



Endpoints And Indications For The Older Population

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Outline

- Functional Endpoints and Geriatrics
- Sarcopenia and reduced mobility as indications
- Geriatric Indications

Consideration of Older Patients

- Aging Effects
 - Loss of skeletal muscle (sarcopenia), changing body composition, reduced blood volume/kg weight, impaired regulation of appetite and thirst, decreased GH, IGF1, Testosterone, Estradiol
- Geriatric Patients
 - Multiple chronic diseases, poly-pharmacy, frailty, inflammation

Short Physical Performance Battery

Functional measurement for trials that include elderly people

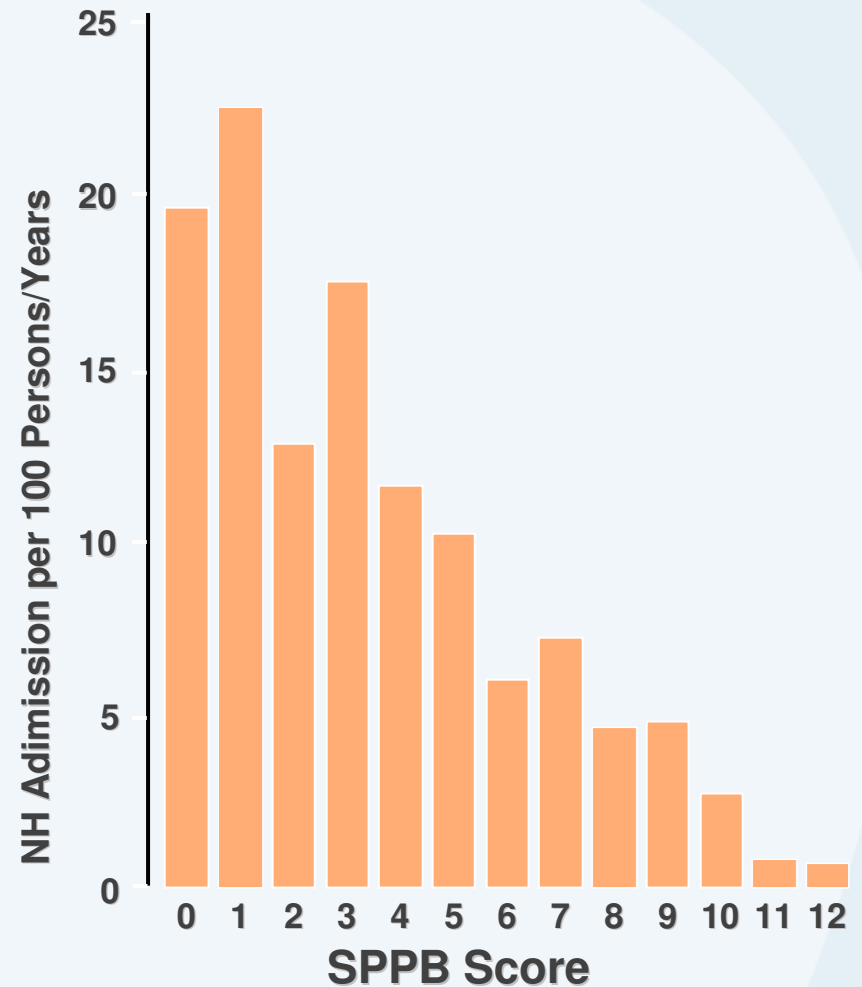
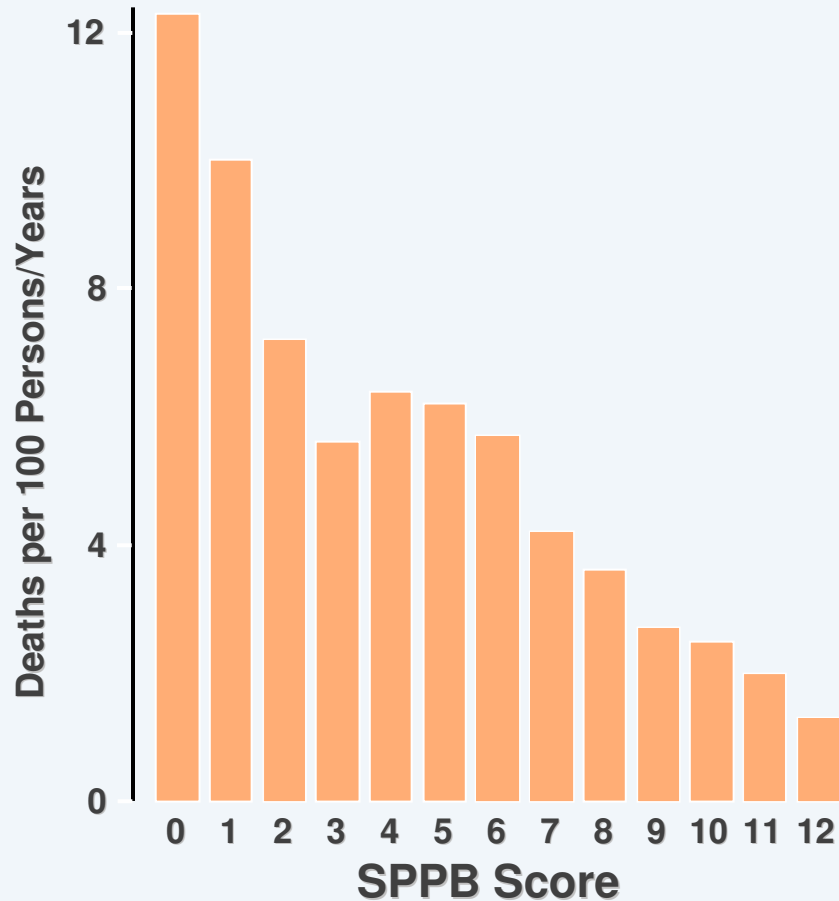
- Developed at the National Institute on Aging (NIA) for use in the Established Population for the Epidemiologic Studies of the Elderly (EPESE)
- **Timed standing balance (up to 10 seconds)**
 - Side-by-side stand
 - Semi-tandem stand
 - Tandem stand
- **Timed 4-meter walk** (habitual gait speed)
- **Chair rise**
 - Single
 - Timed multiple (5) chair rises
- Six minute walk distance: validated in clinical populations, difficult to perform by health care provider

SPPB Development and Scoring

SCORE	5 Chair Stands (time)	4 m Walking (time)	Balance
0	Unable	Unable	Side-by-Side 0-9 s
1	> 16.6 s	> 7.5 s	Semitandem 0-9 s
2	13.7-16.6 s	5.4-7.5 s	Tandem 0-2 s
3	11.2-13.6 s	4.1-5.3 s	Tandem 3-9 s
4	< 11.2 s	< 4.1 s	Tandem 10 s

2-Year Mortality and Nursing Home Admission According to Baseline SPPB (EPESE)

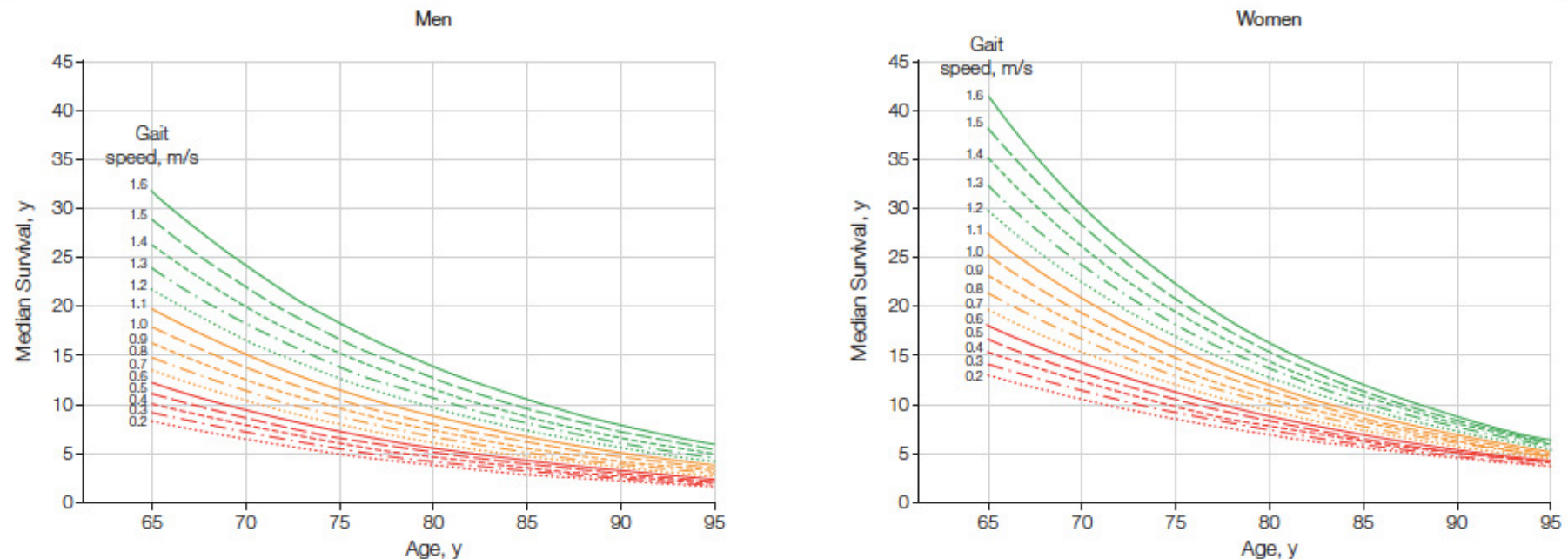
Guralnik JM, Simonsick EM, Ferrucci L et al. - J. Gerontol 1994



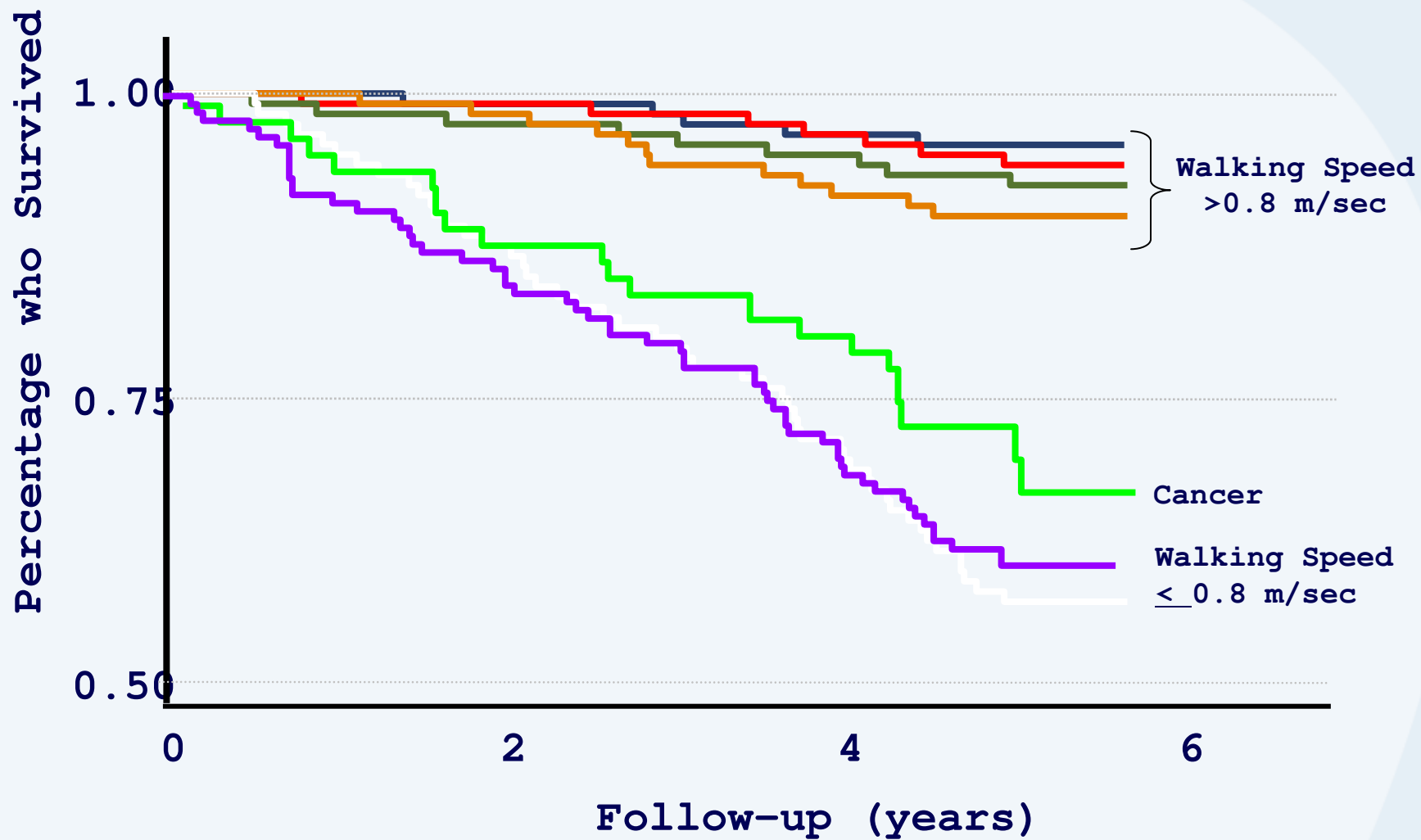
Gait Speed and Survival in Older Adults

JAMA. 2011;305(1):50-58

Figure 2. Predicted Median Life Expectancy by Age and Gait Speed

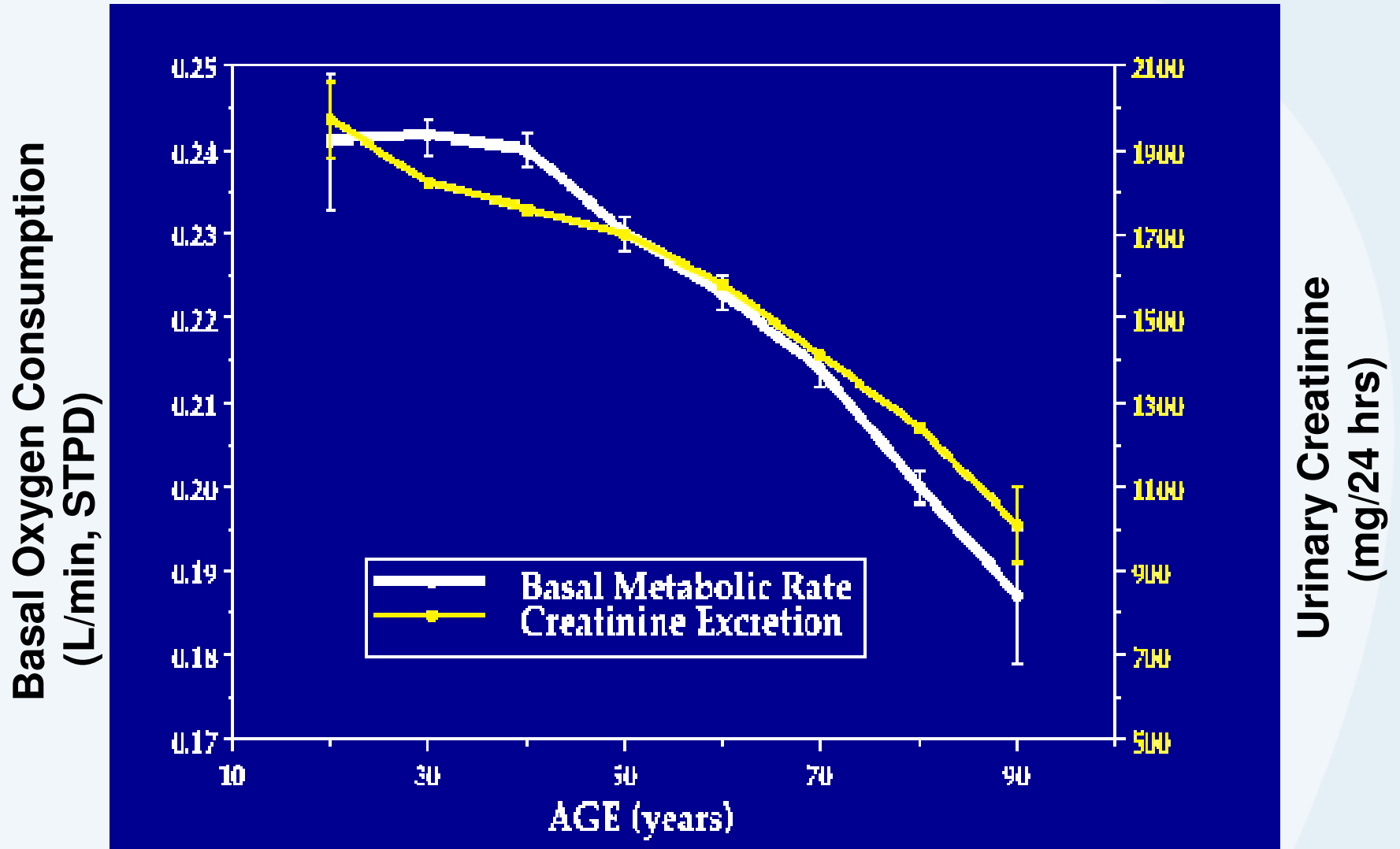


Walking Speed Predicts Mortality



Ble & Ferrucci (unpublis

Tzankoff and Norris, Effect of muscle mass decrease on age-related BMR changes, J Appl Physiol 43: 1001, 1977

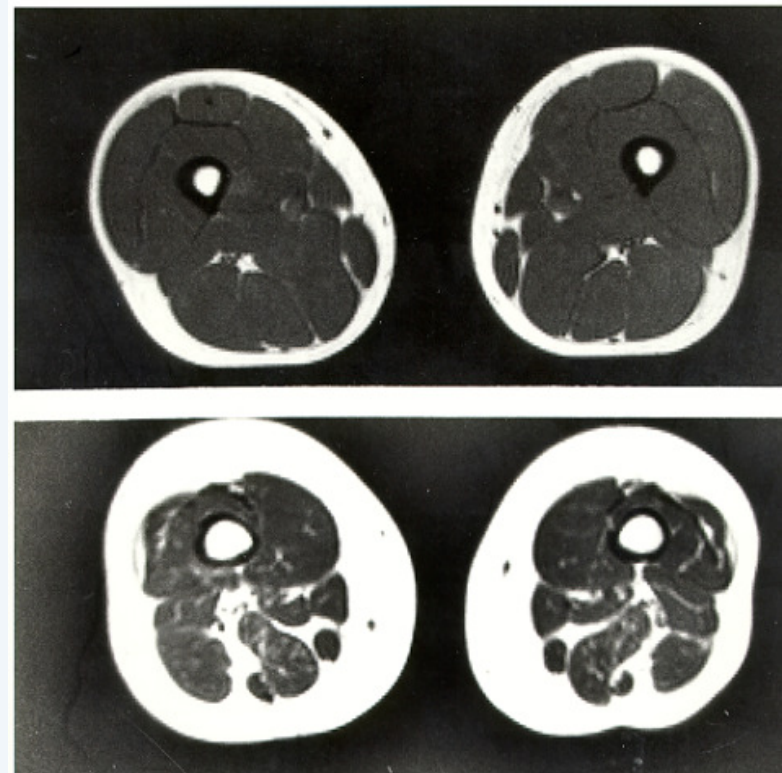


Sarcopenia

Age related loss of skeletal muscle mass and function

Evans, W What is Sarcopenia, *J. Gerontol.*, 50A: 5-8, 1995.

Evans, W Sarcopenia and age-related changes in body composition and functional capacity, *J. Nutr.*, 123: 465-468, 1993.



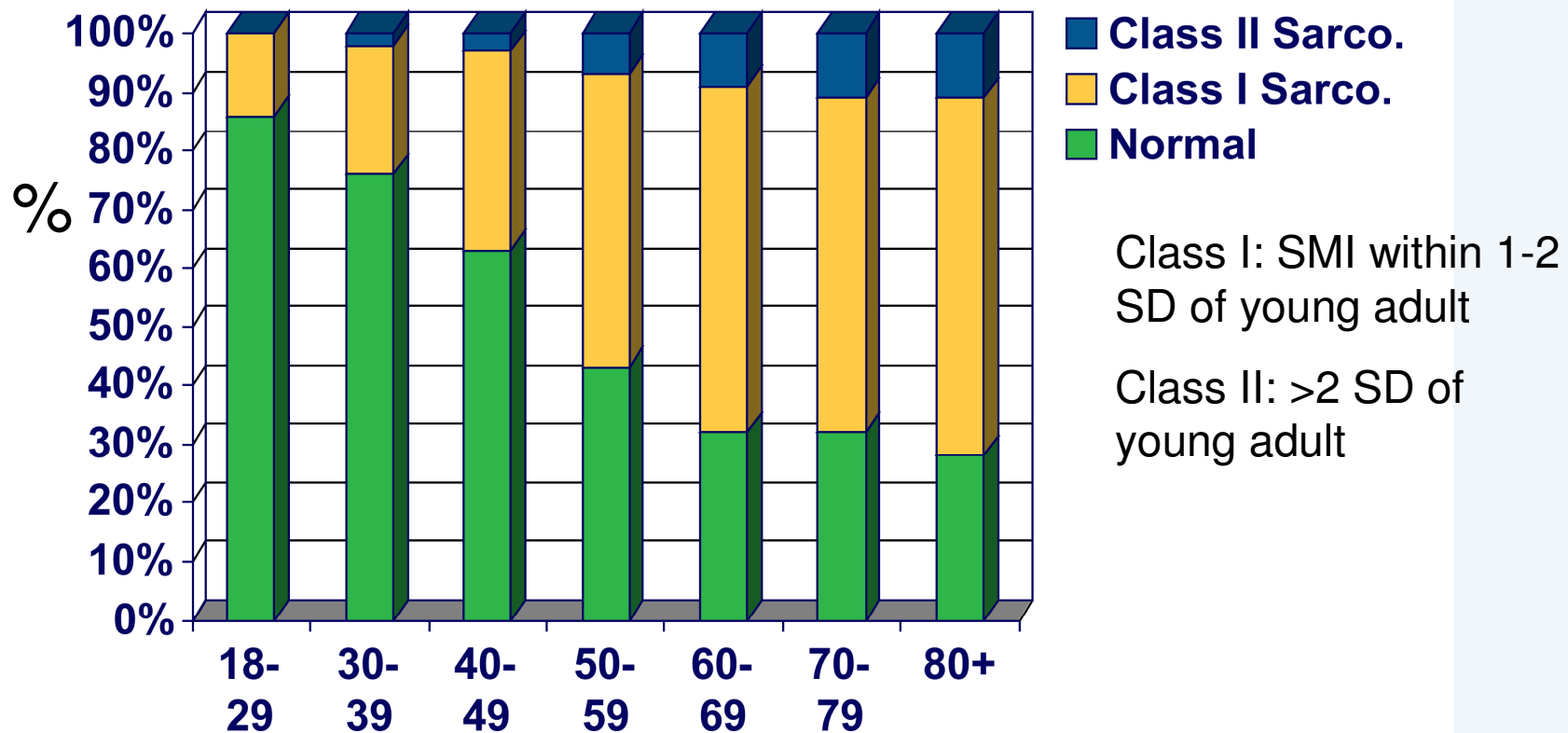
Sarcopenia: An undiagnosed condition in older adults. Current consensus definition

JAMDA, 2011

- “Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multifactorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance and nutritional deficiencies.”
- **“Sarcopenia represents a major cause of disability and increased health costs in older persons. It is very common, but like most geriatrics syndromes, seldom recognized by physicians”**
- Diagnosis of sarcopenia:
 - **Habitual gait speed of < 1 m/sec**
 - Objectively measured low muscle mass
 - **Appendicular lean mass (DEXA)**
 - **$\leq 7.23 \text{ kg/m}^2$ (Men)**
 - **$\leq 5.67 \text{ kg/m}^2$ (Women)**

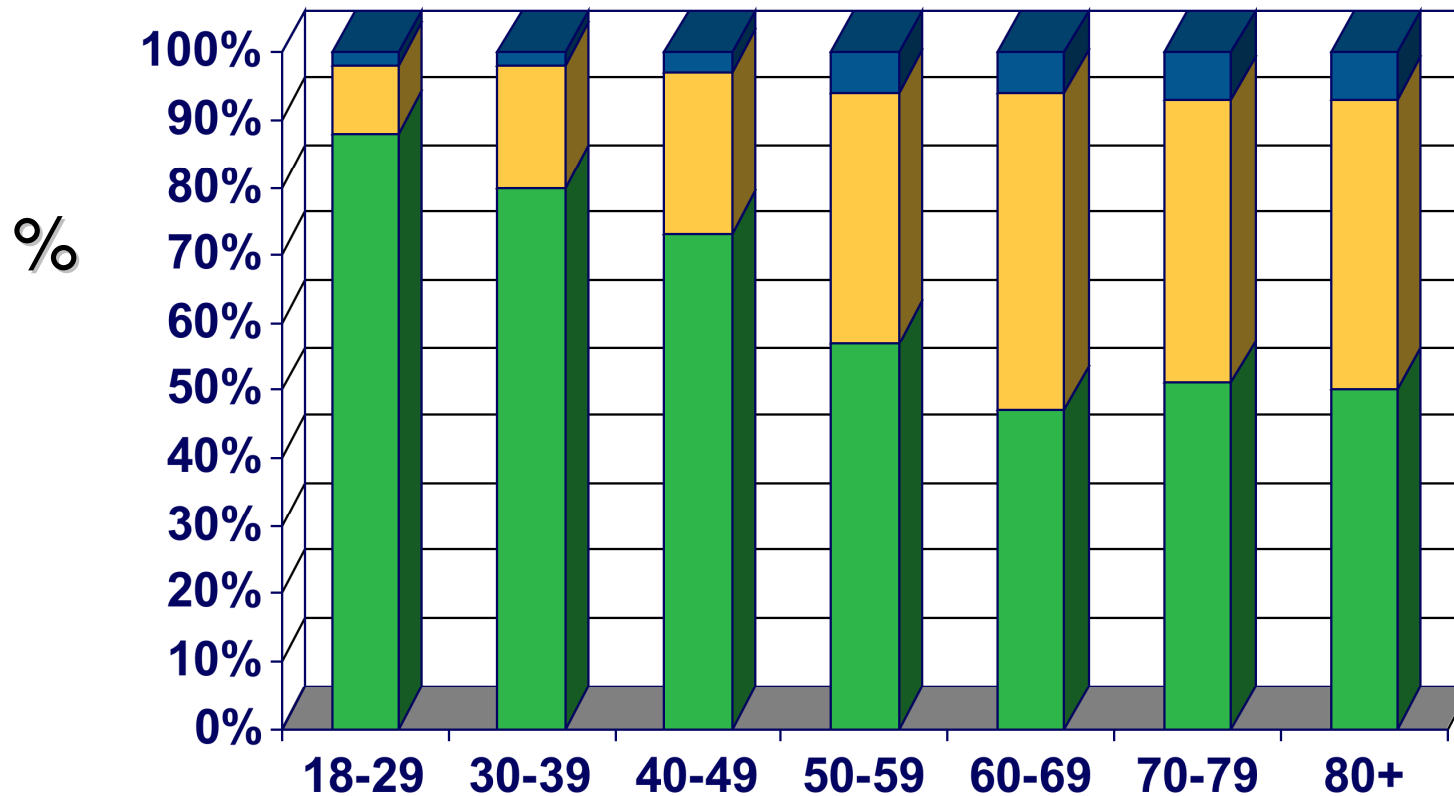
Prevalence of sarcopenia, Women

JAGS, 50:889-896, 2002 - NHANES III

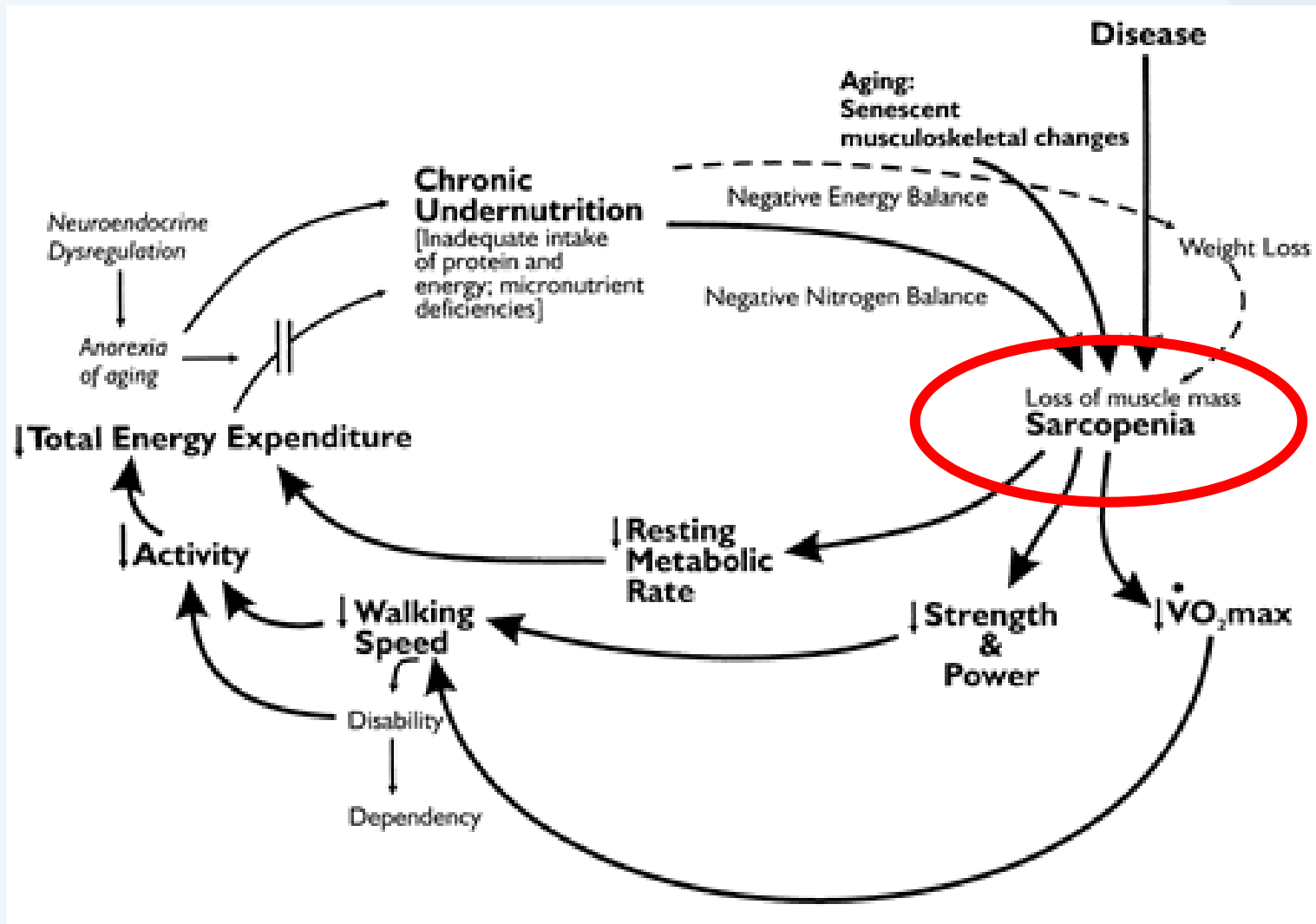


Prevalence of sarcopenia, Men

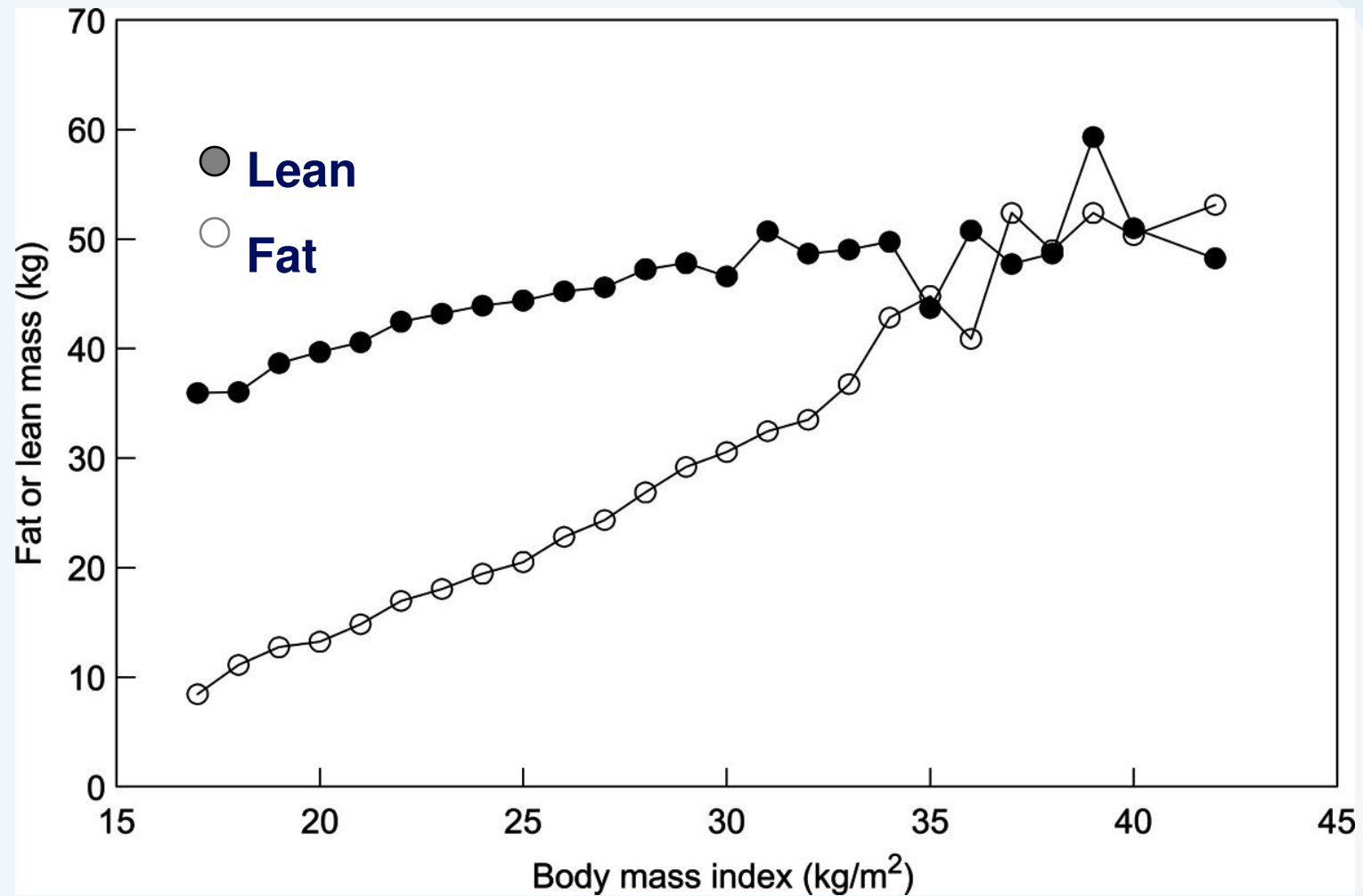
JAGS, 50:889-896, 2002 - NHANES III



Etiology of Frailty (Fried model)



Body Composition in post-menopausal women by BMI



Sarcopenic Obesity

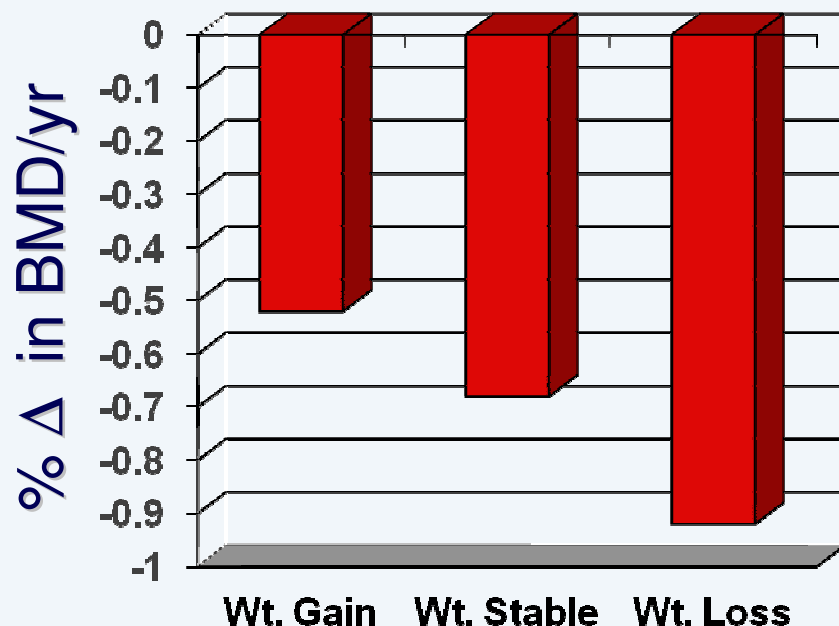
Int J Obesity 28: 234, 2004

“Obesity was strongly associated with self-reported physical functional health, ***equivalent to being 11 years older for men and 16 y for women.***”

“In clinical practice, BMI may be considered as a simple to obtain marker of the risk of functional impairment in the elderly.”

Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women,

Ensrud, et al, *J Am Geriatr Soc* 51: 1740-1747, 2003



- 6,785 women > 65 yrs examined over an average of 5.7 yrs
- Wt. Loss > 5% from baseline
 - Asked about intention to lose weight
 - Wt. Loss: 78.3 ± 5.3
 - Wt. Stable: 76.4 ± 4.7
 - Wt. Gain: 75.4 ± 4.2

Undesirable side effect of weight loss in elderly people

- “Older women who experience weight loss in later years have increased rates of hip-bone loss and a two-fold greater risk of subsequent hip fracture, irrespective of current weight or intention to lose weight.”

“These findings indicate that even voluntary weight loss in overweight elderly women increases hip fracture risk.”

Changes associated with aging

↓ Fatty acid oxidation

↓ Muscle mass

↑ Body and visceral fat

↑ Insulin resistance

↓ Strength functional capacity

↓ Bone density

Changes associated with BEDREST

↓ Muscle protein synthesis

↑ Cortisol sensitivity

↑ Insulin resistance

↓ Fatty acid oxidation

↓ Strength

↓ Bone density

↑ Nitrogen loss

↑ Dietary protein needs

↓ Muscle mass

↑ Intramuscular triglyceride

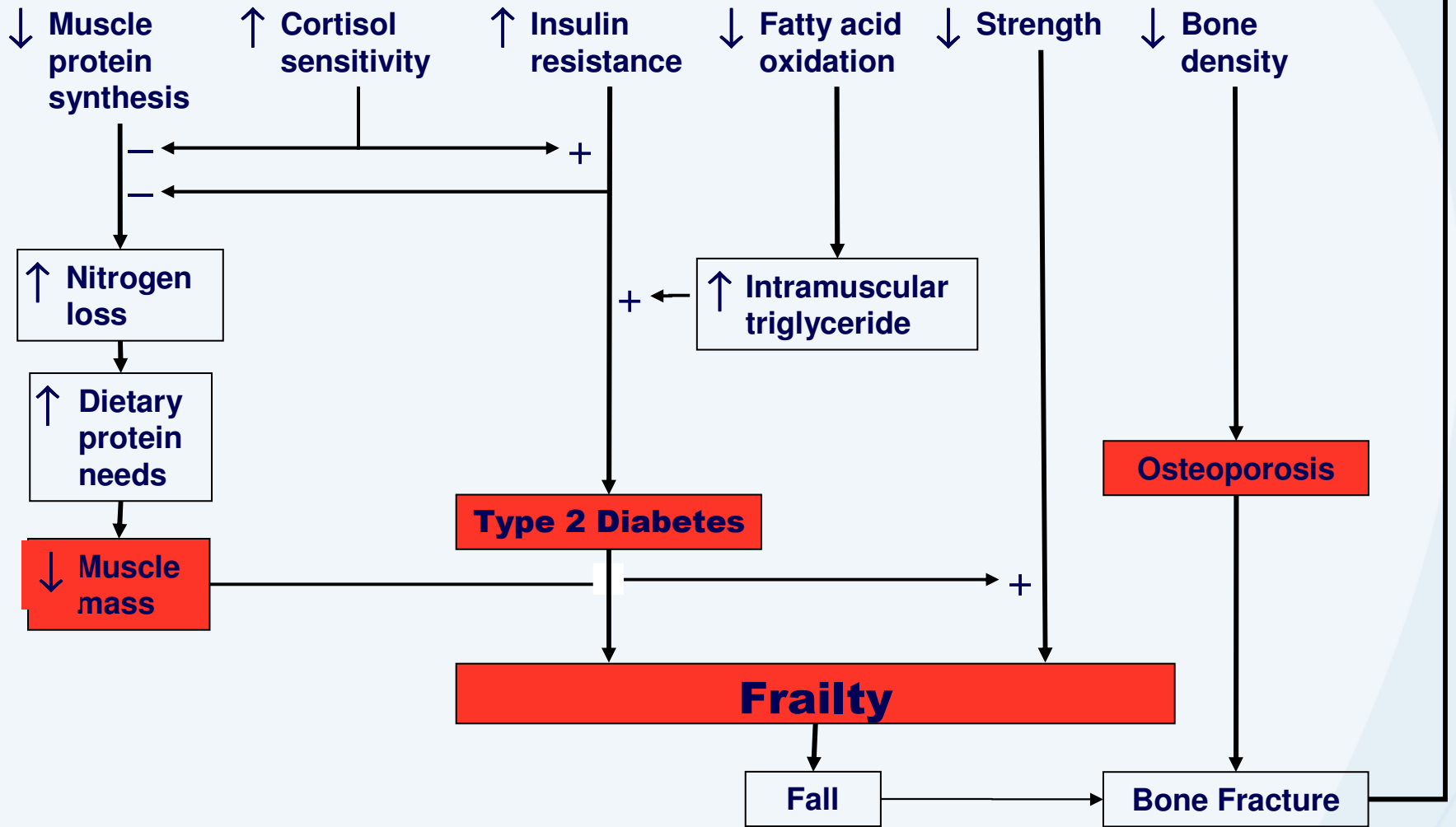
Type 2 Diabetes

Osteoporosis

Frailty

Fall

Bone Fracture



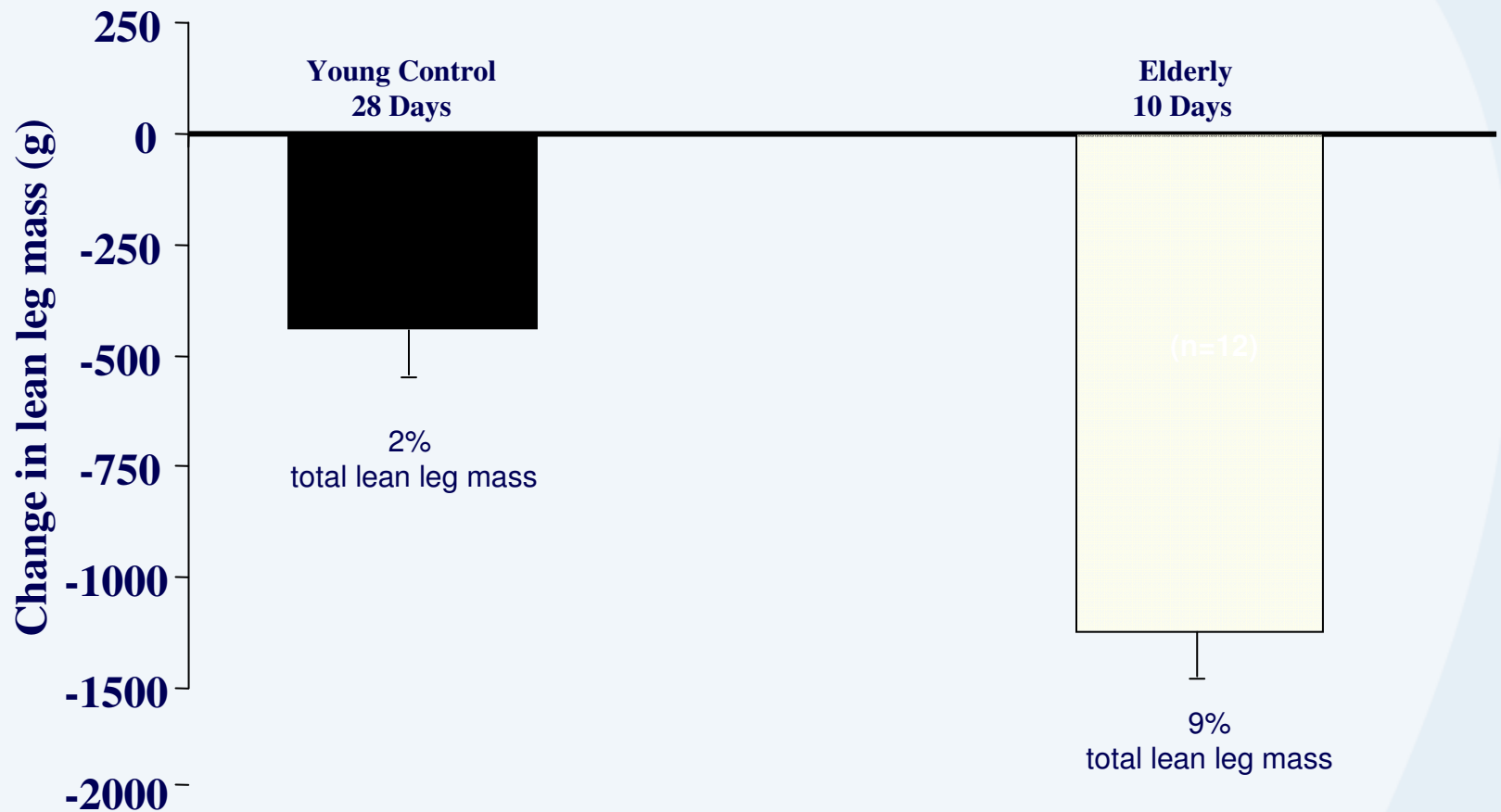
Effect of 10 days of bed rest on skeletal muscle in healthy older adults, *JAMA* 297: 2007

- 10 days complete bedrest
- 12 subjects, 67 ± 5 years
- Eucaloric diet, 0.8g protein/kg/d
- Body composition (DEXA)
- Fractional Synthetic Rate of muscle protein
 - 24-h infusion of $^{13}\text{C}_6$ -phenylalanine, vastus lateralis biopsy pre-post infusion

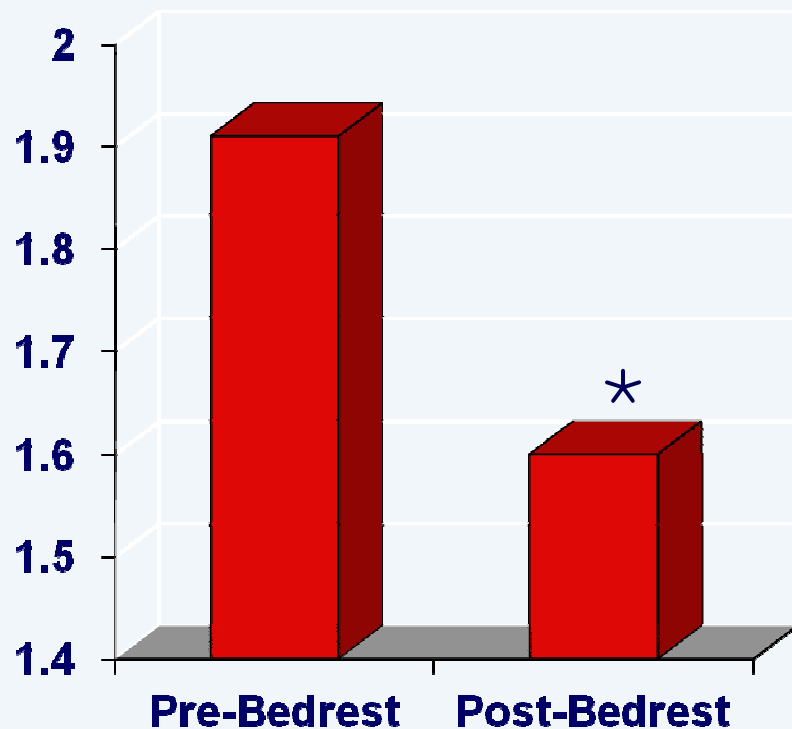
Loss of Leg Muscle Mass: DEXA

Effect of 10 days of bed rest on skeletal muscle in healthy older adults, *JAMA* 297: 2007

40% reduction in rate of muscle protein synthesis



Effects of bed rest on physical activity and $\text{VO}_{2\text{max}}$



- **-15.1±4.3% change**
- **-1% reduction/year with normal aging**
- **10 d bedrest = 15 years of aging**
- **20% reduction in physical activity**

*P = 0.017

Functional impact of ten days bed rest in healthy older adults, *J. Gerontol. Med Sci.* 63: 1076-1081, 2008.

Unmet Need for Medicines in Geriatrics *Opportunities:*

- **Frailty**
 - Concerns about criteria for diagnosis -
- **Sarcopenia and Sarcopenic Obesity**
 - Consensus on diagnostic criteria
 - Fat is a powerful predictor of late-life dysfunction
- **Deconditioning/Mobility Limitations**
 - Caused by illness, depression, fear of falling, loss of muscle mass
- **Anorexia of Aging/Involuntary Weight loss**
 - Strong mortality risk, increased risk < 24 BMI
- **Consequences of Hospitalization**
 - Rapid and progressive loss of physical and cognitive function
 - Elderly people often receive different level of care and have different needs – nutritional support, pain medication, reduced immune function and increased risk of infection, orthostatic intolerance