Muscle and Mobility in Old Age

Frailty, Strength, Physical Performance, Sarcopenia

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March 1, 2019

Outline

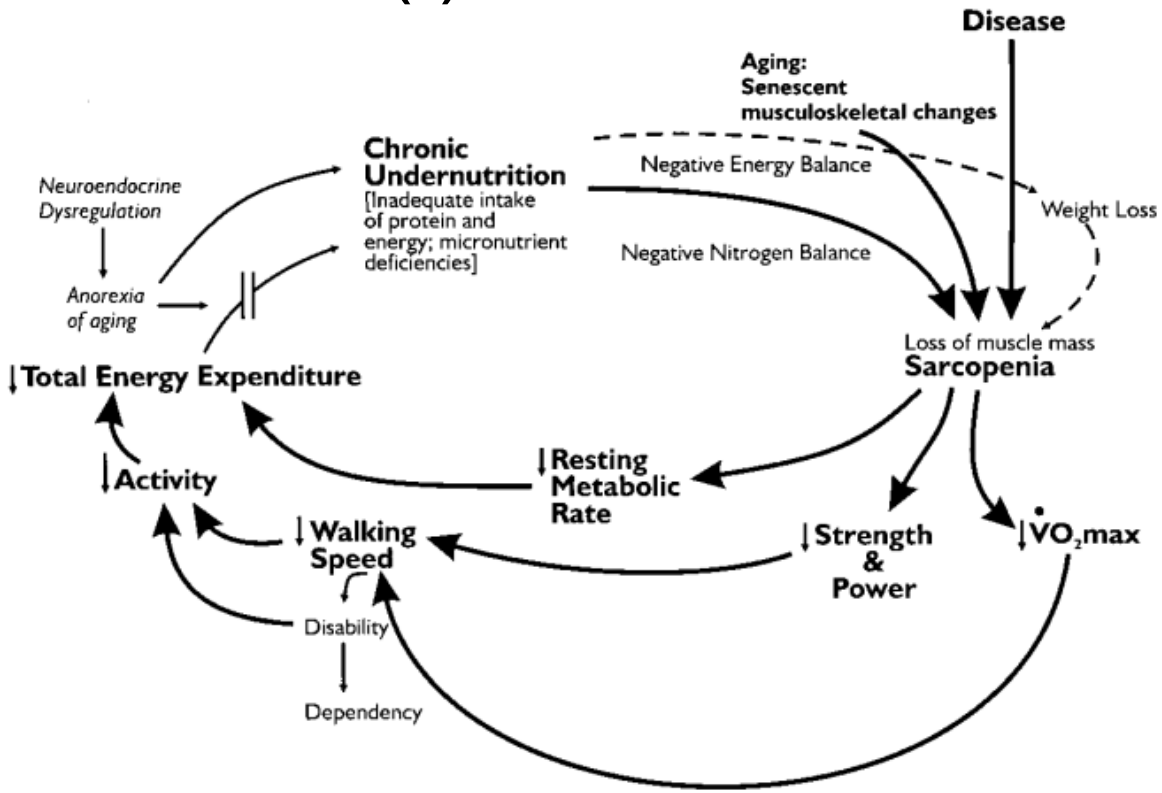
- Frailty
- Strength & physical performance
- Sarcopenia

What is frailty?

- “I know it when I see it”

Frailty

- Operational definition published by Fried in 2001 – 11,000 (!) citations



Fried JGMS 2001

Frailty - Fried

Table 1. Operationalizing a Phenotype of Frailty

A. *Characteristics of Frailty*	B. *Cardiovascular Health Study Measure**
Shrinking: Weight loss (unintentional) Sarcopenia (loss of muscle mass)	Baseline: >10 lbs lost unintentionally in prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance; Exhaustion	"Exhaustion" (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week
	C. *Presence of Frailty*
	Positive for frailty phenotype: ≥3 criteria present
	Intermediate or prefrail: 1 or 2 criteria present

*See Appendix.

Fried JGMS 2001

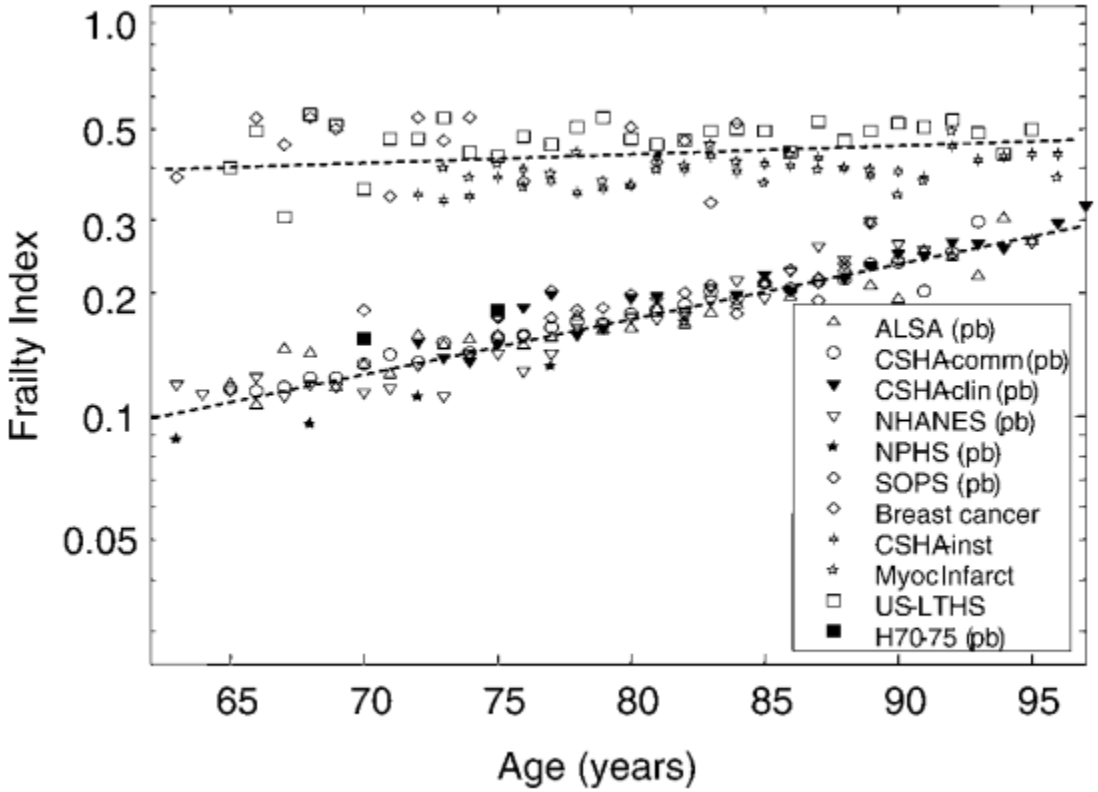
Frailty – Modifications

Table 1. Characteristics of 6701 Participants

Variable	Patients, No. (%)
Age, mean (SD), y	76.7 (4.8)
Frailty status by CHS index	
Robust	2462 (37)
Intermediate	3152 (47)
Frail	1087 (16)
Frailty status by SOF index	
Robust	3117 (47)
Intermediate	2440 (36)
Frail	1144 (17)
Individual CHS index components	
Unintentional weight loss[a]	783 (12)
Weakness	1303 (20)
Reduced energy level	2880 (43)
Slowness	1332 (20)
Low physical activity level	1211 (18)
Individual SOF index components	
Weight loss[b]	1017 (15)
Inability to rise from chair[c]	779 (12)
Reduced energy level	2880 (43)

Ensrud Arch Intern Med 2008

Frailty – Accumulated Deficits



Rockwood JGMS 2007

Wide application

- Nakajima Y et al. **Relationship between Perceived Indoor Temperature** and Self-Reported Risk for Frailty among Community-Dwelling Older People. Int J Environ Res Public Health. 2019
- Mascarella MA et al Evaluation of a Preoperative Adverse Event Risk Index for Patients Undergoing **Head and Neck Cancer Surgery**. JAMA Otolaryngol Head Neck Surg. 2019
- Li Z et al. Frailty in patients undergoing **transcatheter aortic valve implantation**: a protocol for a systematic review. BMJ Open. 2019
- Liu H et al. **Clinically Relevant Frailty Index for Mice.** The Journals of Gerontology: Series A, 2014

Frailty: Strengths

- Strongly related to poor outcomes
- Wide applications in aging and other disciplines

Frailty: Limitations

- Circular? measure of comorbidity predicts … subsequent co-morbidity
- Is frailty an distinct biological entity in and of itself, or just a collection of physiologic deficits? (What is the **truth**?) Distinct from disability?

Terminology

Muscle size

Lean mass from DXA

Fat-free mass from BIA

Cross-sectional area from CT

D_3Cr muscle mass from D3-creatine dilution

Physical performance

Walking speed

Chair stands

Timed up and go

Self-reported function

Limitations

Disability

Muscle function

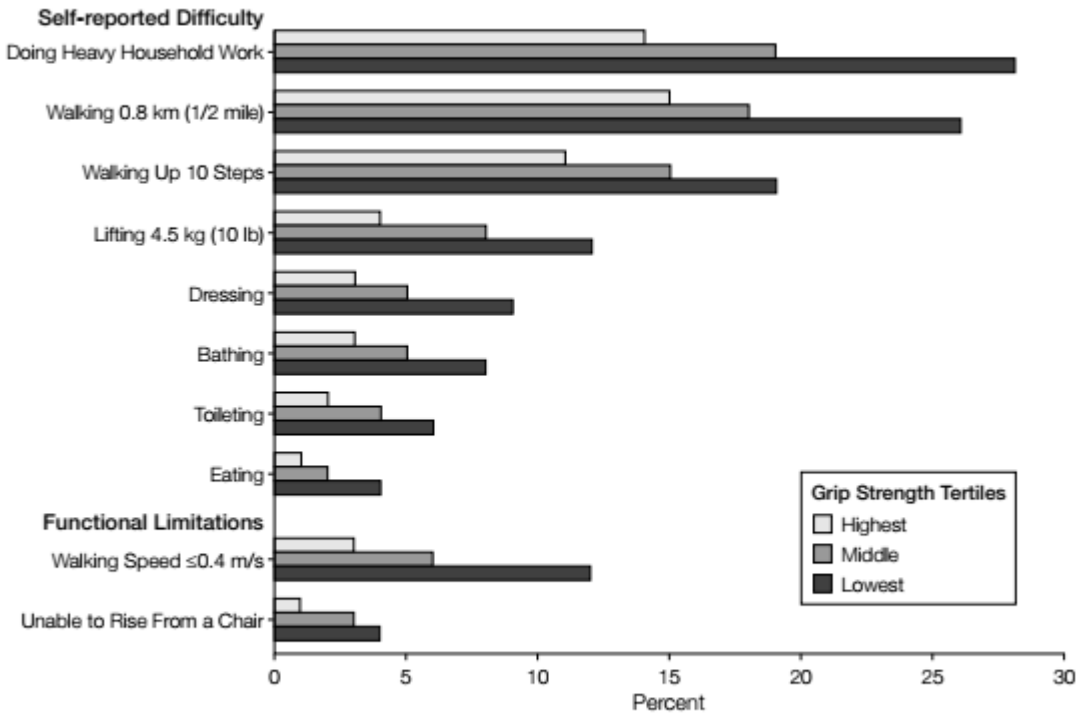
Strength

Power

Strength

- Muscle function: strength and power

Figure. Functional Limitations 25 Years After Assessing Grip Strength



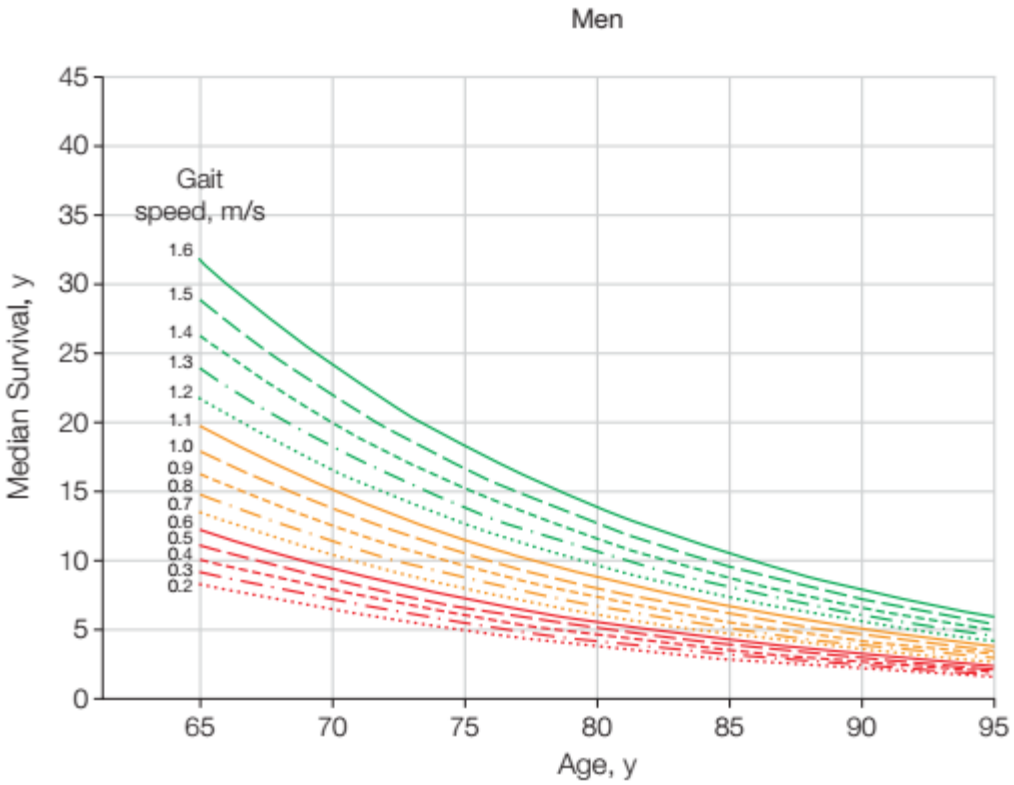
Proportion of subjects with functional limitations and disability according to baseline (1965-1970) grip strength tertiles in 3218 initially healthy 45- to 68-year-old men at exam 4 from 1991-1993.

Rantanen JAMA 1999

Performance

- Chair stands, walking speed

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



Studenski JAMA 2011

SPPB

Short

Physical

Performance

Battery:

chair stands, gait speed, standing balance

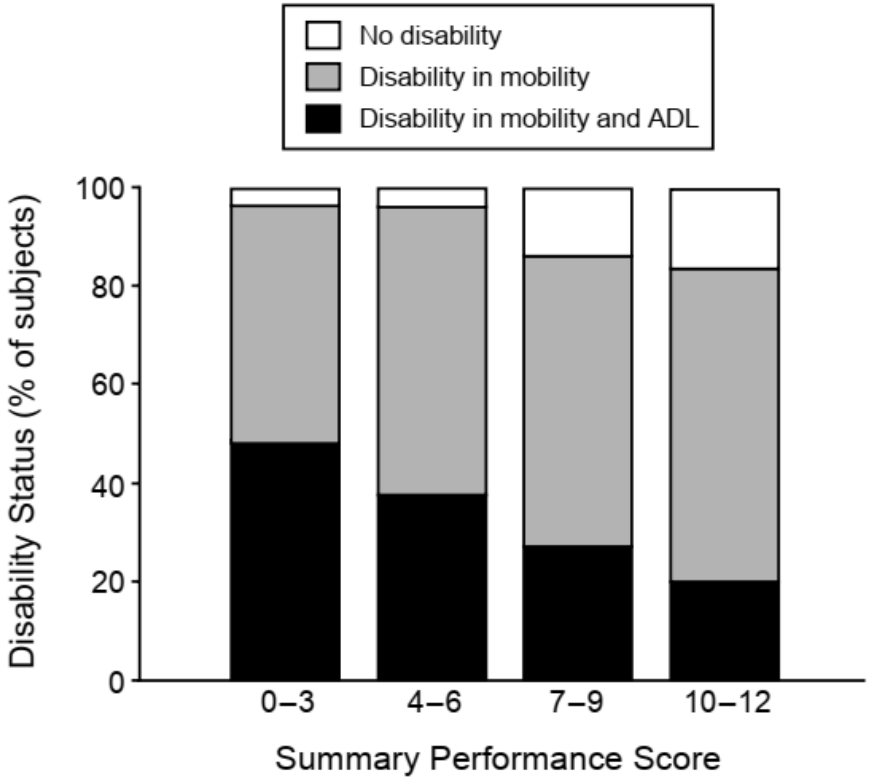


Figure 2. Disability Status at Four Years According to the Base-Line Summary Performance Score among 359 Subjects with Mobility-Related Disability at Base Line.

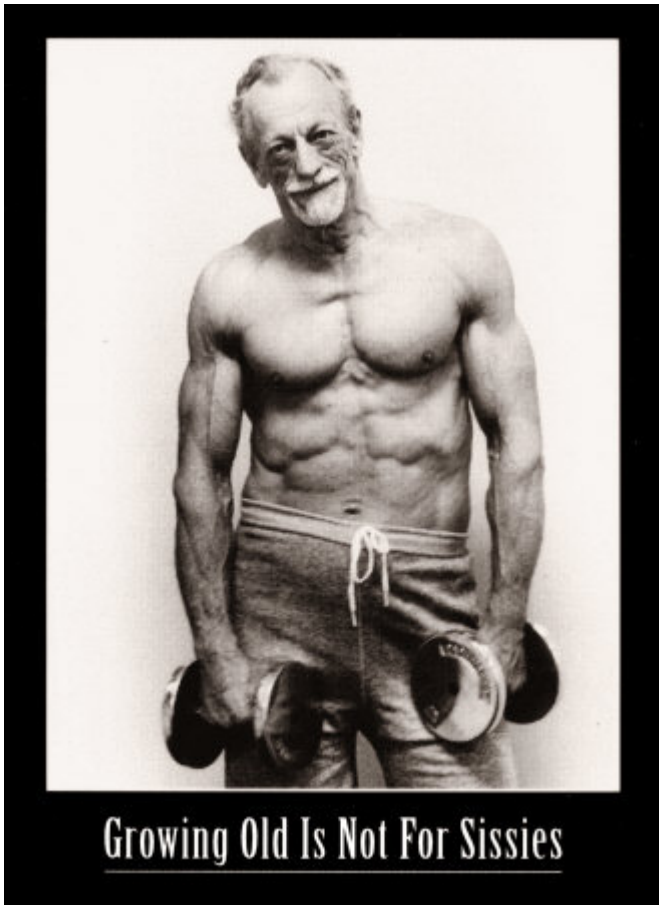
ADL denotes activities of daily living.

Guralnik NEJM 1995

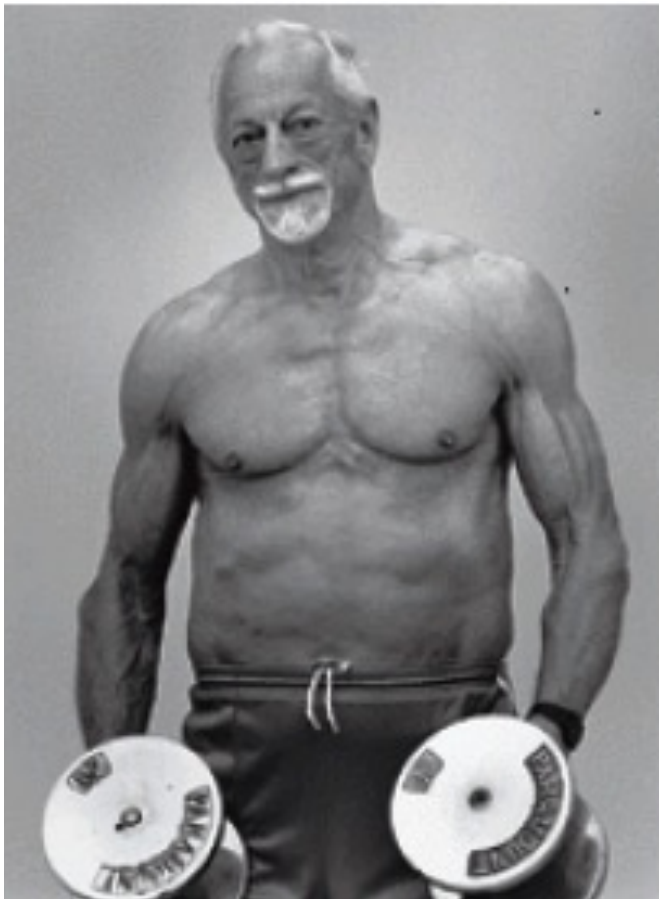
Strength & Performance Discussion

- Grip strength relatively easy to measure … only moderately related to lower extremity strength
- Power and lower extremity strength very difficult to assess
- Lots of “flavors”
  - 400 m walk, 20 m walk, 6 minute walk, timed up and go, etc.

Muscle loss occurs with age, even in those who exercise



John Turner, age 67



John Turner, age 79

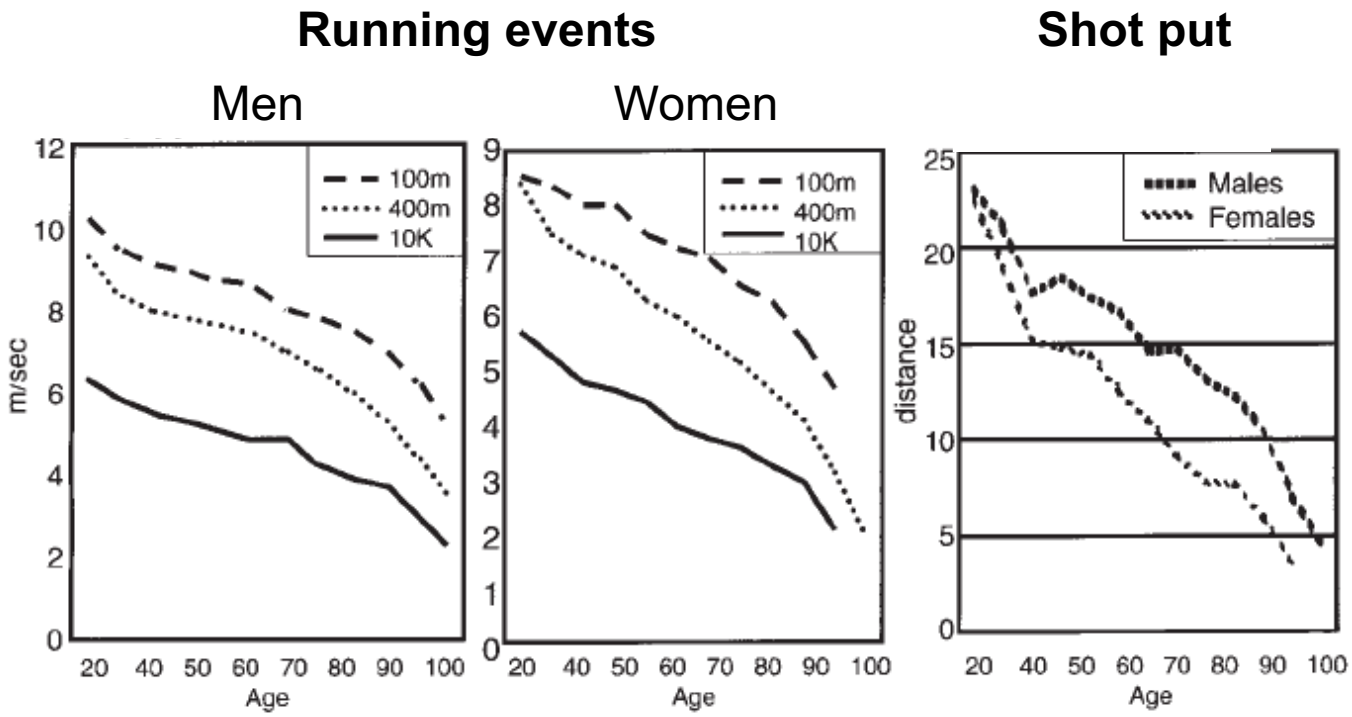
Sarcopenia

"sarco" = flesh, "penia" = poverty

- Age-related muscle loss
- No consensus on a single definition
  - Early definitions relied solely on measures of muscle size or lean mass
  - Recent research adds measures of strength and/or function

Baumgartner. AJE. 1998; Newman. JAGS. 2003

World record times in track over the lifespan



Morley. Journal of Gerontology. 2000

Muscle size and lean mass

- Dual x-ray absorptiometry
  - Lean mass, % fat
- QCT, pQCT, MRI
  - Muscle cross sectional area, muscle volume, muscle density (marker of myosteatosis or fatty infiltration)
- BIA (bioelectrical impendence analysis)

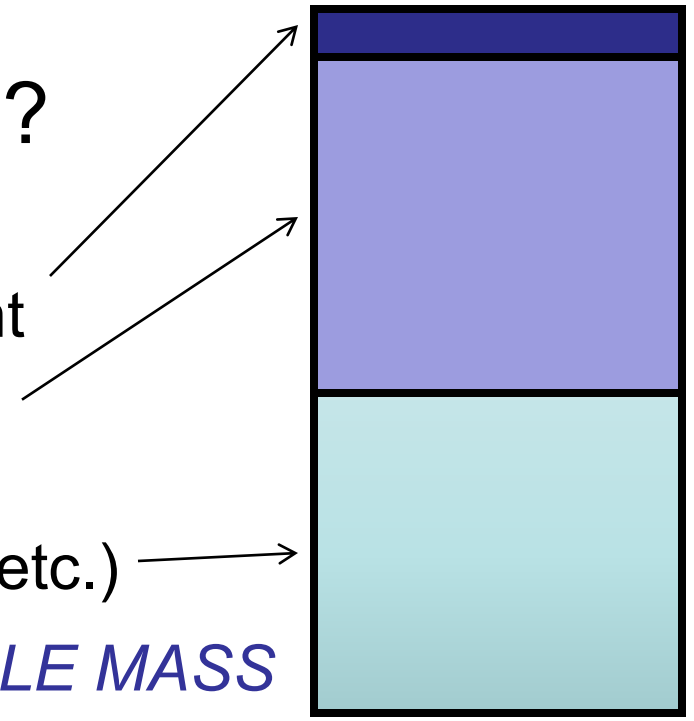
How to measure ~~muscle~~ *lean* mass?

- Dual energy x-ray absorptiometry (DXA)
  - Became widespread in 1990s to measure bone mineral density for the diagnosis of osteoporosis
- What does DXA measure?
  - 3 compartment model

Bone mineral content

Fat mass

Lean mass
(includes water, protein, etc.)



NOT A DIRECT MEASURE OF MUSCLE MASS

First operational definition Baumgartner

American Journal of Epidemiology
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Vol. 147, No. 8
Printed in U.S.A.

Epidemiology of Sarcopenia among the Elderly in New Mexico

$$\text{Sarcopenia} = \frac{\text{ASM (kg)}}{\text{height (m)}^2}$$

2 standard deviations below young adult mean:

- 7.26 kg/m^2 in men
- 5.45 kg/m^2 in women

ASM = appendicular skeletal ~~muscle~~ (lean) mass by DXA

Baumgartner AJE 1998

First operational definition Baumgartner

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Epidemiology of Sarcopenia among the Elderly in New Mexico

TABLE 4. Associations of sarcopenia* with physical disability or a history of injury, New Mexico Elder Health Survey, 1993–1995

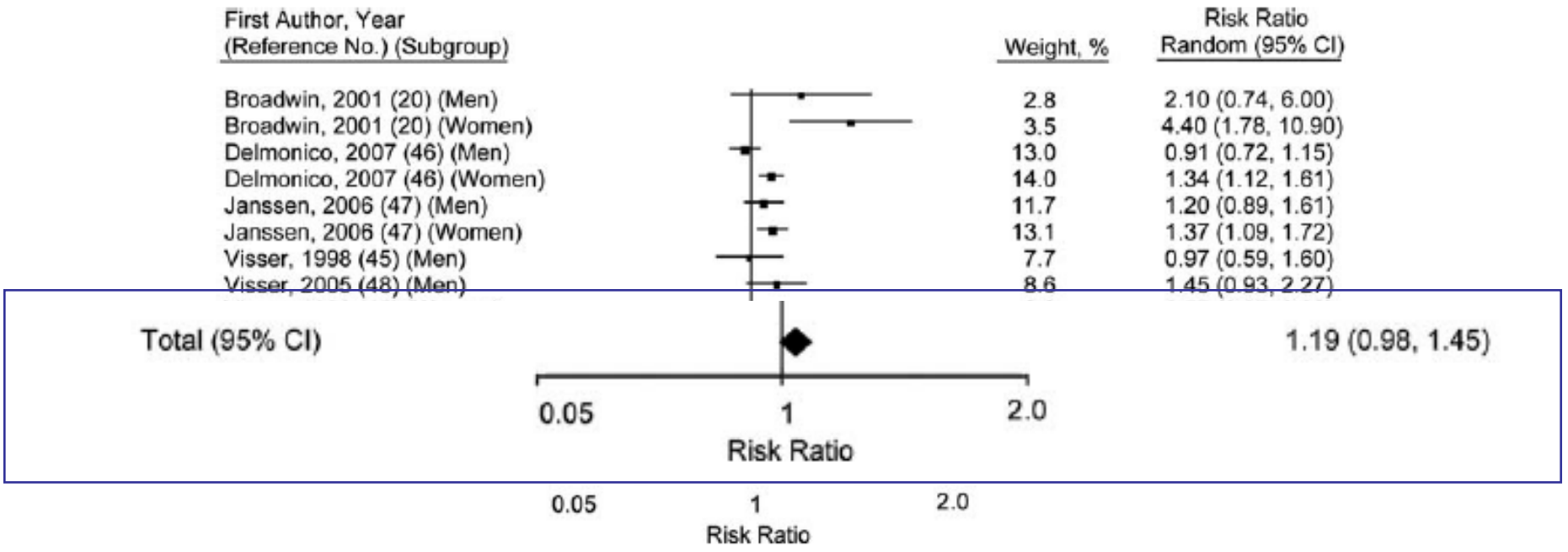
	Men			Women		
	%	Odds ratio†	95% CI‡	%	Odds ratio†	95% CI
≥3 disabilities	16	3.66	1.42–10.02	33	4.08	1.52–11.31
>1 balance abnormality	28	3.23	1.13–9.74	8	1.77	0.48–5.75
>1 gait abnormality	25	1.87	0.94–3.74	21	1.12	0.43–2.73
Use of cane/walker	14	2.29	1.09–4.88	17	1.79	0.67–4.60
Fell during past year	22	2.58	1.42–4.73	31	1.28	0.60–2.67
History of bone fracture	11	0.52	0.20–1.25	24	1.31	0.56–2.89

* Appendicular skeletal musc
for young adults from the Rosett
† Odds ratios for ≥3 disabilitie
score, current smoking, and com
comorbidity, and alcohol intake.
‡ CI, confidence interval.

Values imputed for ~75% of participants – measurement error and misclassification

Baumgartner AJE 1998

Muscle “mass” and functional decline

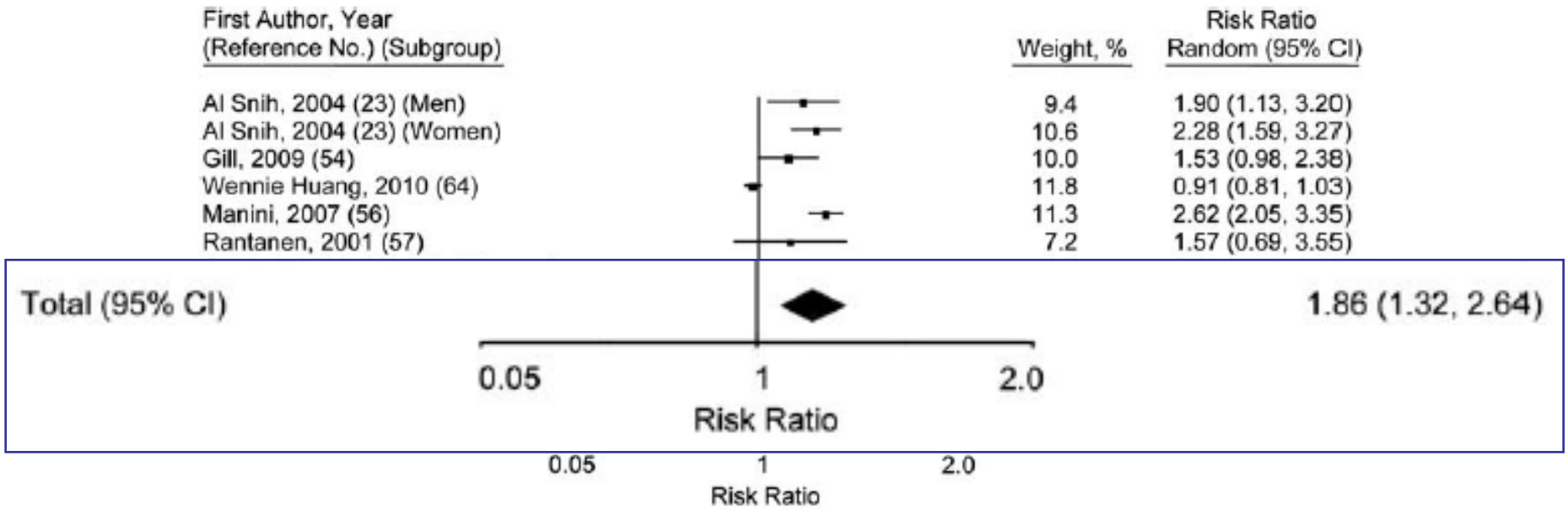


Poor muscle mass≠ functional decline

Figure 3. Forest plot of poor muscle mass and functional decline (year range: 1998–2007). The following definitions of low muscle mass were used: Broadwin (20) (bioelectrical impedance analysis): percent fat-free mass, <35.5 for men and <45.6 for women; Delmonico (46) (dual-energy x-ray absorptiometry): use of linear regression to model appendicular lean mass on height and fat mass (the 20th percentile of the distribution of the residuals was used as the cutoff value for sarcopenia); Janssen (47) (bioelectrical impedance analysis): skeletal muscle index (muscle mass/height^2), ≤8.50 kg/m^2 for men and ≤5.75 kg/m^2 for women; Visser (45) (bioelectrical impedance analysis): fat-free mass, <43.5 kg for men and <29.0 kg for women; Visser (48) (computed tomography): midthigh muscle cross-sectional area, <230 cm^2 for white men, <245 cm^2 for black men, <152 cm^2 for white women, and <181 cm^2 for black women; and Zoico (42) (dual-energy x-ray absorptiometry): appendicular skeletal muscle mass/height^2, <7.6 kg/m^2 for men and <5.4 kg/m^2 for women. Heterogeneity: $\tau^2 = 0.10$, $\chi^2 = 22.56$, df = 5 ($P < 0.0004$); $I^2 = 78\%$. Test for overall effect: $Z = 1.22$ ($P = 0.22$).

Schaap Epidemiologic Reviews 2012

Muscle strength and functional decline



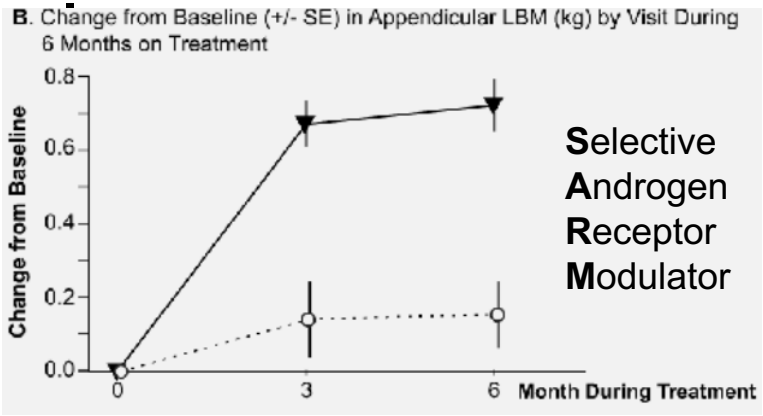
Poor muscle strength = ↑ functional decline

Figure 4. Forest plot of poor muscle strength and functional decline (date range: 2001–2010). The following definitions of low muscle strength were used: Al Snih (23) (grip strength): <22.01 kg for men and <14.00 kg for women; Gill (54) (grip strength): lowest sex- and body mass index-specific quintiles, exact number not given; Wennie Huang (64) (grip strength): continuous levels used; Manini (56) (knee extensor strength): <1.13 Nm/kg for men and <1.01 Nm/kg for women; Rantanen (57) (knee extensor strength): <10.6 kg for women; Shinkai (60) (grip strength): ≤27 kg for men aged 65–74 years, ≤20 kg for men aged ≥75 years, ≤7 kg for women aged 65–74 years, and ≤1.9 kg for women aged ≥75 years; Visser (48) (knee extensor strength): <109 Nm for white men, <110 Nm for black men, <67 Nm for white women, and <71 Nm for black women. Heterogeneity: $\tau^2 = 0.04$, $\chi^2 = 66.22$, df = 22 ($P < 0.00001$); $I^2 = 67\%$. Test for overall effect: $Z = 7.88$ ($P < 0.00001$). Nm, Newton meters.

Schaap Epidemiologic Reviews 2012

Disconnect between lean mass and strength in intervention studies

- Interventional trials: maintenance of strength despite loss of weight and lean mass
  - Knee OA *Wang X JGMS 2007*
  - RT and Pioglitazone *Marsh AP JGMS 2008*
- No increase in strength with increase in



Papanicolaou Journal of

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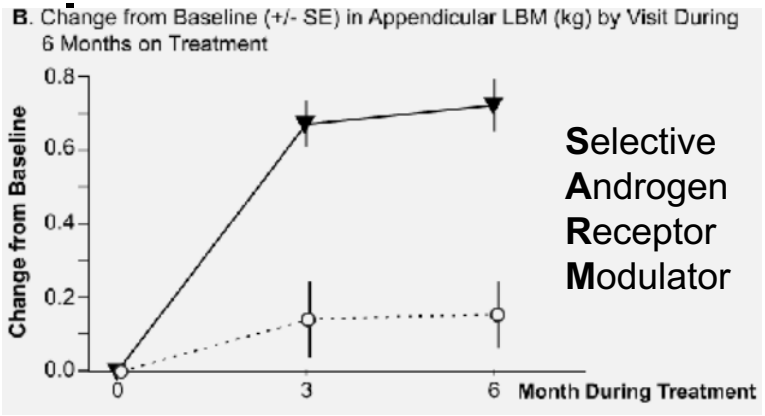

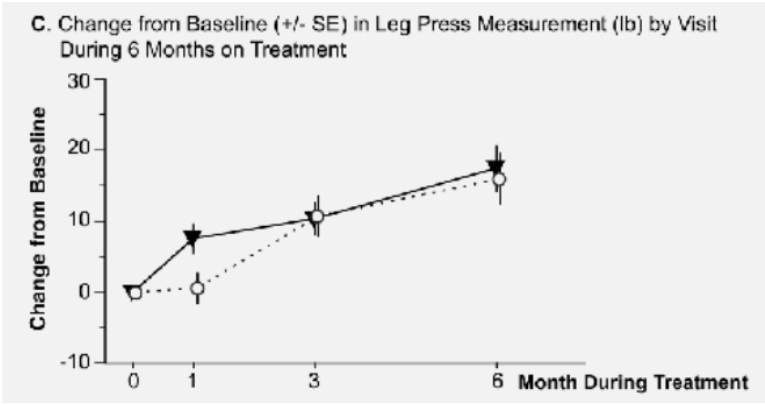

Epidemiology 101

- Measurement error
  - Bias results towards null if non-differential
  - If measurement error varies by outcome status then direction of bias is difficult to impossible to detect
  - DXA lean mass is highly likely to be subject to measurement error and no gold standard exists

Sarcopenia: Definitions

Defining sarcopenia: issues

- Disconnect between lean mass, strength and performance: how to integrate into a single definition?
- Sarcopenia is complex; reflects a syndrome
  - Dementia, incontinence

For sarcopenia, as with many clinical tests, there are three groups

1. Those clearly normal
2. Those clearly with sarcopenia
3. Those in the grey area in the middle

Any classification of these groups can introduce measurement error

EWGSOP
European Working Group on Sarcopenia in Older Persons

Table 3. EWGSOP conceptual stages of sarcopenia

Stage	Muscle mass	Muscle strength		Performance
Presarcopenia	↓			
Sarcopenia	↓	↓	Or	↓
Severe sarcopenia	↓	↓		↓

Cruz-Jentoft Age & Ageing 2010

Competing consensus statements

EWGSOP
International Working Group
Asian Working Group
Foundation for NIH (analysis based)
+ At least 5 others

Similarities

- Syndrome, multicomponent
- Muscle size + other factors

Differences

- Cut-points (when provided)
- Specific measure for component

Defining sarcopenia: issues

- Disconnect between lean mass, strength and performance: how to integrate into a single definition?
- Sarcopenia is complex; reflects a syndrome
  - Dementia, incontinence
- No “gold standard” outcome to evaluate diagnostic criteria

Creatine biology & muscle mass

- Nearly all creatine in muscle (>98%) & at relatively constant concentration

Total body creatine pool size ≈ Total body muscle mass

- Creatine → creatinine at constant rate
  - Determine creatine pool size from 24 hour urine
  - Limitations: dietary control, timing issues, incomplete bladder emptying, renal problems

Mr. OS

D_3-creatine dilution

1. Orally dose with D_3-creatine
2. Reach isotopic steady state (3 days)

   creatine → creatinine

   D_3-creatine → D_3-creatinine
3. Fasting morning spot urine: measure

   D_3-creatinine & creatinine
4. Calculate creatine pool size
5. Calculate total body muscle mass

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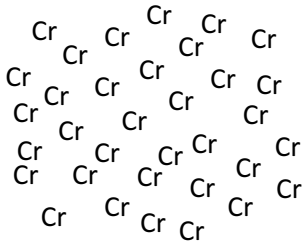
Large muscle mass:

↑ creatine pool size



↓ D_3-creatinine:total creatinine

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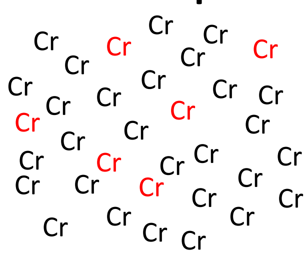

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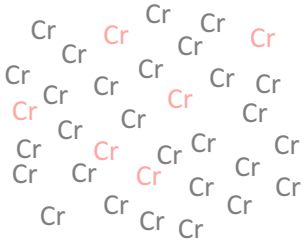
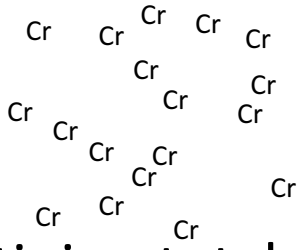


↓ D_3-creatinine:total creatinine

Small muscle mass:

↓ creatine pool size



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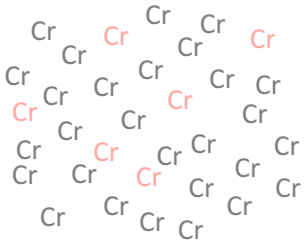

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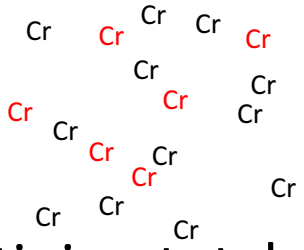
Small muscle mass:

↓ creatine pool size



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Large muscle mass:
↑ creatine pool size
↓ D_3-creatinine:total creatinine

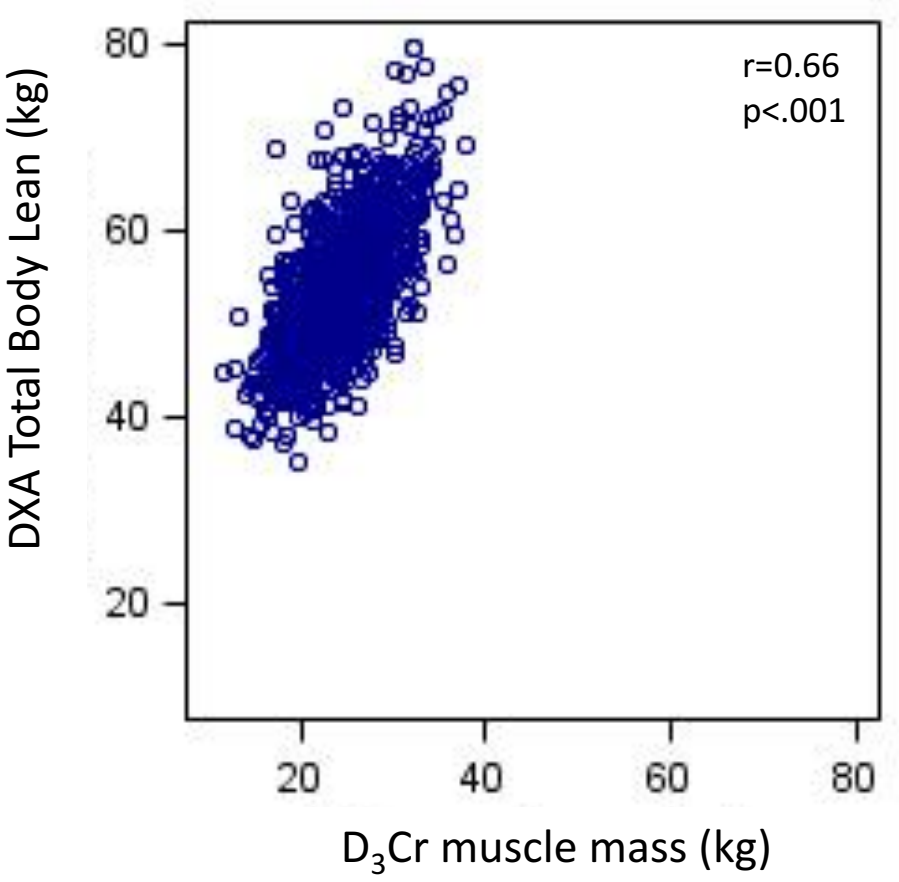
Small muscle mass:
↓ creatine pool size
↑ D_3-creatinine:total creatinine

Validated against MRI muscle volume in humans (r=0.87, p<.001)
Not dependent on renal function

Clark J Appl Physiol 2014

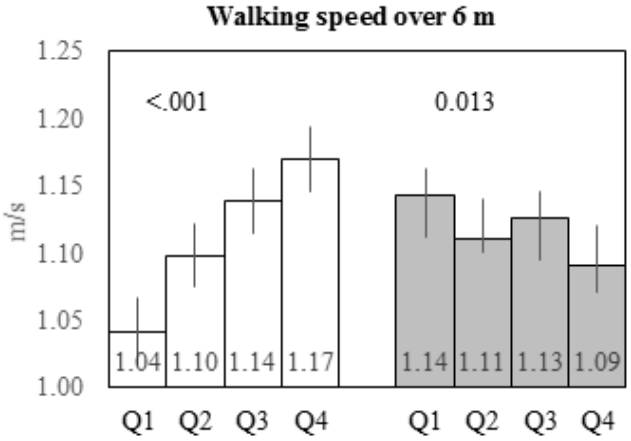
Background: Muscle ≠ Lean

- Previous studies: inconsistent associations of approximations of muscle mass with disability
- Unlike D_3Cr dilution, DXA does not measure muscle mass per se

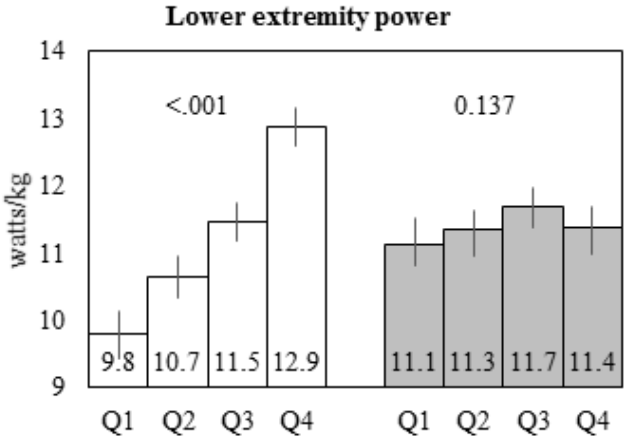


Cawthon JGMS 2018

D_3Cr muscle mass & strength, physical performance



D_3Cr muscle mass/wgt ALM/ht^2



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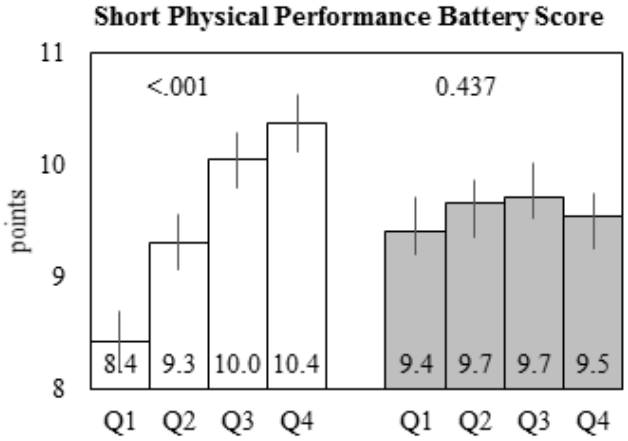
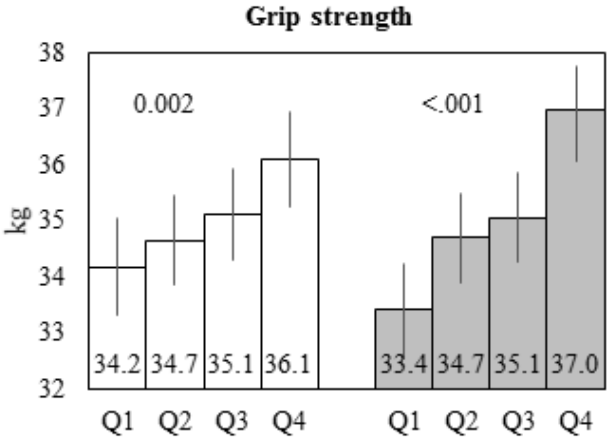


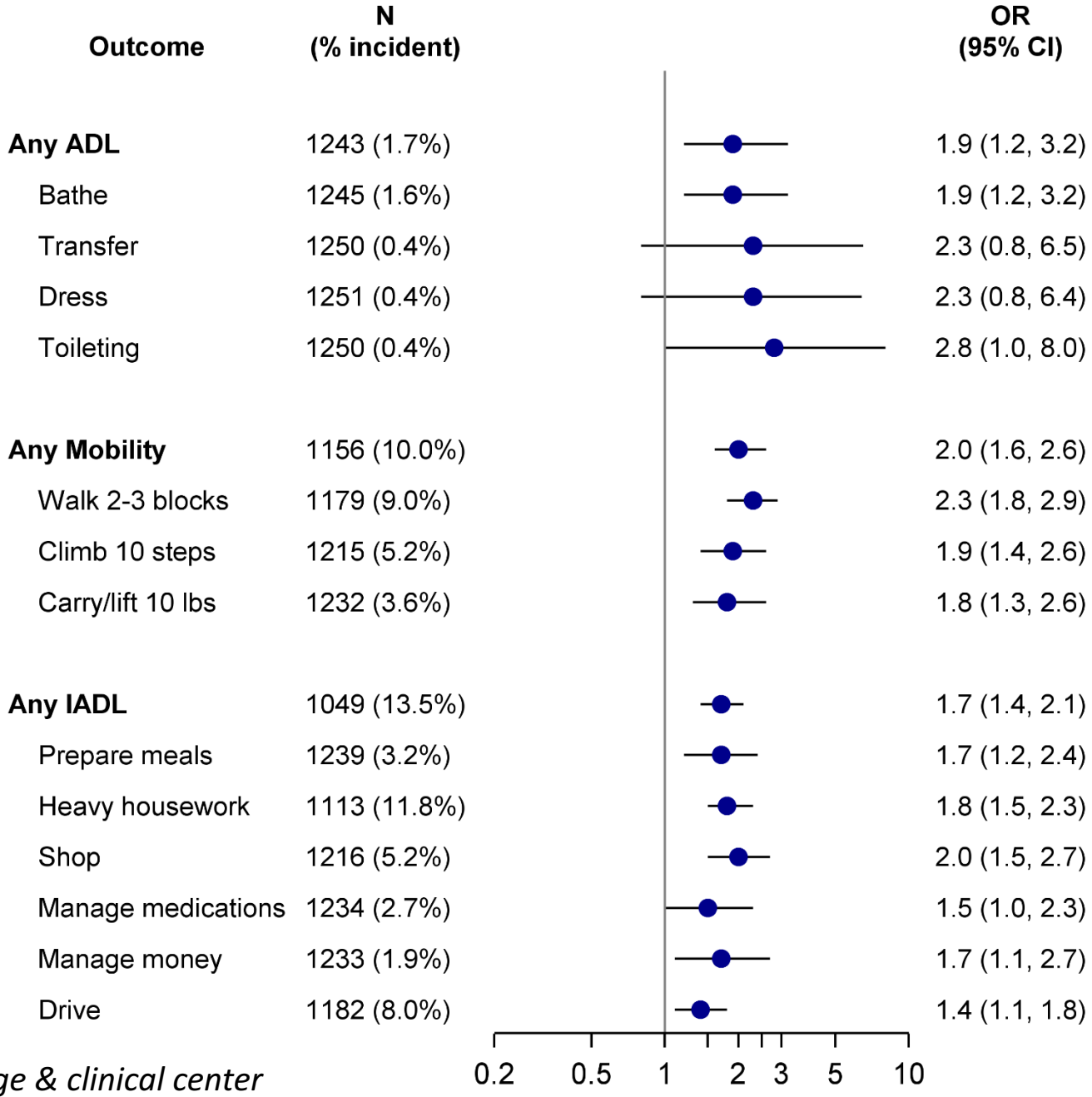
D_3Cr muscle mass/wgt ALM/ht^2



D_3Cr muscle mass/wgt ALM/ht^2

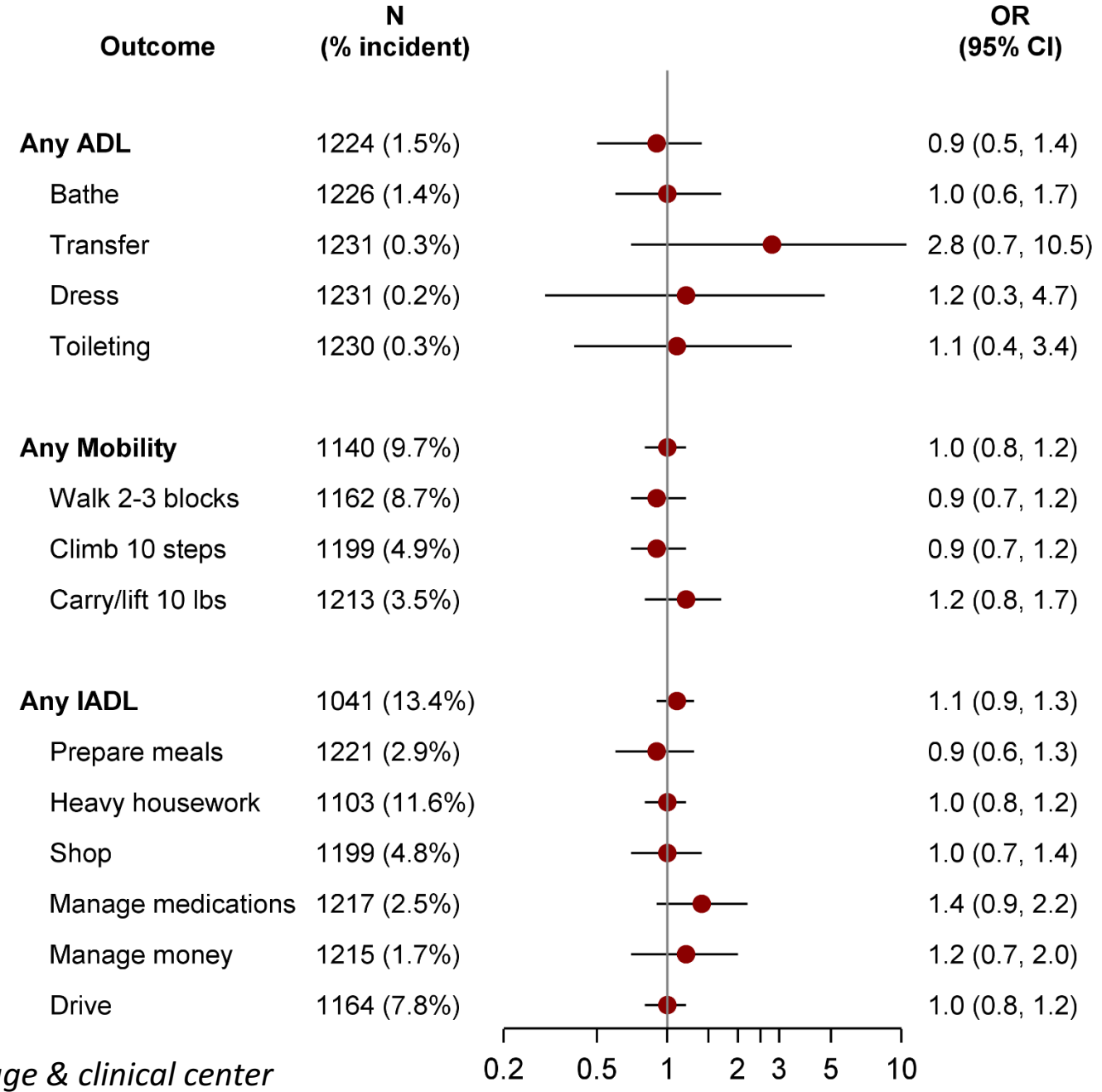
Cawthon JGMS 2018

D_3Cr muscle mass/wgt, Odds ratio per SD



Adjusted for age & clinical center

DXA ALM/ht^2, Odds ratio per SD



Adjusted for age & clinical center

Sarcopenia: issues

- Lots of competing definitions with confusing and inconsistent terminology
- Would strength, performance have been integrated into definitions if DXA lean mass has been strongly related to outcomes?
- Is D_3Cr muscle mass the answer?
  - More data needed!

THE TAKEAWAY

muscle is important but field is confounded by measurement and technical issues