ACP-INDIANA and IMDA -
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Frailty, Strength, and the Promise of Vitamin D

Douglas K. Miller, MD

Fairbanks Professor in Aging Research

Associate Director, IU Center in Aging Research

Scientist, Regenstrief Institute, Inc.

INDIANA UNIVERSITY

School of Medicine
Department of Medicine
Division of General Internal Medicine and Geriatrics
Center for Aging Research

Regenstrief Institute

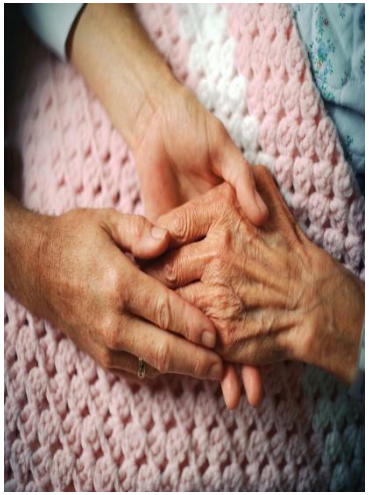
IU Geriatrics

Frailty
General Considerations

- "Hard to define but I know it when I see it "
- Vulnerability to adverse health outcomes
  - Falls, incident disability, poor recovery from acute illness, etc.
- "Potato Chip," "Teetering," "Weak and wobblies."
- Often exposed by "stress" – acute illness, new meds, surgery, pain, social loss, change in environment or support
- Thus, surgery & Illness = frailty stress tests

General Considerations …

- **BUT: Separate from Disability, disease states("comorbidities) … and age**
- **Ideally operational definitions would indicate where & how to intervene to prevent (either frailty or its sequela)**
- **Social Impacts modulated by adap-tations in physical & social environ.**



Consensus Pathophysiological Conceptualization

- **"Biological syndrome of decreased [personal] reserve and resistance to stressors resulting from cumulative declines across multiple physiologic systems**." [Fried, JGMS 2001; 61:146-56]
- **That is, frailty is a result of deficits/↓reserves in multiple functions.**

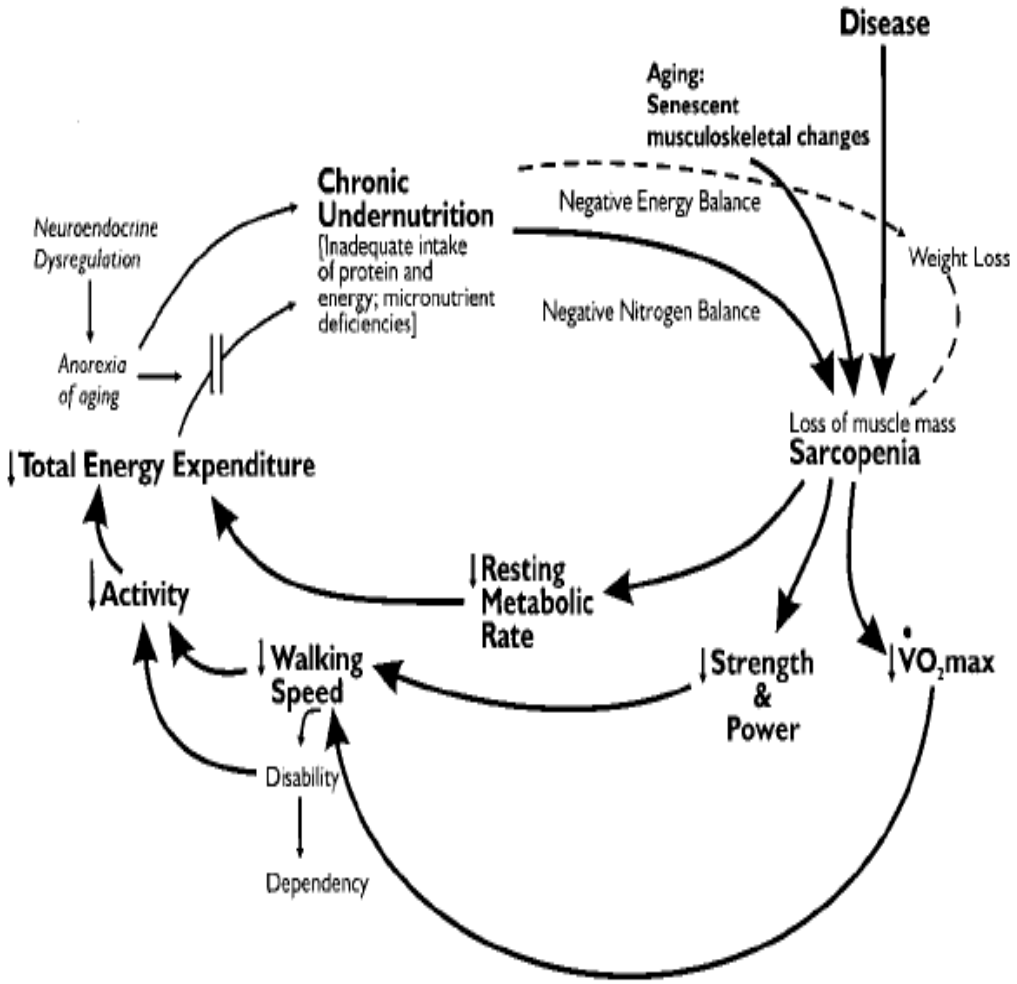


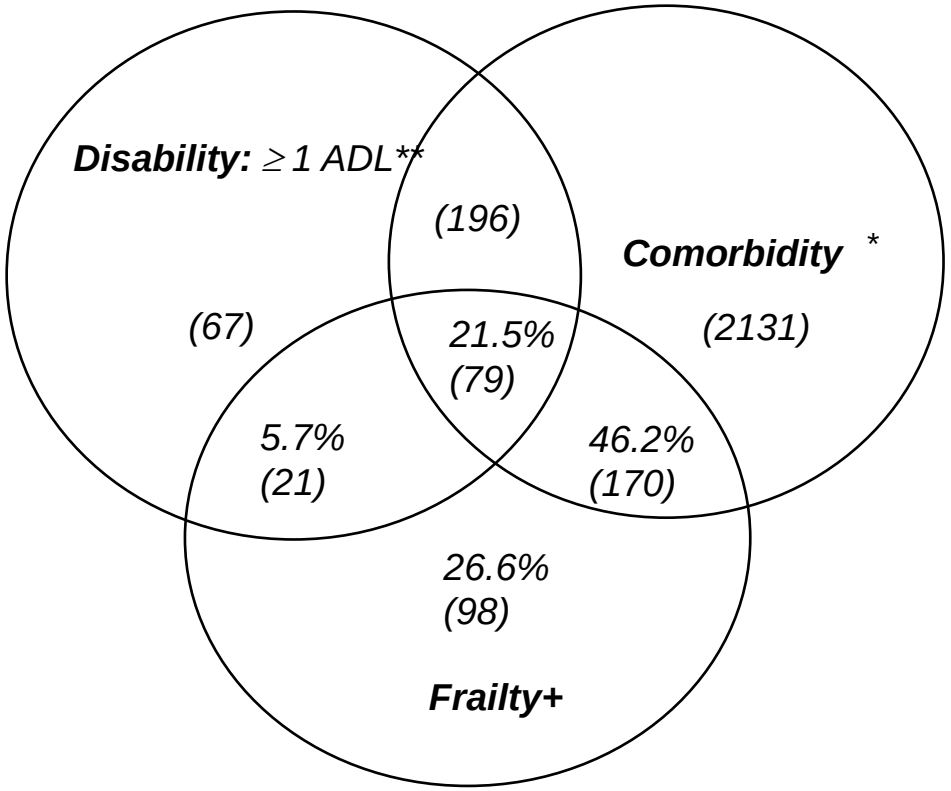
Figure 1. Cycle of frailty hypothesized as consistent with demonstrated pairwise associations and clinical signs and symptoms of frailty. Reproduced with permission from (14).

Operational Definitions: Fried's Phenotype of Frailty (JGMS 2001; 61:146-56)

- Unintentional weight loss (10 lbs in past year)
- Self-reported exhaustion
- Weak grip strength [lowest 20% of referent population]
- Slow preferred walking speed [lowest 20%]
- Low physical activity [lowest 20%]
- Frail = 3 or more criteria
- Pre-frail = 1-2 criteria

Fried's Frailty Phenotype …

- Validated
- "Separate" from disability and comorbidity (and age)
- Decent job of indicating places to intervene



Total represented: 2,762 subjects who had comorbidity and/or disability and/or frailty.

+ n=368 frail subjects (both cohorts).

** n=2,576 with 2 or more out of the following 9 diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, COPD. Of these, 249 were also frail.*

***n=363 with an ADL disability; of these, 100 were frail.*

From: Fried LP, et al., "Frailty in Older Adults; Evidence for a Phenotype." JGMS 2001;56:M146

Other Operational Definitions

- **FRAIL Scale from Geriatric Advisory Panel of International Academy of Nutrition and Aging** [Abellan van Kan, J Nutr H Aging 2008; 12:29-37]
- **Frailty Index from the Study of Osteoporotic Fractures [SOF;** Cawthon JAGS 2007; 55:121-23]
  - **(1) Inability to do 5 chair rises without using arms, (2) weight loss of any type > 5% / 2y, & (3) not full of energy**
-

- ***Rockwood & Mitnitsky Frailty Index (count of problems=burden of illness)*** *[Mech Ageing Dev 2004; 125: 517-9]*
- ***Edmonton Frail Scale by Rolfson et al.,(8 domains from cognition to social support)*** *[Clin Invest Med 2000;23:336]*
- ***Fatigue and nutritional assessments (e.g., Mini-Nutritional Assessment, MNA)***
- ***One criticism: inadequate inclusion of cognition … but I prefer separating physical from cognitive frailty***

"FRAIL Scale"

- **Fatigue** (by self-report)
- **Resistance** (reported inability to walk up 10 steps without stopping)
- **Ambulation** (reported inability to walk ¼ mile on own without aids)
- **Illnesses** (more than 5 illnesses)
- **Loss of weight** (reported 10+ lb of wt loss in past year)

Proposed Advantages of FRAIL Scale

- **Easier & quicker to administer than Fried's phenotype**
- **Less overlap with disability**
- **Performed more easily in NH residents [?]**
- **(More direct indication of where/how to intervene)**

Recommendation

- **Research – Pick one definition and stick with it** ('comparative validity' in process)
- **Clinically:**
  - **Know at least one, if not more, indicator**
  - **If positive on any indicator** (including gestalt of potato chipness), **then do aggressive CGA and restitution.**
  - **If need firm Dx for reimbursement – know several of the easier, validated ones, e.g., SOF, MNA … Fatigue report, or FRAIL Scale**

Sarcopenia (low muscle mass) and Dynapenia (lack of strength)

- A component of most frailty definitions
- Caveat

Sarcopenia: The Previous Paradigm (i.e., 'Outmoded')

- **Term attributed to Rosenberg, literally "poverty of flesh"** [J Nutr 1997; 127:990-1S]
- **People lose muscle mass as they age**
- **People get weak, wobbly, and vulnerable to falls & physiological decline as they age**
- **Hence, the weak and wobblies must be due to sarcopenia.**

Reality is Much More Complex

- **Longitudinal epidemiology studies show that strength is not perfectly correlated with muscle mass and adds explanatory value over and above muscle mass.**
- **With age, strength often decreases more quickly than muscle mass, & volume of muscle predicts strength relatively poorly (in some groups)**
- **Train the right leg only**

and the left leg gets stronger!.....

Reality is Much More Complex …

- ***(Thankfully)*** **weight loss plus PRT can produce decline in muscle mass but increase in strength!**
- **Easiest way to explain these phenomena is via neuromuscular connections … "neuromuscular strength**

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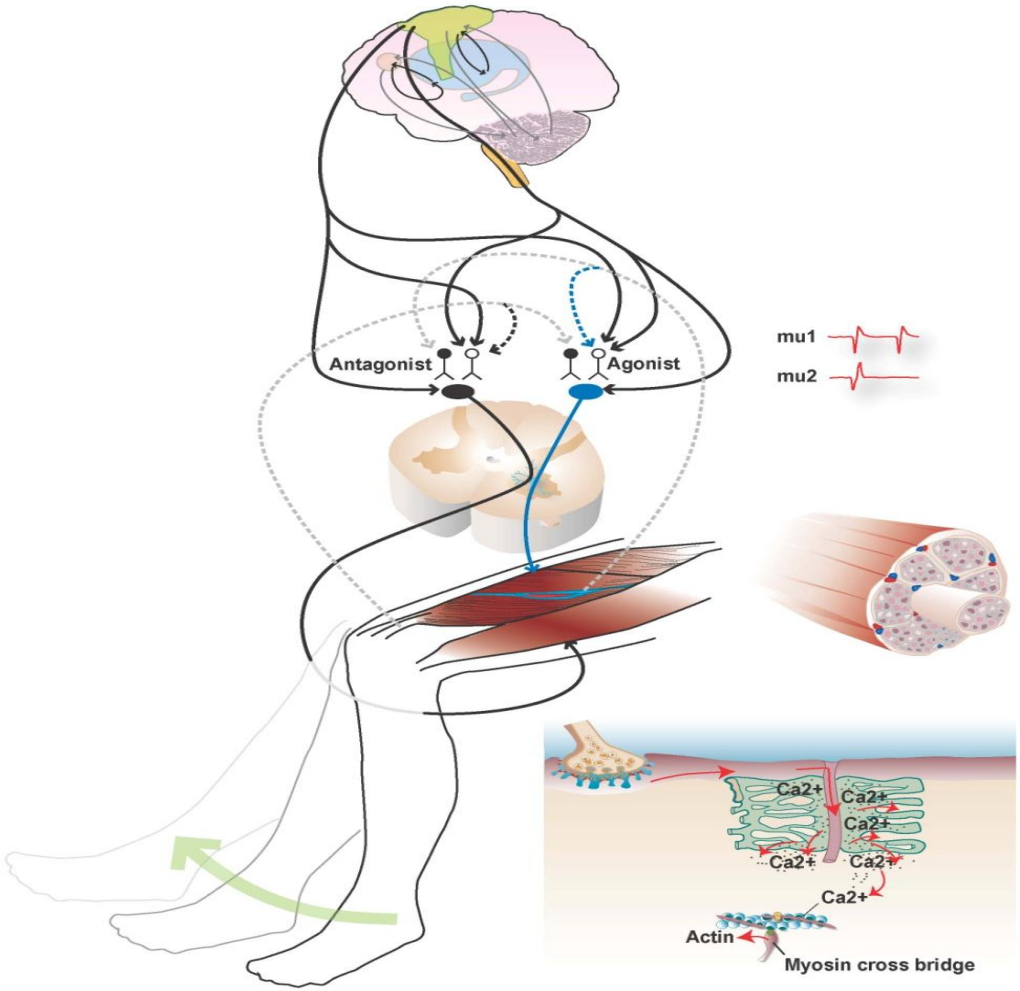
Potential Neuromuscular Mechanisms

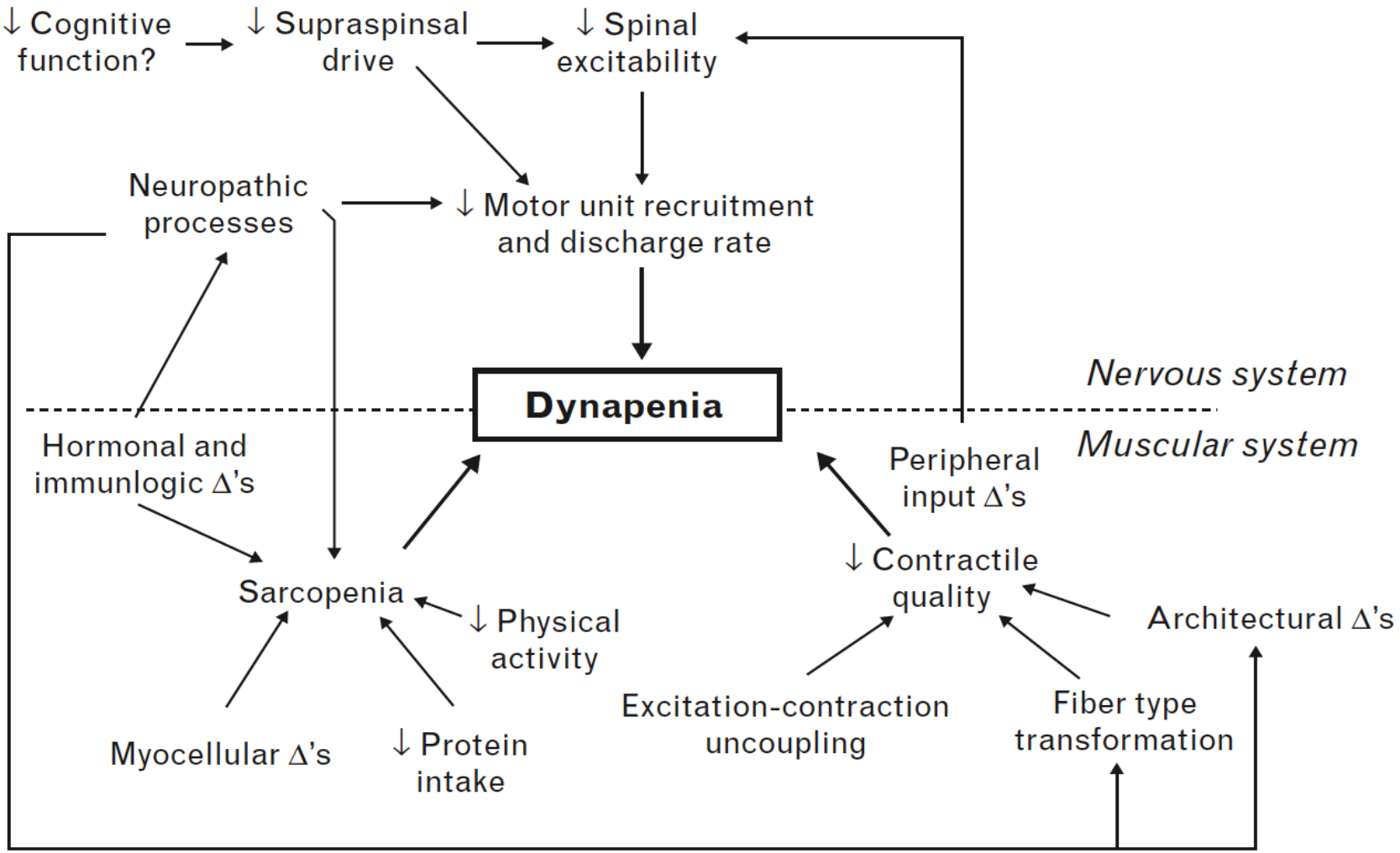
- Decreased drive from cortical and spinal centers
- Antagonistic muscle activity
- Slowed nerve conduction
- Excitation-contraction uncoupling (largely via decreased # of dihydropyridine receptors)
- Decreased motor unit recruitment and “rate of coding”

- Muscle architectural changes (e.g., tendon stiffness and decreased fascicle length & pennation angle)
- Increased myocellular lipid content
- (Probably other factors as well)

Nomenclature Conundrum

- **Does ‘sarcopenia’ include ‘dynapenia’ or**
- **Should separate terms be used**
- **I favor the latter, but former is still very common.**

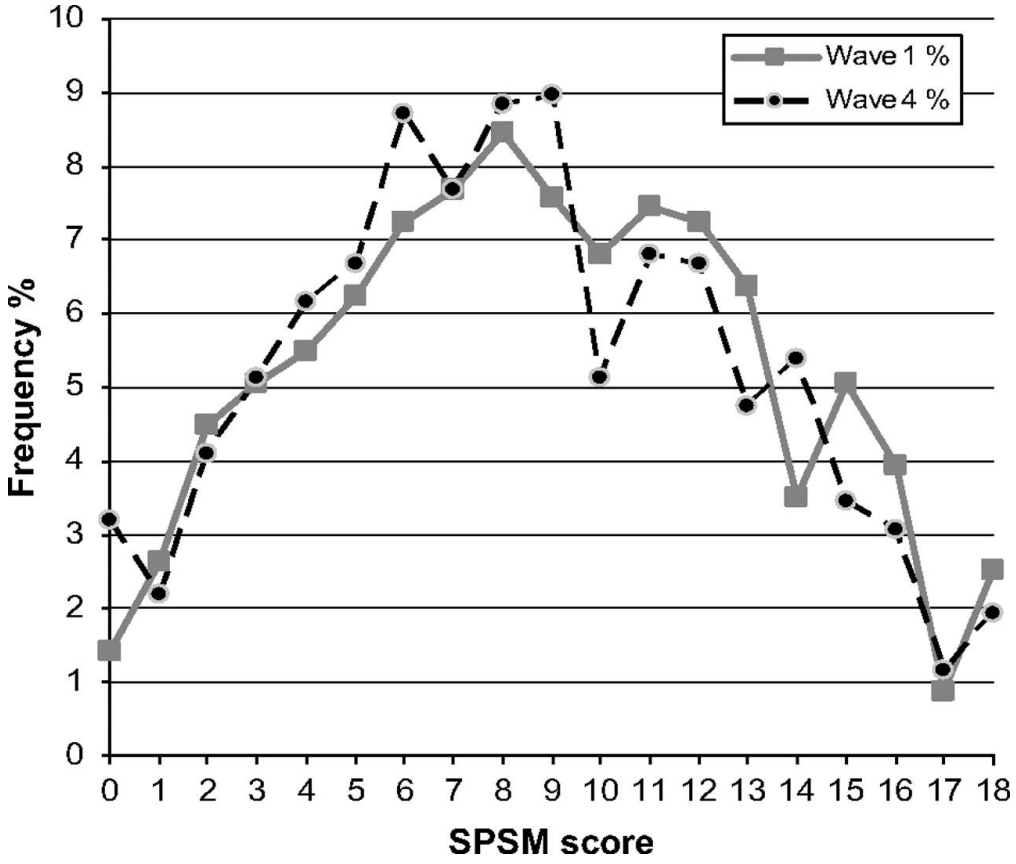

Antagonist
Agonist
mu1
mu2
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Actin
Myosin cross bridge


↓ Cognitive function?
↓ Supraspinsal drive
↓ Spinal excitability
Neuropathic processes
↓ Motor unit recruitment and discharge rate
Dynapenia
Nervous system
Muscular system
Hormonal and immunlogic Δ's
Peripheral input Δ's
↓ Contractile quality
Sarcopenia
↓ Physical activity
Architectural Δ's
Myocellular Δ's
↓ Protein intake
Excitation-contraction uncoupling
Fiber type transformation

Short-Portable Sarcopenia-Dynapenia Measure (SPSDM) [Miller JGMS 2009; 64:388-94]

- Epidemiological (research) measure
- Weighted sum of:
  - Grip strength / height (0-4, weighted x2)
  - Lean BMI (BMI * % lean by bioelectrical impedance; 0-4, weighted x1.5)
  - Chair rise time (0-4, weighted x1)
- 8.5 lb of equipment, 12.4 min to complete on average.
- Excellent score distribution
- Good validity cross-sectionally with muscle function, body composition, physical performance, & functional limitation and longitudinally with changes in muscle function and body composition

SPSM unweighted score distributions for Wave 1 (baseline) and Wave 4 (36-month follow-up).



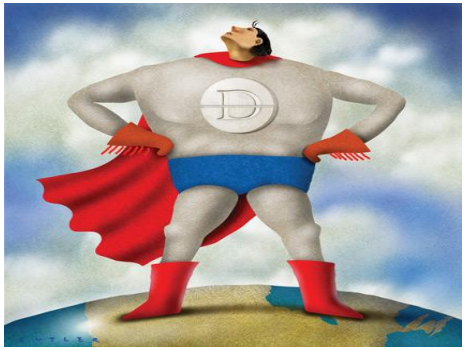
Miller D K et al. J Gerontol A Biol Sci Med Sci 2009;64A:388-394

Clinical Implications

- Beware of claims that muscle mass explains all things muscular!
- Grip strength - in general populations
- Hand-held dynamometers, isokinetic dynamometers, and related instruments = research tools
- Chair rise time or stair climb time
- Preferred gait speed is a tremendous indicator of age-associated vigor (or lack thereof)

The Promise of Vitamin D

- "Not just for bones anymore"
- Tremendous interest and lots of emerging research
- Important roles range from bone to muscle to balance to falls to diabetes control to CV disease to cancer to MS to schizophrenia (to marital harmony??)
- MANY unanswered questions
- My caveats
  - Limited 'expertise'
  - Focus on only a couple areas
  - Claims probably excessive for the reality … but
- Exciting story and lots of potential



"Normal Level"

- Differentiate between 'normal' and optimal levels
- Best measure = serum 25(OH)D (but beware of variability!)
- Optimal level for bone claimed to be > 11, >20 or >30 ng/ml, but ? for other functions
  - Some have argued for optimal level at 50-99 ng/ml
  - Adverse side effects start at 90-120 ng/ml; "toxic level = > 88 ng/ml" … or > 150 … or > 200 [kidney stones=biggest risk]
  - Up to 1 billion people worldwide are < 30 ng/ml, especially home-bound and darker skinned (and obese)
  - Worse during winter and early spring (duh)
  - Some evidence levels decreasing over time, attributed to greater use of sun screens
    - Add transdermal vitamin D??

Cautionary Tales & Age of Lost Innocence

- **Antioxidant therapy (HD beta-carotene & Vit E supplementation increased mortality; Bjelakovic JAMA 2007; 297:842-57)**
- **Folic Acid supplementation (Bazzano JAMA. 2006; 296:2720-6)**
- **Encainide and flecainide (CAST trial, JAMA. 1993;270:2451-2455)**

Data on Falls Prevention

- In a meta-analysis of 8 trials, Vit D (200-1,000 IU cholecalciferol equivalent) showed average 19% fewer falls than Ca alone or placebo (NNT=15) (Bischoff-Ferrari BMJ 2009; ;339:b3692)
- Dose < 700 IU/d or achieved 25(0H)D level < 24ng/m. were INEFFECTIVE.

- **Substantial agreement from Kalyani's MA in JAGS 2010; 58:1299-1310:**
  - **Better in community-dwelling < 80 yo, adjunctive Ca Rx, no H/O falls or Fx, Rx > 6 mo**
- **Caveats: > 1 fall or injurious falls, mechanisms?, optimal serum level, optimal replacement regimen,**
- **Similar for fracture prevention: 700-800 IU/d reduced risk of hip fracture by 26% and any nonvertebral fracture by 23%; 400 IU/d ineffective.** [Bischoff-Ferrari JAMA 293: 2257-64]
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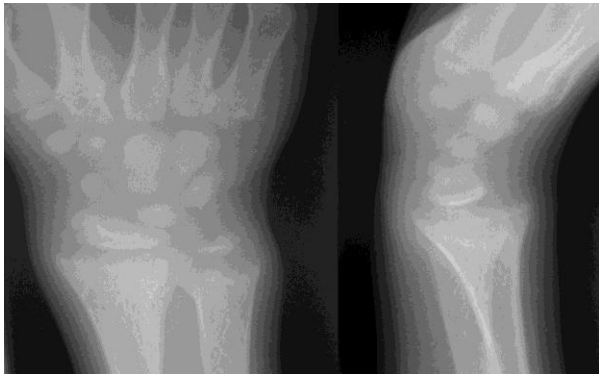


Vitamin D and Physical Performance

- **2009 systematic review of 16 studies showed that this relationship remains controversial**
  [Annweiler J Nutr Health Aging 2009; 13:893-8]
- **Observational studies suggested a relationship**
- **Intervention trials were either negative or unimpressive.**

Role in Health Disparities in Heart Disease?

- **10 y follow-up of 15,363 representative sample, 18+ years from NHANES III Epi Follow-up** **(Fiscella et al., Ann Fam Med 2010; 8:11-18)**
- **AAs have lower mean 25(OH)D levels (skin pigmentation, lower intake, less sun, etc.)**
- **AAs had 38% higher CV mortality….**

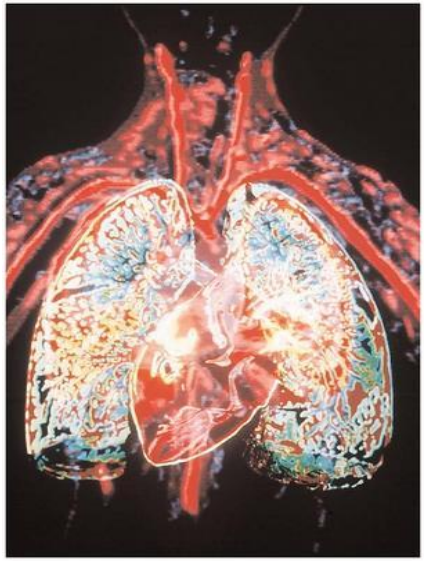
- *Low Vit D appeared to account for ~ two-thirds of increased risk.*
- *Vit D & income levels together explained entire difference in CV mortality between AAs and NHWs*
- *(Smooth muscle proliferation, inflammation, thrombosis, Ca-channel fluxes, 2º hyperpara-thyroidism)*

Data on CVD and Vitamin D

- **Observational studies tend to show worse CV outcomes in those with low Vit D levels**
- **BUT, only two trials of Vit D in general populations** (Trivedi & WHI), **both of which were inconclusive.**
- **Trivedi** (BMJ. 2003; 326:469) **used**

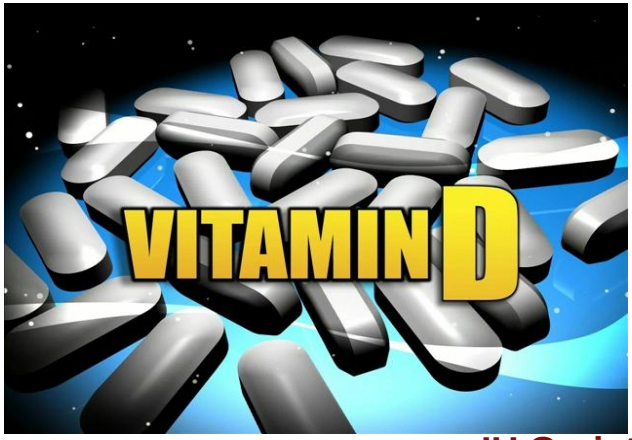
  100,000 IU D_3 every 4 months
- **WHI** (Circulation. 2007;115:846-54)

  used only 400 IU/d plus calcium



Replacement

- Standard has been 800 IU of cholecalciferol per day
- Standard is being reviewed by IOM expert committee; may be raised to 1,000-2,000 IU/d.
- Some data suggest that even more that 2,000 IU will be required for some people (at least short term); clarifying studies are in process…..
- NEXT Q: For how long at that level?



- *In meantime, some people are using much higher daily doses, and some are using very high loading doses (e.g., 50,000/d for some days-weeks) followed by maintenance dose. This hasn't been standardized yet*
- *May need calcitriol analogs (doxercalciferol and paricalcitol) for pts with significant renal disease; being studied…….*

IU Geriatrics

- **Beware of:**
  - **Normocalcemic hyperparathyroidism => risk for hypercalcemia**
  - **High dose intermittent therapy (see next slide)**
- **Target is probably 30-60 ng/ml until better data available**

Concern about High Dose Intermittent Therapy

- **500,000 IU p.o. once a year** (most with normal Vit D levels) **actually INCREASED falls and fractures compared to placebo**

  [Sanders JAMA 2010; 303:1815-22]

  - Dawson-Hughes: compensatory mechanisms, any went > 120 ng/ml.

- **300,000 IU once showed a non-significant increased point estimate for falls (RR 1.12)** [Latham JAGS 2003; 51:291-9]