ENRGISE Study Design And Rationale

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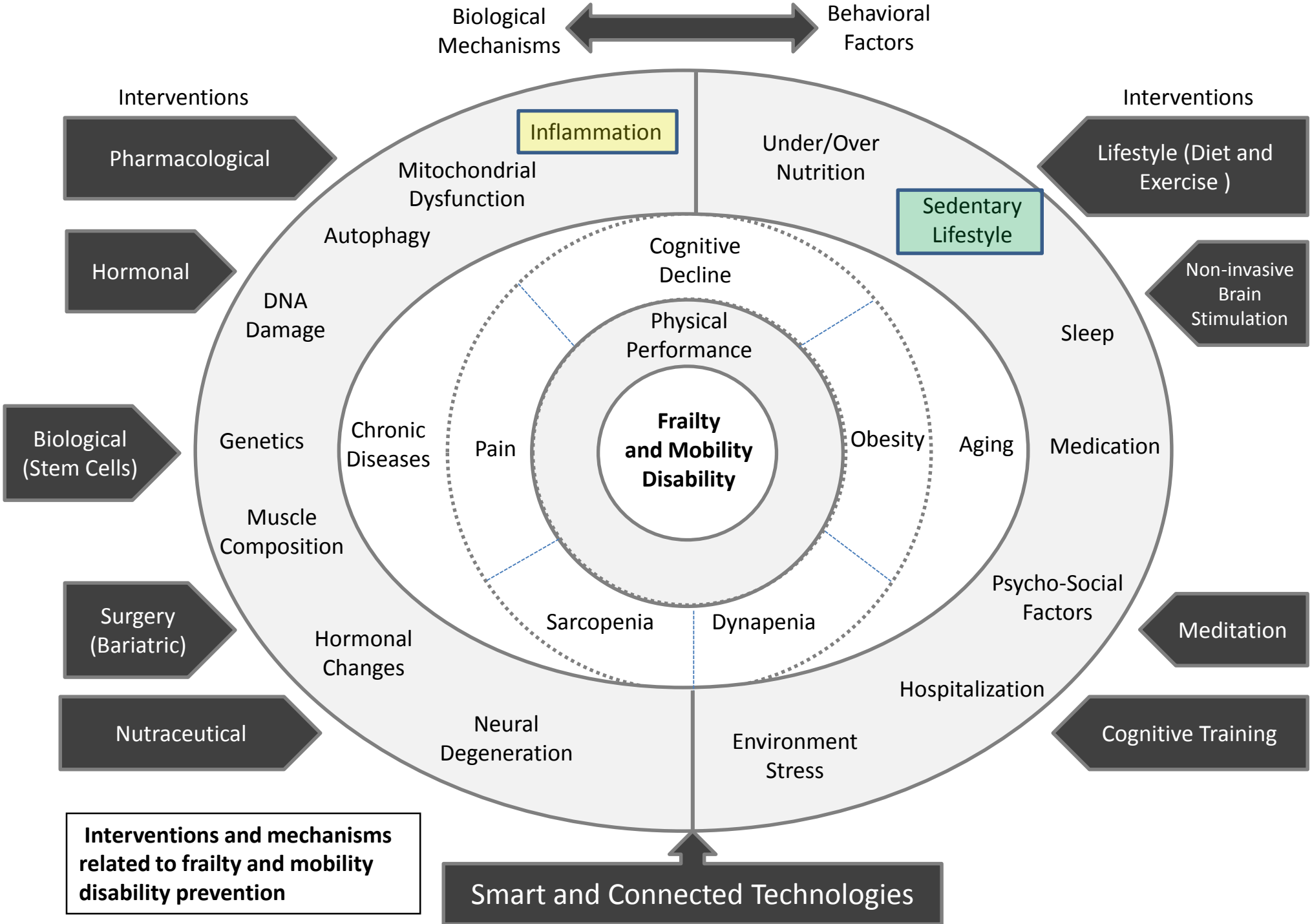
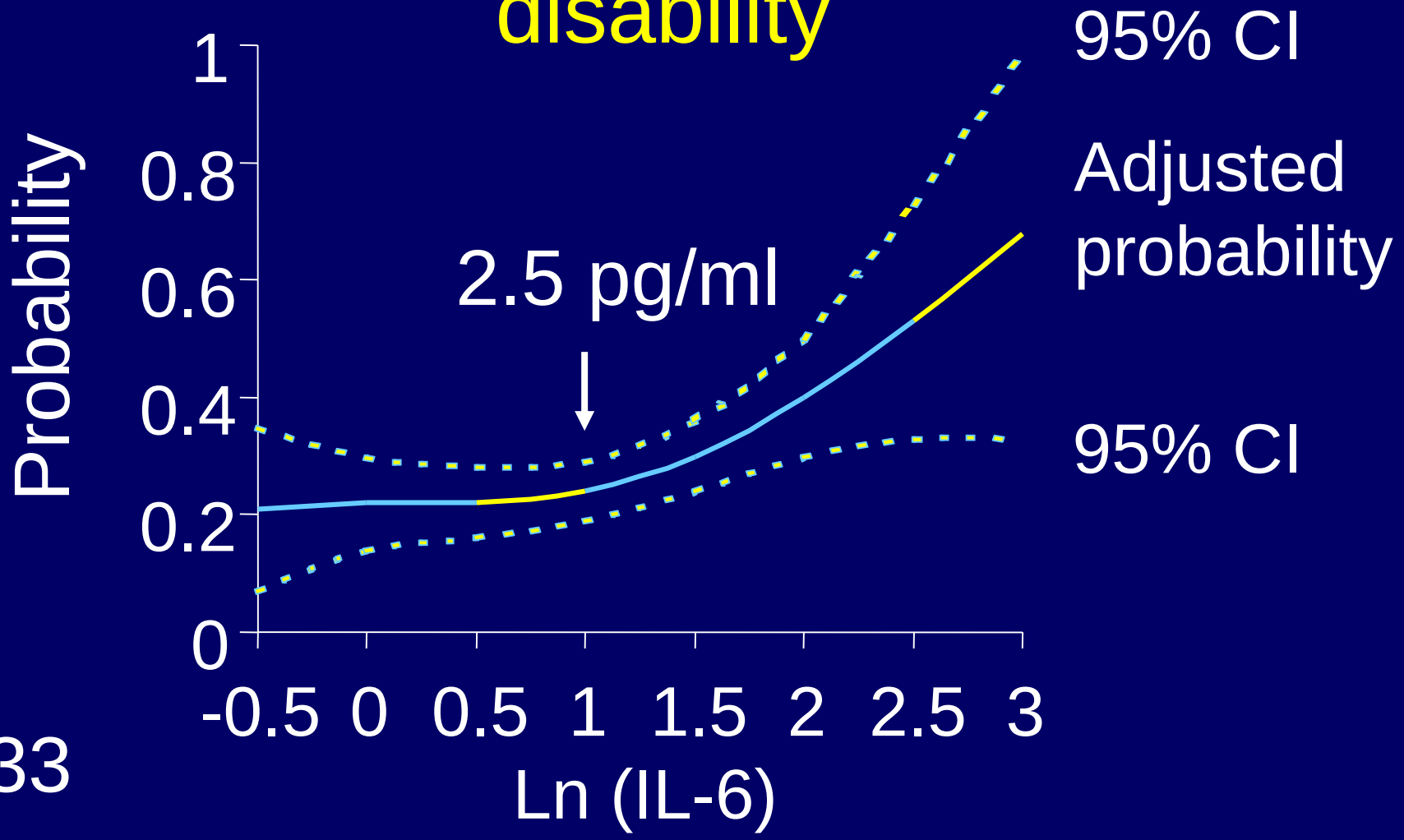

Biological Mechanisms
Behavioral Factors
Interventions
Pharmacological
Hormonal
Biological (Stem Cells)
Surgery (Bariatric)
Nutraceutical
Interventions
Lifestyle (Diet and Exercise)
Non-invasive Brain Stimulation
Meditation
Cognitive Training
Inflammation
Mitochondrial Dysfunction
Autophagy
DNA Damage
Genetics
Muscle Composition
Hormonal Changes
Neural Degeneration
Under/Over Nutrition
Sedentary Lifestyle
Sleep
Medication
Psycho-Social Factors
Hospitalization
Environment Stress
Cognitive Decline
Physical Performance
Chronic Diseases
Pain
Obesity
Aging
Sarcopenia
Dynapenia
Frailty and Mobility Disability
Smart and Connected Technologies
Interventions and mechanisms related to frailty and mobility disability prevention

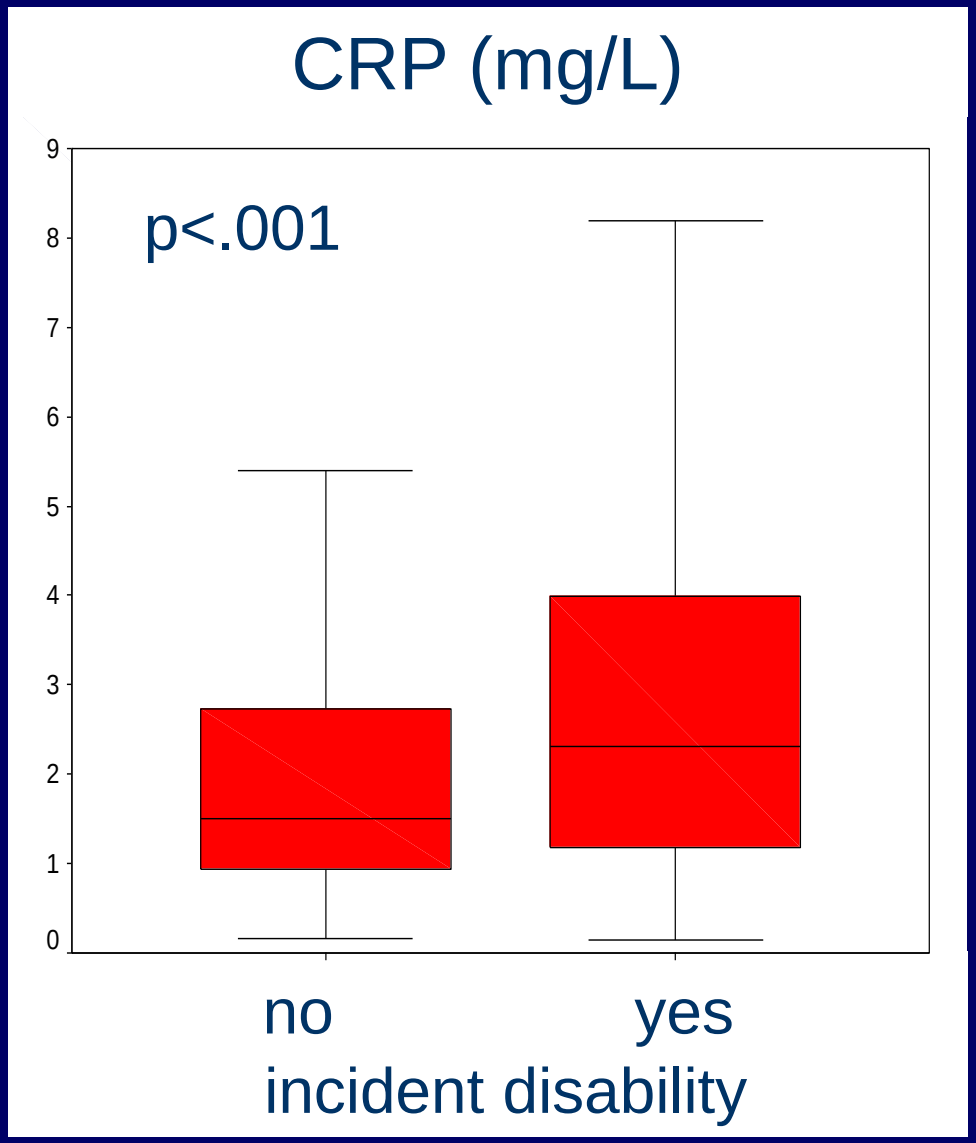
EPESE - IL-6 and 4 year incident mobility disability

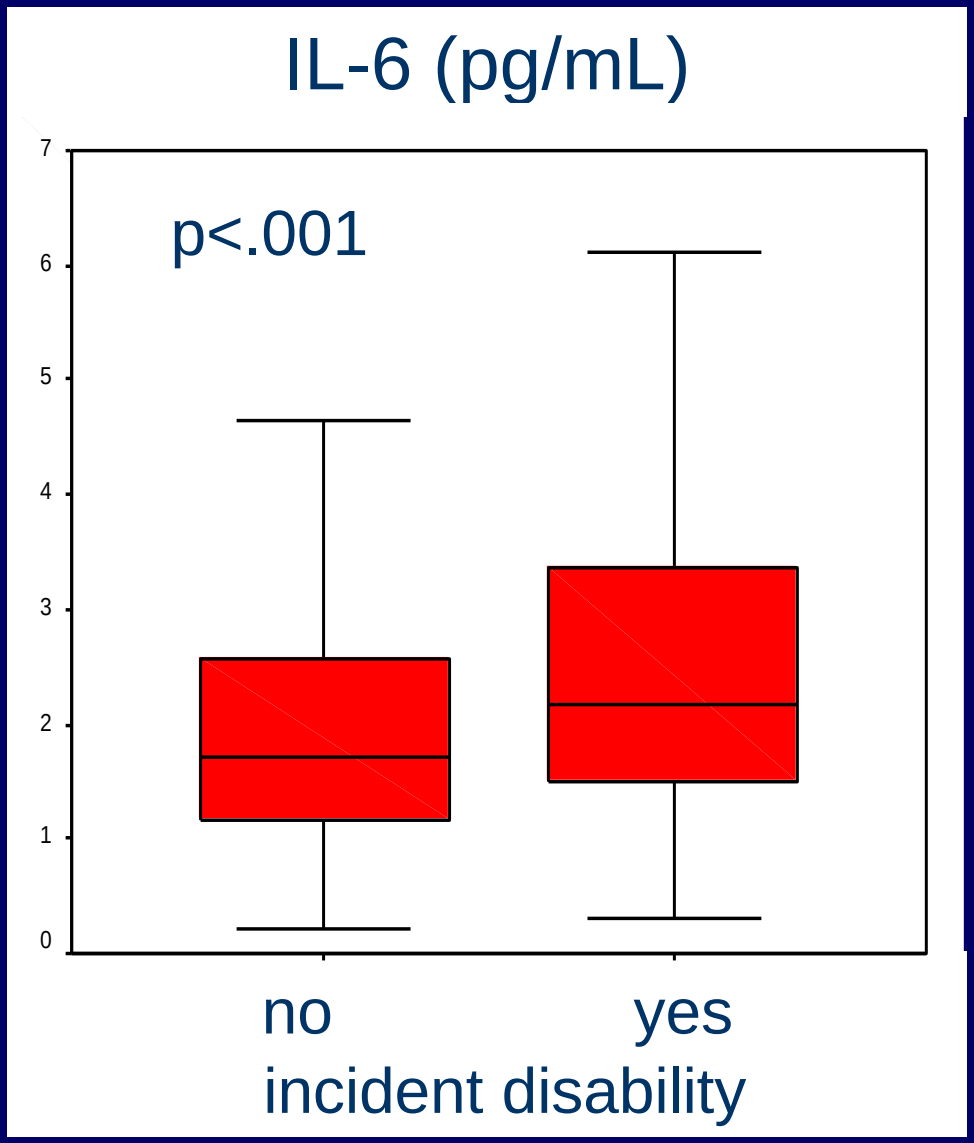


n=633

Ferrucci et al *JAGS 1999;47:639*

HABC - Inflammation markers by mobility disability





Penninx et al JAGS *2004;52:1105*

HABC - Inflammation & incidence of mobility disability

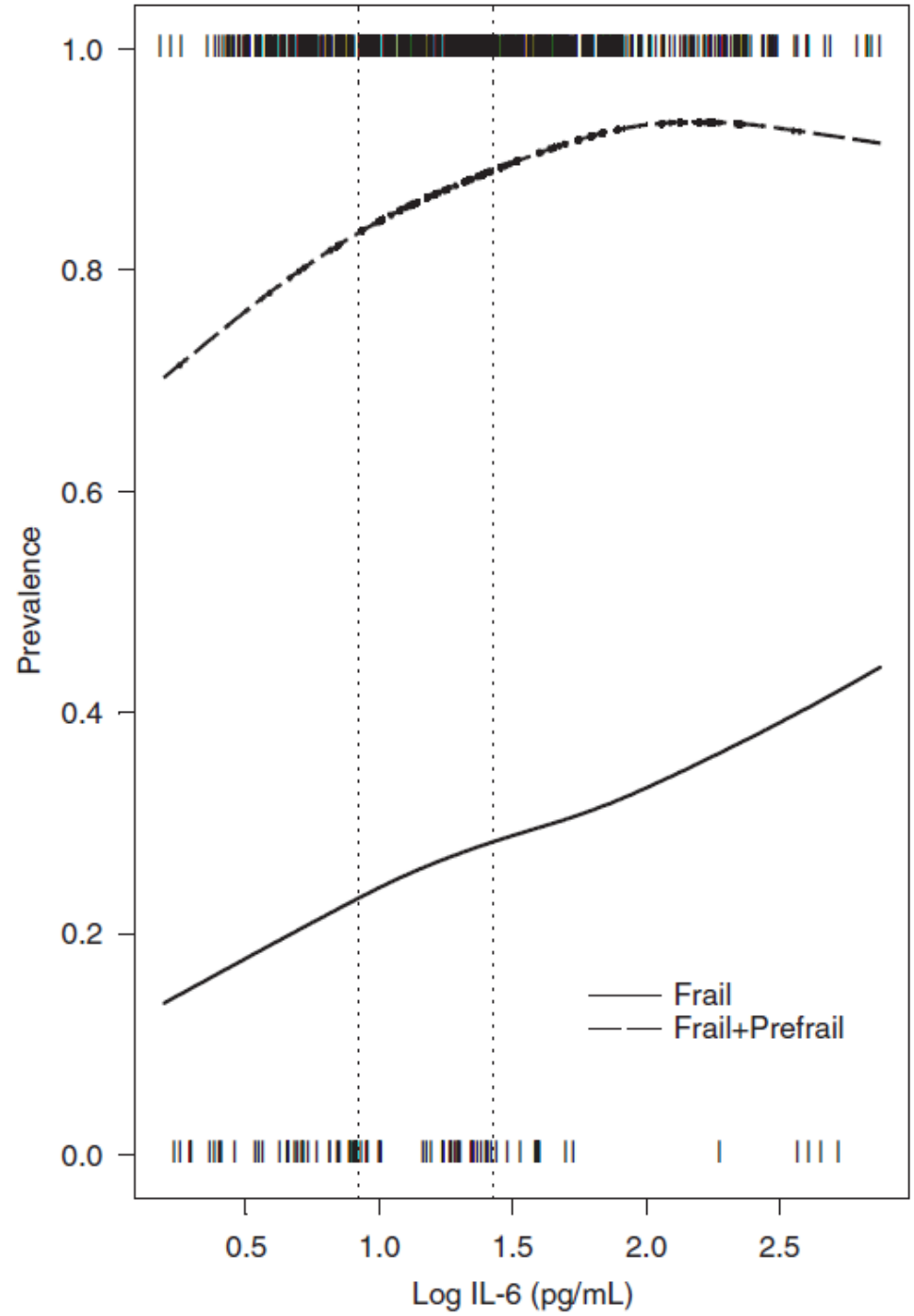
	tertile	incidence	RR*	95% CI
CRP	I	22.2%	1	
	II	26.9%	1.05	0.88-1.26
	III	41.4%	1.40	1.18-1.68
IL-6	I	19.8%	1	
	II	30.6%	1.34	1.11-1.62
	III	40.2%	1.65	1.37-1.98
TNF-α	I	25.0%	1	
	II	28.7%	1.09	0.91-1.30
	III	36.1%	1.18	0.99-1.41

*adjusted for age, gender, race, education, fat mass, smoking, CVD, COPD, diabetes, cancer, arthritis, NSAIDs, corticosteroids albumin, creatinine, EPESE perf.

Penninx et al JAGS *2004;52:1105*

Inflammation and Prevalence of Frailty in Older Women Enrolled in WHAS

Leng et al.
JAGS 55:864–871, 2007



Criteria for prioritizing the interventions in RCTs

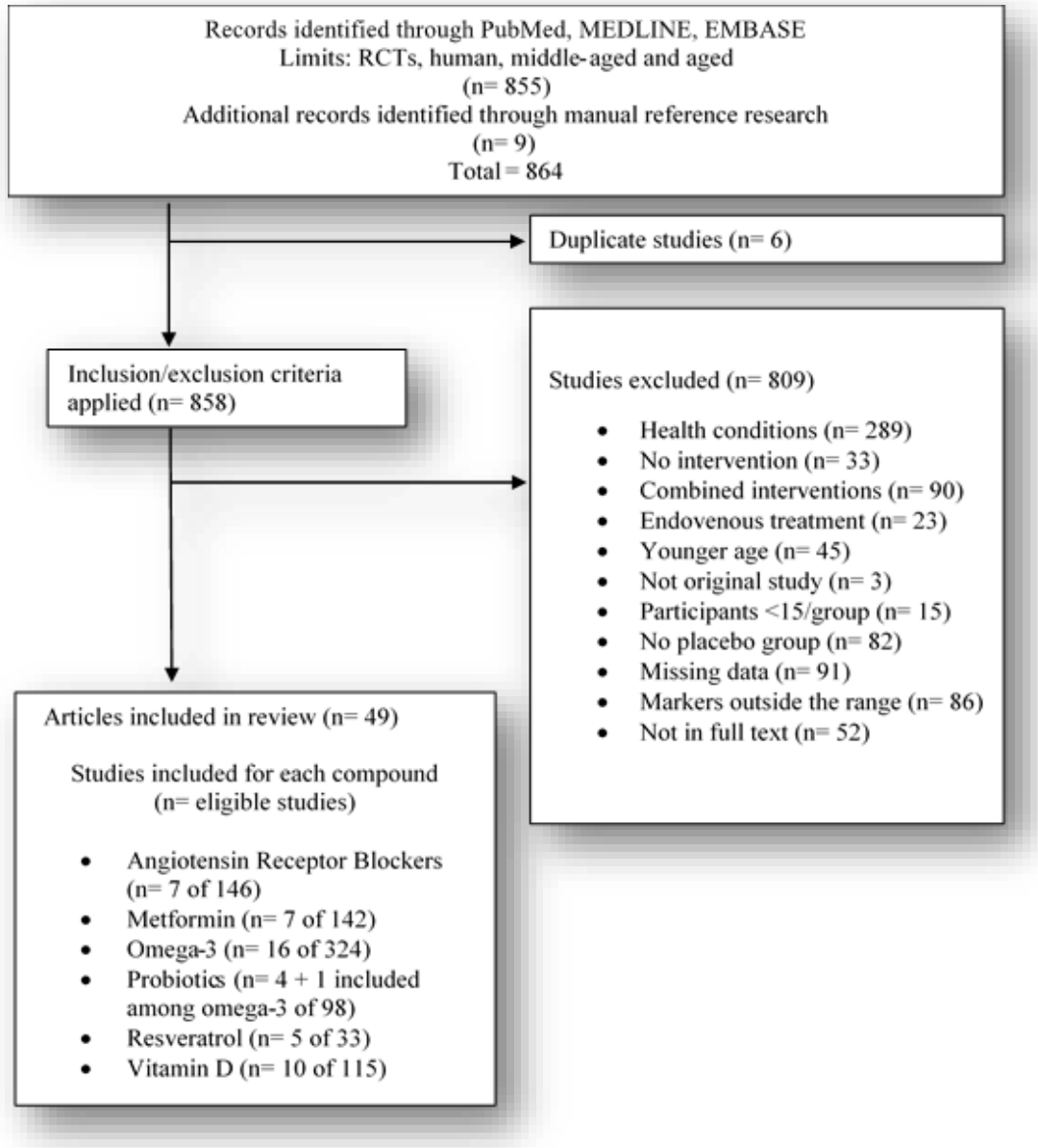
Safety, tolerability and acceptability are key criteria. Vulnerable older persons use multiple drugs and have multiple comorbidities, and thus, are at high risk of adverse drug reactions. Newer drugs are often tested in younger or middle age adults for the treatment of a single condition and therefore, their safety and tolerability in older persons is not fully known. Furthermore, for the prevention of mobility limitations, vulnerable or frail older persons may not be willing to take, and their providers may not be willing to prescribe drugs that bear a risk of severe adverse events. Finally, we exclude interventions that may negatively affect skeletal muscle or neuromuscular metabolism.
Benefit on inflammation, and physical performance and/or skeletal muscle
Innovation. We prioritize interventions that have not been, or are not being tested in RCTs for preventing mobility limitations.
Biological mechanisms are considered to prioritize interventions that target different mechanisms or may have synergistic effects. We exclude interventions that may negatively affect skeletal muscle metabolism.
Practical and affordable for implementation in the US health care system. **Cost** is a major factor for this criterion to maximize the public health impact of the trial

Methods

- To maximize the public health impact of our meta-analysis, we selected compounds based on four criteria:
    - safety
    - tolerability/acceptability
    - innovation
    - practicality/affordability
- Once we identified potential compounds, we applied one more criterion, which was to select compounds that had sufficient evidence from RCTs (> 3 trials) conducted in middle-aged and older adults with chronic low grade inflammation.
- Six compounds met all the selection criteria and on these we performed meta-analysis:
    1. Angiotensin receptor blockers (ARBs)
    2. Metformin
    3. Omega-3
    4. Probiotics
    5. Resveratrol
    6. Vitamin D

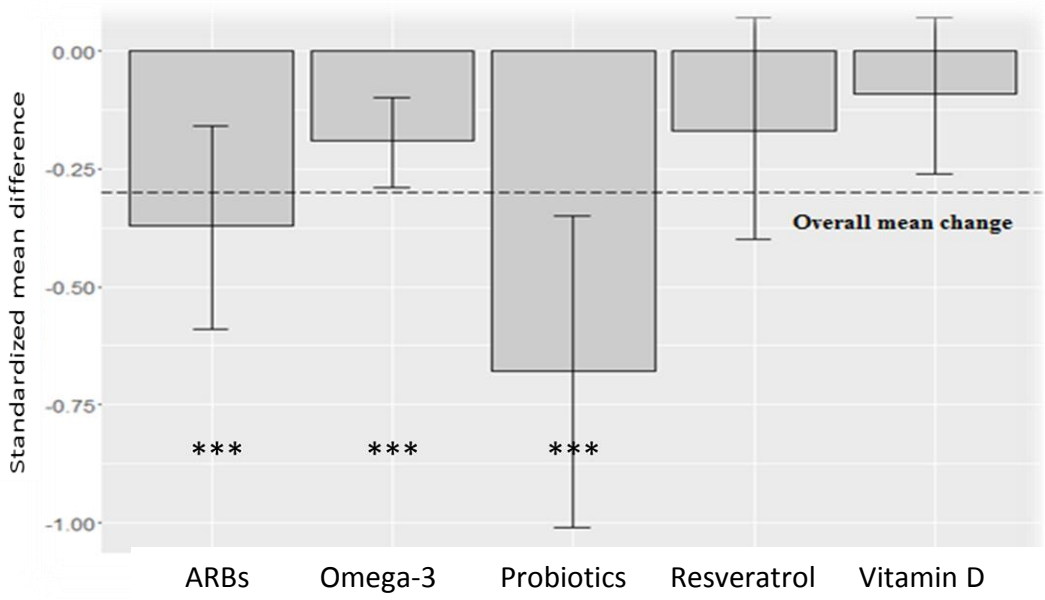
Methods

- A systematic literature search in MEDLINE, PubMed and EMBASE database using combinations of the target compounds with: “inflammation” OR “c-reactive protein” OR “interleukin-6”.
- To be included, studies were limited to randomized controlled trials with placebo or control group receiving no treatment.
- Other key inclusion criteria: participants 45 years and older with chronic low-grade inflammation as defined by IL-6 levels between 2.5 and 30 pg/ml and/or CRP levels between 2 and 10 mg/L.

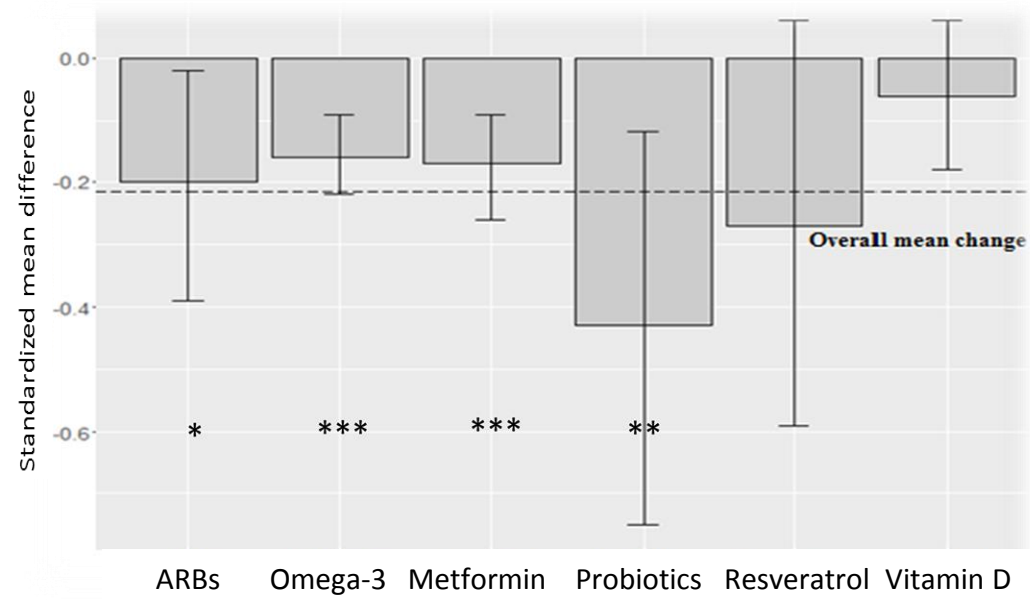


Results

Mean decrease in IL-6 by compound



Mean decrease in CRP by compound



P-value for significant decrease compared to placebo; *: P <0.05; **: P <0.01; ***: P <0.001

enrgise

ENabling Reduction of low-Grade Inflammation in Seniors - Pilot Study

Funding: NIA U01AG050499

Abbott grant for study drug – the company has no other involvement with the study

Manini et al JAGS 2017; 65:1961

Selection of the Interventions

Criteria / Interventions	1. Safe, tolerable, acceptable	2. IL-6 redu-ction	3. Physical performance	4. Inno-vation	5. Mecha-nism	6. Practical, affordable
ACEIs, ARBs	+	+	+	+	+	+
ω-3	+	+	+	+	+	+
Mediterranean diet	+	+	+	+	+	-
Physical activity, weight loss	+	+	+	-	+	+?
Vitamin D	+	+	+	-	+	+
Anti-TNF-α, -IL6,-IL1; methotrexate thiazolidinediones	-	+	?	+	+	?
Statins, chloroquine, colchicine	-	+	- ?	+	-	+
Corticosteroids, aspirin, NSAIDs, cox-2 inhibitors	-	+	?	+	+	+
Metformin, fosinopril, ghrelin, lactoferrin, oxytocin, salsalate, curcuma, creatine, probiotics, resveratrol	+	- ?	- ?	+	+ ?	+
+ positive evidence, - negative evidence, ? evidence lacking						

- Double-blinded, 2x2 factorial randomized pilot trial
- 5 field centers
- Coordinating Center: University of Florida
- Data Management Quality Control: Wake Forest University
- n=300 – follow-up duration 12 months

ClinicalsTrials.gov NCT02676466

Specific Aims

Conduct a pilot RCT in 300 older persons at risk of mobility decline to assess:

- Compared with placebo, the effects of losartan, ω-3, and losartan+ω-3 on IL-6, walking speed, SPPB and frailty;
- The recruitment yields, the target population, adherence, retention, tolerability of the interventions
- The primary outcome, sample-size, design, and cost for the main trial;
- The dosage and safety of the interventions

Manini et al JAGS 2017; 65:1961

Design

- Double-blind, placebo controlled RCT to test losartan, ω-3, and their combination in a 2 x 2 factorial design
- Recruitment to last 1 year
- Each participant will be followed for 1 year

Manini et al JAGS 2017; 65:1961

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The ENRGISE Pilot Study will provide preliminary data to design a definitive clinical trial to assess whether the reduction of chronic low-grade inflammation may prevent of major mobility disability

Manini et al JAGS 2017; 65:1961