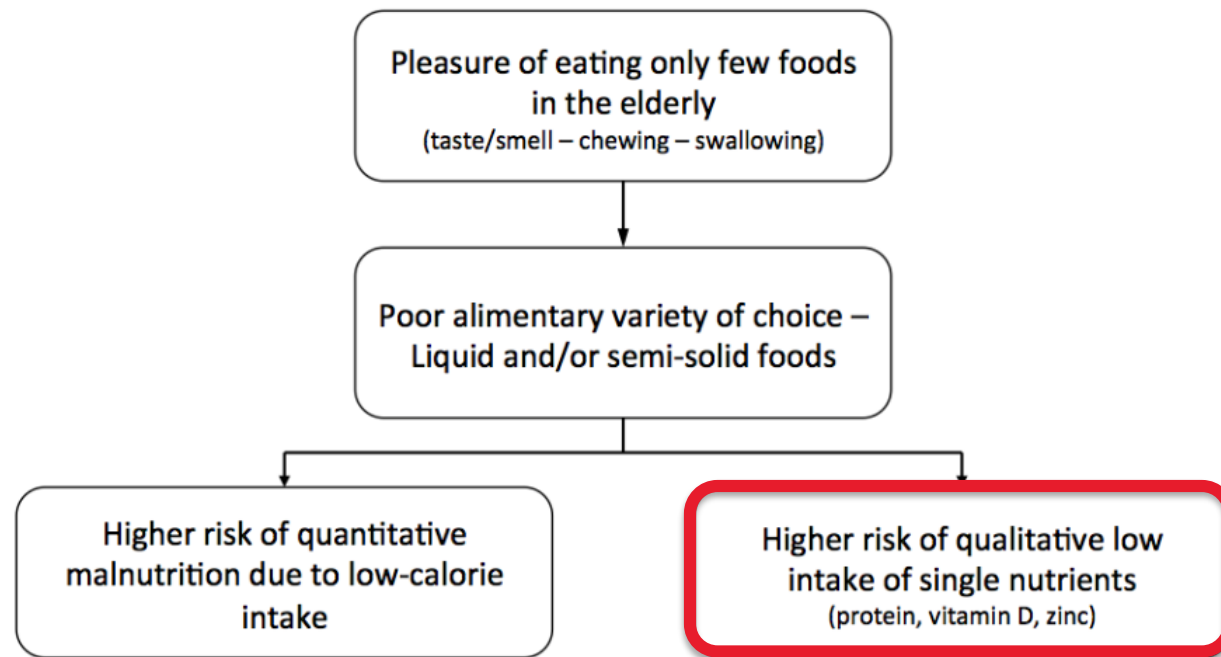
*nutrients*



*Review*

## Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments

Francesco Landi \*, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Elena Ortolani, Giulia Savera, Alex Sisto and Emanuele Marzetti



**Figure 2.** Anorexia of aging and risk of malnutrition.

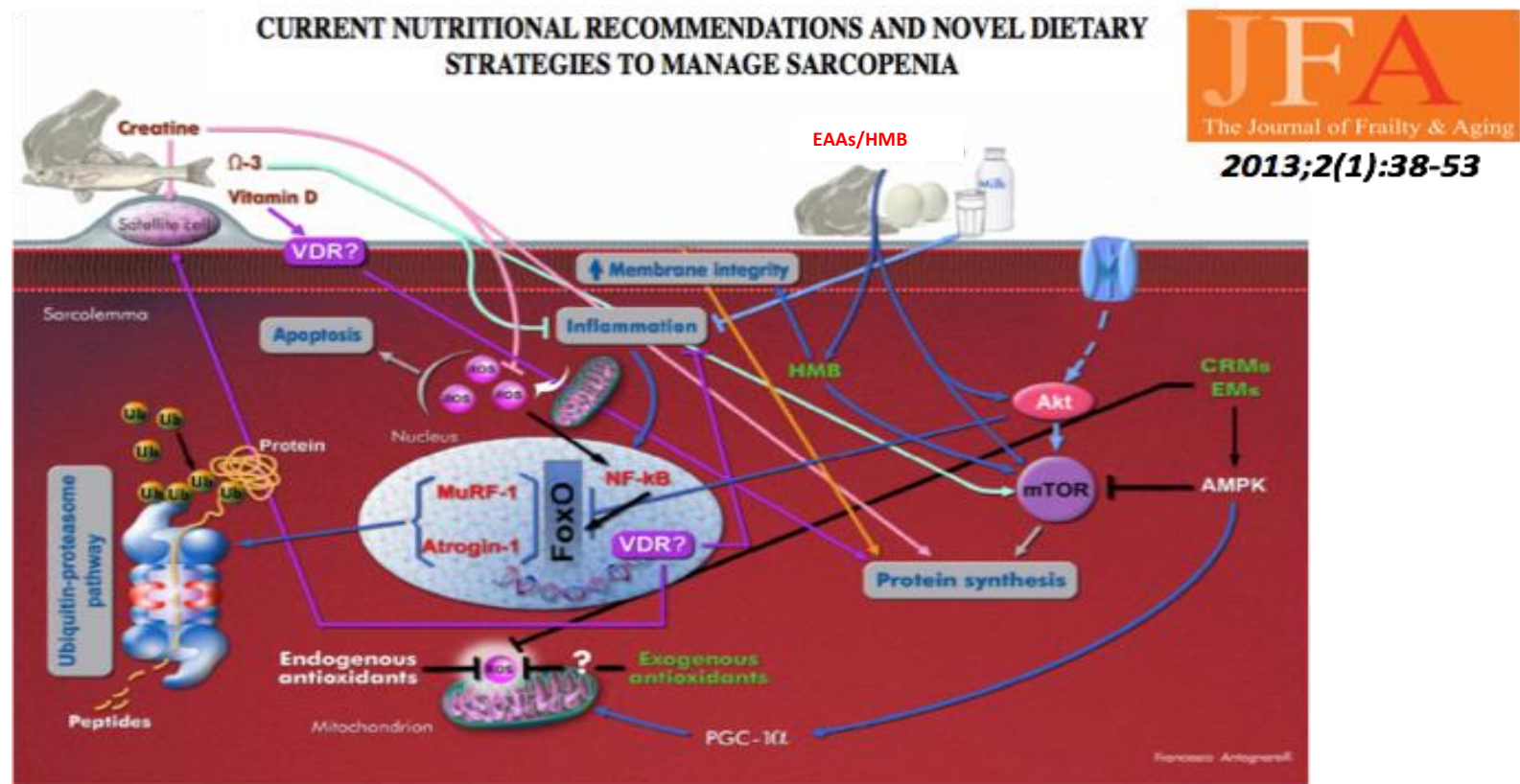
*Nutrients* 2016 Jan 27;8(2).





## 2.0 PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS

Overview of potential pathways whereby resistance exercise and nutritional interventions may influence cellular events implicated in the regulation of muscle mass



Landi F. et al. The New Metabolic Treatments  
For Sarcopenia. *Aging Clin Exp Res*: 2013

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# 2.0 PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS



JAMDA

journal homepage: [www.jamda.com](http://www.jamda.com)



Perspective: Protein: What Kind, How Much, When?

Francesco Landi, MD, PhD

Emanuele Marzetti, MD, PhD

Roberto Bernabei, MD

Department of Geriatrics

Catholic University of the Sacred Heart

Rome, Italy

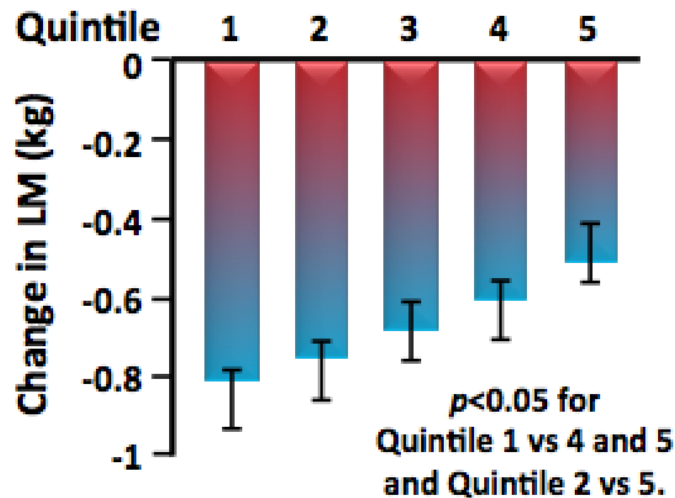




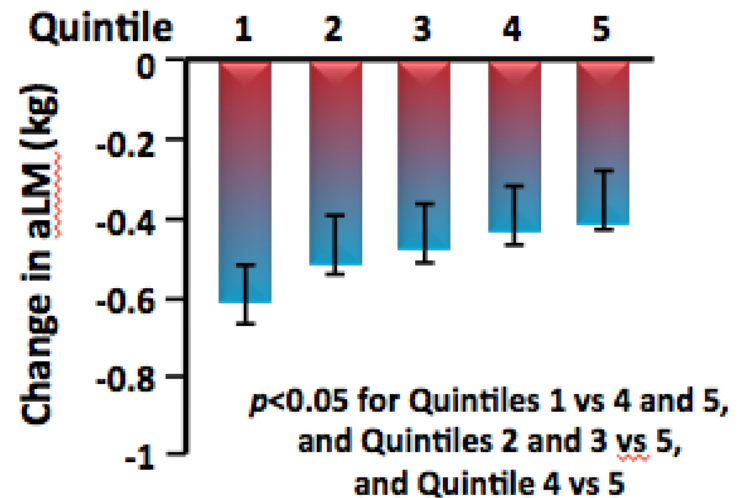
### 3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

DIETARY PROTEIN INTAKE EVIDENCE: A prospective analysis including 2000+ elderly adults in the health, aging, and body composition (Health ABC) study

**Overall lean body mass (LM)  
by quintile of protein intake**



**Appendicular (ARM+LEG) lean mass (aLM)  
by quintile of protein intake**



**Protein is important in the maintenance and rebuilding of lean body mass in aging adults: participants in the top fifth of protein intake lost 40% less lean mass (LM) – Overall and appendicular – than did those in the bottom fifth of protein intake, a difference that is statistically significant ( $p < 0.01$ )**





# 3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?



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frontiers in  
**AGING NEUROSCIENCE**

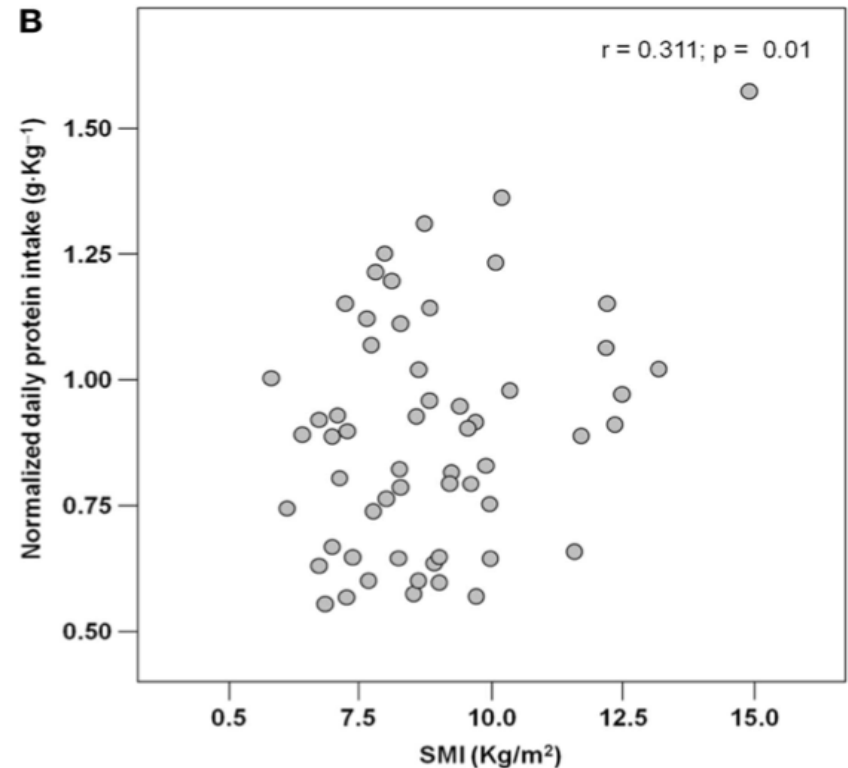
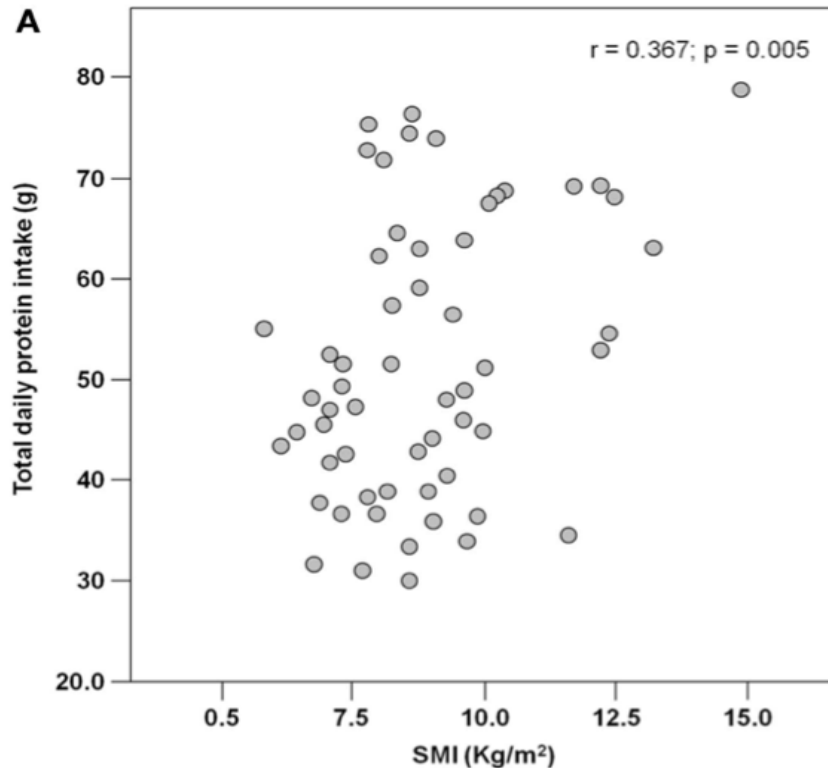
ORIGINAL RESEARCH ARTICLE

published: 19 November 2014  
doi: 10.3389/fnagi.2014.00269



## Pre-hospital dietary intake correlates with muscle mass at the time of fracture in older hip-fractured patients

**Riccardo Calvani<sup>†</sup>, Anna Maria Martone<sup>†</sup>, Emanuele Marzetti, Graziano Onder, Giulia Saveria, Maria Lorenzi, Elisabetta Serafini, Roberto Bernabei and Francesco Landi \***



Calvani R, Landi F et al. 2015

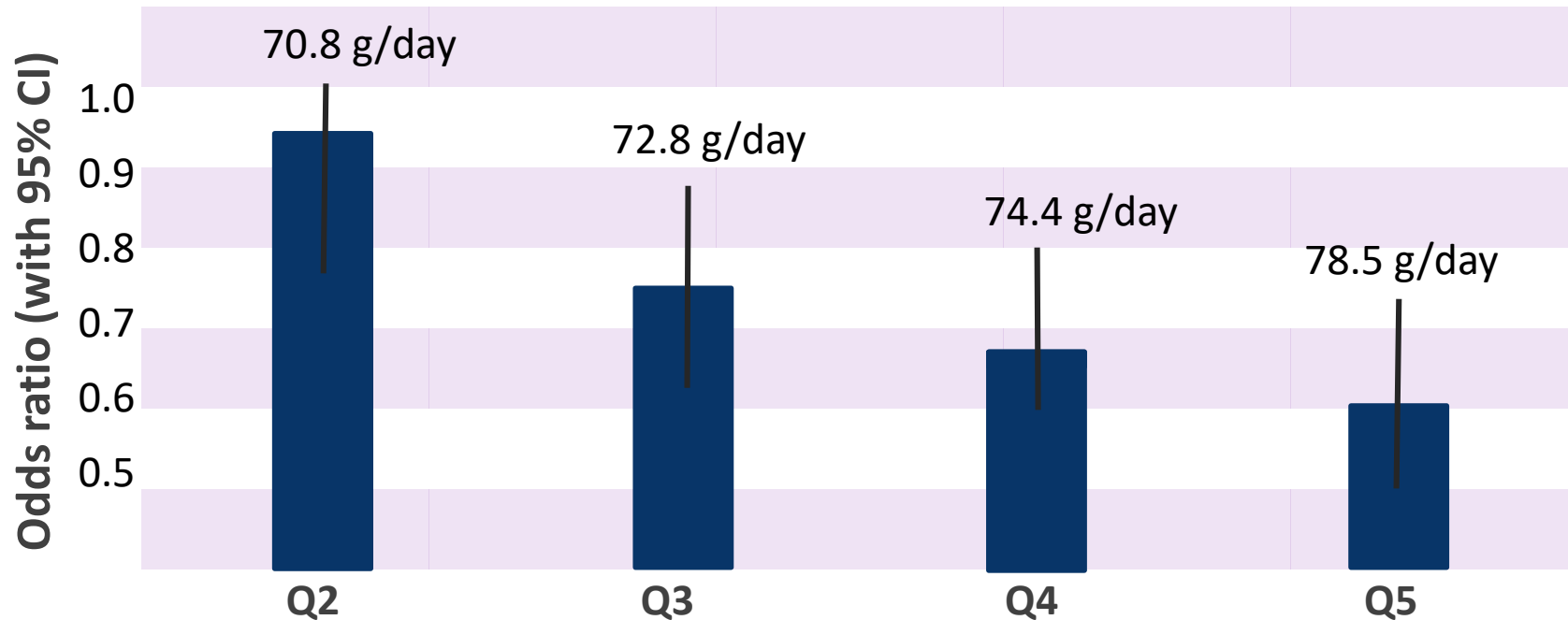
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### 3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

Lower quintiles of protein intake are associated with higher risk of frailty



Risk of frailty by quintile of protein intake (% kcal) (n= 24,417)

Increasing dietary protein intake, % of kcal

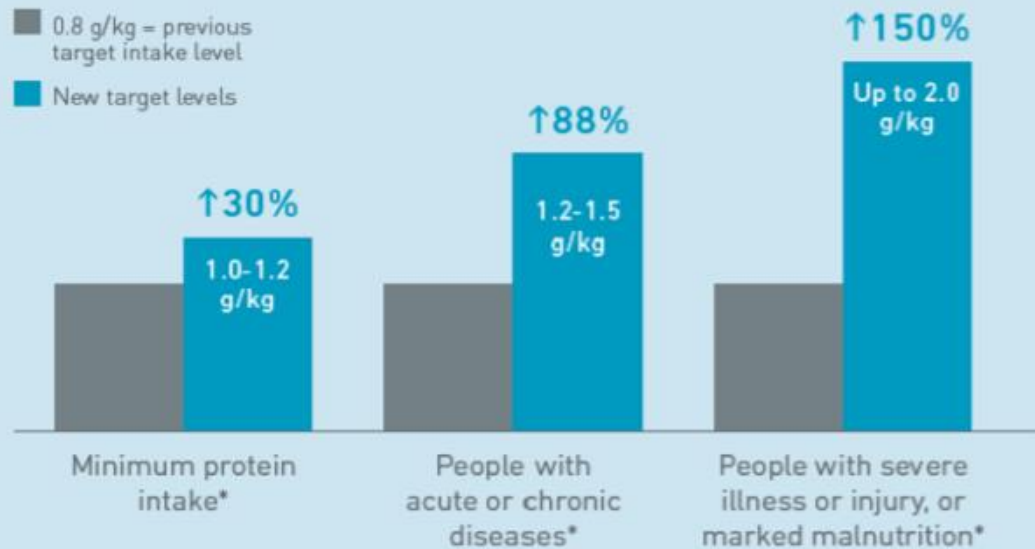




### 3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

## PROT-AGE summary

New recommendations call for higher protein intake  
(g per kg of bodyweight) in those aged >65 years<sup>1</sup>



\*Caution needed among those with severe kidney disease [i.e. estimated Glomerular Filtration Rate <30mL/min/1.73m<sup>2</sup>], calculating their needs differently.





# 4.0 PROTEIN QUALITY: **WHAT** IS THE BEST PROTEIN SOURCE?



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## 4.1 FAST VERSUS SLOW PROTEINS

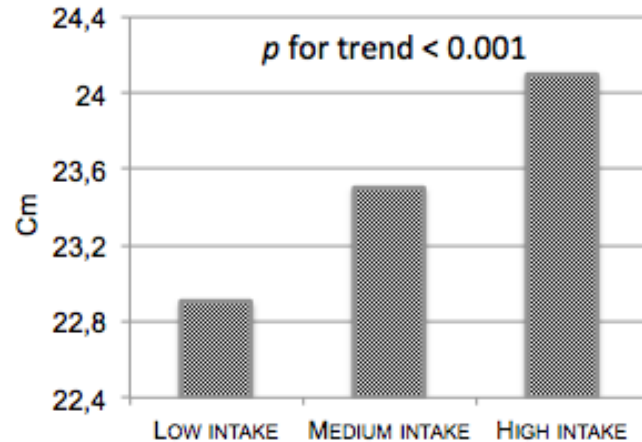
- **No evidences** are available in terms of animal versus plant based protein. This issue is of interest considering that proteins are absorbed at different rates upon digestion.
- The concept of “**fast**” protein (i.e. whey protein) versus “**slow**” protein (i.e. casein and animal protein) is of particular relevance taking into consideration the anabolic response following the ingestion of different foods and/or oral nutritional supplements

~ 1.0–1.2 g/kg/day

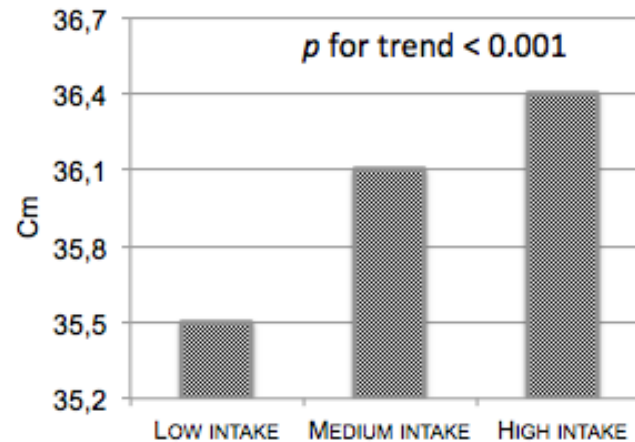




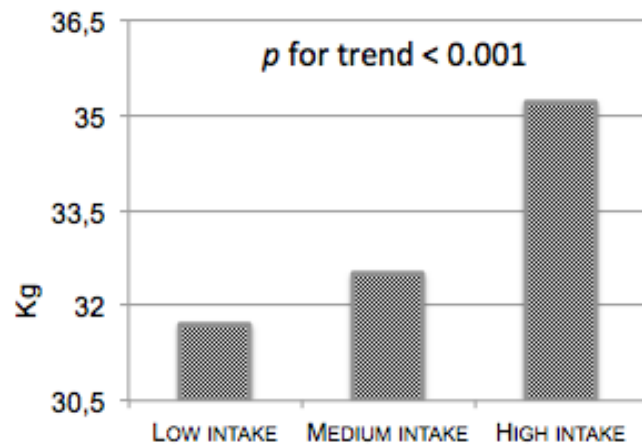
## 4.2 ANIMAL VERSUS PLANT-DERIVED PROTEINS



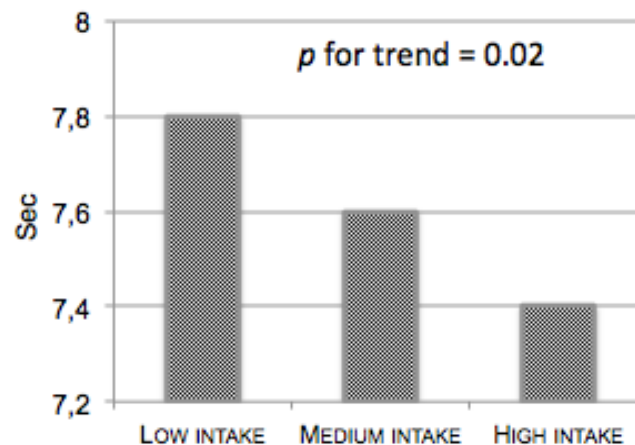
Panel A. Mid Arm Muscle Circumference



Panel B. Calf Circumference



Panel C. Hand Grip Strength Test



Panel D. Chair Stand Test

V-I-P  
VERY IMPORTANT  
PROTEINS

The mean animal-derived protein intake:

- I tertile 17.7 g/day
- II tertile 27.3 g/day
- III tertile 39.1 g/day



## 5.0 PROTEIN DISTRIBUTION:

### WHEN IS IT BETTER TO CONSUME PROTEIN?

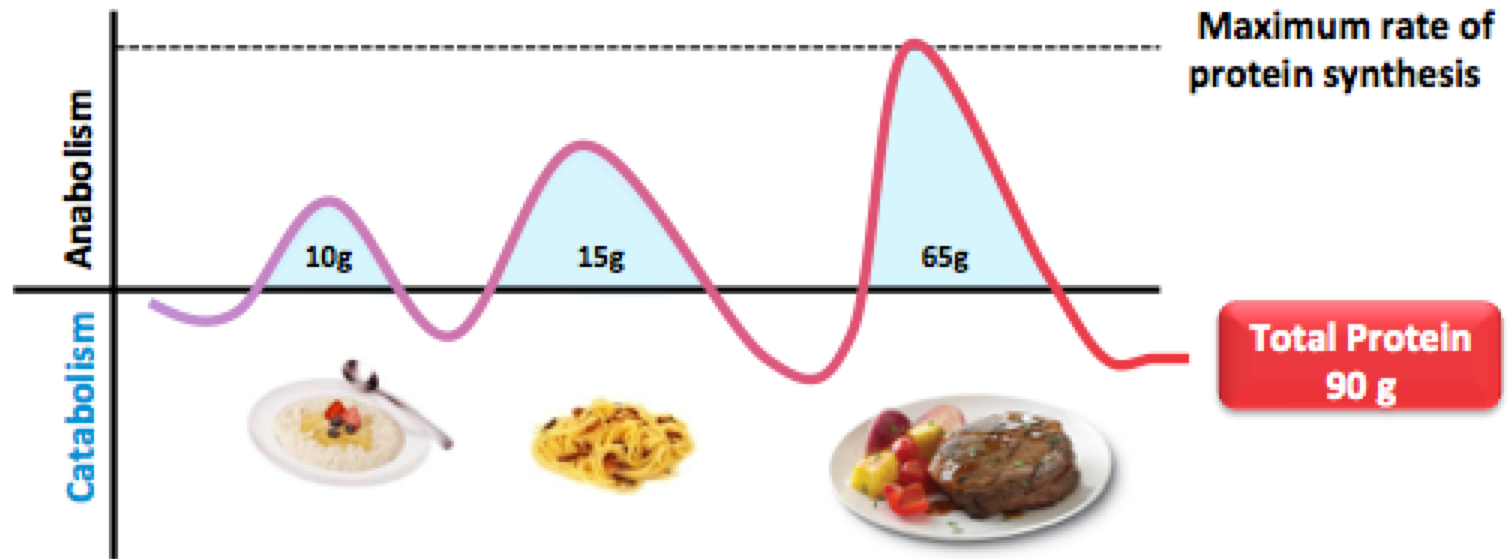
- ◆ A daily protein intake of 1.0-1.2 g/kg body weight per day has been recognized by the PROT-AGE Study Group as the minimum quantity necessary to preserve muscle health during aging.
- ◆ Nevertheless,
  - the timing of protein ingestion and
  - the synergistic effect of protein intake with physical activity may also be critical to optimize muscle health.





# 5.1. PROTEIN TIMING

## Daily protein distribution – typical?



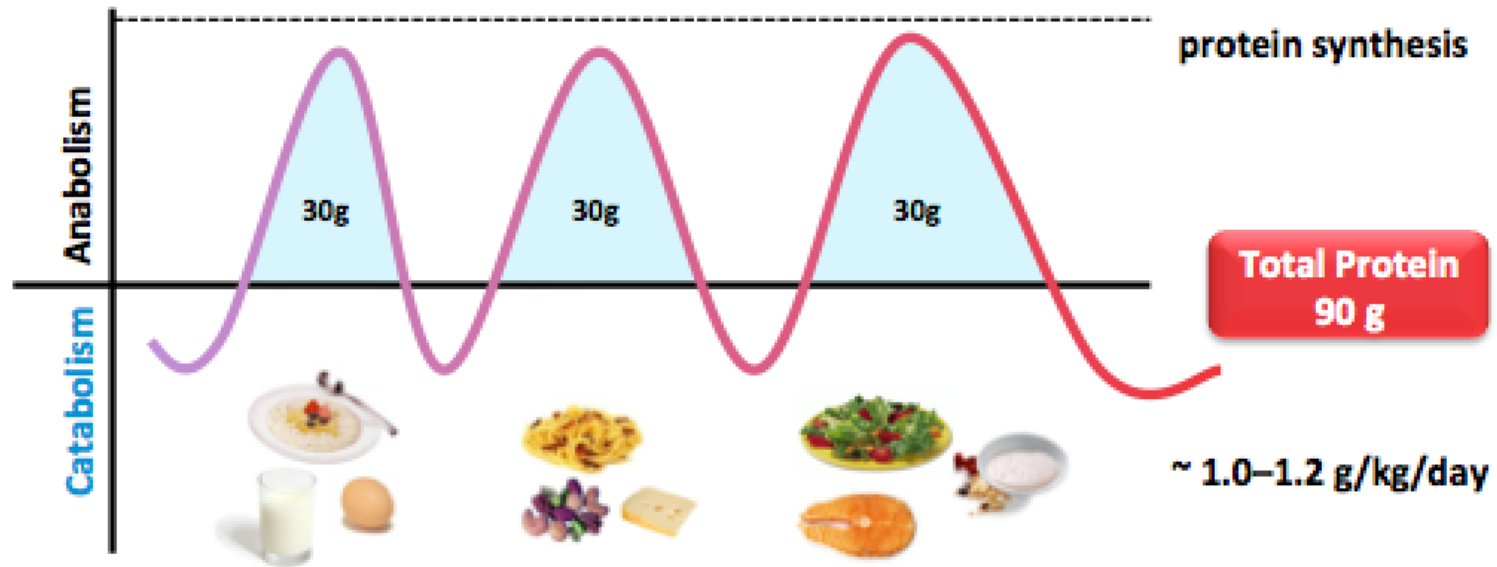
**A skewed daily protein distribution fails to maximize potential for muscle growth**





# 5.1. PROTEIN TIMING

## Daily protein distribution – optimal



**Repeated maximal stimulation of protein synthesis  
→ increase / maintenance of muscle mass**





## 5.2. PROTEIN INTAKE AND PHYSICAL EXERCISE



Original Study

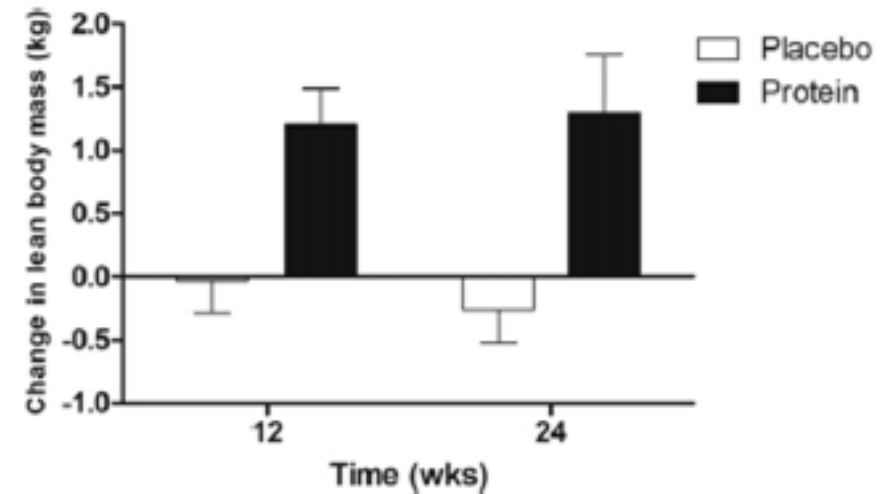
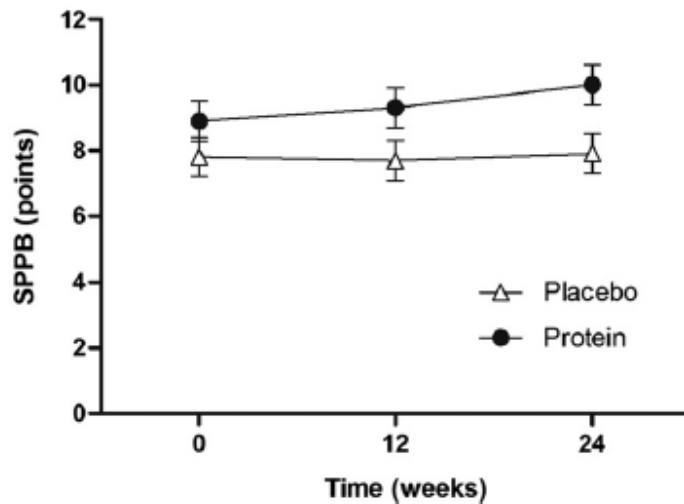
Protein Supplementation Improves Physical Performance in Frail Elderly People:  
A Randomized, Double-Blind, Placebo-Controlled Trial



Original Study

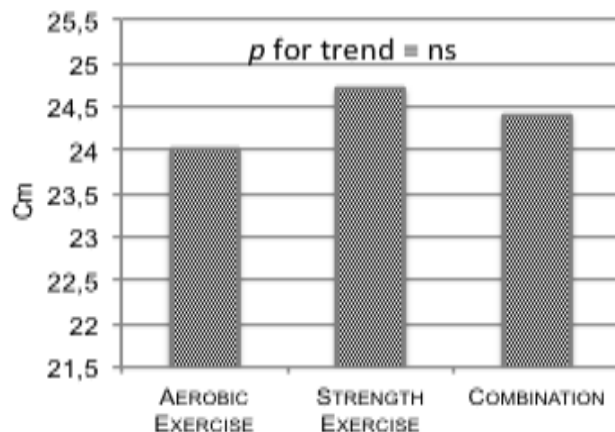
Protein Supplementation Increases Muscle Mass Gain During Prolonged  
Resistance-Type Exercise Training in Frail Elderly People: A Randomized,  
Double-Blind, Placebo-Controlled Trial

Michael Tieland MSc<sup>a,b,\*</sup>, Marlou L. Dirks MSc<sup>c</sup>, Nikita van der Zwaluw MSc<sup>b</sup>, Lex B. Verdijk PhD<sup>a,c</sup>,  
Ondine van de Rest PhD<sup>b</sup>, Lisette C.P.G.M. de Groot PhD<sup>a,b</sup>, Luc J.C. van Loon PhD<sup>a,c</sup>

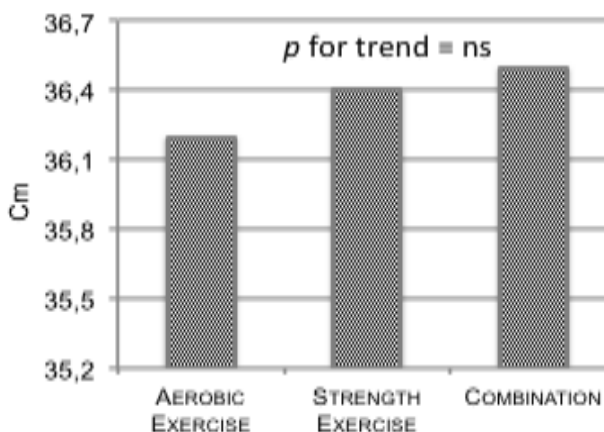




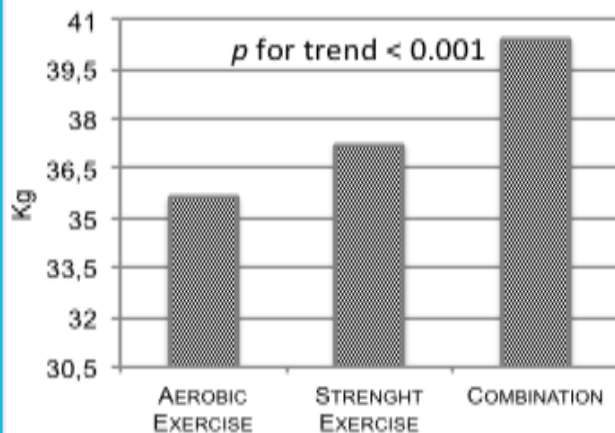
## 5.2. PROTEIN INTAKE AND PHYSICAL EXERCISE



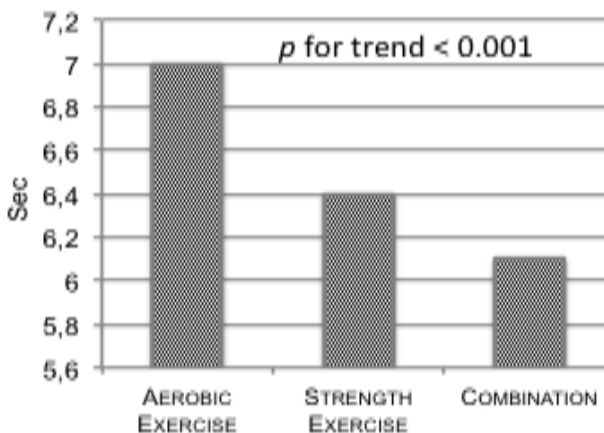
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V-I-P  
VERY IMPORTANT  
PROTEINS

The mean animal-derived protein intake:

➤ III tertile 39.1 g/day



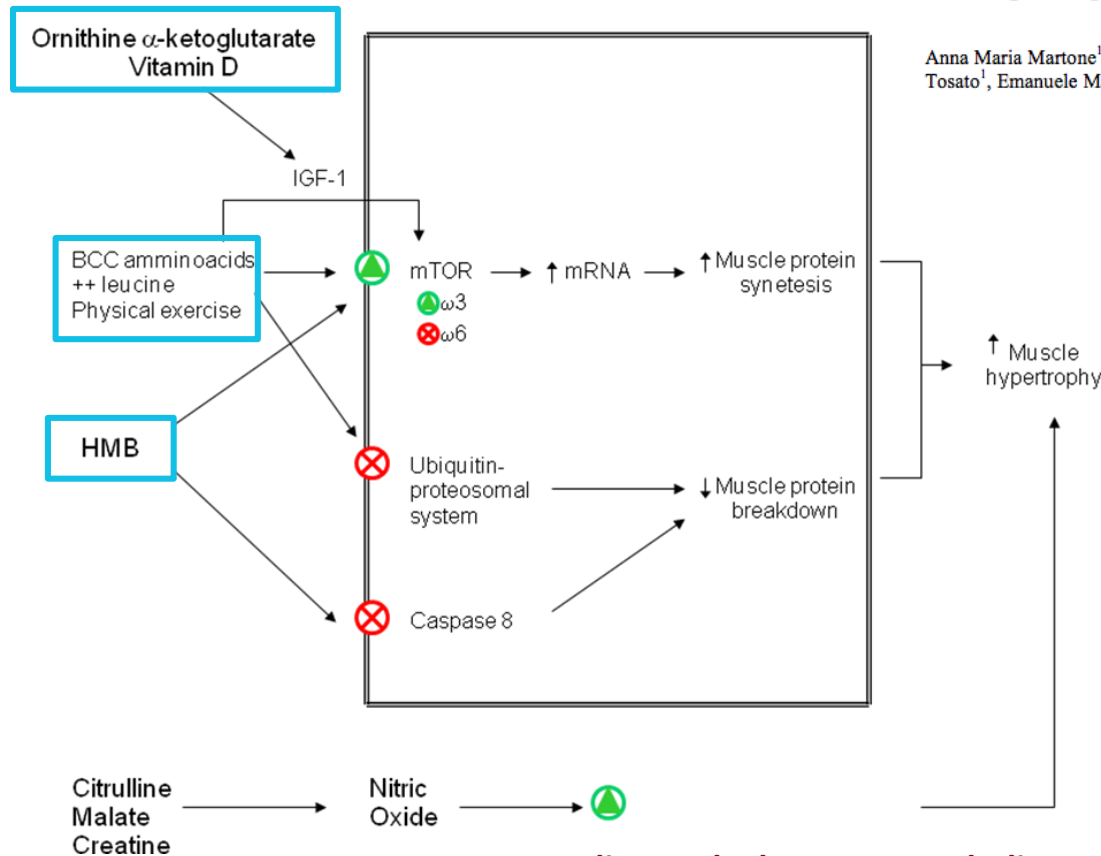
## 6.0. PROTEIN SUPPLEMENTATION: NEW EVIDENCE

### Overview of potential pathways whereby resistance exercise and nutritional interventions may influence cellular events implicated in the regulation of muscle mass

*Current Pharmaceutical Design, 2015, 21, 000-000*

#### Treating Sarcopenia in Older and Oldest Old

Anna Maria Martone<sup>1\*</sup>, Fabrizia Lattanzio<sup>2</sup>, Angela Marie Abbatecola<sup>2</sup>, Domenico La Carpia<sup>1\*</sup>, Matteo Tosato<sup>1</sup>, Emanuele Marzetti<sup>1</sup>, Riccardo Calvani<sup>1</sup>, Graziano Onder<sup>1</sup> and Francesco Landi<sup>1#</sup>



Landi F. et al. The New Metabolic Treatments For Sarcopenia  
*Aging Clin Exp Res: 2013*

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Università Cattolica del Sacro Cuore





## 6.0. PROTEIN SUPPLEMENTATION: NEW EVIDENCE

### Nutrition-muscle connection

#### HMB is a metabolite of the amino acid leucine

- Calcium beta-hydroxy beta-methylbutyrate (CaHMB) is a source of HMB
- HMB regulates protein in muscle cells
  - Supports muscle protein synthesis and slows down muscle protein breakdown<sup>1,2</sup>
  - Helps rebuild muscle mass lost naturally over time<sup>1,3,4</sup>
  - Helps rebuild LBM to support muscle strength and functionality<sup>4,5</sup>

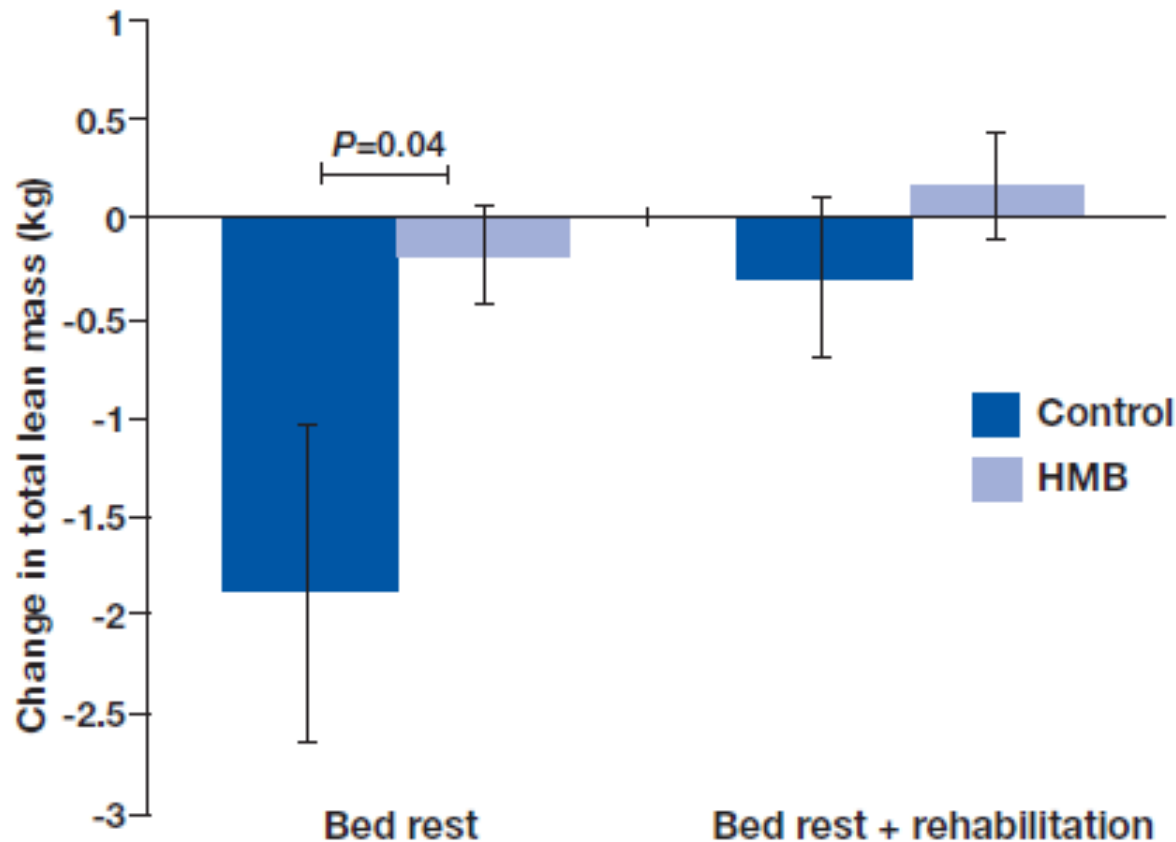


1. Wilson GJ, et al. *Nutr Metab (Lond)*.: 2008;5:1.
2. Eley HL, et al. *Am J Physiol Endocrinol Metab*.: 2008;295:E1409–1416.
3. Nissen S, Abumrad NN. *J Nutr Biochem*.: 1997;8:300–311.
4. Vukovich MD, et al. *J Nutr*.: 2001; 131: 2049–2052.
5. Flakoll P, et al. *Nutrition*.: 2004;20:445–451. (HMB + arginine + lysine)



# Effect of HMB on bed rest-associated loss of total lean mass

Lean body mass is maintained by  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) during 10 days of bed rest in elderly women







ELSEVIER

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

Randomized control trials

Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial

- Malnourished older adults hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease
- Interventions: standard-of-care plus high-protein ONS containing HMB (HP-HMB) or a placebo supplement (2 servings/day)



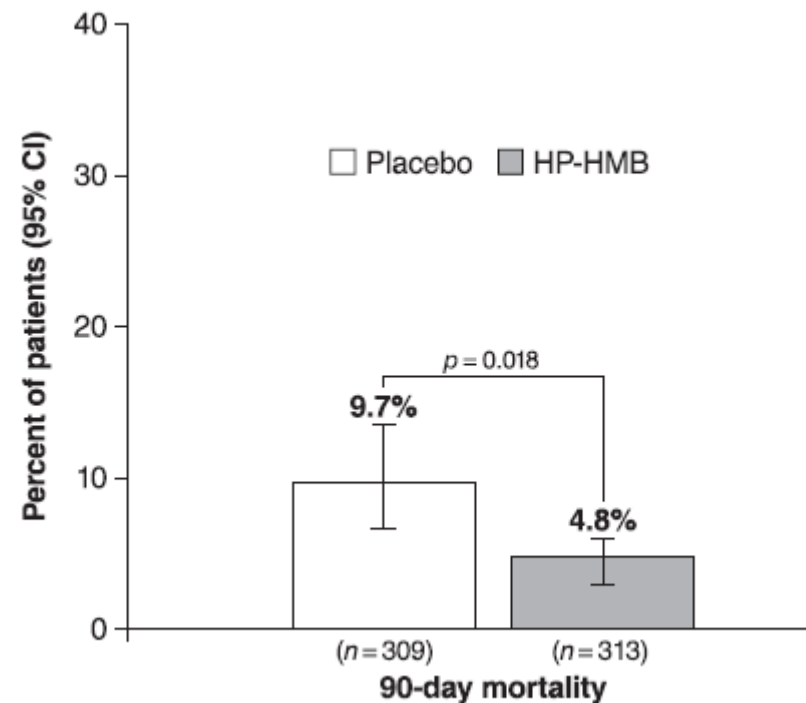
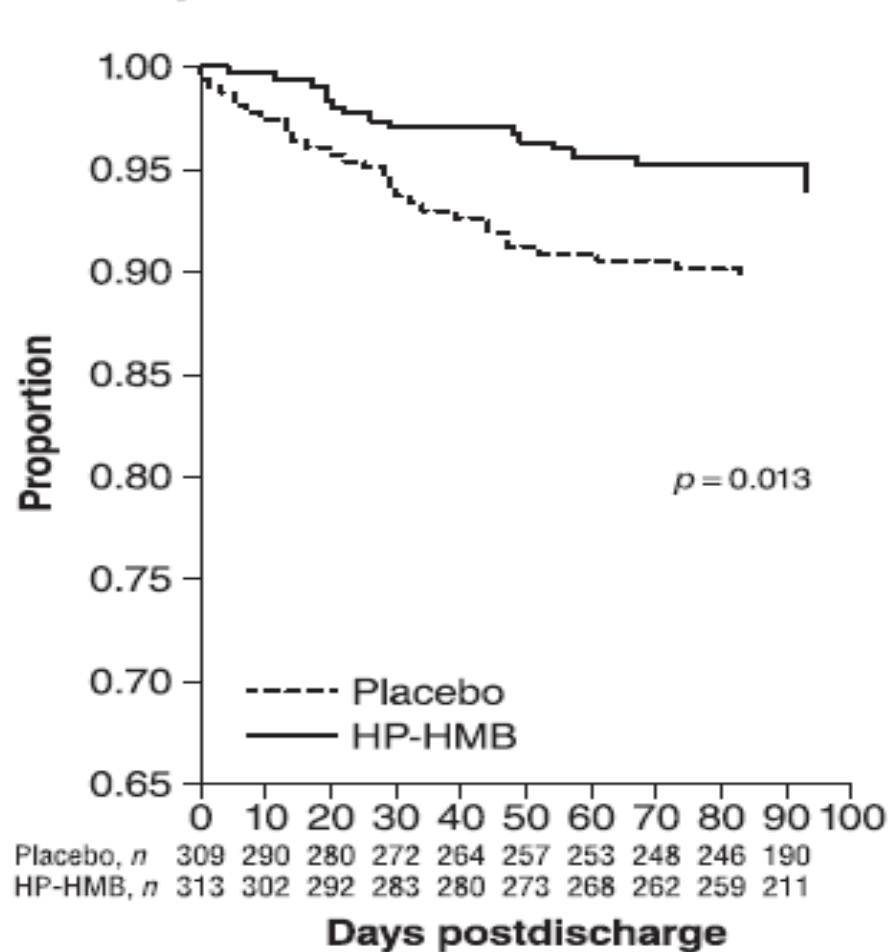


- **I pazienti sono stati randomizzati nell'arco delle 72 ore di ospedalizzazione (N=652)**
  - GRUPPO SPERIMENTALE: standard di cura + supplemento nutrizionale orale (ONS) ipercalorico, ad alto contenuto proteico con CaHMB  
(350 kcal, 20 g. di proteine di alta qualità, 1,5 g CaHMB, vitamine e minerali)
  - GRUPPO DI CONTROLLO: standard di cura + supplemento Placebo ipocalorico, senza proteine (48 calorie)
- **Due volte al giorno durante il ricovero ospedaliero e per 90 giorni dopo la dimissione**
- **Compliance= assunzione di  $\geq 75\%$  di entrambe le somministrazioni**





## D. Kaplan-Meier Survival Curve: Mortality





# Number Needed to Treat (NNT) e proiezione di aspettativa di vita



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- Per il gruppo con supplemento HP+HMB, la stima NNT è stata di 20.3 soggetti da trattare (95% CI 10,9 to 121,4) per prevenire un decesso
- I dati del modello economico attraverso lo studio NOURISH ha osservato un incremento di aspettativa di vita pari a 8 mesi e mezzo



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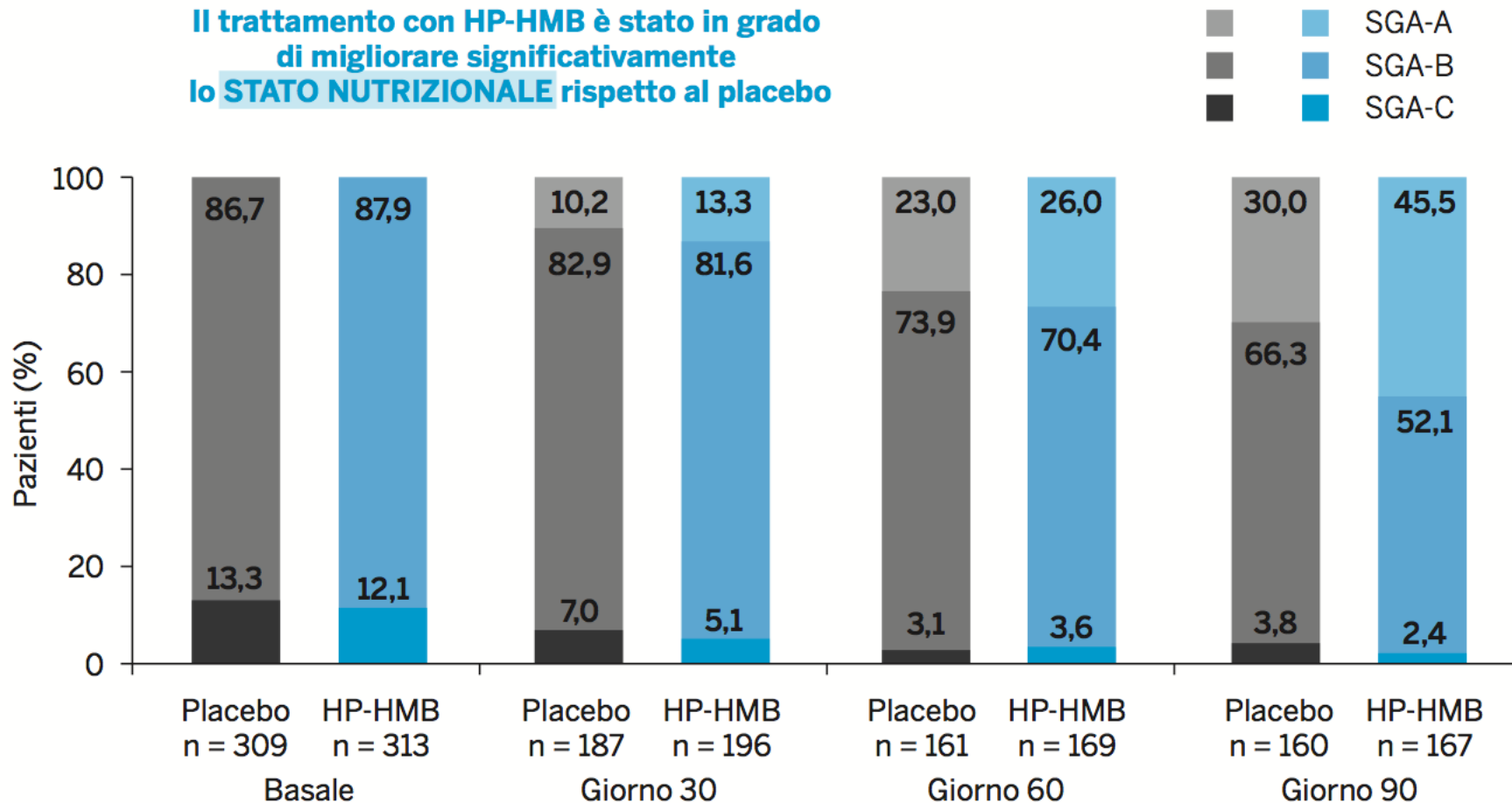


# Stato nutrizionale significativamente migliorato, con alto contenuto proteico + HMB



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Il trattamento con HP-HMB è stato in grado di migliorare significativamente lo **STATO NUTRIZIONALE** rispetto al placebo



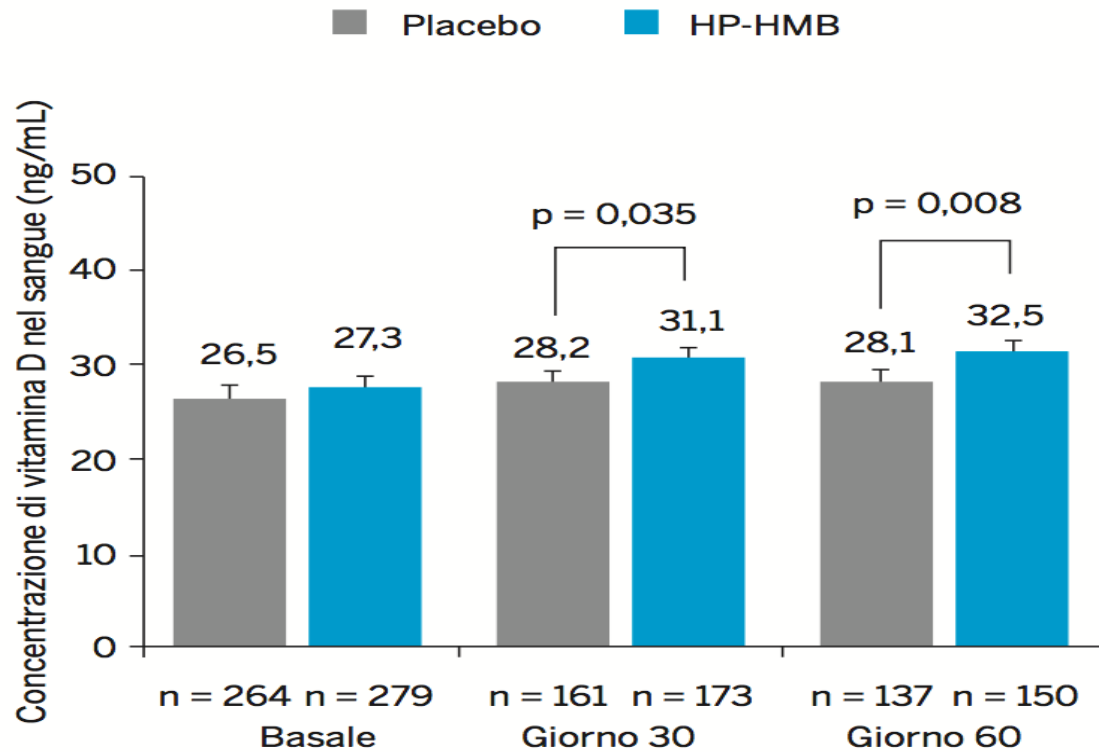
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# VITAMINA D sierica significativamente più elevata, con alto contenuto proteico + HMB

**In pazienti anziani malnutriti, il supplemento nutrizionale orale a base di HP-HMB ha consentito un aumento significativo dei livelli sierici di VITAMINA D rispetto al placebo**





# Evaluation of an Oral Nutritional Supplement Containing HMB



JAMDA

journal homepage: [www.jamda.com](http://www.jamda.com)



## Original Study

### Impacts of High-Protein Oral Nutritional Supplements Among Malnourished Men and Women with Sarcopenia: A Multicenter, Randomized, Double-Blinded, Controlled Trial



Joel T. Cramer PhD<sup>a,\*</sup>, Alfonso J. Cruz-Jentoft MD, PhD<sup>b</sup>, Francesco Landi MD, PhD<sup>c</sup>, Mary Hickson PhD, RD<sup>d</sup>, Mauro Zamboni MD<sup>e</sup>, Suzette L. Pereira PhD<sup>f</sup>, Deborah S. Hustead PhD<sup>f</sup>, Vikkie A. Mustad PhD<sup>f</sup>



ClinicalTrials.gov Identifier: NCT01191125

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# Evaluation of an Oral Nutritional Supplement Containing HMB

## Study design

- Prospective, randomized, double–blind, 24-week intervention trial.
- 330 men and women  $\geq 65$  years with malnutrition (SGA) and sarcopenia (EWGSOP)
- Main outcome measures
  - Knee extensor strength
  - Muscle mass, body composition
  - Grip strength, gait speed, SPPB
  - Dietary intake and compliance
  - ADL, QoL



ClinicalTrials.gov Identifier: NCT01191125



# Evaluation of an Oral Nutritional Supplement Containing HMB

## Subject selection

### ● Main inclusion criteria

- 65-90 years, both genders
- Ambulatory subjects
- Malnourished: SGA of B or C
- Low gait speed AND/OR low hand-grip strength
- Low muscle mass (DXA)
- No resistance exercise program

### ● Main exclusions: diabetes, inflammatory disease, renal impairment, severe GI disorders, malignancy, use of dietary supplements



ClinicalTrials.gov Identifier: NCT01191125



# Evaluation of an Oral Nutritional Supplement Containing HMB

## Intervention

- **Experimental:**

- calorically-dense ONS with complement of protein, HMB, vitamin D and other macronutrients and essential vitamins and mineral

- **Control:**

- commercial calorically-dense ONS (*Ensure<sup>®</sup> Plus HN*, Abbott Nutrition International)

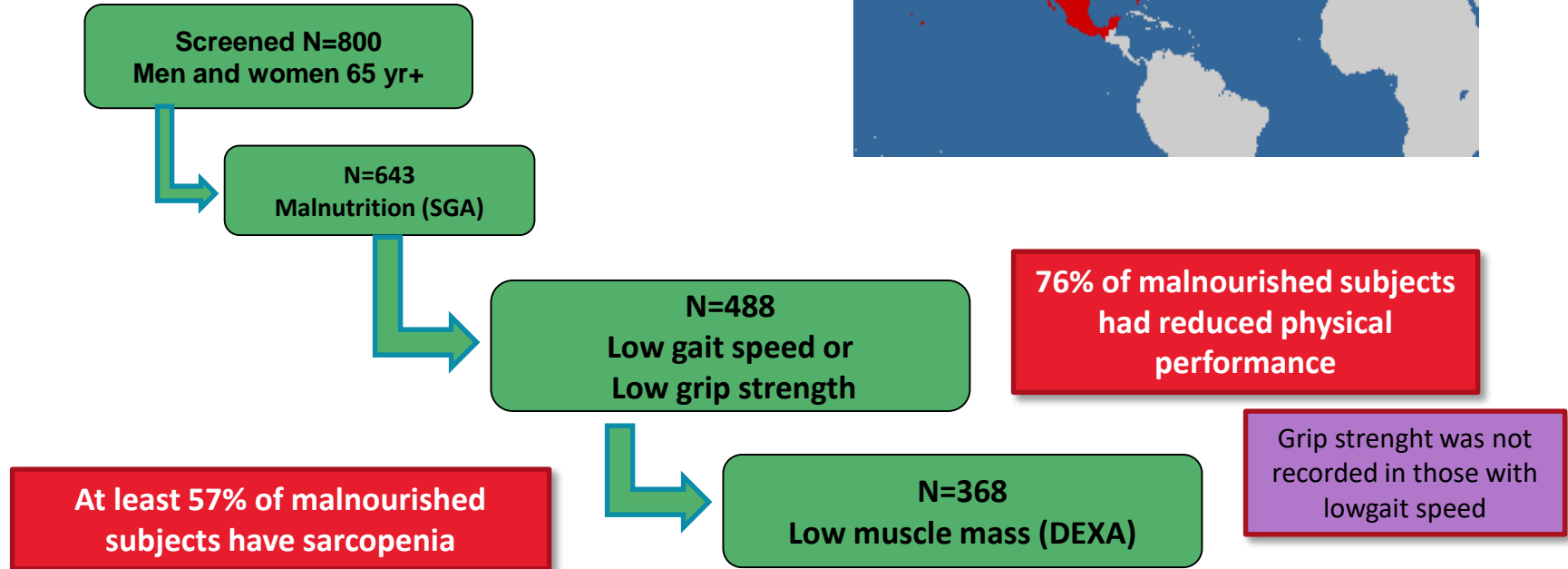
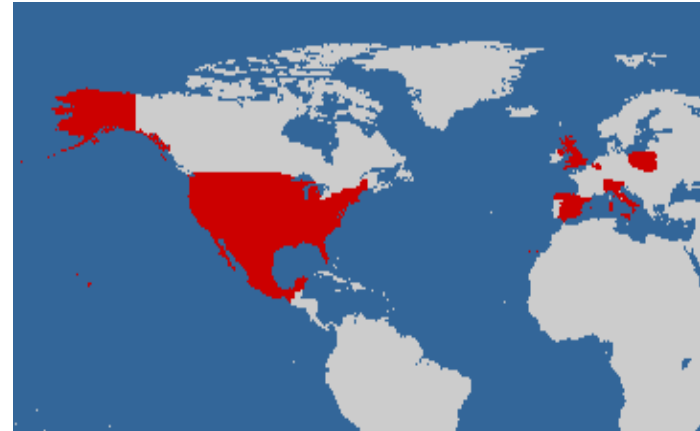


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# Evaluation of an Oral Nutritional Supplement Containing HMB

## Screening and recruitment

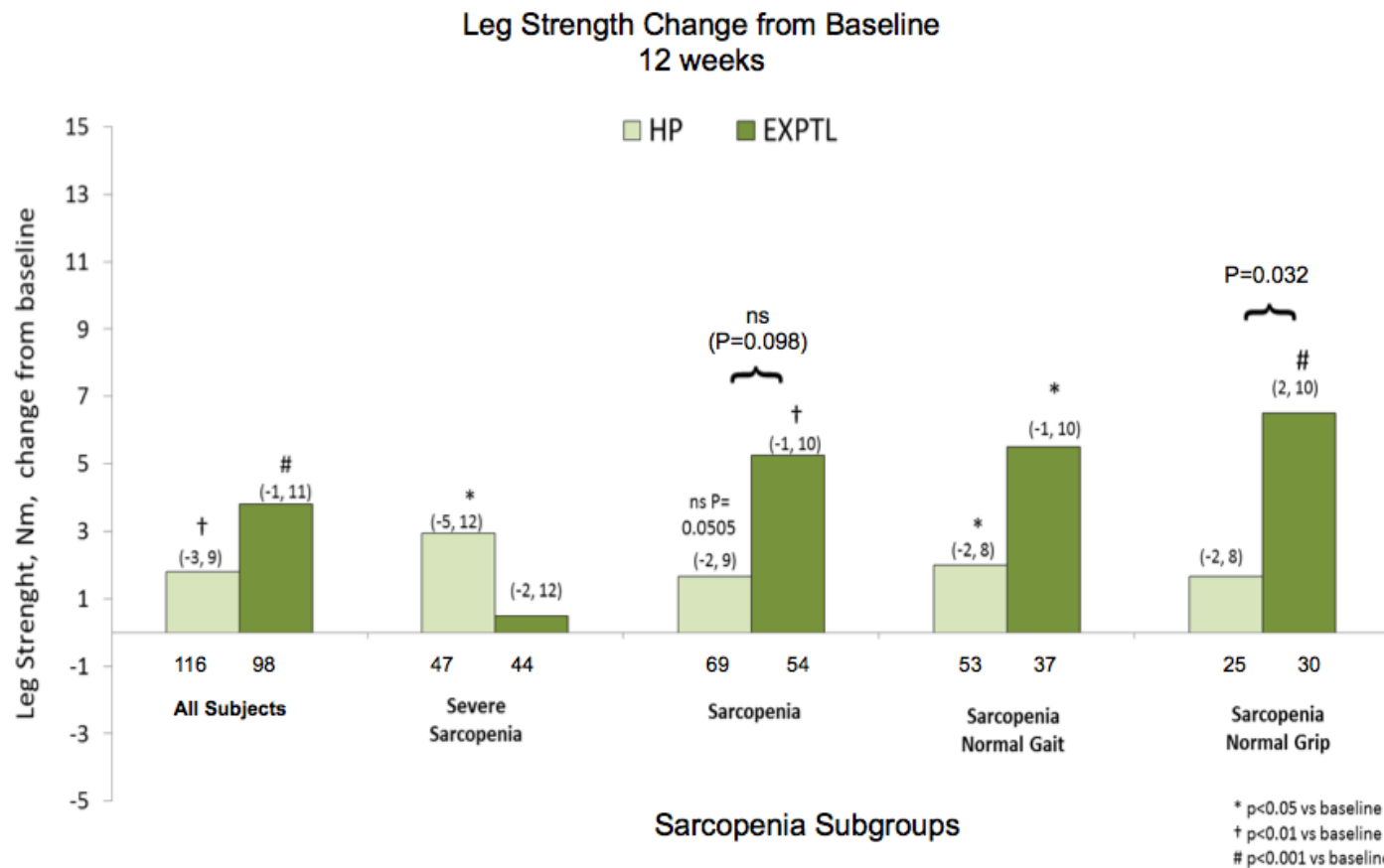


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# Evaluation of an Oral Nutritional Supplement Containing HMB

## Results - Leg Strength (Nm), Change from Baseline at 12 weeks

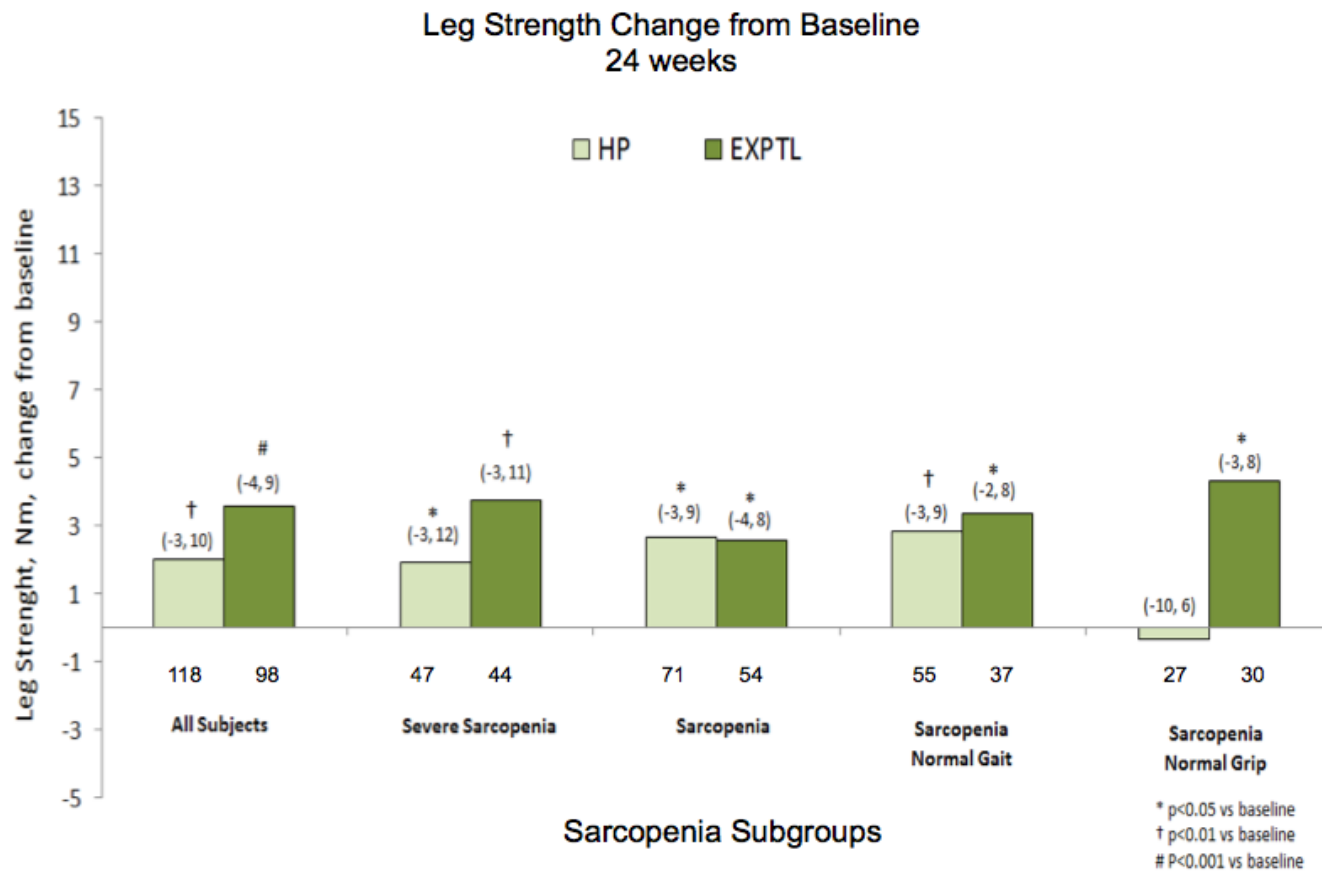


ClinicalTrials.gov Identifier: NCT01191125



# Evaluation of an Oral Nutritional Supplement Containing HMB

## Results - Leg Strength (Nm), Change from Baseline at 24 weeks

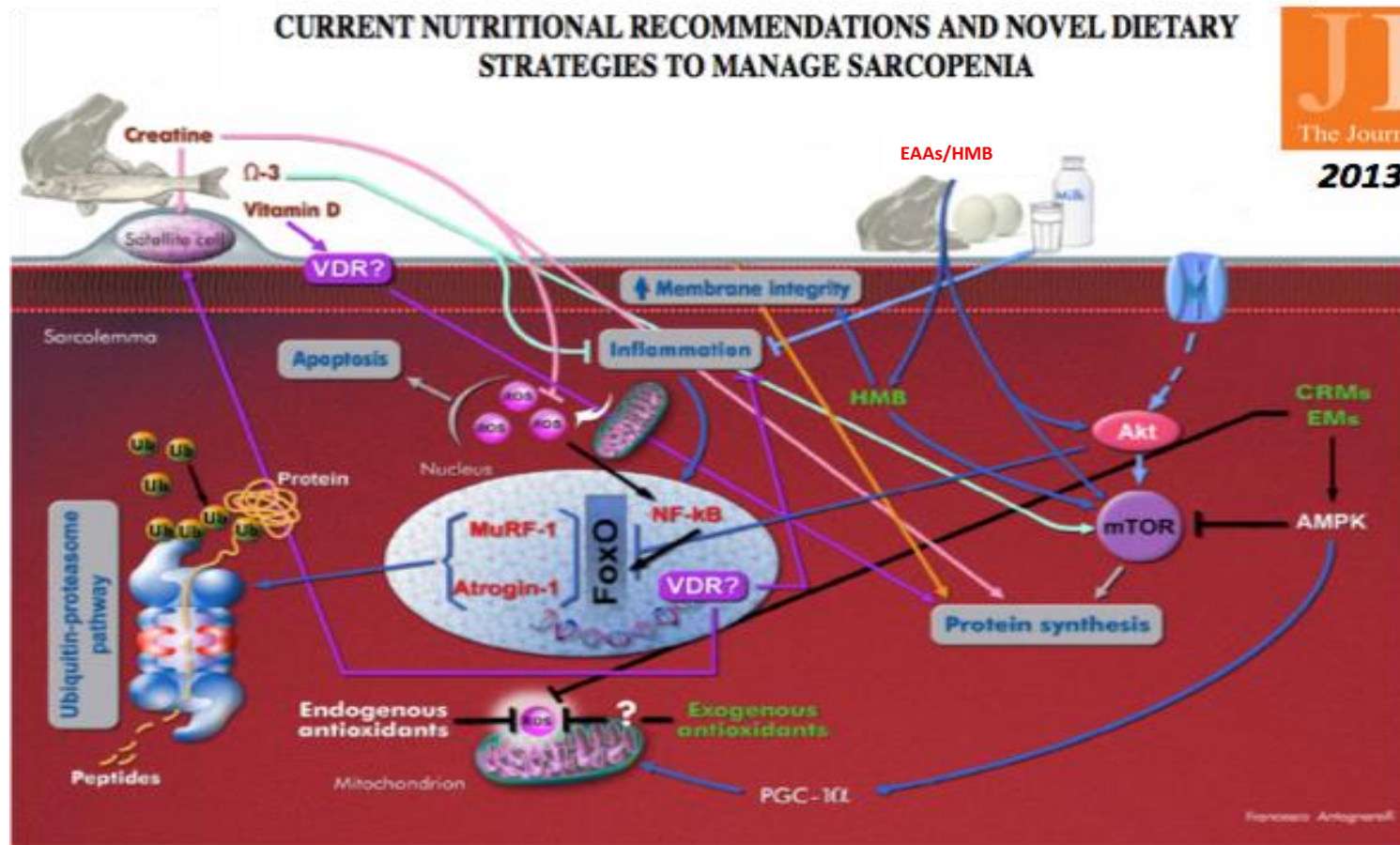


ClinicalTrials.gov Identifier: NCT01191125



# 7.0. CONCLUSION

## Nutrition-muscle connection



**JFA**  
The Journal of Frailty & Aging  
2013;2(1):38-53





# 7.0. CONCLUSION

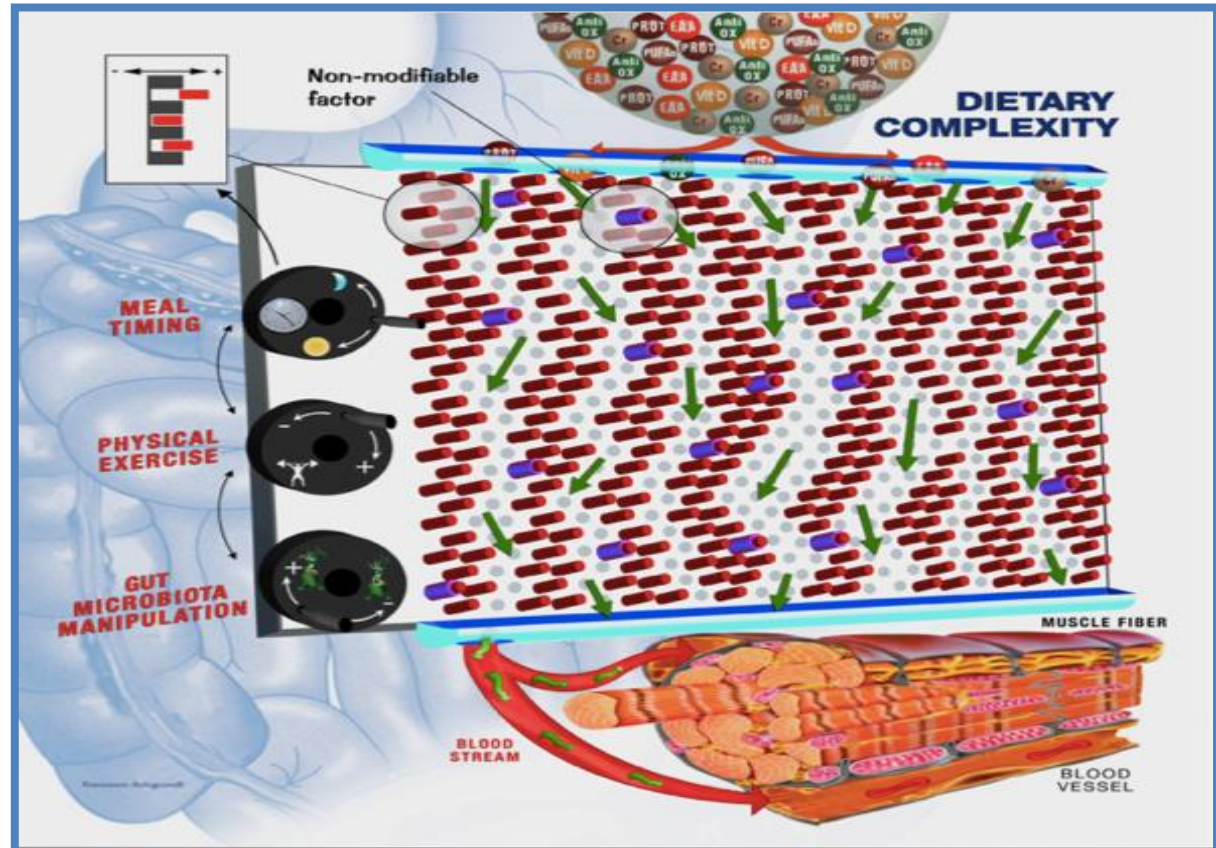


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## Nutrition-muscle connection The “Pachinko Model”



2013;2(1):38-53



**CURRENT NUTRITIONAL RECOMMENDATIONS AND NOVEL DIETARY  
STRATEGIES TO MANAGE SARCOPENIA**



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## 7.0. CONCLUSION



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