

NAPOLI2017  
29 novembre - 2 dicembre

INVECCHIAMENTO:  
SCENARIO 2.0

CONGRESSO  
NAZIONALE  
62 SIGG



# Il Paziente diabetico complesso: dalla epidemiologia al trattamento

## Diabete e sarcopenia

**Stefano Volpato**

Dipartimento di Scienze Mediche – UNIFE  
Dipartimento Medico ad Attività Integrata – OSPFE

# Agenda

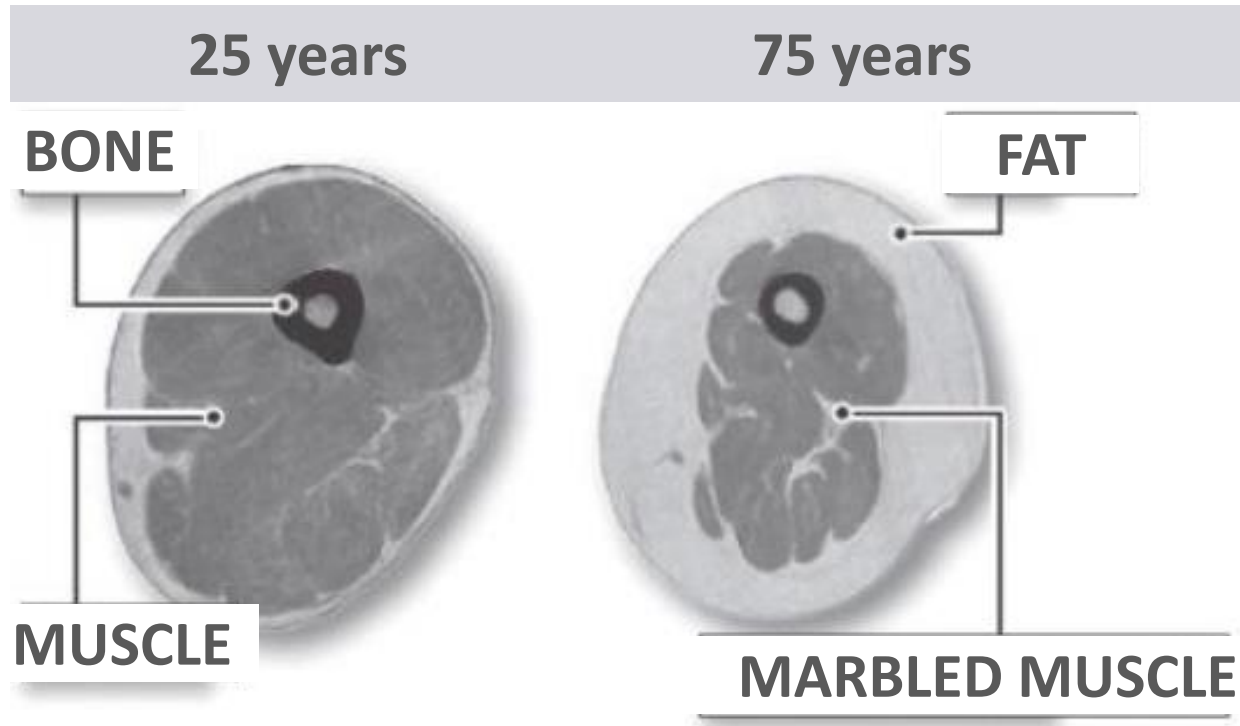
---

- ▶ **Sarcopenia definitions**
- ▶ **Diabetes muscle mass and muscle strenght**
- ▶ **Underlying biological mechanisms**
- ▶ **Functional impact of sarcopenia in older diabetic patients**
- ▶ **Potential treatments**



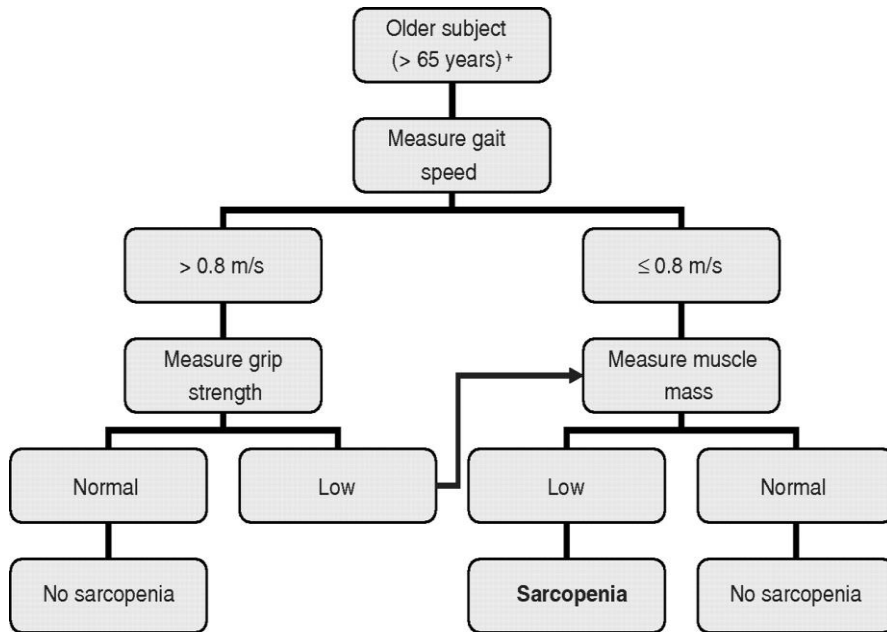
# What is Sarcopenia?

Age-related decline in muscle mass  
and strength (weakness)

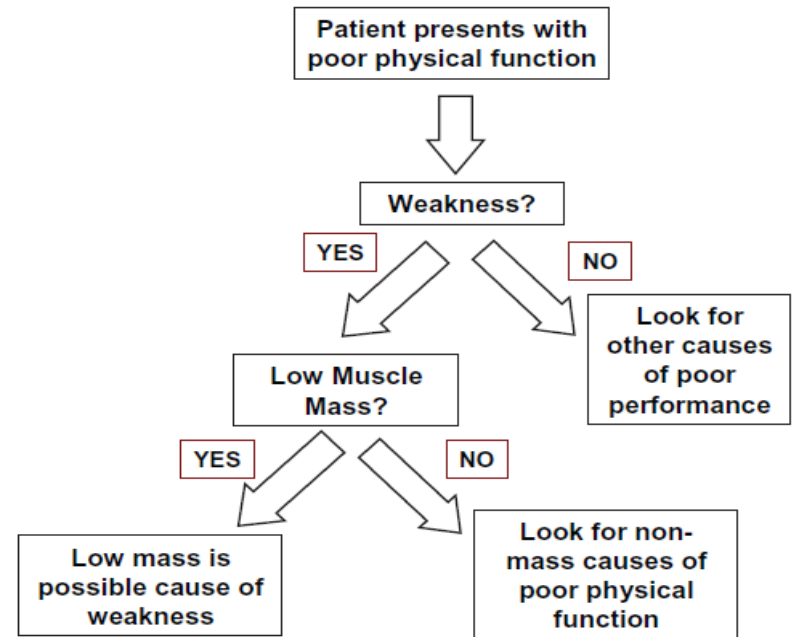


# Sarcopenia: operational definitions

## EWGSOP



## FNIH

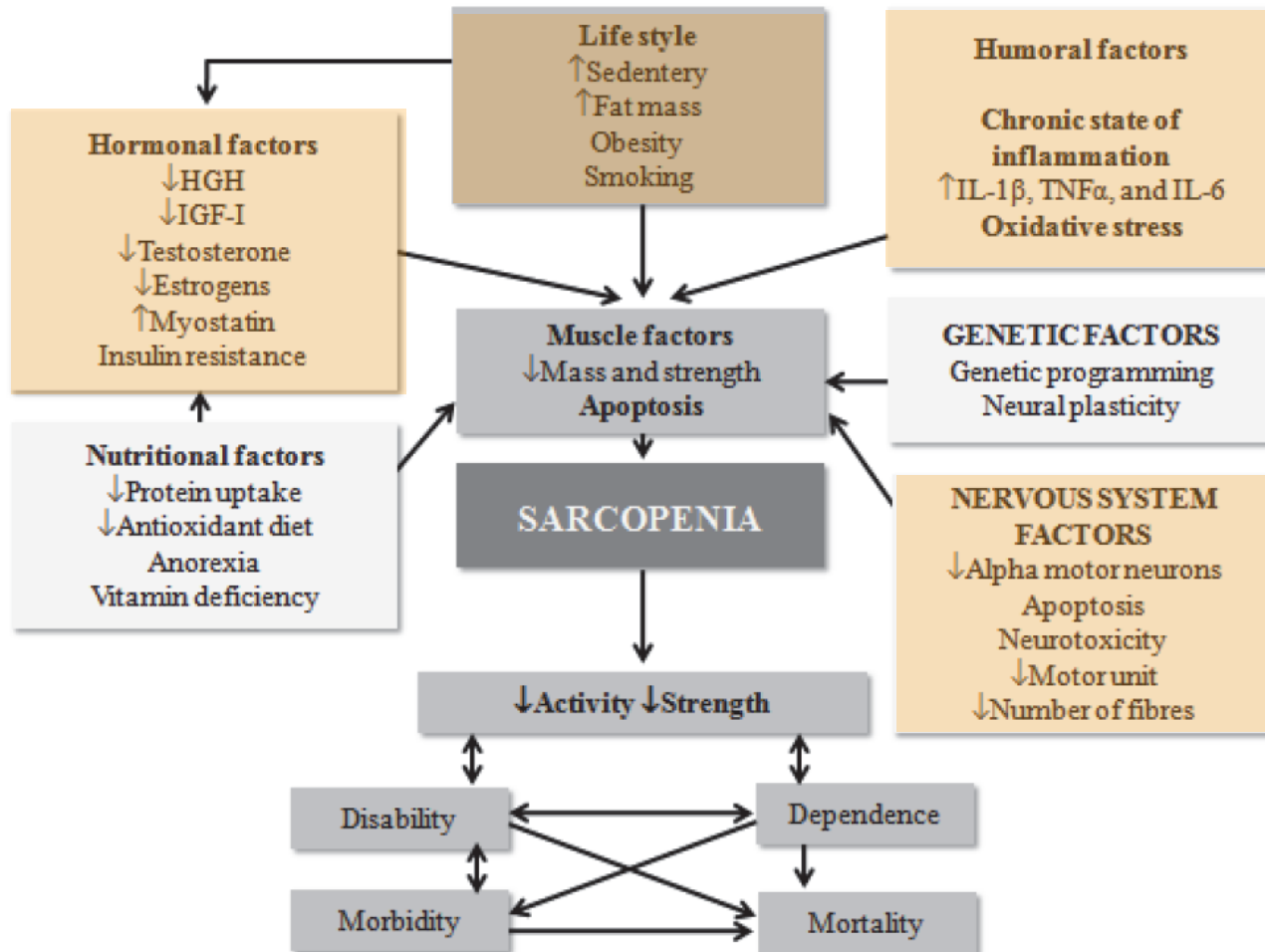


Cruz-Jentoft A J et al. Age Ageing 2010;39:412-423

Studensky et al. JGMS 2014;69:547-558



# Etiopathogenesis and risk factors



# Major population-based studies investigating skeletal muscle mass distribution according to diabetes status

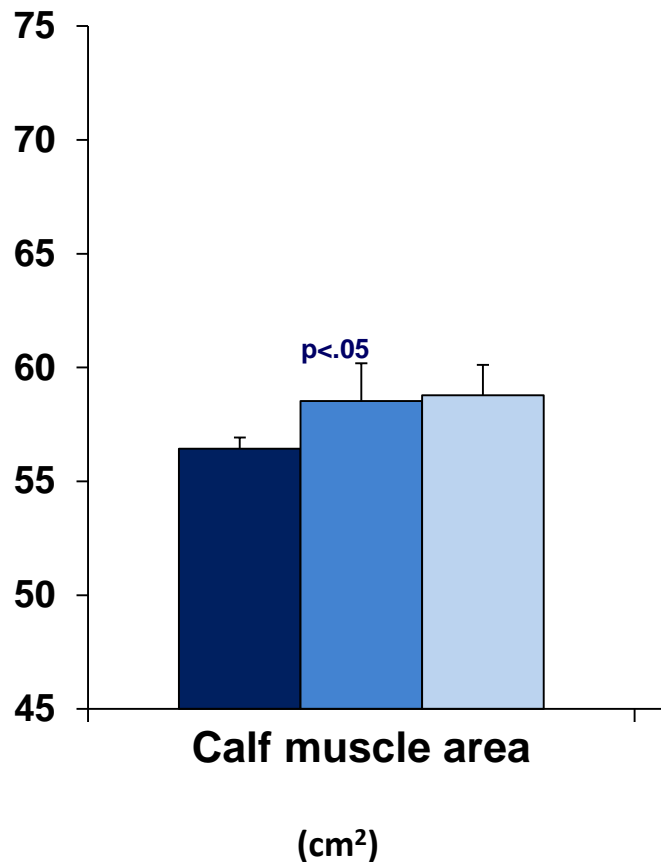
Study reference	Population ( <i>n</i> diabetics) follow-up	Skeletal muscle groups (and methods)	Results
<i>Cross-sectional studies</i>			
Health ABC	2618	Total lean mass (DEXA)	Significantly higher in diabetic participants
Park et al. [10]	(485)	Leg muscle mass (DEXA)	Significantly higher in diabetic participants
		Arm muscle mass (DEXA)	Significantly higher in diabetic participants
InCHIANTI	835	Crude calf muscle area (CT)	Significantly higher in diabetic participants
Volpato et al. [7]	(95)	Standardized calf muscle area (CT)	No difference between groups
Look AHEAD	1560	Whole body lean mass (DEXA)	Significantly higher in diabetic participants
Heshka et al. [11]	(1318)	Trunk lean mass (DEXA)	Significantly higher in diabetic participants
		Leg lean mass (DEXA)	Significantly lower in diabetic participants
		Arm lean mass (DEXA)	No difference
KSOS	810	Total lean mass (DEXA)	Significantly lower in diabetic male participants, no difference in women
Kim et al. [12]	(414)	Appendicular skeletal muscle mass/ height <sup>2</sup> (DEXA)	Significantly lower in diabetic female participants, no difference in men
		Skeletal muscle index (total skeletal muscle mass/weight) (DEXA)	Significantly lower in diabetic participants
Baltimore Longitudinal Study of Aging	587 (-)	Standardized mid thigh muscle area (CT)	Inversely associated with higher fasting and OGTT values of both glucose and insulin
Kalyani et al. [13]			

# Role of Muscle Mass and Muscle Quality in the Association Between Diabetes and Gait Speed

Characteristics	Without Diabetes	With Diabetes		
		Diet	Hypoglycemic agents	All
<b>N</b>	740	37	58	95
<b>Age (yr), mean <math>\pm</math>SD</b>	73.8 $\pm$ 6.5	75.4 $\pm$ 6.8	72.9 $\pm$ 5.7	73.9 $\pm$ 6.2
<b>Gender (%)</b>				
Female	55.9	37.8	48.3	44.2
<b>BMI (kg/m<sup>2</sup>), mean <math>\pm</math>SD</b>	27.3 $\pm$ 3.9	28.7 $\pm$ 3.6	28.7 $\pm$ 4.4	28.7 $\pm$ 4.1*
<b>Physical activity level (%)</b>				
Moderate	43.4	48.6	53.4	51.6
High	41.9	37.8	29.3	32.6
<b>Fasting glucose (mmol/l) mean <math>\pm</math>SD</b>	4.94 $\pm$ 0.62	7.66 $\pm$ 2.41†	8.08 $\pm$ 2.22†	7.92 $\pm$ 2.29†
<b>Duration of diabetes (yr), median (IQR)</b>	-	0 (0-3)	9.5 (4-20)	5.0 (0-13)

# Lower-limb skeletal muscle characteristics in people with and without diabetes: The InCHIANTI Study

■ No diabetes      ■ No hypoglycemic agents      ■ Hypoglycemic agents



All p adjusted for age and gender



# Major population-based studies investigating skeletal muscle mass distribution according to diabetes status

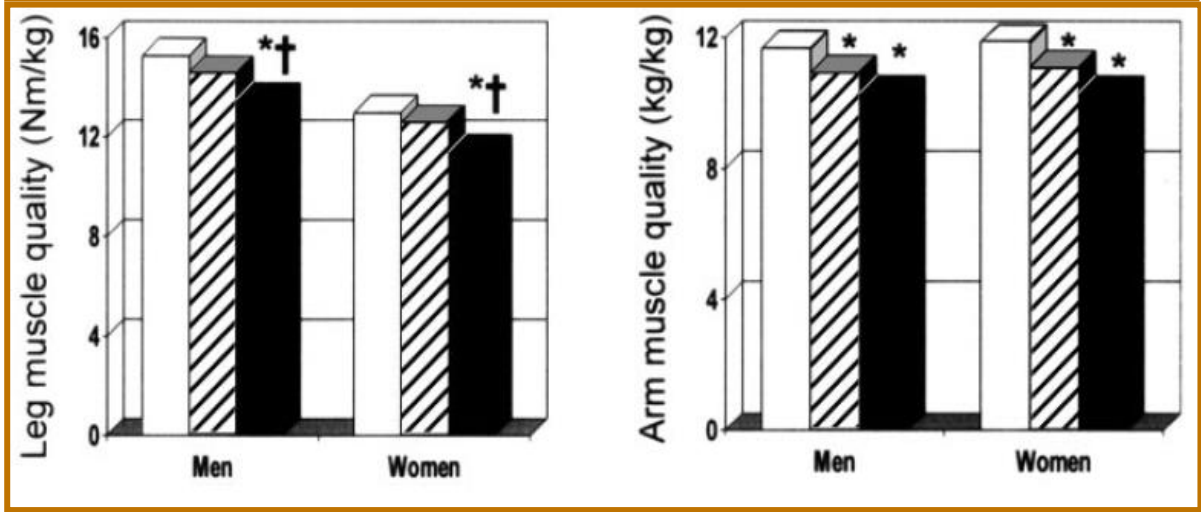
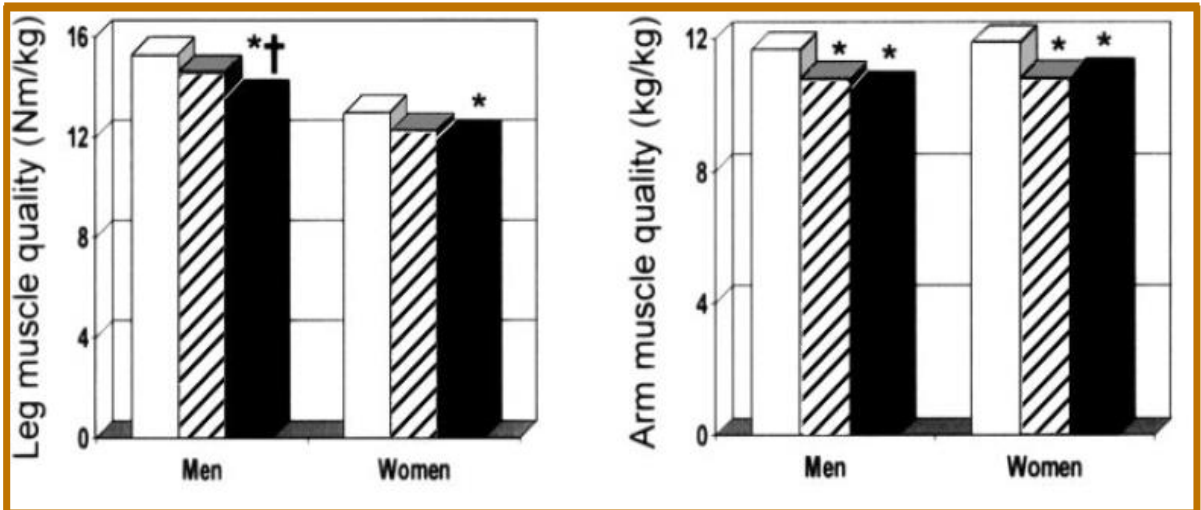
Study reference	Population ( <i>n</i> diabetics) follow-up	Skeletal muscle groups (and methods)	Results
<i>Prospective studies</i>			
Community-dwelling chinese cohort Lee et al. [14]	3153 (442) 4 years	Total lean mass (DEXA) Appendicular lean mass (DEXA)	Significant loss in diabetic participants Significant loss (adjusted for diabetes-related conditions) in diabetic participants
Health ABC Park et al. [15]	2675 (632) 6 years	Mid thigh muscle cross-sectional area (CT) Total lean mass (DEXA) Trunk lean mass (DEXA) Appendicular lean mass (DEXA)	Significant loss in diabetic female Significant loss in undiagnosed diabetic participants No difference Significant loss in undiagnosed diabetic participants
MrOS Lee et al. [16]	3752 (1403 IFG, 496 diabetics) 3.5 ± 0.7 years	Total lean mass and appendicular lean mass (DEXA)	Significant loss in participants with untreated diabetes, diabetes treated without insulin sensitizers, or IFG Significant lower loss for diabetic participants treated with insulin sensitizer

*DEXA* dual-energy X-ray absorptiometry, *CT* computed tomography, *Health ABC* Health, Aging, and Body Composition Study, *InCHIANTI* Invecchiare in Chianti, *KSOS* Korean Sarcopenic Obesity Study, *MrOS* Osteoporotic Fractures in Men Study, *IFG* impaired fasting glucose

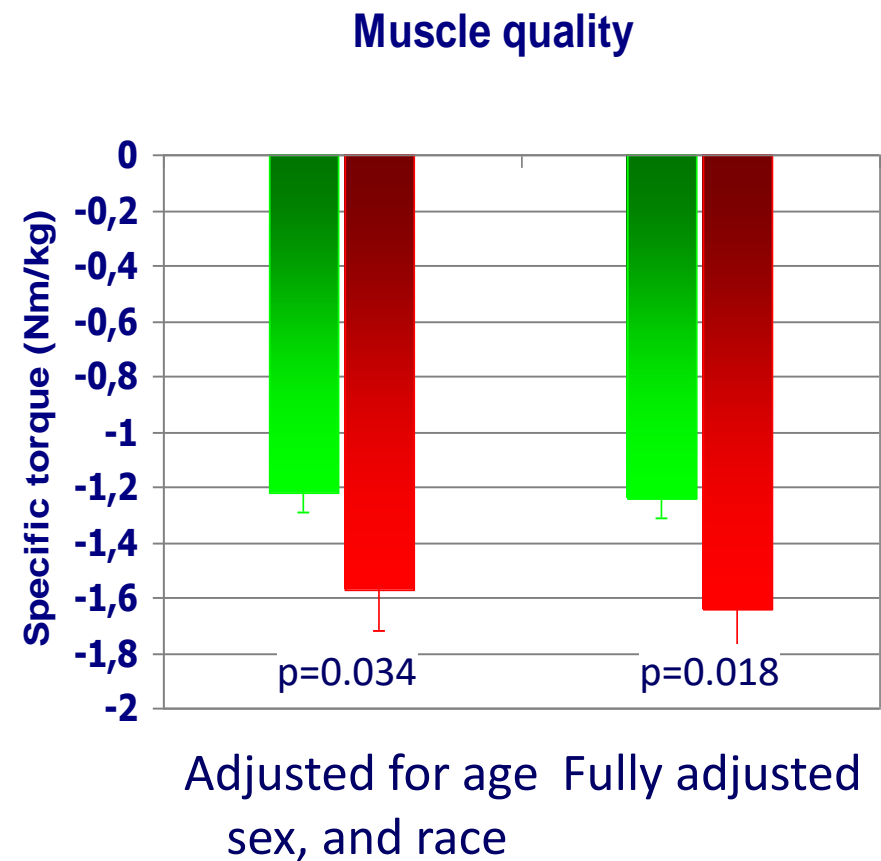
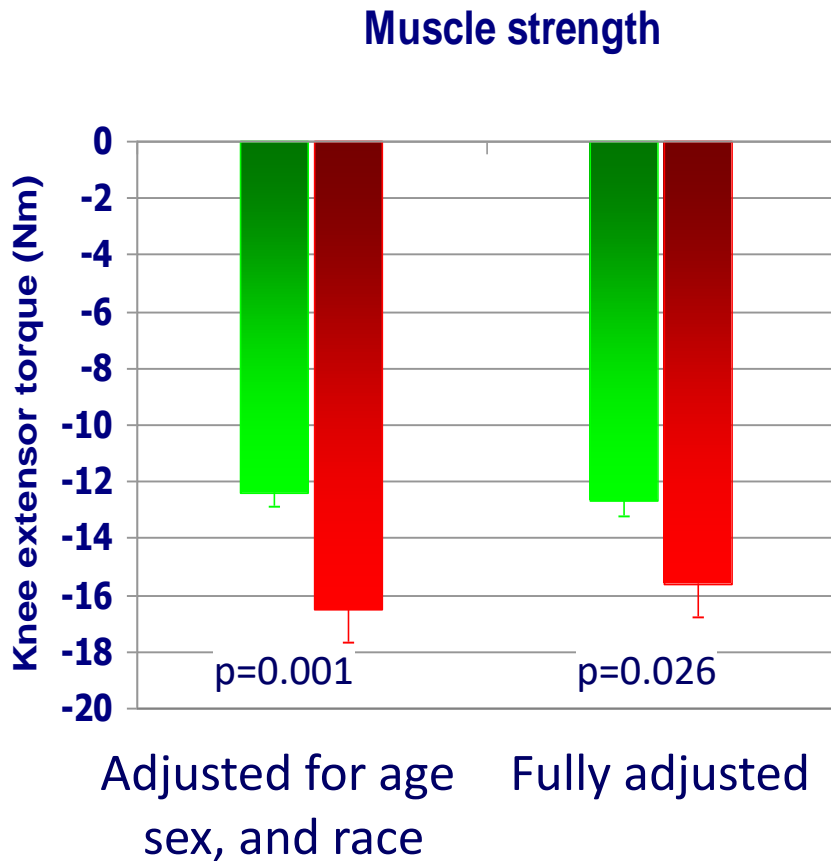
# Major epidemiologic studies investigating skeletal muscle strength according to diabetes

Study	N Follow-Up	Gender	Skeletal Muscle Groups	Significant Association	Statistical Adjustment
<b>Cross-sectional studies</b>					
HEALTH ABC <sup>63</sup>	2618	Men/Women	Knee: extension Hand: grip strength	Yes Yes in men; No in women	Age, race, education, smoking, drinking, body mass index, physical activity, comorbidity
InCHIANTI <sup>21</sup>	835	Men/Women	Hip: abduction or adduction Hip: flexion or extension Knee: extension or flexion Ankle: dorsoplantar flexion	Yes	Age, gender
NHANES1999–02 <sup>19</sup>	2573	Men/Women	Knee: extension	Yes	Demographics, weight, height physical activity, CRP
Hertfordshire Cohort Study <sup>64</sup>	1391	Men/Women	Hand: grip strength	Yes	Body weight
SOF <sup>65</sup>	2864	Women	Hand: grip strength	No	None
<b>Prospective studies</b>					
HEALTH ABC <sup>62</sup>	1840, 3 y	Men/Women	Knee: extension	Yes	Age, gender, race, education, smoking, drinking, body mass index, physical activity, comorbidity
SOF <sup>65</sup>	2864, 4.9 y	Women	Grip strength	No	Age, race, clinic site, baseline physical performance measure, body mass index, self-rated health, hypertension, and estrogen use

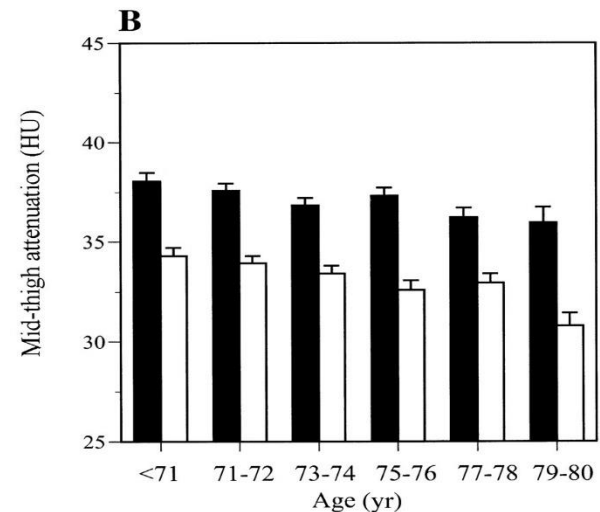
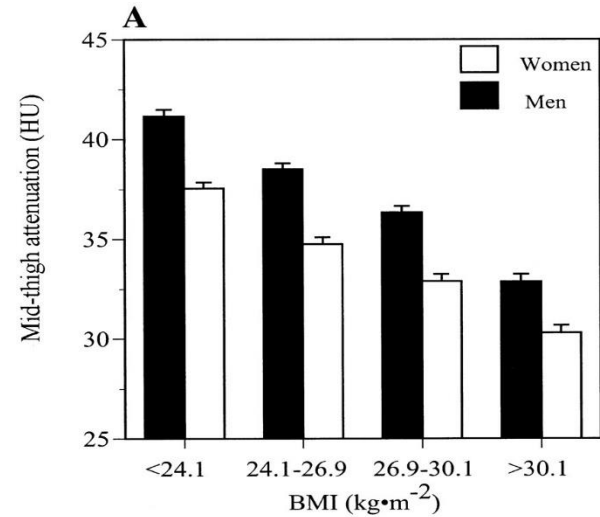
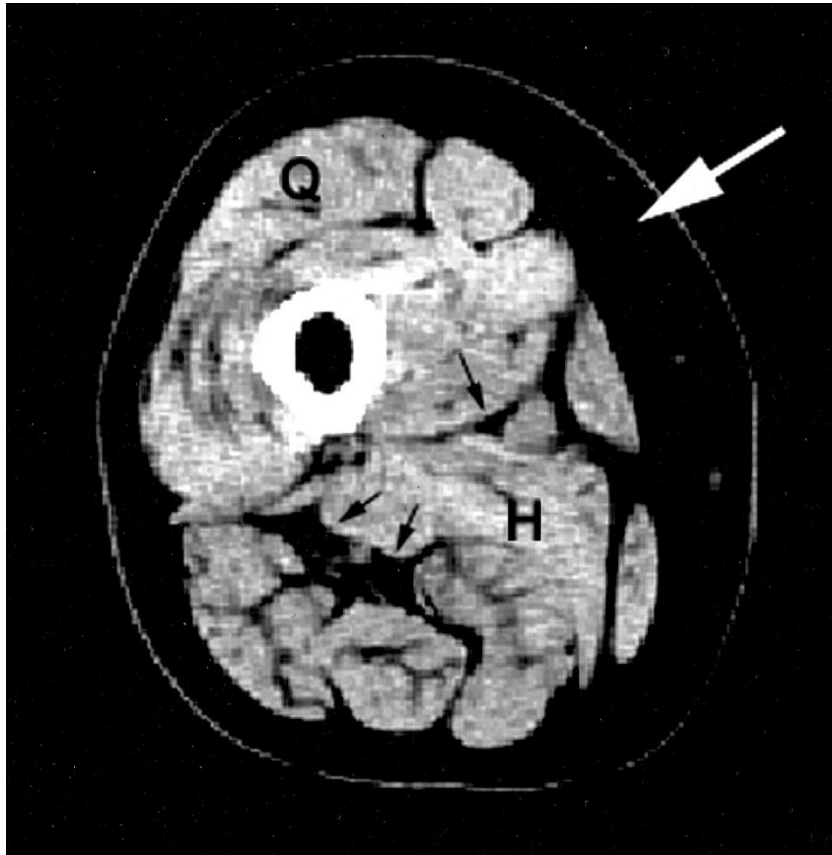
# Decreased Muscle Strength and Quality in Older Adults with Type 2 Diabetes (Health ABC Study)



# 3-year changes in knee extensor strength and muscle quality by diabetes in the Health ABC Study



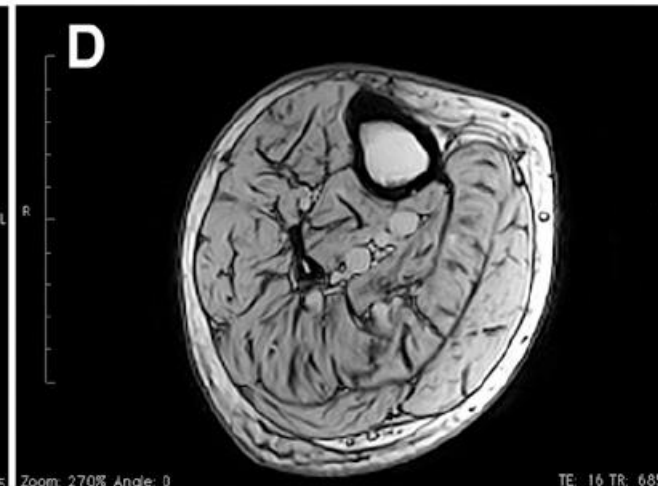
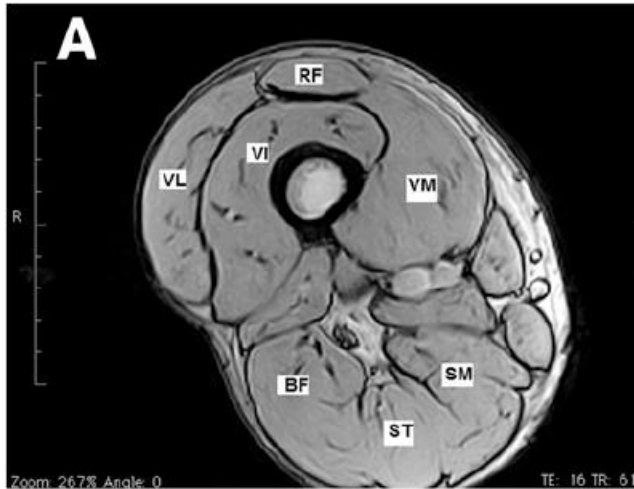
# Skeletal Muscle Mass fat infiltration according to age and adiposity



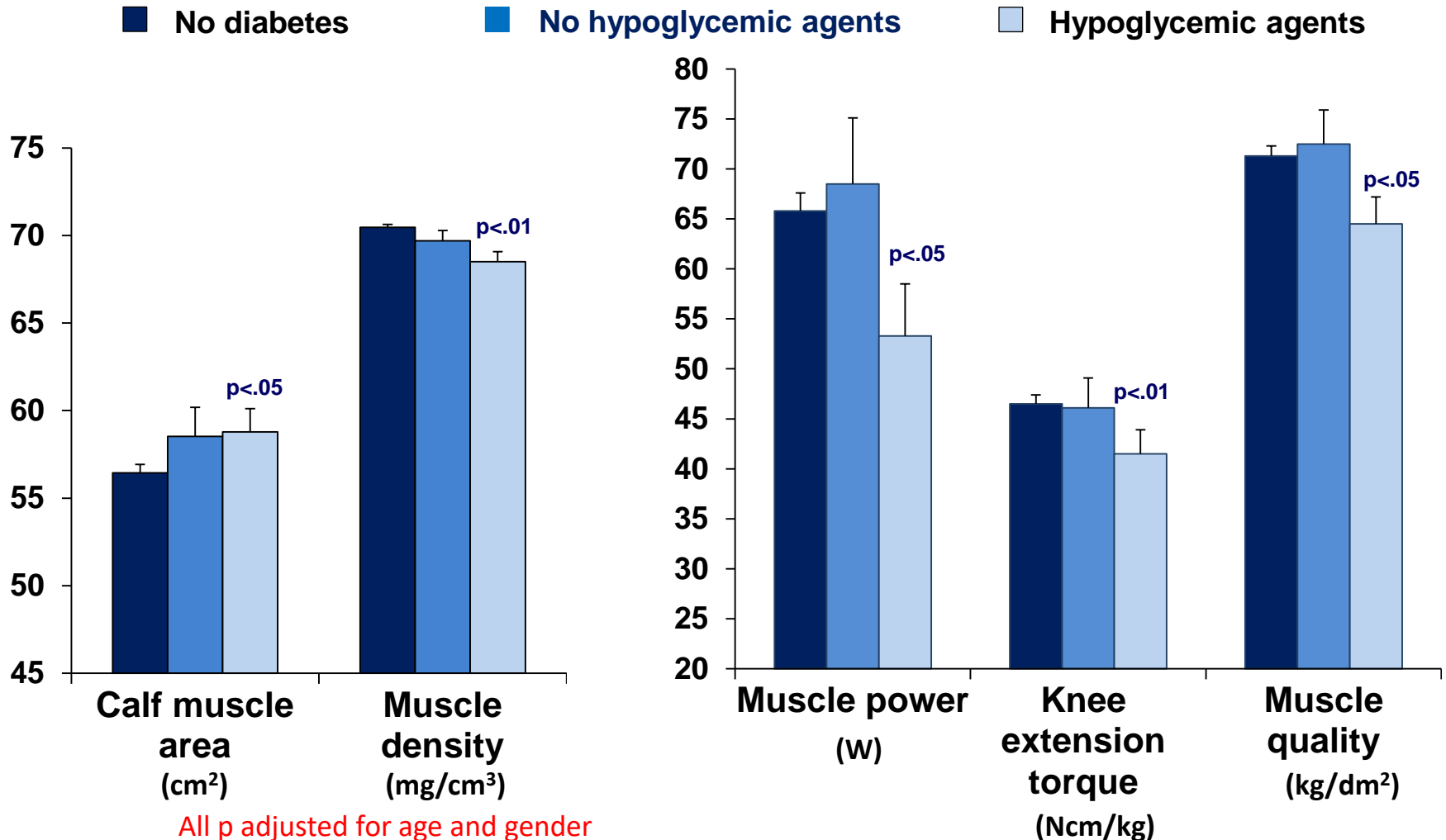
# MRI images of the lower limbs of control subjects vs. patients with type 2 diabetes

Healthy 69-yr control

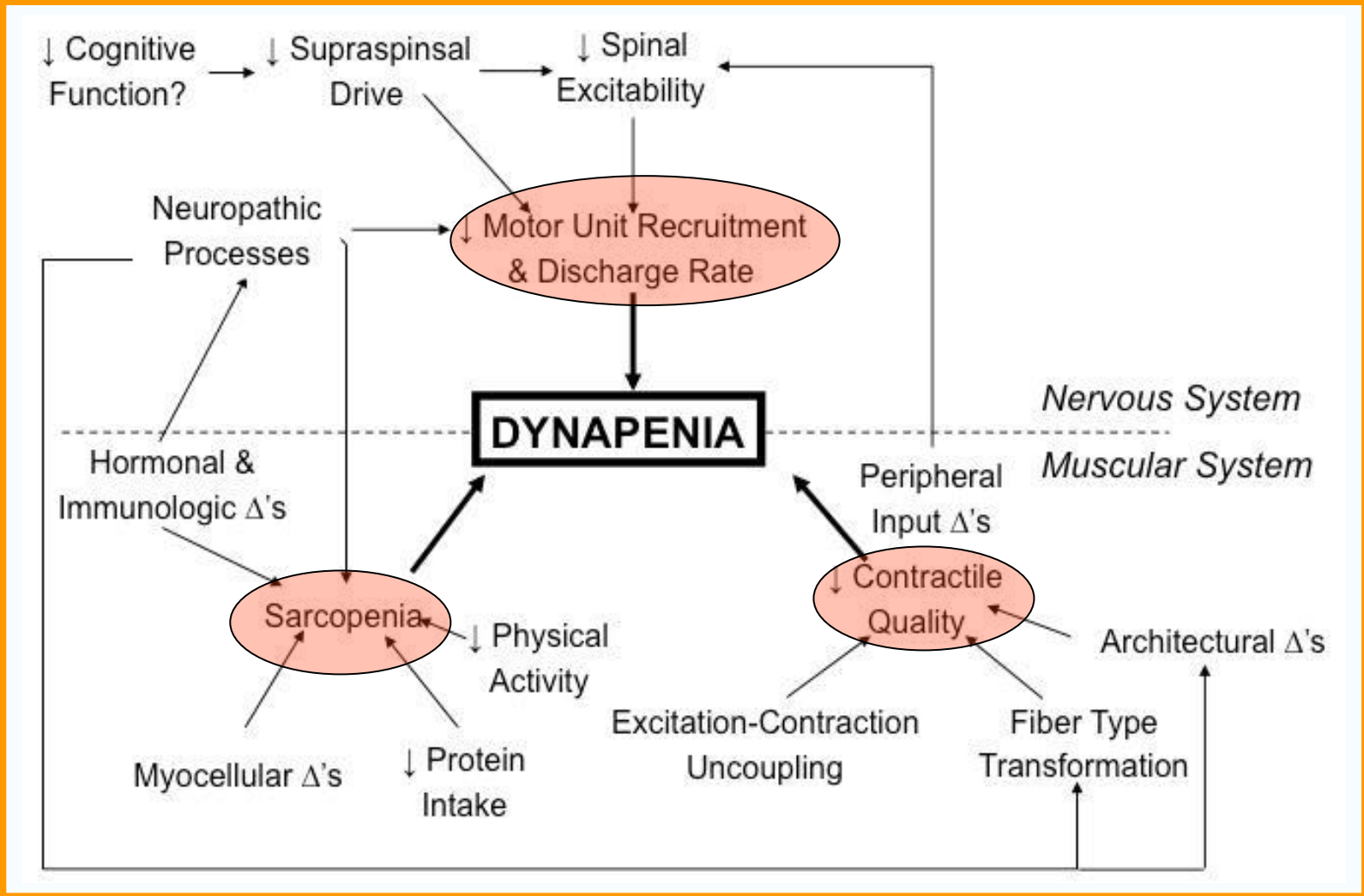
67-yr old diabetic with polyneuropathy



# Lower-limb skeletal muscle characteristics in people with and without diabetes: The InCHIANTI Study

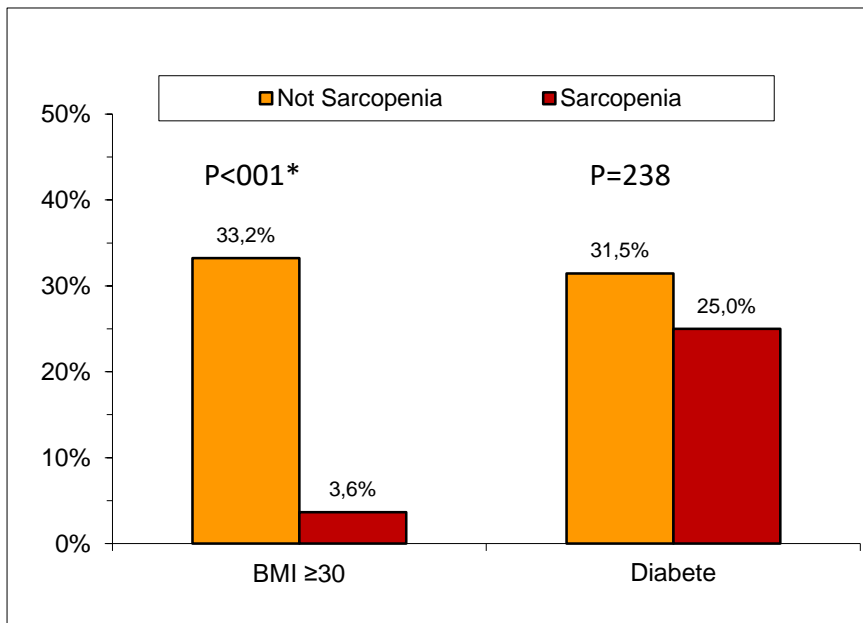


# Sarcopenia ≠ Dynapenia



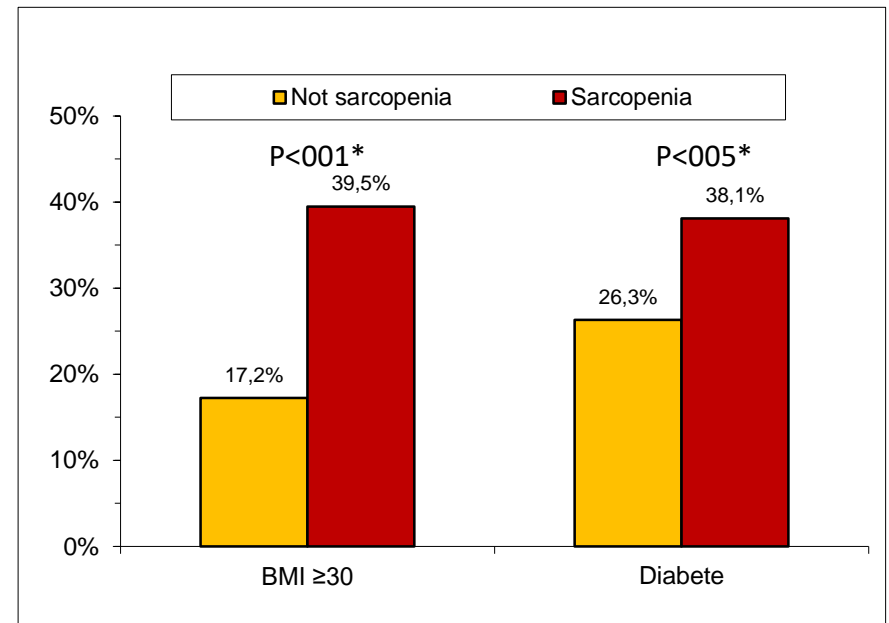
# Relationship of Diabetes with BMI and Sarcopenia: The Glisten Study

## EWGSOP



SMI: Appendicular skeletal muscle mass/height<sup>2</sup>

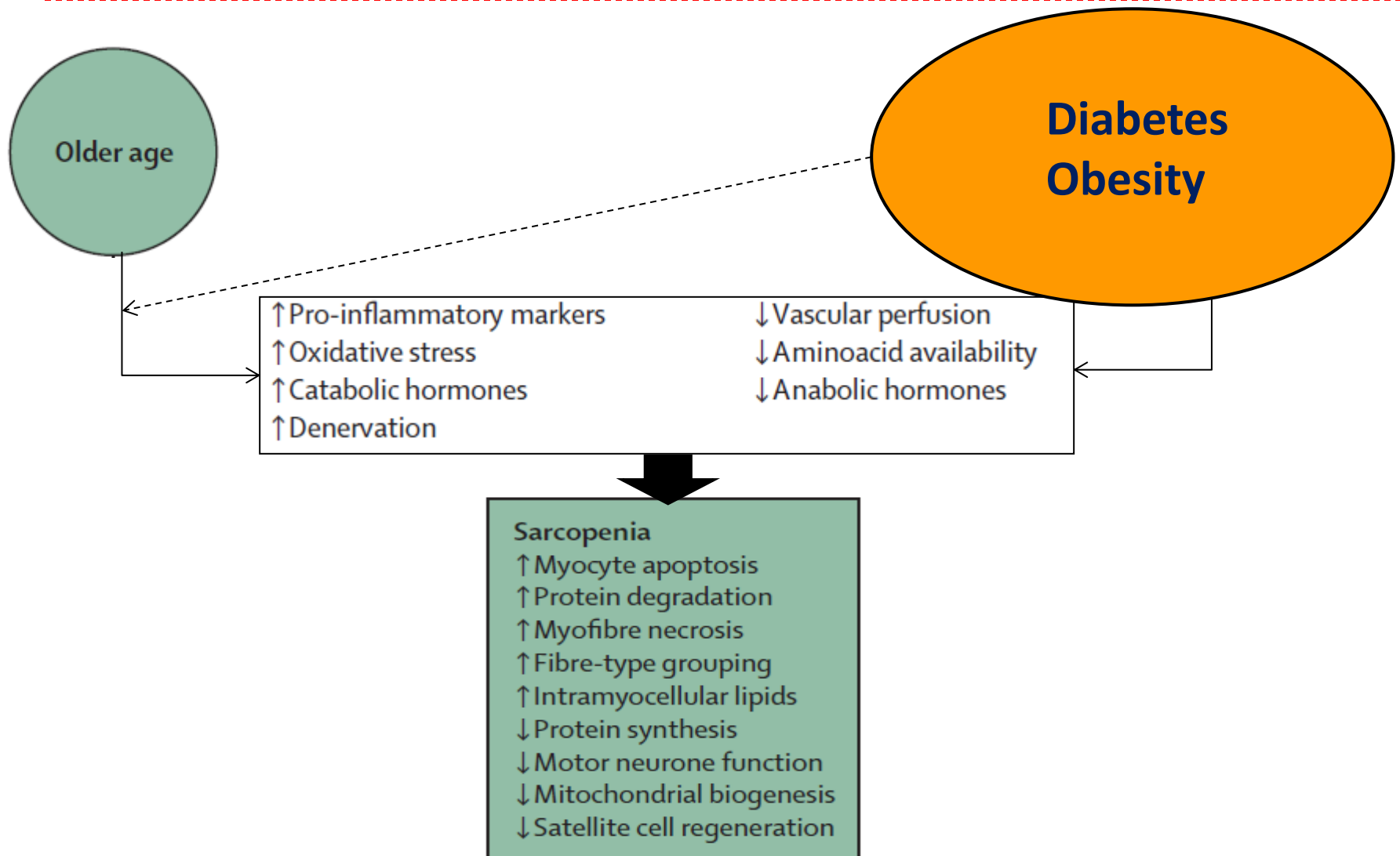
## FNIH



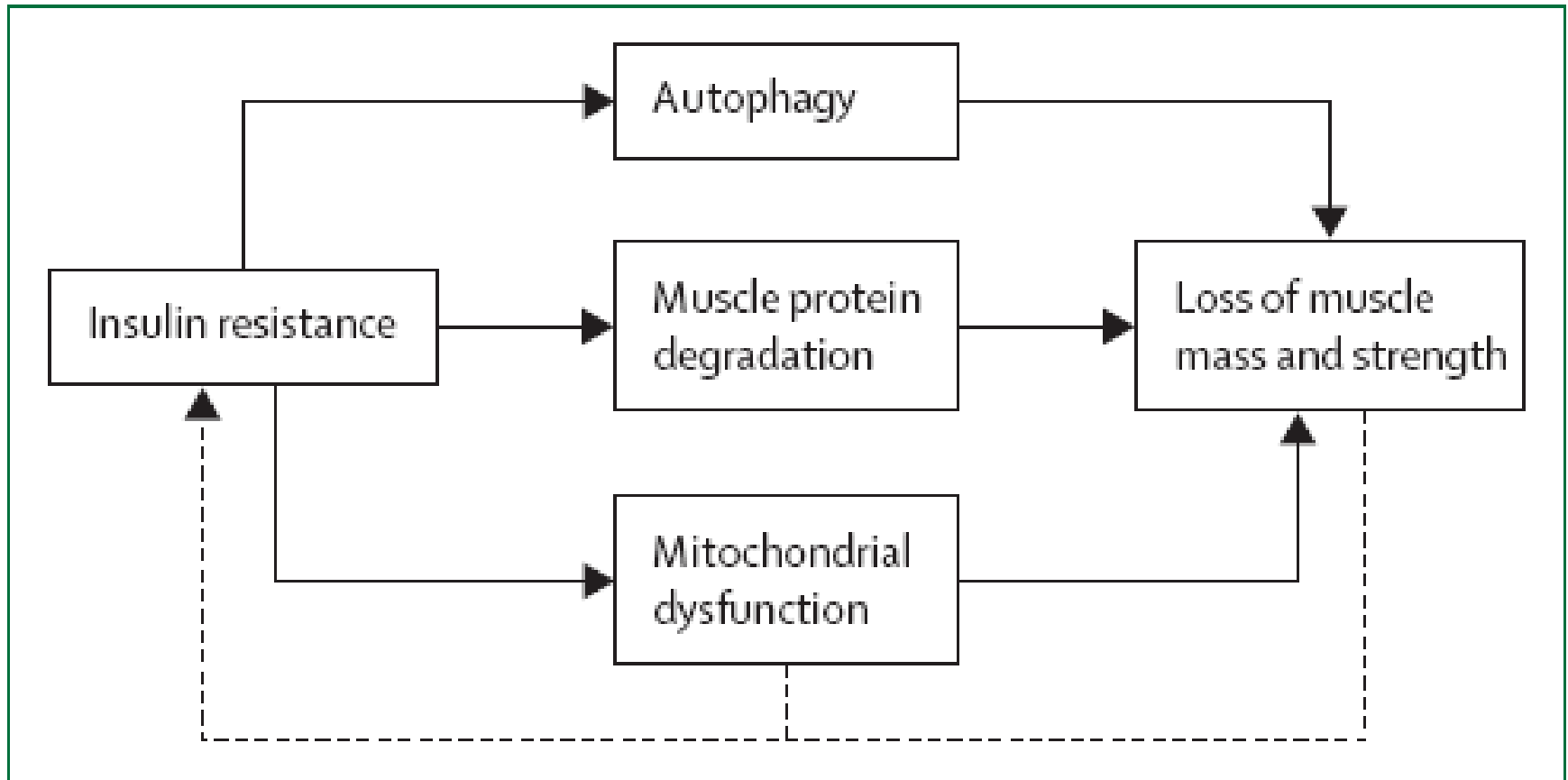
SMI: Appendicular skeletal muscle mass/BMI

\*age and gender adjusted

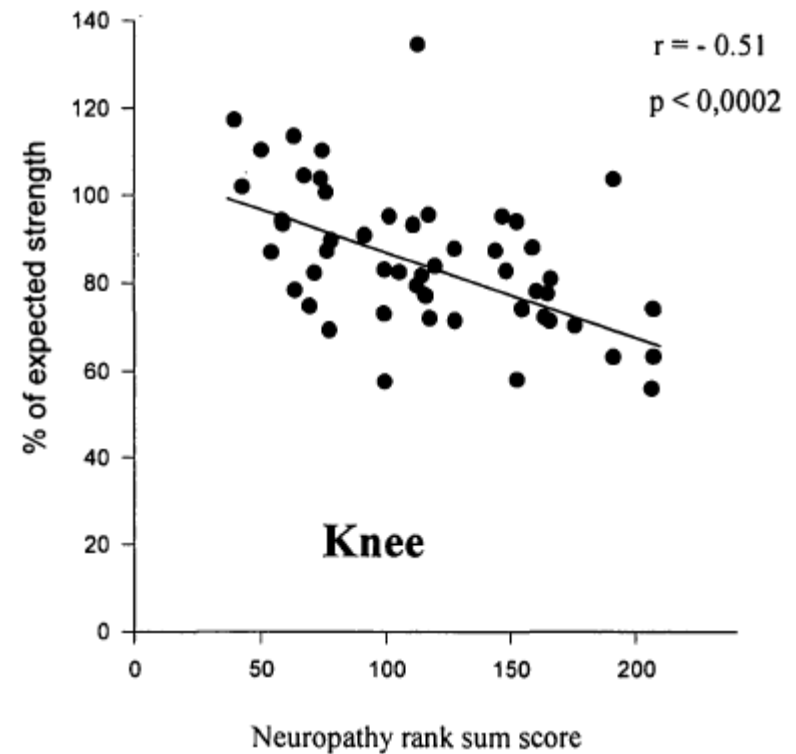
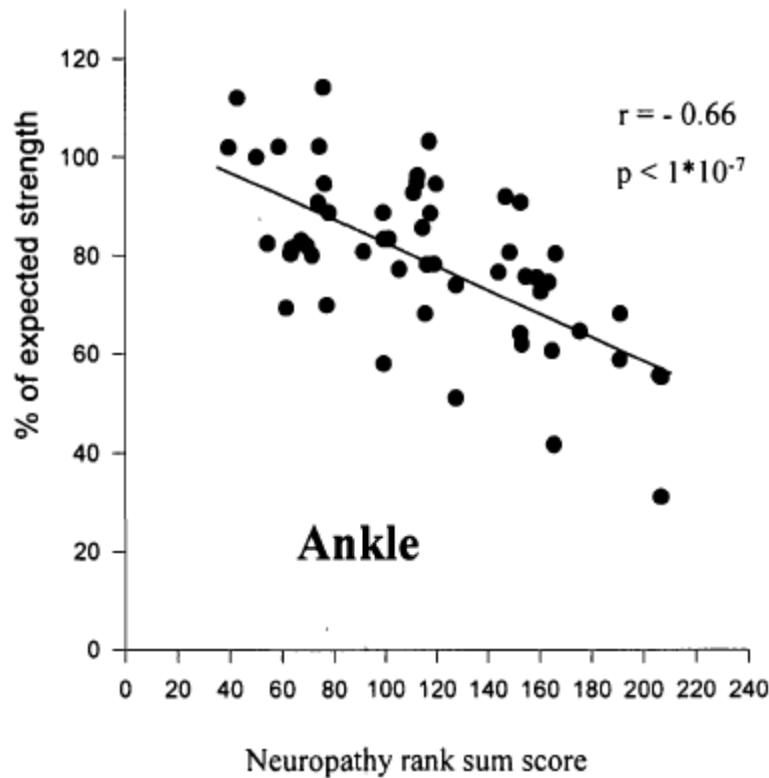
# Potential mechanisms of age-related and disease-related muscle loss



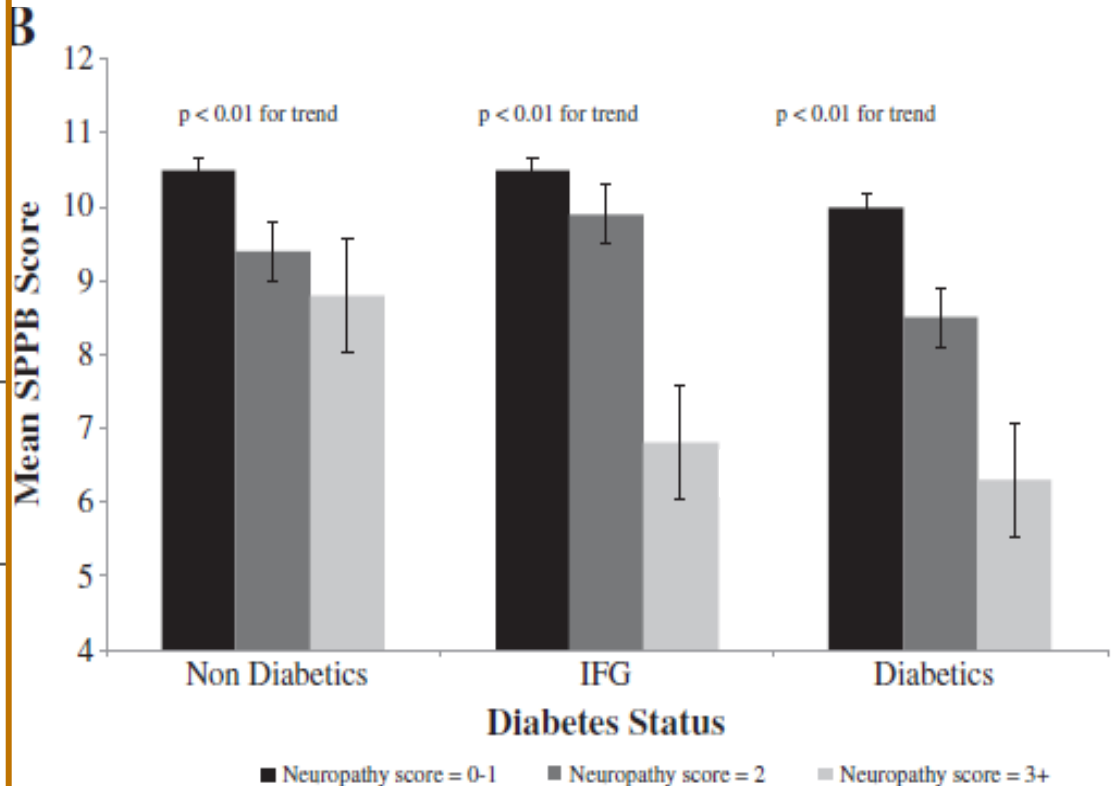
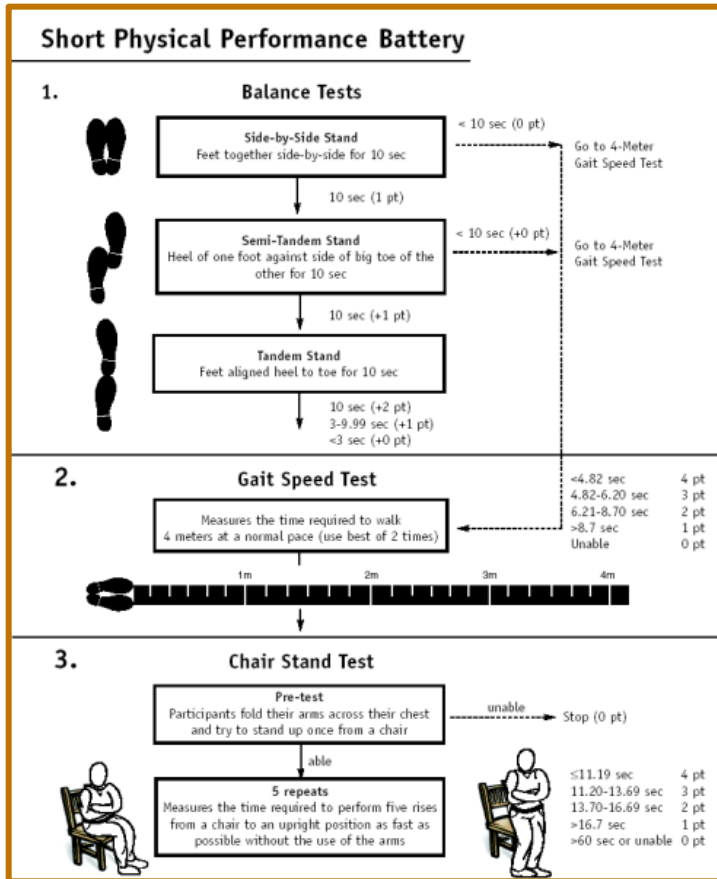
# Pathways of accelerated muscle loss in type 2 diabetes



# Isokinetic Muscle Strength in Long-Term IDDM Patients in Relation to Diabetic complications



# Diabetes, Peripheral neuropathy and lower extremity function: InChianti Study



# Potential biological mechanism explaining the diabetes-related muscle dysfunction

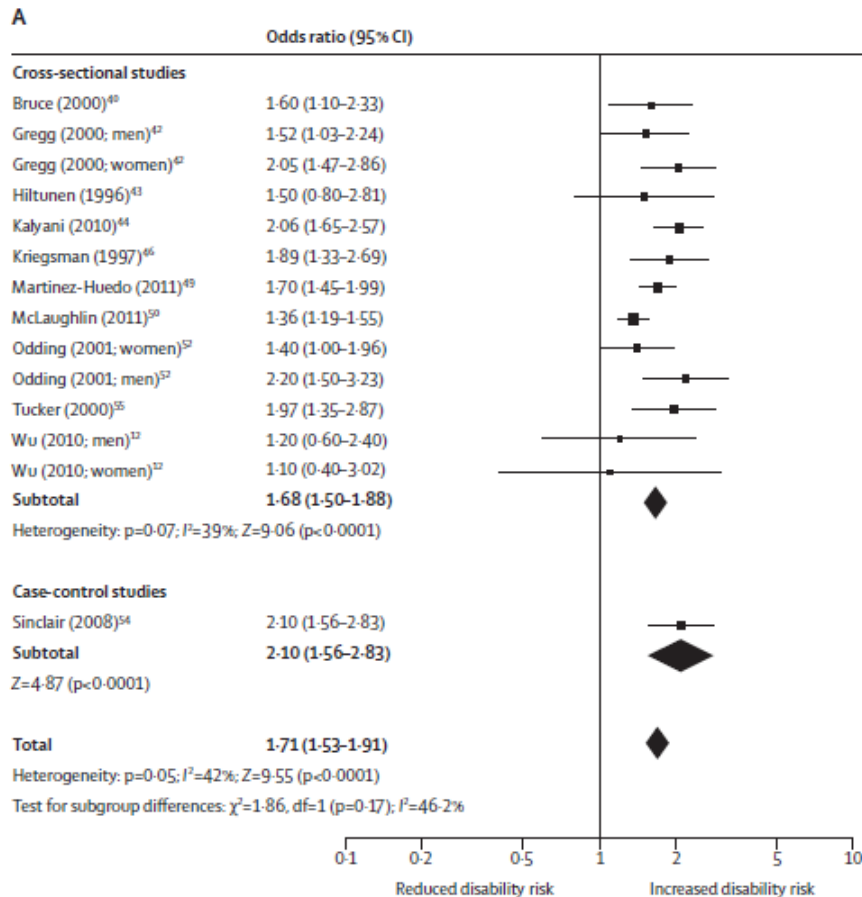
Insulin Resistance	<ul style="list-style-type: none"> <li>Increased protein degradation</li> <li>Decreased protein synthesis</li> <li>Mitochondrial dysfunction</li> </ul>
Hyperglycemia	<ul style="list-style-type: none"> <li>Mitochondrial dysfunction</li> <li>Glycation of skeletal muscle myosin</li> <li>Oxidative Stress</li> </ul>
Chronic inflammation and oxidative Stress	<ul style="list-style-type: none"> <li>Deregulation of protein synthesis and breakdown</li> <li>Mitochondrial dysfunction</li> <li>Muscle apoptosis</li> <li>GLUT-4 down-regulation</li> <li>Inhibition of insulin receptor activity</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>Muscle fat infiltration</li> <li>Reduced insulin sensitivity</li> <li>Worse inflammatory status</li> <li>Reduced oxidative activity and maximal aerobic capacity</li> </ul>
Physical inactivity	<ul style="list-style-type: none"> <li>Increased weight</li> <li>Worse glycemic control and glucose tolerance</li> <li>Increased insulin resistance</li> <li>Increased risk of diabetic complications</li> <li>Worse inflammatory status</li> <li>Increased intermuscular adipose tissue</li> </ul>
Diabetes complication	<ul style="list-style-type: none"> <li>Muscle atrophy</li> <li>Muscle apoptosis</li> <li>Worse oxidative metabolism</li> <li>Worse NVC</li> <li>Muscle atrophy</li> </ul>
Peripheral arterial disease	
Diabetic peripheral neuropathy	

# Diabetes and risk of physical disability in adults: a systematic review and meta-analysis

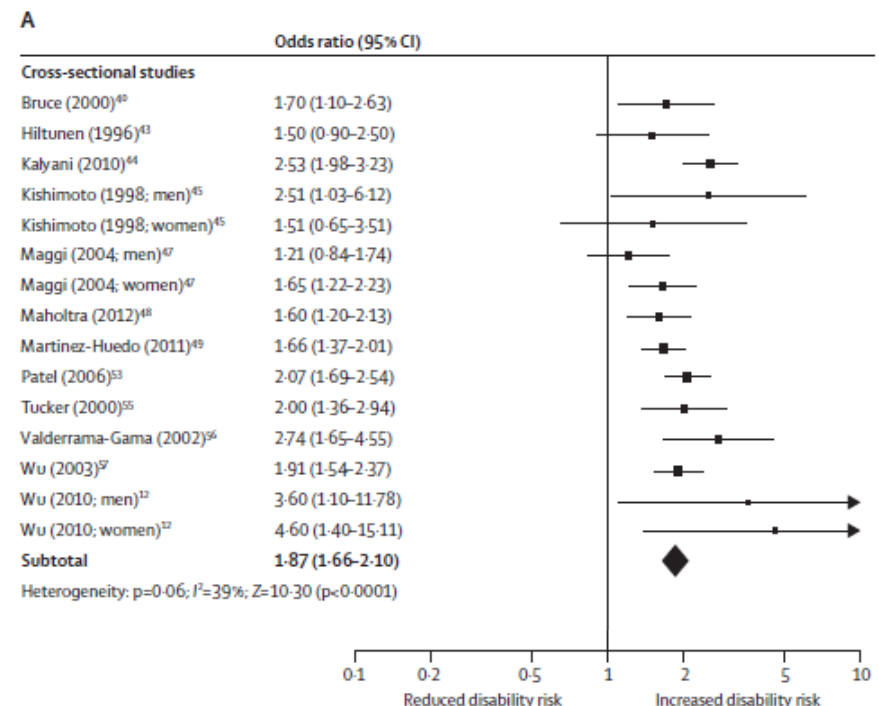


## Cross-sectional and case-control studies

### Mobility Disability



### ADL Disability

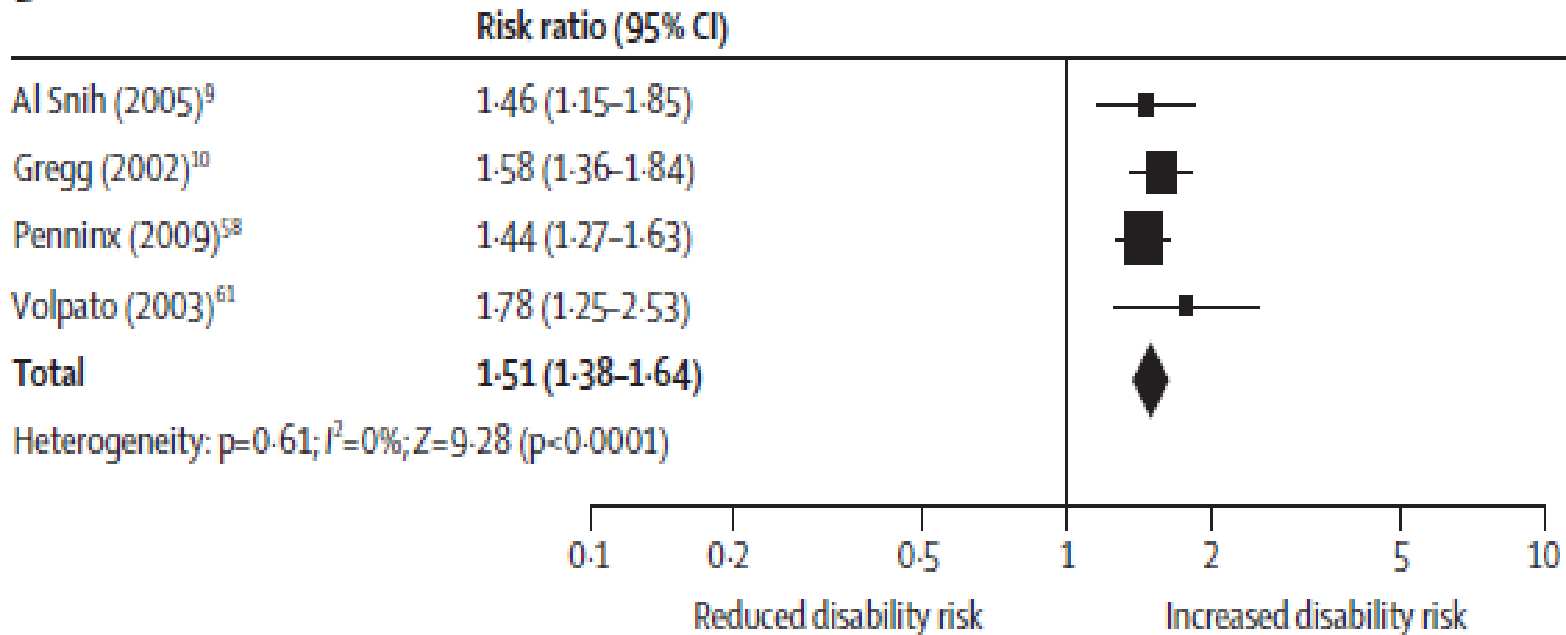


# Diabetes and risk of physical disability in adults: a systematic review and meta-analysis



## Longitudinal studies: Mobility Disability

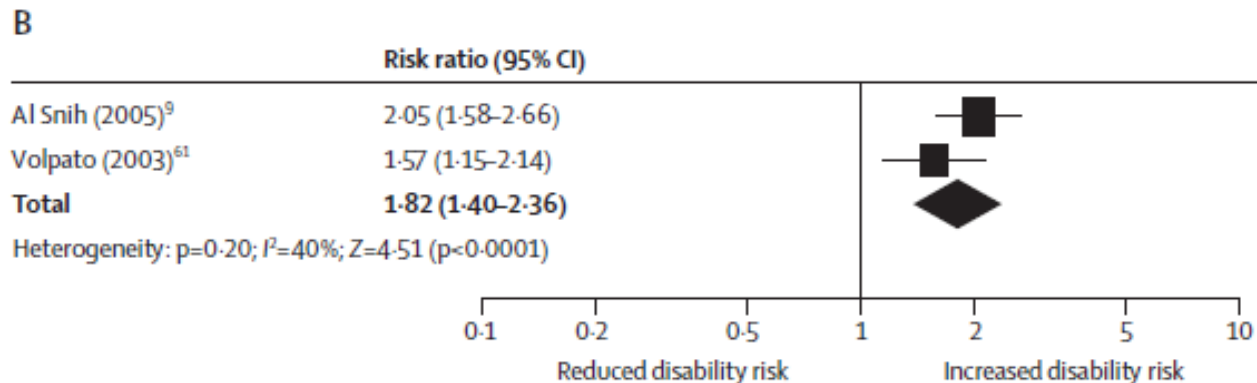
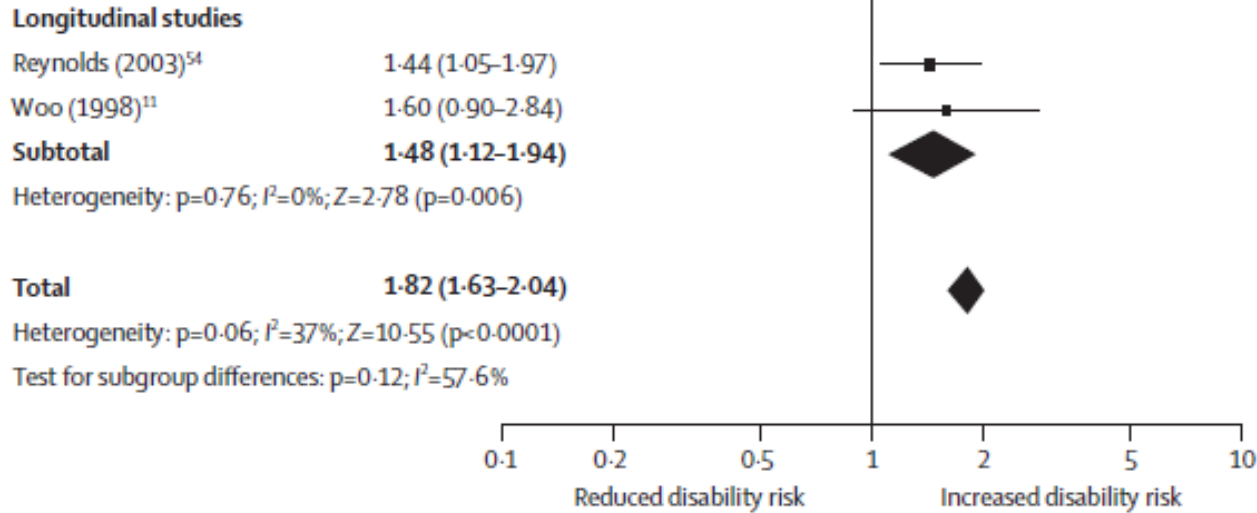
B



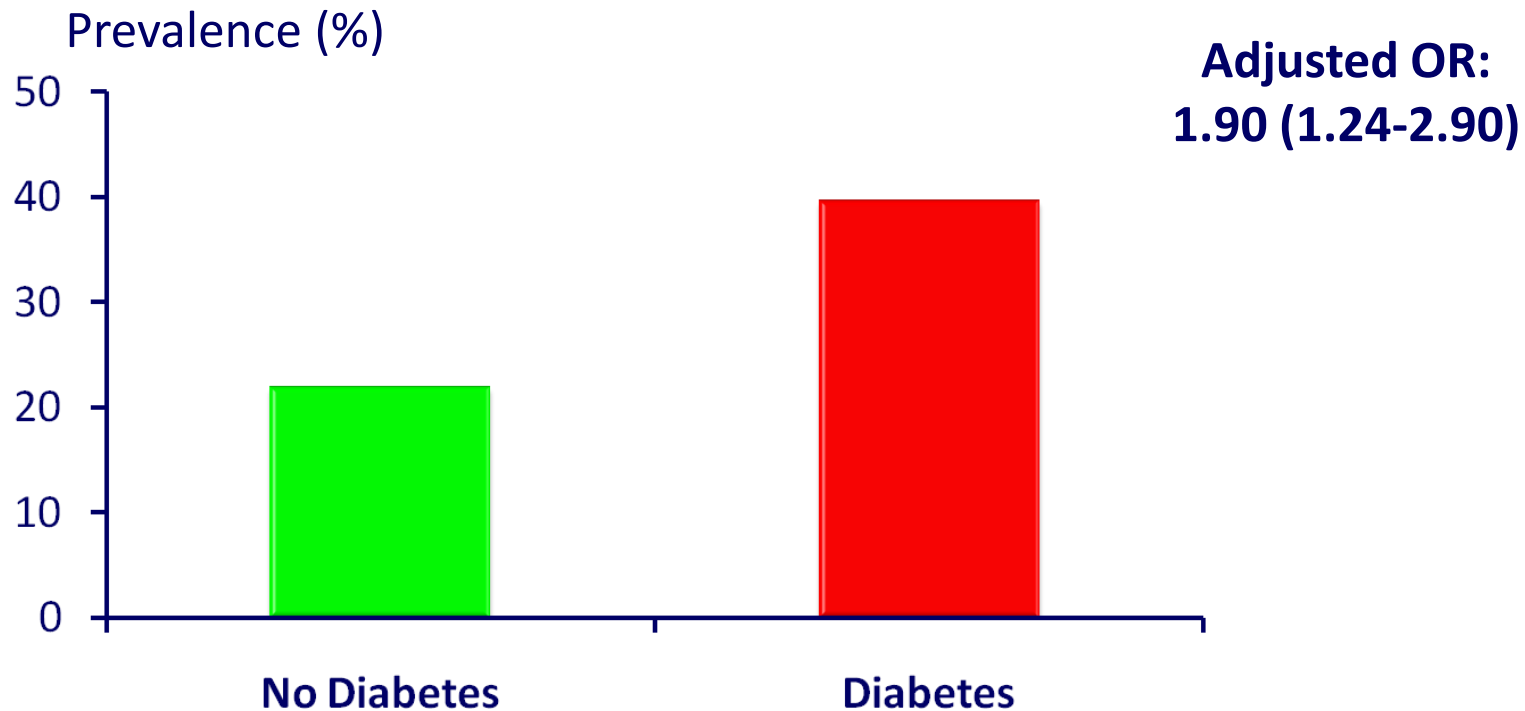
# Diabetes and risk of physical disability in adults: a systematic review and meta-analysis



## Longitudinal studies: ADL Disability



# Walking disability (walking speed <0.4 m/s) in older women (Women Health and Aging Study)



Adjusted for age, race, smoking, education, BMI, knee osteoarthritis, cognitive impairment, depressive symptoms

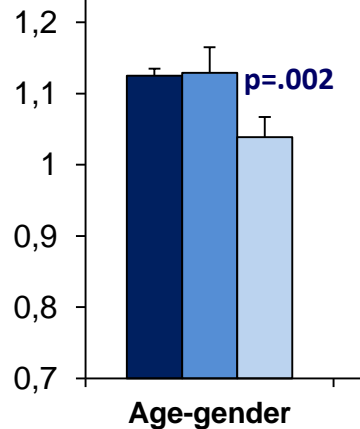


# Association of diabetes and gait speed: Multivariable linear regression analyses

4-m gait speed (m/s)



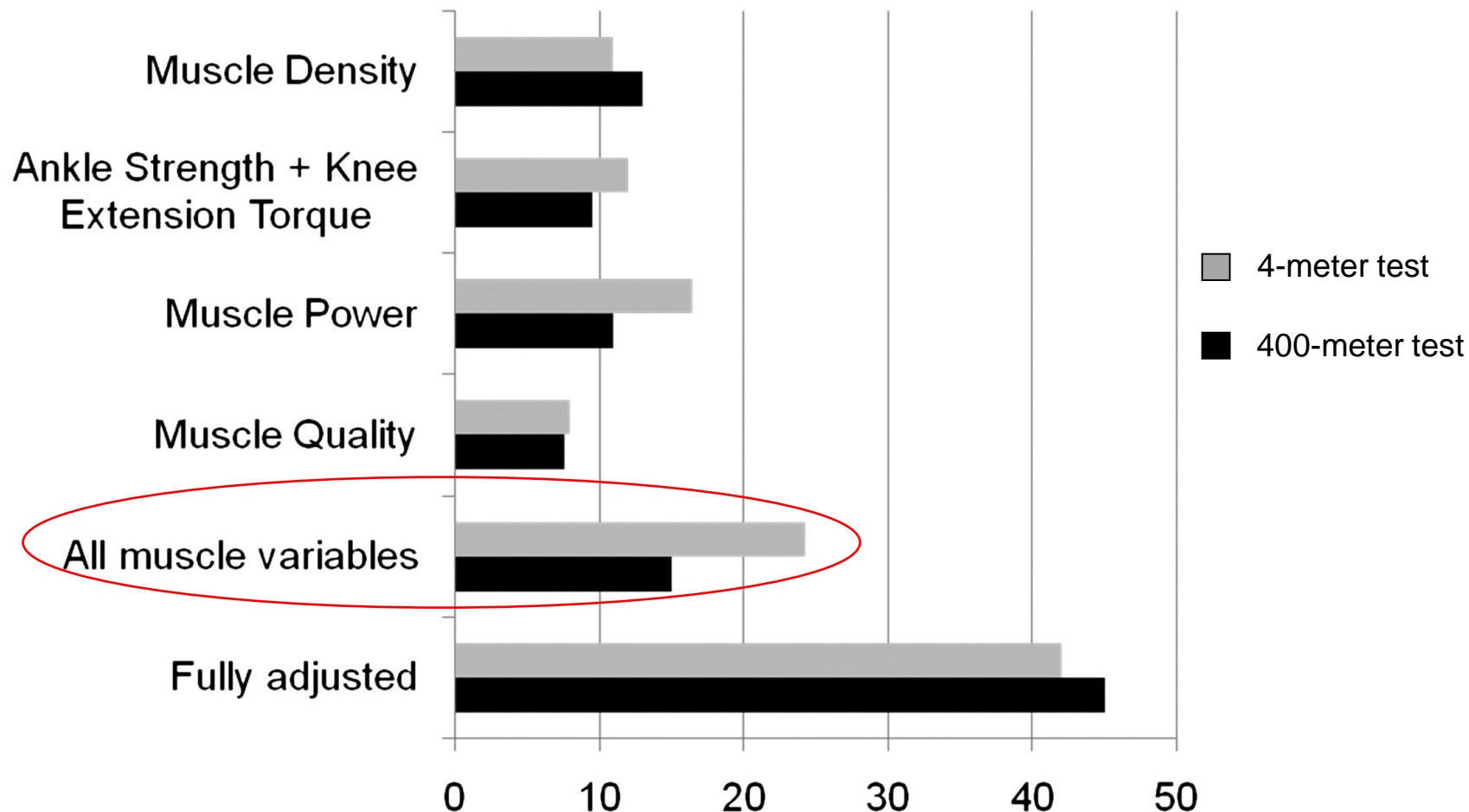
400-m gait speed (m/s)



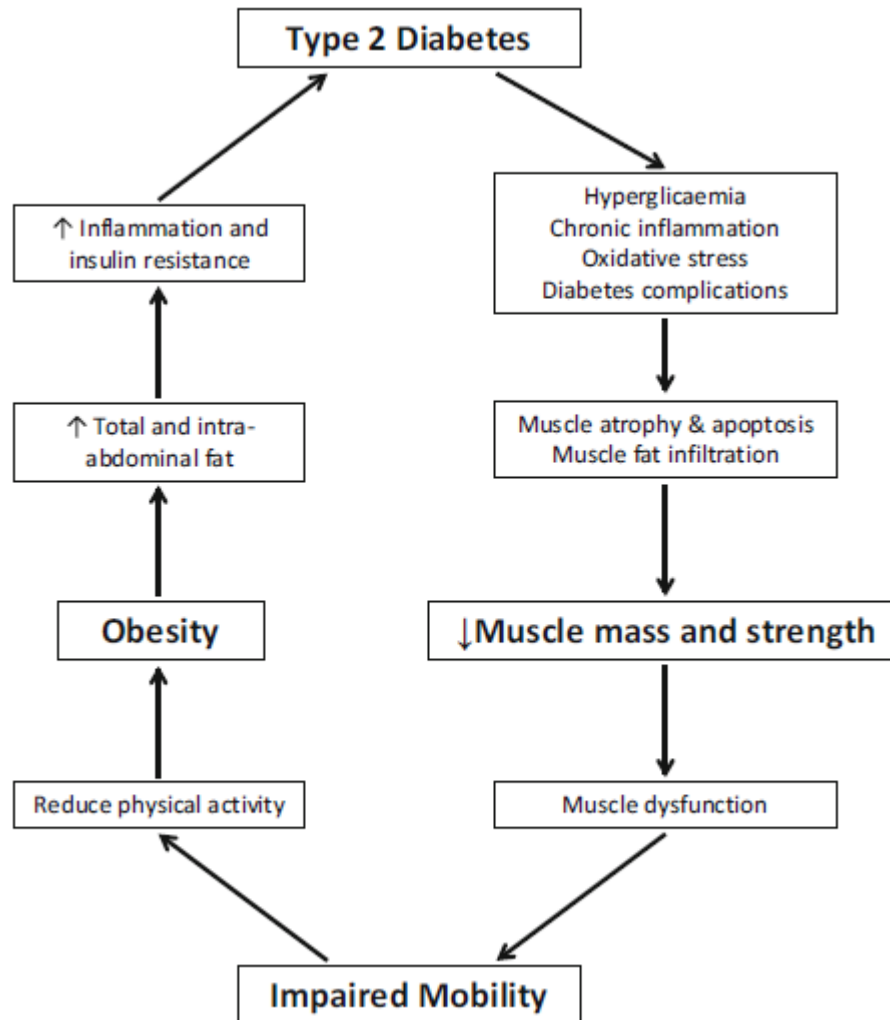
## Muscle variables:

- muscle density
- knee extension torque
- ankle strength
- muscle power
- muscle quality

# Percent reduction in the association between diabetes and gait speed after adjustment for potential mediators



# Putative model of the pathway from diabetes to impaired mobility



# Potential treatments for age-related and diabetes-related disability and muscle impairment

---

## ▶ Diet

- ▶ High quality protein supplementation?

## ▶ Strict glycemic control

- ▶ No evidence available
- ▶ Risk of hypoglycemia in older people

## ▶ Insulin sensitizer agents

- ▶ Thiazolidinediones ?? No evidence available

## ▶ Exercise

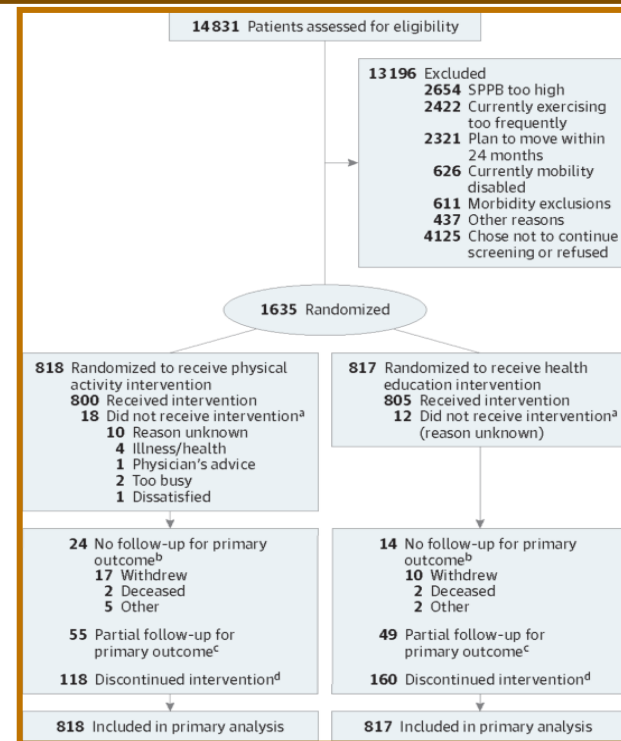
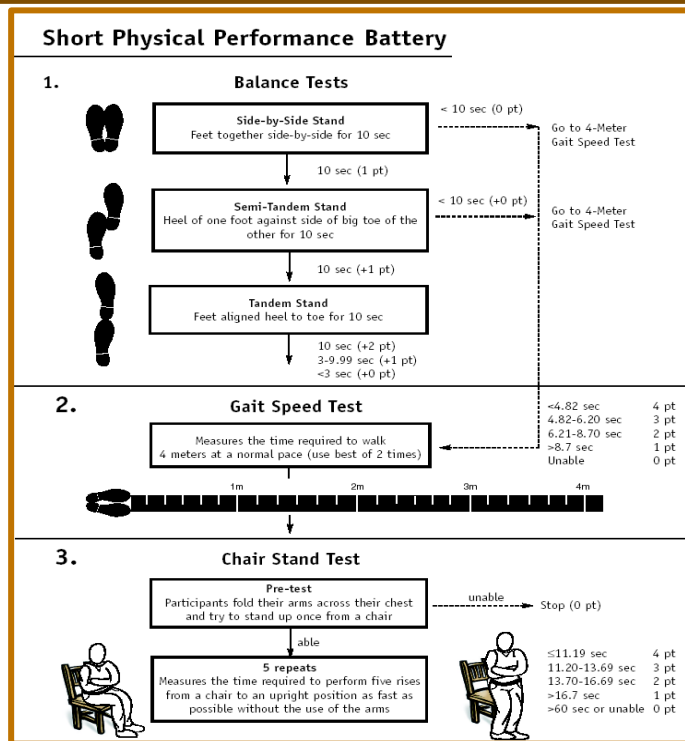
- ▶ Yes but specific RCT are missing

Original Investigation

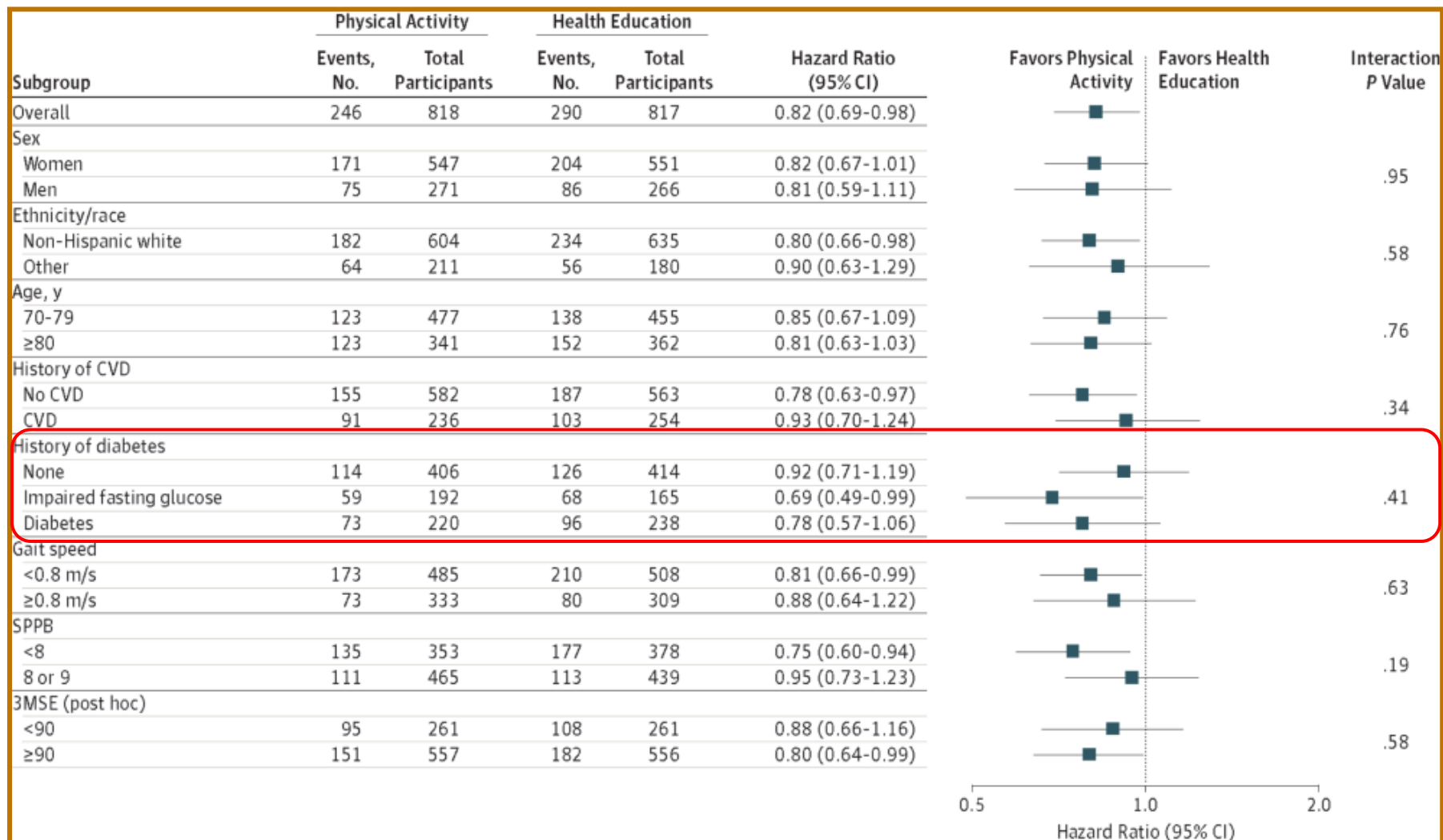
# Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults

## The LIFE Study Randomized Clinical Trial

Marco Pahor, MD; Jack M. Guralnik, MD, PHD; Walter T. Ambrosius, PhD; Steven Blair, PED; Denise E. Bonds, MD; Timothy S. Church, MD, PhD, MPH; Mark A. Espeland, PhD; Roger A. Fielding, PhD; Thomas M. Gill, MD; Erik J. Groessl, PhD; Abby C. King, PhD; Stephen B. Kritchevsky, PhD; Todd M. Manini, PhD; Mary M. McDermott, MD; Michael E. Miller, PhD; Anne B. Newman, MD, MPH; W. Jack Rejeski, PhD; Kaycee M. Sink, MD, MAS; Jeff D. Williamson, MD, MHS; for the LIFE study investigators



# Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults: The LIFE Study Randomized Clinical Trial



# Conclusions

---

- ▶ Diabetes accelerates the age-related decline in muscle strength and quality
- ▶ The mechanism explaining the excess risk of disability in older diabetic patients is multifactorial, however sarcopenia is an important mediator linking diabetes to disability
- ▶ Structured physical activity programs might prevent or postpone disability onset in older people with diabetes and sarcopenia

