Vrije Universiteit Brussel

Evaluatie, preventie en behandeling van Sarcopenie

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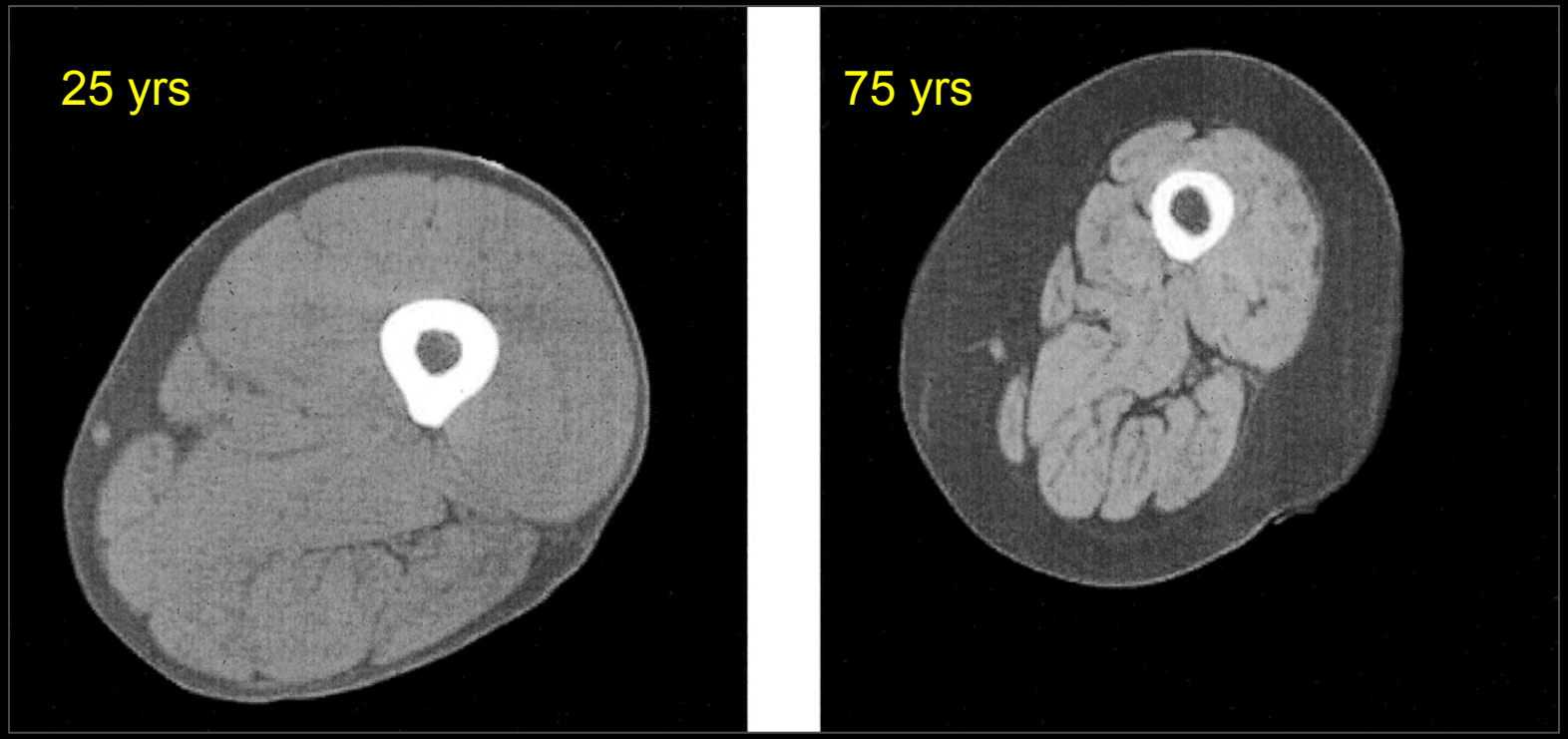
Frailty in Ageing research group

www.vub.ac.be/FRIA

Sarcopenia

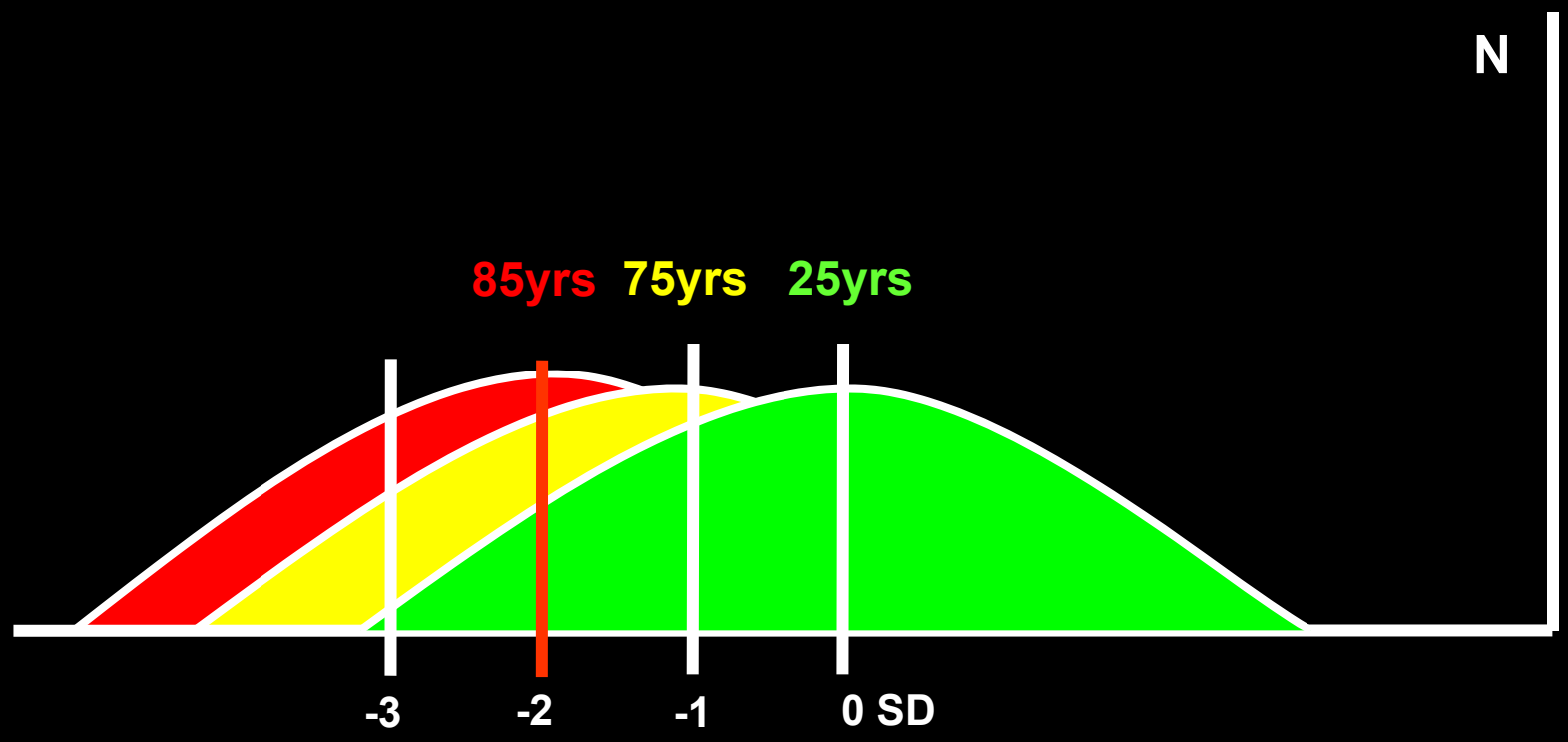
Rosenberg *J Nutr 1997*

Age-related loss of muscle mass and muscle strength



Roubenoff R. *J Gerontol 2003*

$$\text{T-score} = \frac{X_i - \text{mean}X_{young}}{SD_{young}}$$



- **Baumgartner ea. 1998**
  - **New Mexico, USA**
    N-Hisp: 205M, 173F
  - **Reference group**
    N-Hisp, 107M, 122F aged 18-40yrs
    - >80 yrs = ♂ 53%, ♀43%

- **Janssen ea. 2000**
  - **NHANES III, USA**
    2224M, 2278F aged≥60yrs
  - **Reference group**
    3116M, 3298F aged 18-39yrs
    - Class 1: -1≥T≤-2
      >80 yrs = ♂ 43%, ♀61%
    - Class 2: T<-2
      >80 yrs = ♂ 7 %, ♀11%

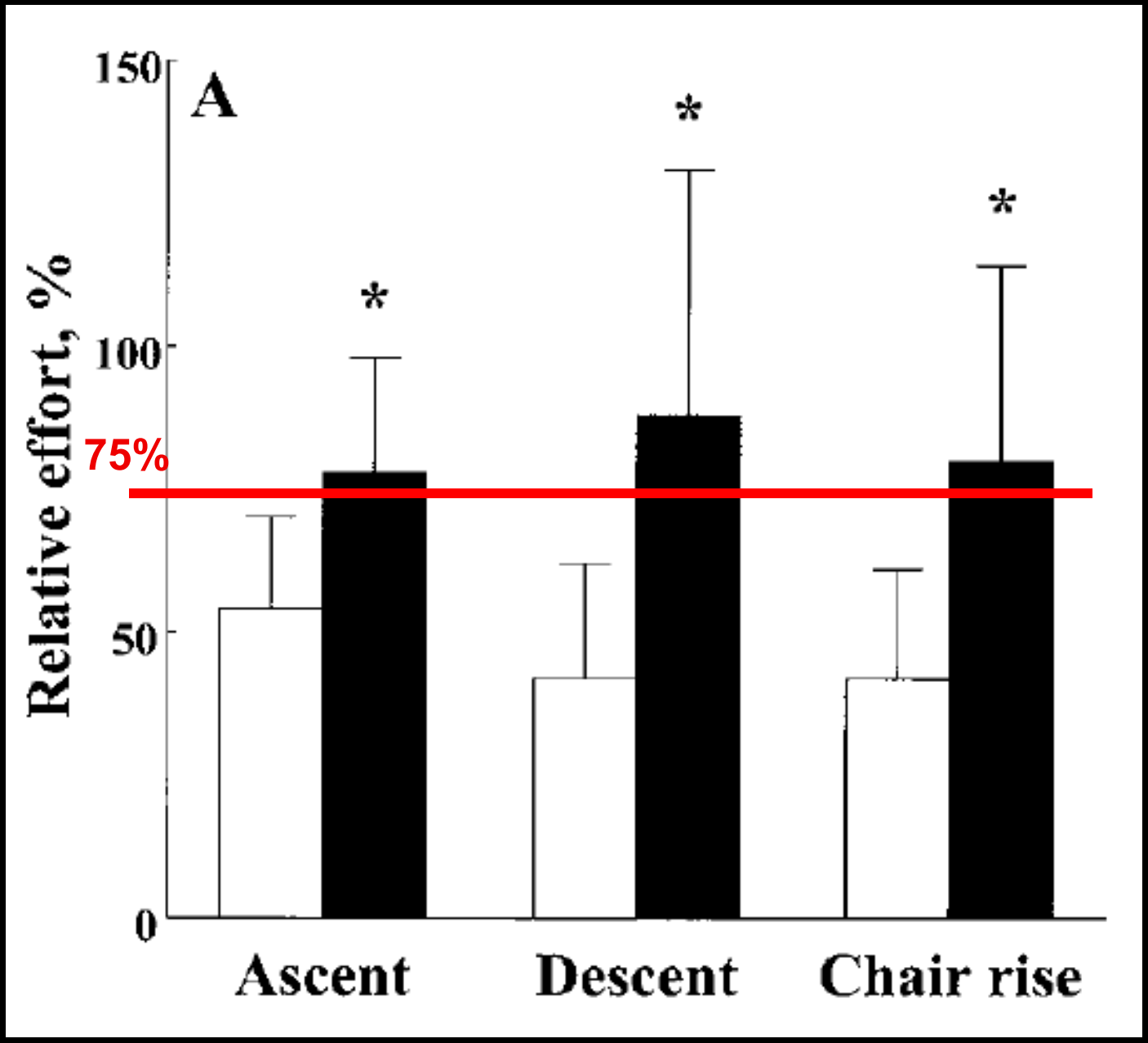
Correction for weight or stature

Table 1. Criteria for the diagnosis of sarcopenia

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)

1. Low muscle mass
2. Low muscle strength
3. Low physical performance

European Working Group on Sarcopenia in Older People *Age&Ageing 2010*



Hortobagyi ea *J Gerontol 2003*

Men:	<30 kg
Women:	<20 kg
Men:	
BMI	≤ 24 ≤ 29 kg
BMI	24.1–26 ≤ 30 kg
BMI	26.1–28 ≤ 30 kg
BMI	> 28 ≤ 32 kg
Women:	
BMI	≤ 23 ≤ 17 kg
BMI	23.1–26 ≤ 17.3 kg
BMI	26.1–29 ≤ 18 kg
BMI	> 29 ≤ 21 kg

Lauretani ea *JApplPhysiol 2003*
Fried ea. *JGerontol 2001*

Table 3. Reference values (in Kpa) for maximal grip strength

	Male		*Female*	
Age	*Threshold value*	*Median*	*Threshold value*	*Median*
70-74 years	66 KPa	91 KPa	54 KPa	67 KPa
75-79 years	57 KPa	82 KPa	48 KPa	63 KPa
80-84 years	50 KPa	75 KPa	43 KPa	59 KPa
≥85 years	37 KPa	64 KPa	35 KPa	54 KPa

All reference values are valid for the dominant and non-dominant hand using the Martin Vigorimeter. The threshold value corresponds to the p=0.05 level. Adapted from Merkies et al.(60)

Bautmans ea. *Acta Clinica Belgica 2009*

Criteria Used to Define Frailty

- **Weight loss:** "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year − current measured weight)/(weight in previous year) = K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.
- **Exhaustion:** Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion c

"How often in the last week did you feel this way?"

(a) I felt that everything I did was an effort;
(b) I could not get going.

0 = rarely or none of the time (<1 day),
1 = some or a little of the time (1–2 days),
2 = a moderate amount of the time (3–4 days),
3 = most of the time.

Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.

BMI 23.1–26	≤17.5
BMI 26.1–29	≤18
BMI > 29	≤21

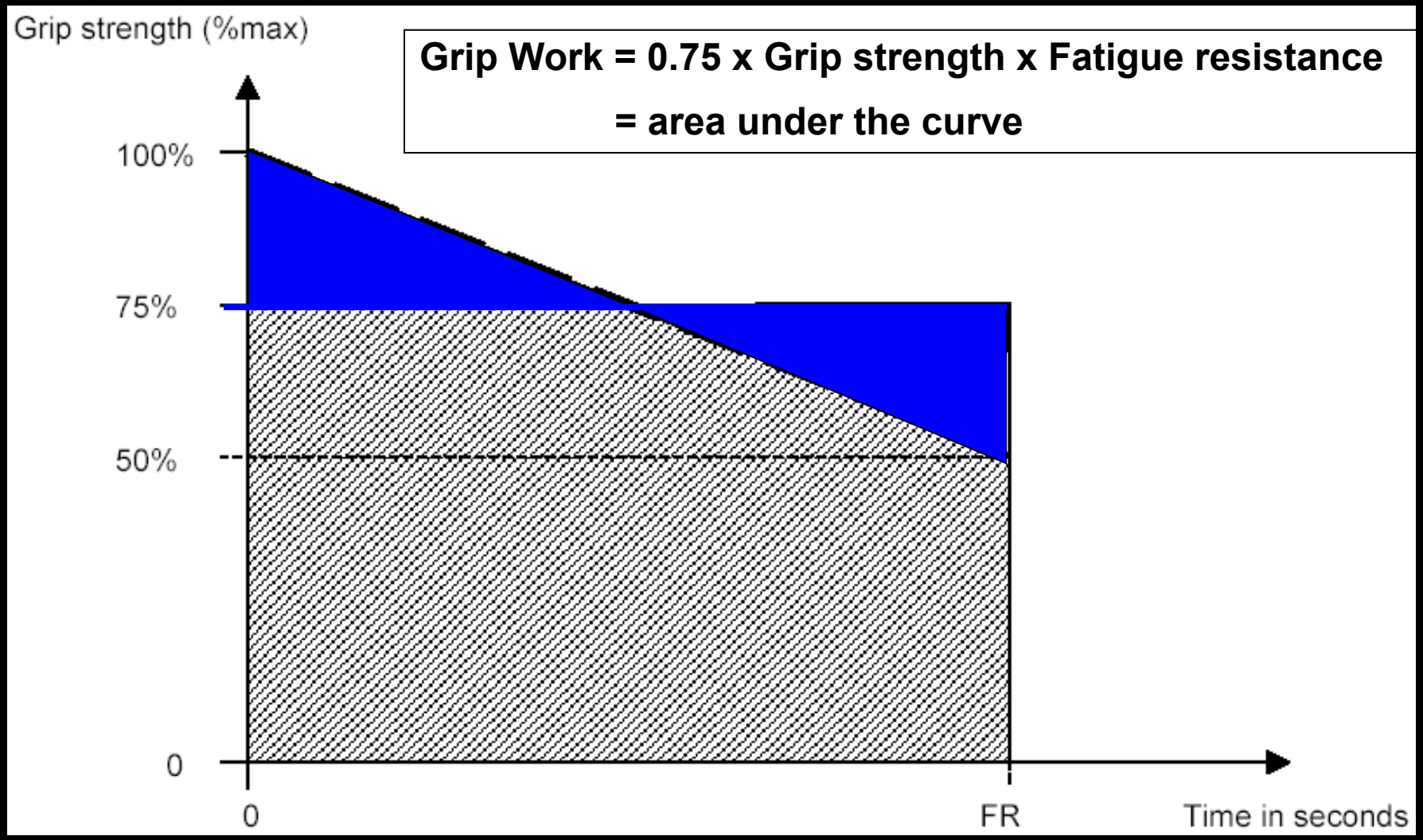
Fried ea. *JGerontol 2001*

Fatigue resistance

- Based on max. grip strength
- Time (seconds) until grip strength ↓ to 50%Max
- Reliability
  - Inter-observer ICC(3,1)= 0.77 – 0.91
  - Intra-observer ICC(3,1)= 0.82 – 0.94

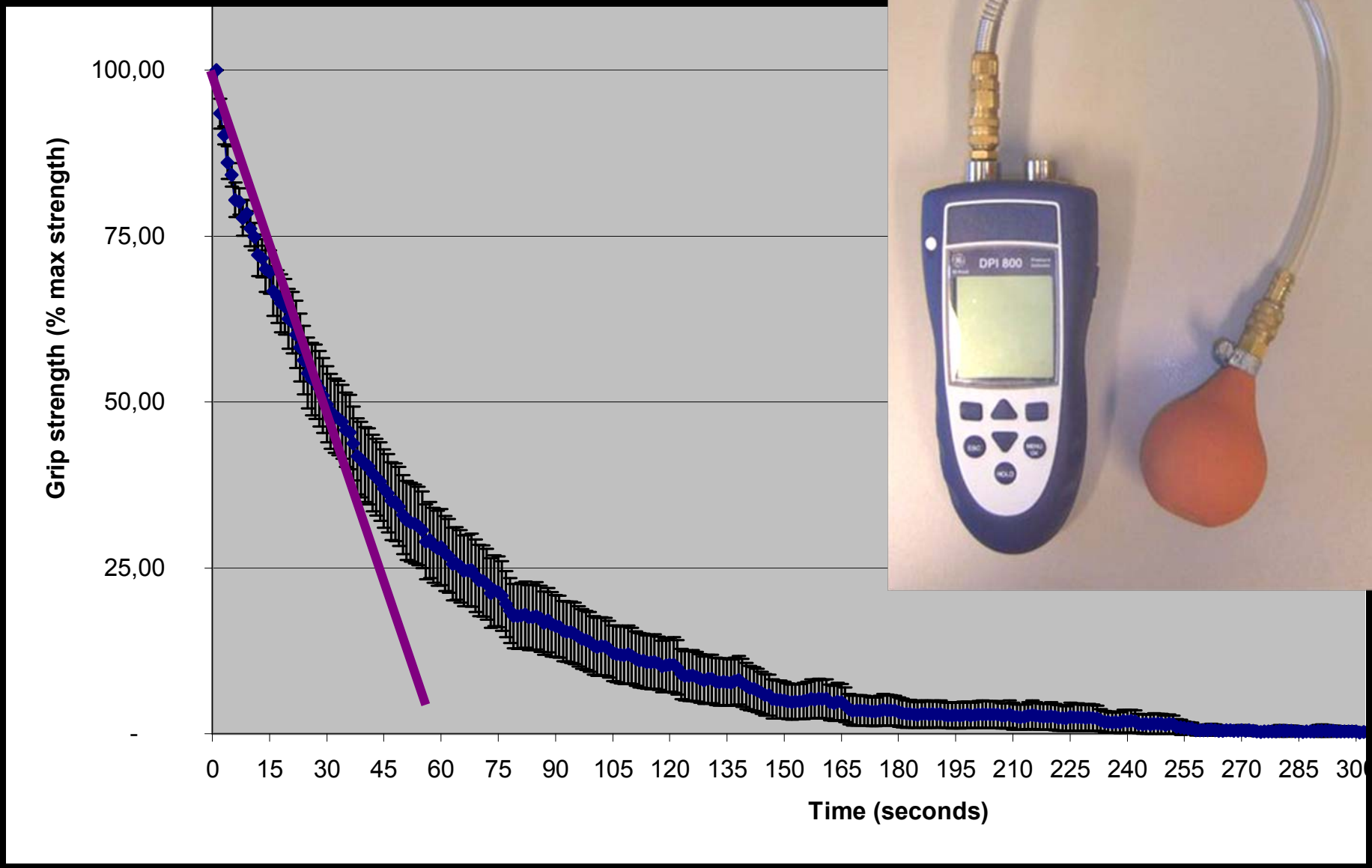
Bautmans & Mets *J Ageing Clin Exp Research 2005*

STRENGTH ENDURANCE

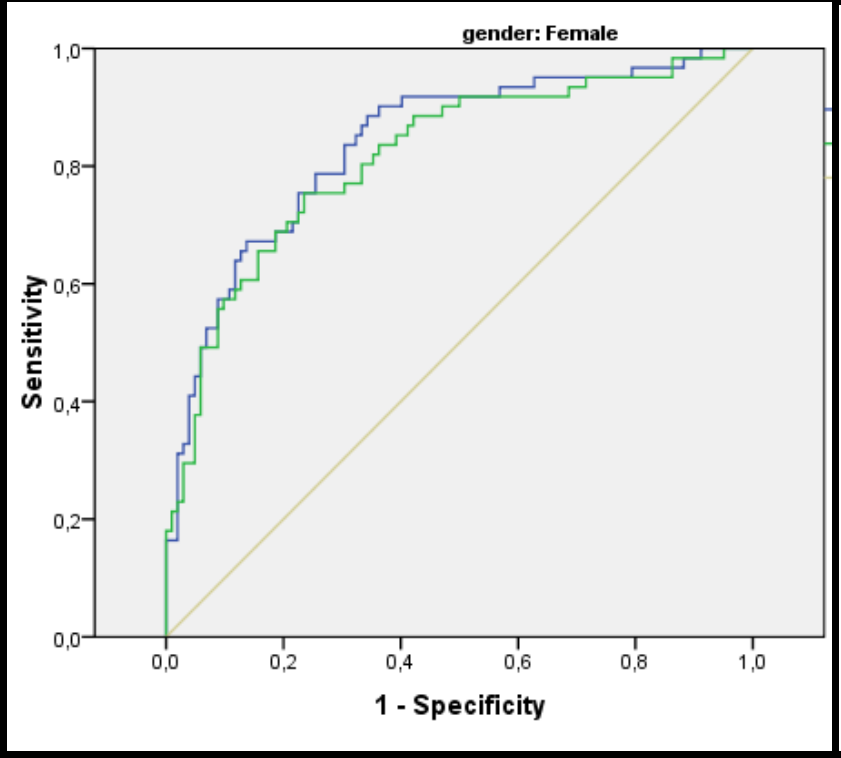


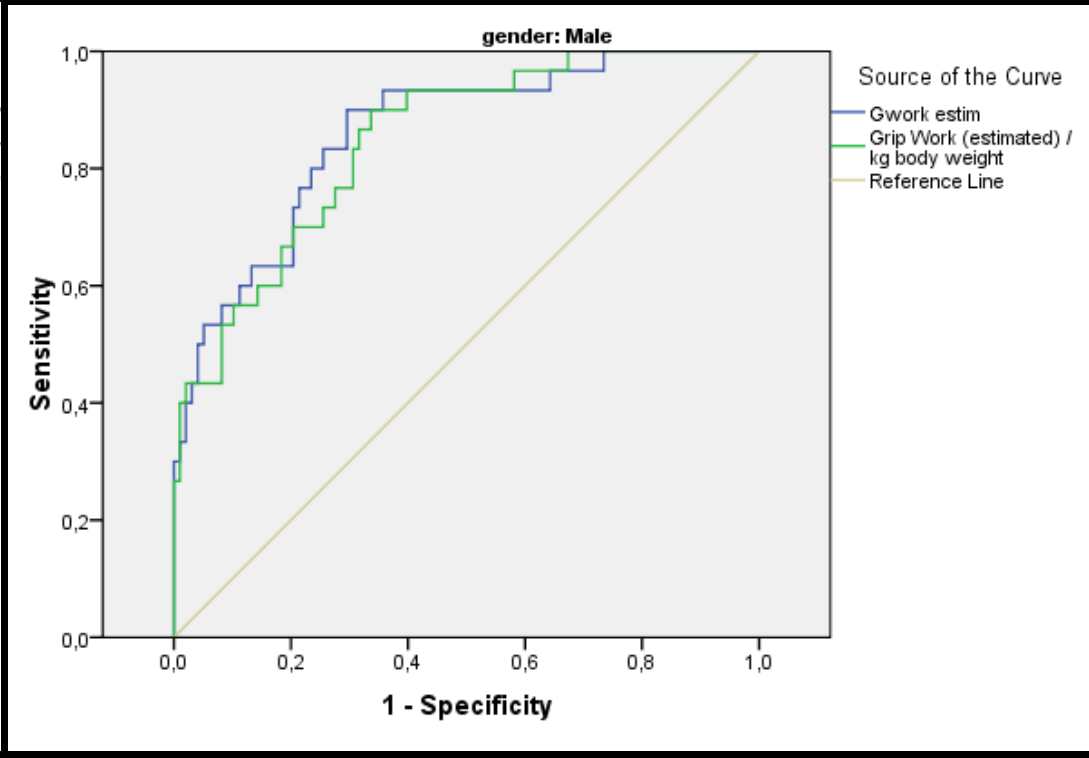
Bautmans ea. *BMC Geriatrics 2007, JAGS 2008, JGerontol 2010*

N=291, age 20-93 yrs



Bautmans ea. *J Nutr Health & Ageing 2011*





	Grip Work		Grip Work/kg Body mass
	Male	Female	Male & Female
Cutoff	3000 KPa*sec	2500 KPa*sec	40 KPa*sec/kg
AUC	86%	84%	83%
Sens	90%	80%	80%
Spec	70%	70%	68%

Bautmans ea. *Acta Clinica Belgica 2009*

Muscle weakness & Fatigue

Underlying mechanisms

Table 2. Factors Contributing to Sarcopenia.

	Type	Factor
↓ Anabolism	Endogenous	↓ Hormonal stimulation (Growth Hormone, IGF-1, Testosterone, Oestrogen)
		Loss of motorneurones, denervation of muscle fibres
		↑ non-contractile tissue in muscle
	Exogenous	↓ Physical activity
		Bed rest, immobilisation
		Malnutrition
↑ Catabolism	Endogenous	↑ Basal inflammatory profile (IL-6, TNF-α)
	Exogenous	Stress-induced inflammation: Life events, Depression
		Disease

Bautmans ea. *Acta Clinica Belgica, 2009; 64-4*

Increase of 0.016 pg/mL per year in healthy subjects

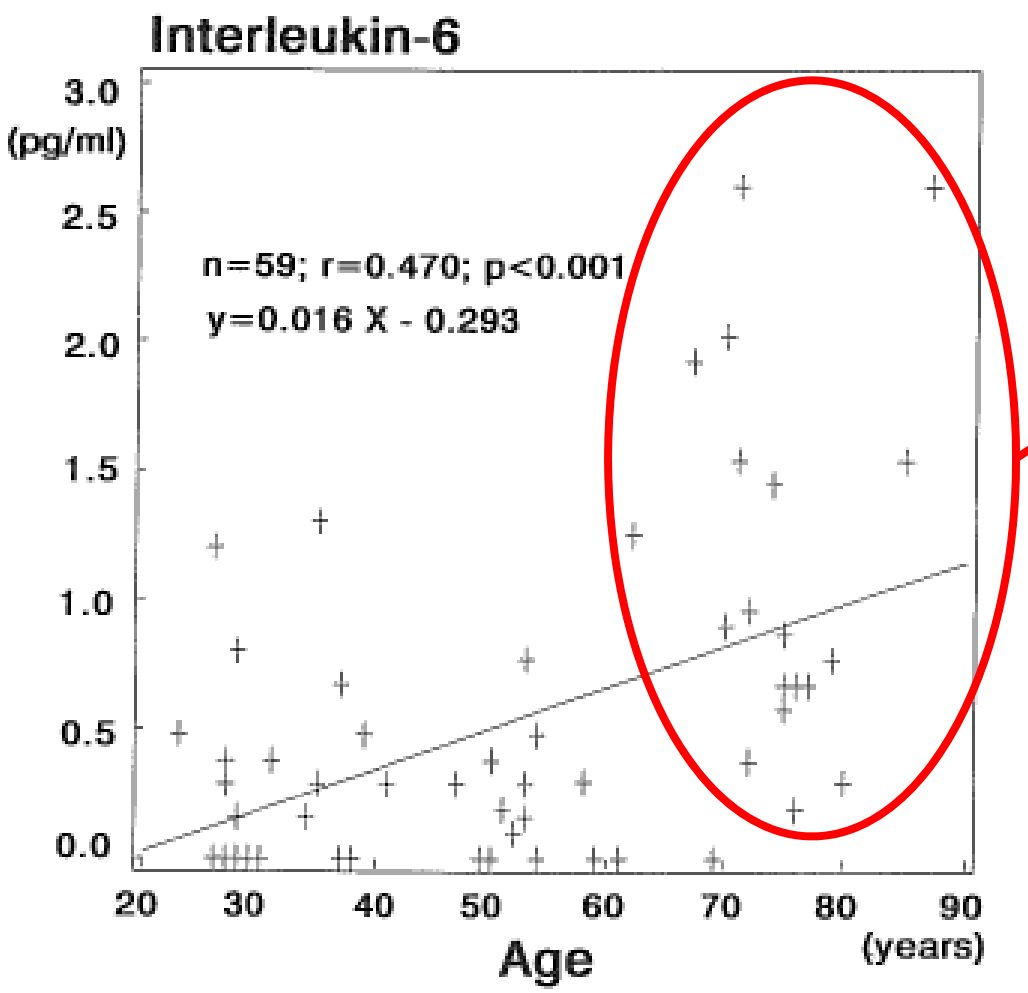


FIG. 1. Correlation of interleukin-6 and donor age.

Basal inflammatory profile

- ↑IL-6, TNF-α, …
- Muscle weakness
- Muscle atrophy

Cesari ea *J Gerontol 2004*

Hager ea *Neurobiol of Ageing 1994*

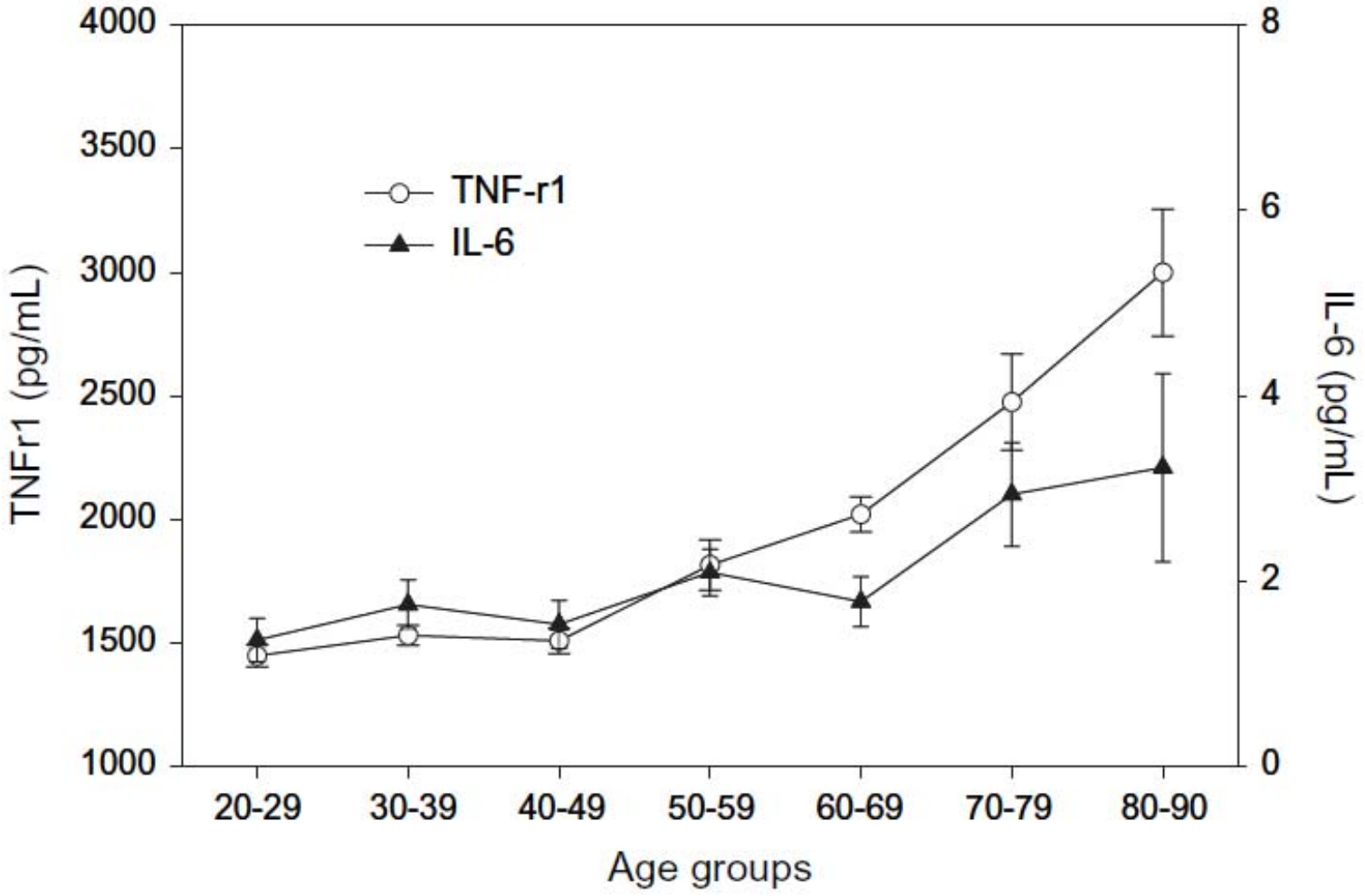


Figure 1. Plasma levels of tumor necrosis factor-receptor 1 (TNF-r1) and interleukin (IL)-6 (mean ± *SE*) by age (n = 1,411).

Stowe ea. *J Gerontol 2009; 65A: 429-433*

N=79, age= 80 years, 5 years follow-up

158 *P. Hämäläinen et al.*

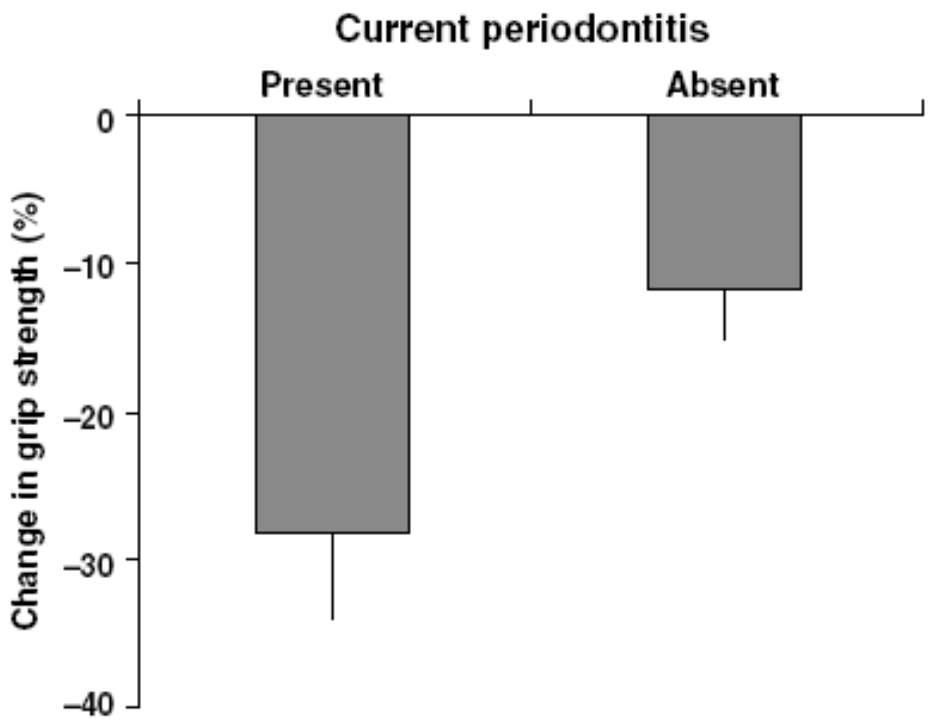


Figure 2 Percentage change in handgrip strength over 5 years among those with and without periodontitis at baseline ($p = 0.015$). Values are adjusted for gender, height, weight, number of chronic conditions and physical activity. Means with standard errors are shown.

Hamalainen ea *Gerodontology 2004: 21; 155–160*

BED REST

N=680, non-disabled, aged >70 yrs, 18 months follow-up

60% at least 1 episode bed rest!

Gill ea. *J Gerontol 2004*

11 healthy subjects, aged 67±5 yrs, 10days bed rest

Table 2. Lower Extremity Muscle Performance and Aerobic Capacity

Test	Pre-Bed Rest	Post-Bed Rest	% Change	*p* Value
Knee extension ($N = 11$)				
1-RM	–	–	−13.2 ± 3.5	.004
Isometric (N)	133.7 ± 15.1	117.6 ± 13.6	−11.2 ± 3.9	.017
Concentric 180° (N · m/s)	69.9 ± 8.1	60.1 ± 7.0	−13.5 ± 4.4	.011
Knee flexion ($N = 11$)				
Isometric (N)	76.8 ± 10.0	68.1 ± 10.5	−14.2 ± 3.6	.003
Concentric 60° (N · m/s)	80.3 ± 8.8	71.6 ± 9.4	−11.8 ± 4.6	.03
Concentric 180° (N · m/s)	51.8 ± 7.7	46.6 ± 8.2	−13.2 ± 4.3	.01
Stair ascent power (N · m/s) ($N = 8$)	403 ± 67	337 ± 48	−14.0 ± 4.1	.01
VO_{2max} (mL/kg/min) ($N = 9$)	22.7 ± 2.0	19.72 ± 1.7	−12.2 ± 4.5	.04

Notes: All values are mean ± standard error of the mean.
1-RM = one repetition maximum; VO_{2max} = maximal oxygen uptake.

Kortebein ea. *J Gerontol 2008*

Immobilisation

Inflammation

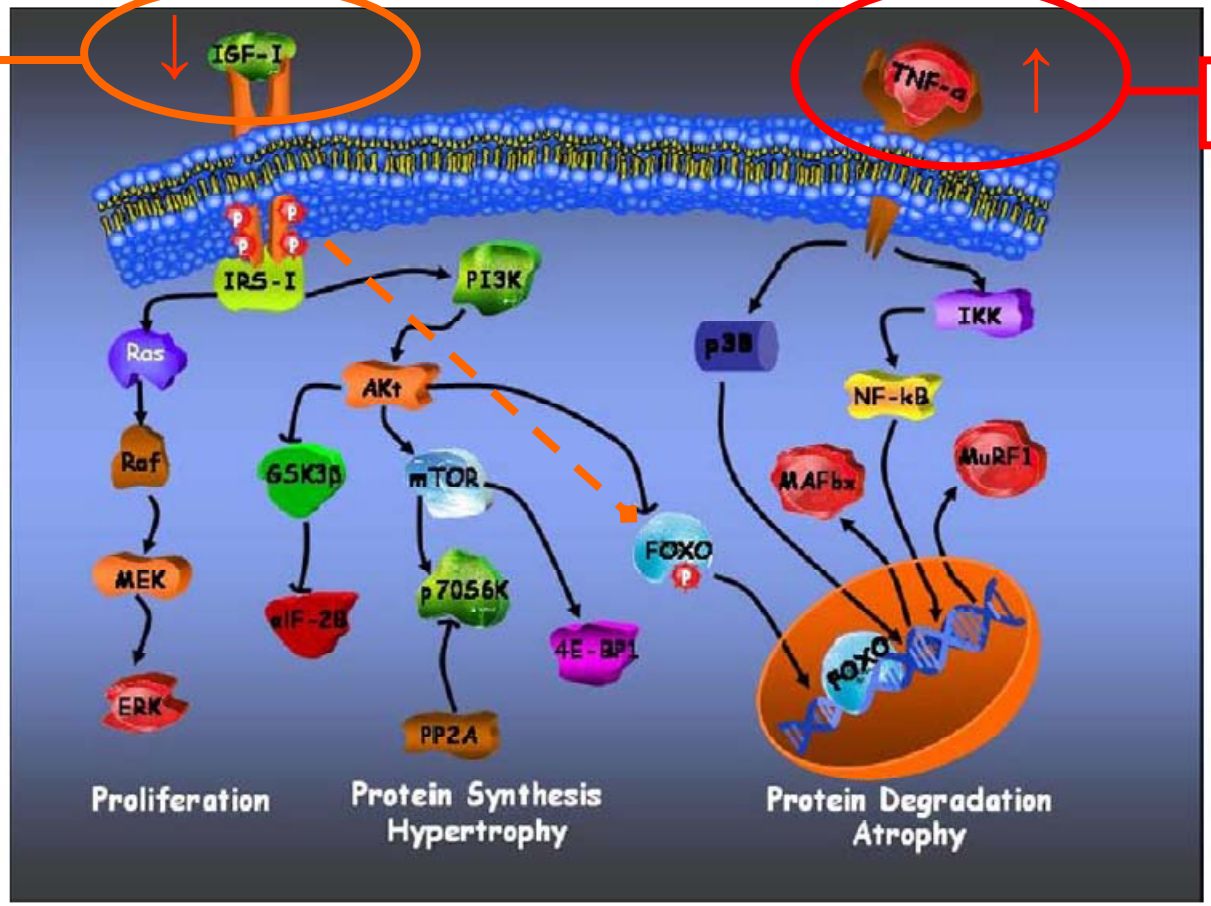


Fig. 5. Hypertrophy and atrophy signalling via Akt. Increases in RAS/RAF/MEK/ERK signalling results in an up regulation of cellular proliferation in response to IGF-I binding to its receptor. Activation of IRS-I/PI3K/Akt1 pathway leads to an increase in hypertrophy via mTor and p70S6k up regulation. Akt activation inhibits FOXO binding to DNA preventing MAFbx and MuRF1 activity and subsequent protein breakdown. NF-κB activation occurs following the degradation of its associated inhibitory protein IκB, leading to the nuclear transport of NF-κB transcription factors and MAFbx and MuRF-1 activity, resulting in protein breakdown.

Saini ea. *Ageing Research Reviews 2009;8:251–267*

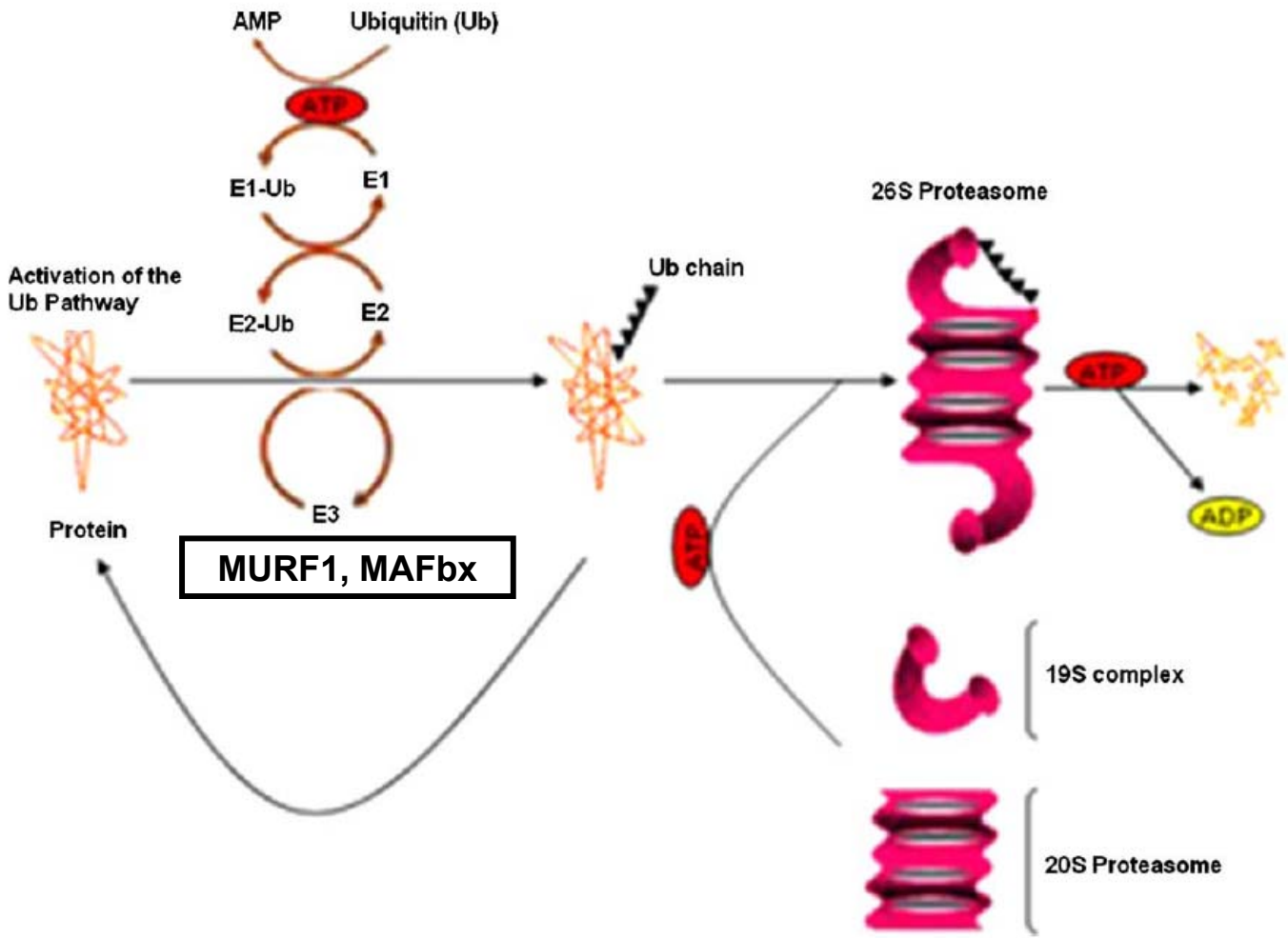


Fig. 6. The Ub-proteasome pathway which results in intracellular protein breakdown. Proteolysis is catalysed by the 26S proteasome which degrades ubiquitinated proteins into small peptides following the tagging of the whole protein via the ATP dependent activation of the E1 and E2 proteins. The ubiquitinated proteins are then presented to the proteasome for disassembly into their constituent peptides (Lecker et al., 1999, with permission).

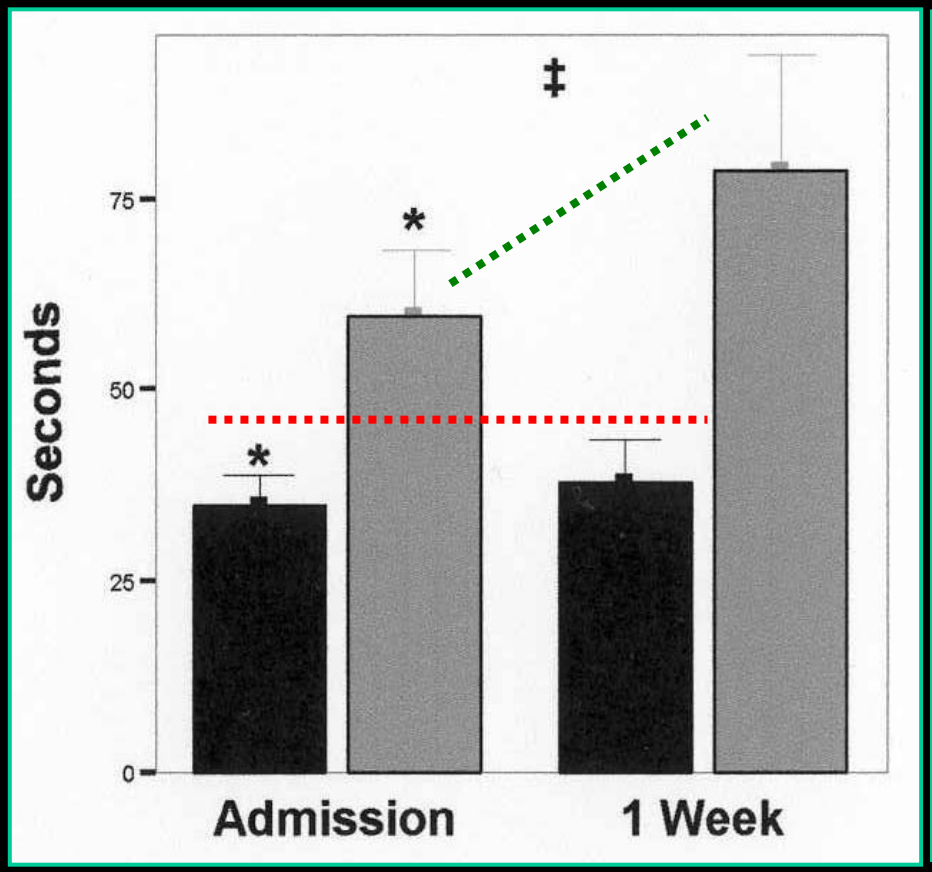
Saini ea. *Ageing Research Reviews 2009;8:251–267*

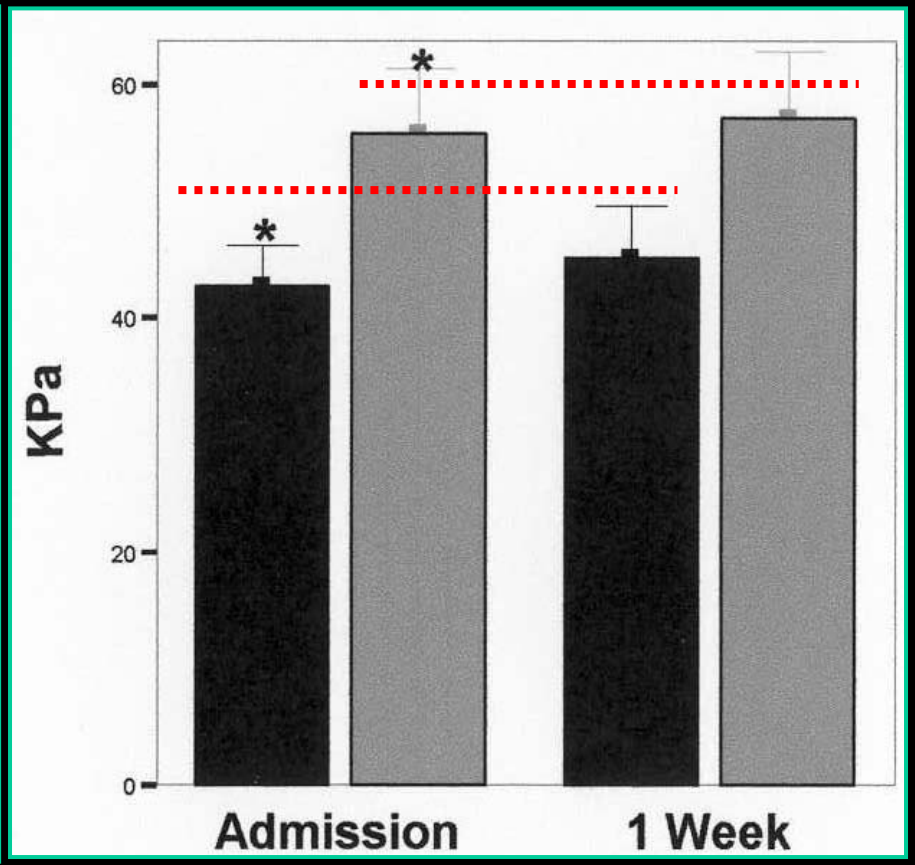
Acute accelerating factors

- Serious systemic inflammation
  - Inflammatory conditions (e.g. infection, surgery)

N=63, Age=70-98 yrs

Bautmans ea. *J Gerontol 2005*





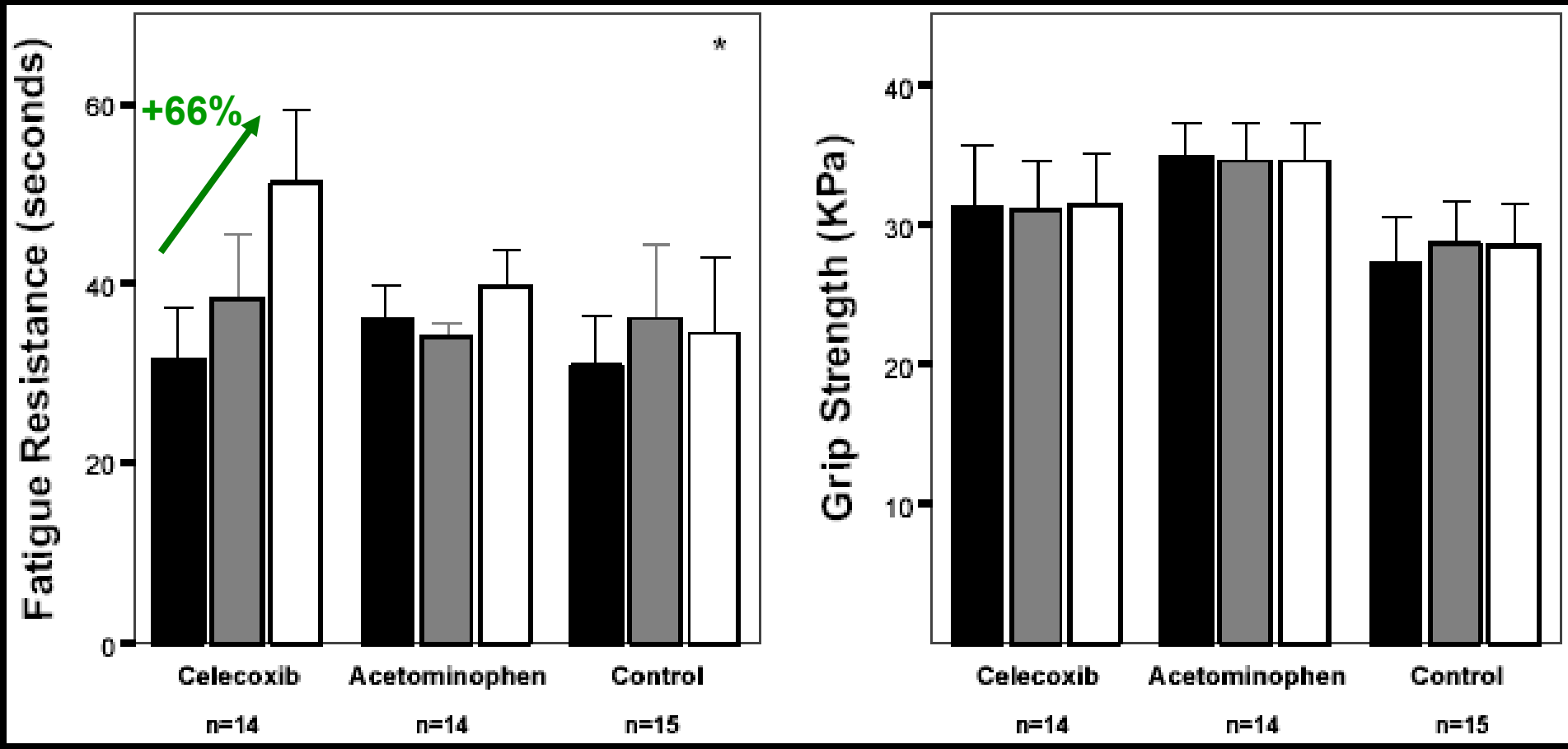
Inflammatory Patients **Non-inflammatory Patients**

* Inflammatory Patients Significantly Weaker than Non-Inflammatory ($p<0.05$)

‡ Significant difference in evolution ($p<0.05$)

Hospitalized geriatric patients with acute infection, N=43, aged 84 ± 6 years

Mets, Bautmans ea. *Am J Geriatr Pharmacother 2004*

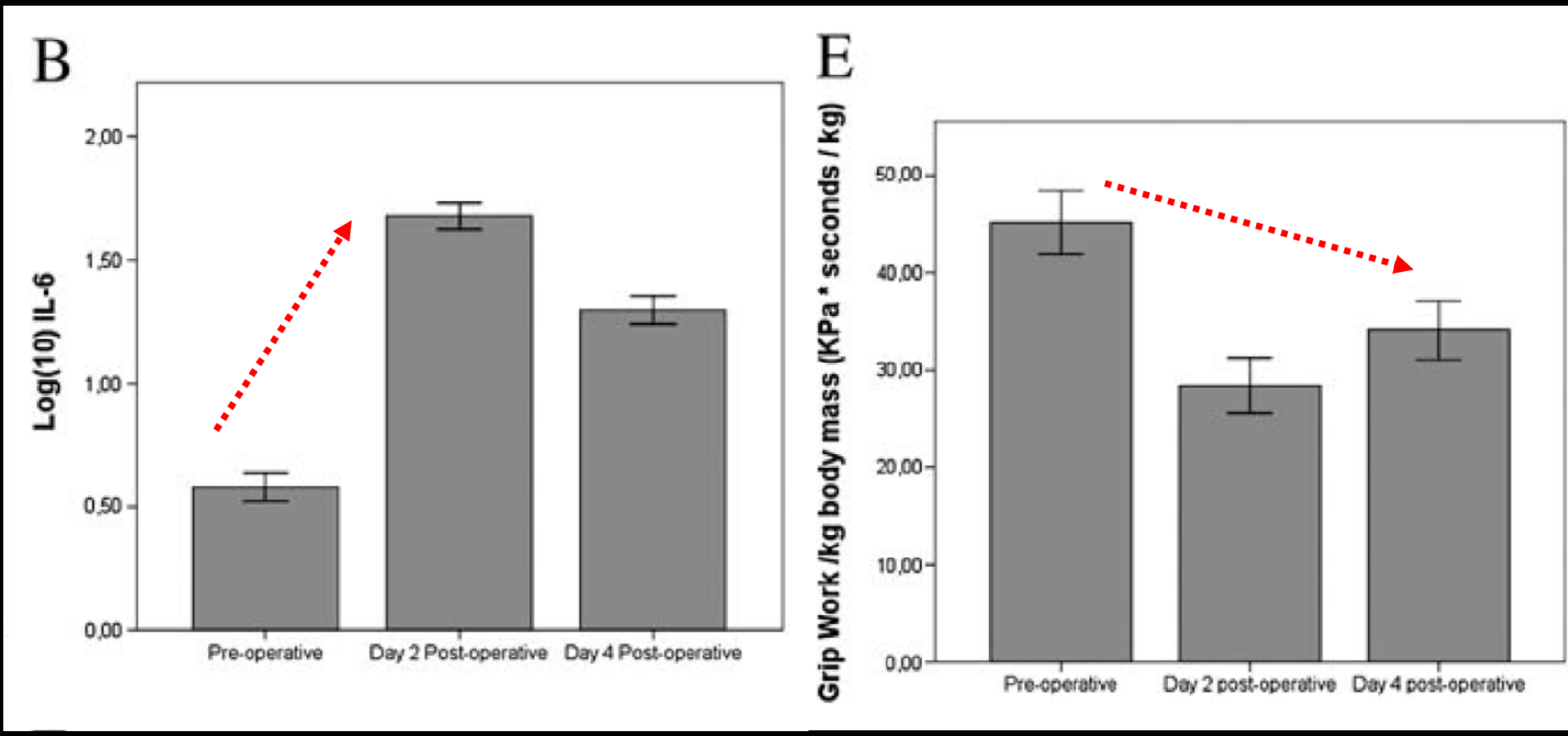


Admission | After 1 Week | After 2 weeks

* Evolution FR significantly different between 3 groups ($p=0.021$) and improvement celecoxib group significantly better than acetaminophen group ($p<0.05$) control group ($p<0.05$)

SURGERY

N=66, age 24-91 yrs, elective abdominal surgery



Bautmans ea. *J Gerontology 2010*

N=66, age 24-91 yrs, elective abdominal surgery

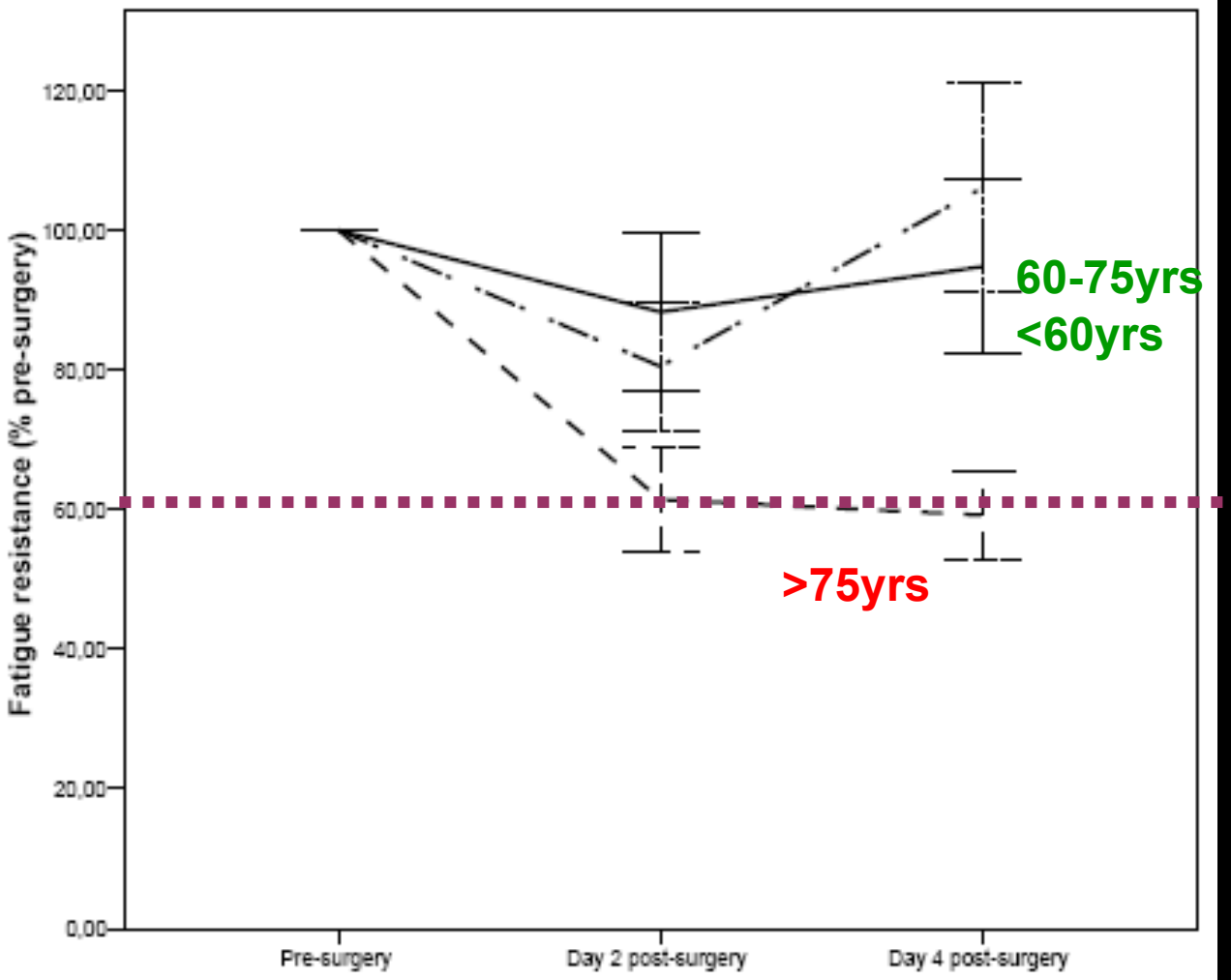


Figure 2 - Evolution of post-surgical muscle fatigue resistance according to age. Patients aged >75 years (N=20, dotted line) worsened significantly more and recovered significantly less rapidly for fatigue resistance at day4 post-surgery compared to the younger (age<60 years: N=29, plain line; aged 60-75 years: N=29, semi-dotted line) patients (Repeated measures ANOVA, interaction between age and fatigue resistance $p<0.05$).

Bautmans ea. *J Gerontology 2010*

Sarcopenia

Partly reversible

Cost of Sarcopenia USA 2000

Group	Muscle Mass Range, kg/m^2	Prevalence in Population, %	Relative Risk Disability	Population Attributable Risk for Disability, %*	Cost, billion $
Older men					
Normal muscle	≥10.76	35.7	1.00	—	—
Moderate sarcopenia	8.51–10.75	53.1	3.48	56.8	7.18
Severe sarcopenia	≤8.50	11.2	4.60	28.7	3.63
Older women					
Normal muscle	≥6.76	68.7	1.00	—	—
Moderate sarcopenia	5.76–6.75	21.9	1.46	9.2	2.70
Severe sarcopenia	≤5.75	9.4	3.15	16.8	4.96

* [prevalence (RR − 1)]/[1+prevalence (RR − 1)].

Janssen ea J Am Geriatr Soc 2004

Total 18,5 billion dollar!

10% reduction of sarcopenia = 1,1 billion dollar savings!

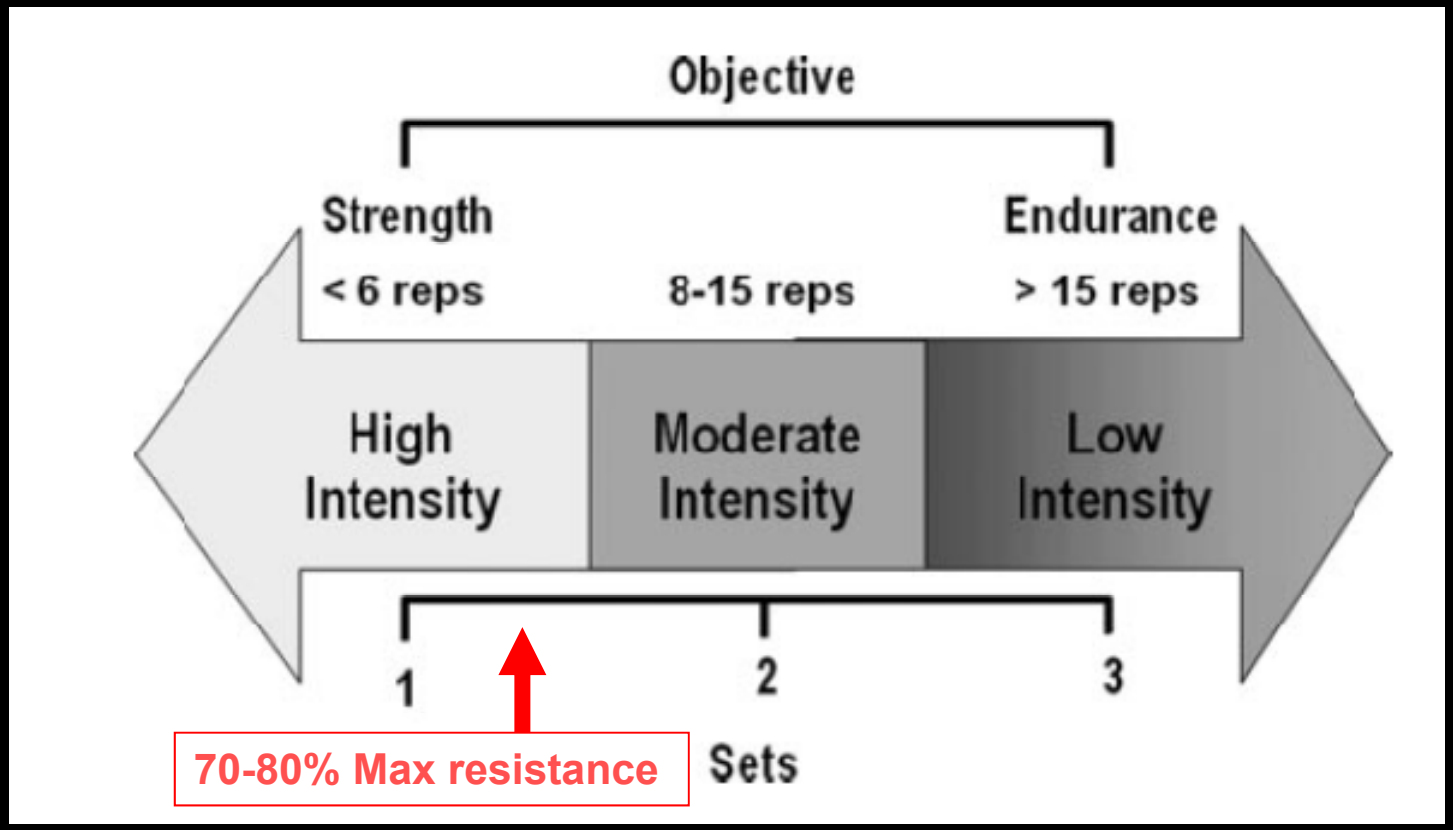
Countering Sarcopenia

Bautmans ea. *Gerontology 2005*

Bennell ea. 2000

Bautmans ea. *BMC Geriatrics 2005*

Bautmans ea. *J Rehab Med 2008*



Adapted from Williams ea *Circulation 2007*

Strength training effective in elderly persons

- **+ 30-170% strength in 6 weeks**
- **Even in oldest old (age >90 yrs)**

Latham ea. *The Cochrane Library 2003*

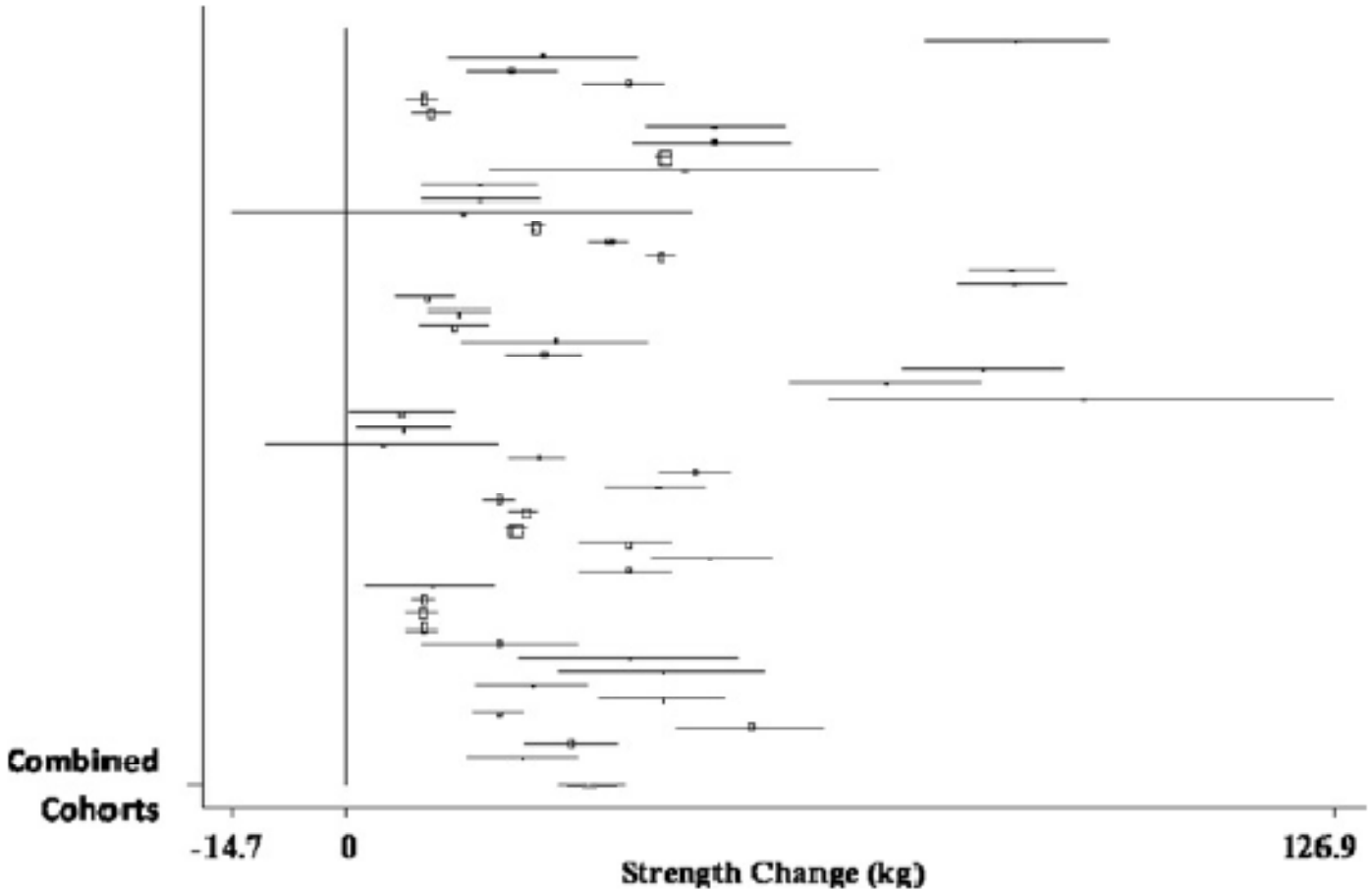


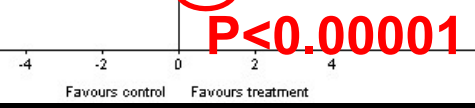
Fig. 2. Forest plot of effect sizes and 95% confidence intervals for all 51 cohorts (32 studies) representing leg press, based on the random-effects meta-analysis results.

Peterson ea. *Ageing Research Reviews 2010*

Review: Progressive resistance strength training for physical disability in older people
Comparison: 01 Strength
Outcome: 01 Main Lower Limb Strength (LL) Measure - PRT versus control

Study	Treatment N	Mean (SD)	Control N	Mean (SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Ades 1996	12	46.00 (16.00)	12	29.00 (13.00)		2.0	1.13 [0.25, 2.00]
Baker 2001	19	40.60 (31.00)	19	34.80 (16.40)		2.7	0.23 [-0.41, 0.87]
Bermon 1999	16	23.60 (4.00)	16	19.20 (3.60)		2.3	1.13 [0.37, 1.88]
Brandon 2000	43	60.10 (19.90)	42	47.30 (13.60)		3.6	0.74 [0.30, 1.18]
Buchner 1997	22	99.00 (31.00)	29	84.00 (32.00)		3.0	0.47 [-0.09, 1.03]
Castaneda 2001	14	55.90 (22.40)	12	38.80 (14.00)		2.2	0.87 [0.06, 1.68]
Chandler 1998	44	63.70 (27.00)	43	48.30 (23.00)		3.6	0.61 [0.18, 1.04]
Charette 1991	13	33.90 (7.60)	6	23.10 (3.40)		1.4	1.55 [0.44, 2.67]
Collier 1997	24	53.80 (37.00)	12	32.80 (11.70)		2.5	0.66 [-0.05, 1.37]
Damush 1999	33	58.00 (17.60)	29	52.00 (17.40)		3.3	0.34 [-0.16, 0.84]
Ettinger 1997	120	90.20 (21.90)	127	87.00 (21.40)		4.3	0.15 [-0.10, 0.40]
Haykowsky 2000	10	367.00 (47.00)	8	290.00 (53.00)		1.5	1.48 [0.40, 2.55]
Hortobagyi 2001	18	1122.00 (340.00)	9	877.00 (203.00)		2.1	0.78 [-0.05, 1.62]
Jette 1996	35	52.00 (18.50)	38	45.80 (19.10)		3.5	0.33 [-0.14, 0.79]
Jette 1999	91	15.00 (5.30)	102	13.70 (5.50)		4.2	0.24 [-0.04, 0.52]
Jones 1994	30	55.17 (15.87)	12	50.17 (8.75)		2.6	0.34 [-0.33, 1.02]
Judge 1994	22	8.00 (3.80)	23	6.90 (1.90)		2.9	0.36 [-0.23, 0.95]
Latham 2001	10	12.30 (7.10)	10	7.40 (3.50)		1.9	0.84 [-0.08, 1.76]
Latham 2002	108	12.60 (5.40)	112	12.90 (5.30)		4.3	-0.06 [-0.32, 0.21]
Maiorana 1997	12	132.40 (26.40)	14	116.60 (26.60)		2.2	0.58 [-0.21, 1.37]
McCartney 1995	20	124.00 (22.00)	23	98.00 (18.00)		2.7	1.28 [0.62, 1.94]
Nelson 1994	20	37.80 (10.40)	19	25.80 (8.50)		2.5	1.23 [0.54, 1.93]
Newnham 1995	12	15.30 (7.50)	12	7.40 (3.60)		1.9	1.30 [0.40, 2.19]
Nichols 1993	15	39.20 (12.70)	15	32.20 (9.70)		2.4	0.60 [-0.13, 1.34]
Parkhouse 2000	13	98.00 (21.60)	9	54.00 (18.00)		1.5	2.09 [1.00, 3.18]
Pollock 1991	20	53.40 (21.10)	12	43.20 (20.30)		2.4	0.48 [-0.25, 1.20]
Pu 2001	9	1630.00 (516.00)	7	1292.00 (352.00)		1.6	0.71 [-0.32, 1.73]
Rall 1996	8	47.30 (14.80)	6	32.20 (11.20)		1.4	1.05 [-0.10, 2.21]
Rhodes 2000	20	33.50 (4.30)	18	28.00 (4.00)		2.5	1.29 [0.59, 2.00]
Schilke 1996	10	67.40 (28.60)	10	36.30 (27.80)		1.8	1.06 [0.11, 2.01]
Simpson 1992	14	24.80 (14.00)	14	25.10 (14.00)		2.4	-0.02 [-0.76, 0.72]
Singh 1997	17	3241.00 (191.00)	14	2756.00 (334.00)		2.0	1.78 [0.93, 2.64]
Sipila 1996	12	382.00 (116.00)	10	332.00 (77.00)		2.0	0.48 [-0.37, 1.33]
Skelton 1995	20	239.70 (76.30)	20	242.90 (63.70)		2.8	-0.04 [-0.66, 0.58]
Skelton 1996	9	279.60 (68.10)	9	195.20 (52.80)		1.6	1.32 [0.27, 2.36]
Taaffe 1996	7	159.80 (30.70)	11	116.10 (18.50)		1.4	1.75 [0.60, 2.89]
Taaffe 1999	11	62.60 (10.60)	12	45.00 (10.90)		1.8	1.58 [0.62, 2.54]
Topp 1993	25	101.20 (40.00)	30	87.30 (32.90)		3.1	0.38 [-0.16, 0.91]
Tsutsumi 1997	13	30.90 (7.00)	14	25.80 (9.20)		2.3	0.60 [-0.17, 1.38]
Westhoff 2000	10	88.70 (21.70)	11	75.70 (31.70)		2.0	0.46 [-0.41, 1.33]
Wood 2001	10	229.10 (97.40)	6	201.70 (97.20)		1.6	0.27 [-0.75, 1.28]
Total (95% CI)	991		957			100.0	0.68 [0.52, 0.84]

Test for heterogeneity chi-square=98.35 df=40 p<0.00001
Test for overall effect=8.32 p<0.00001



Latham et al. The Cochrane Library 2003; 2.

Exercise

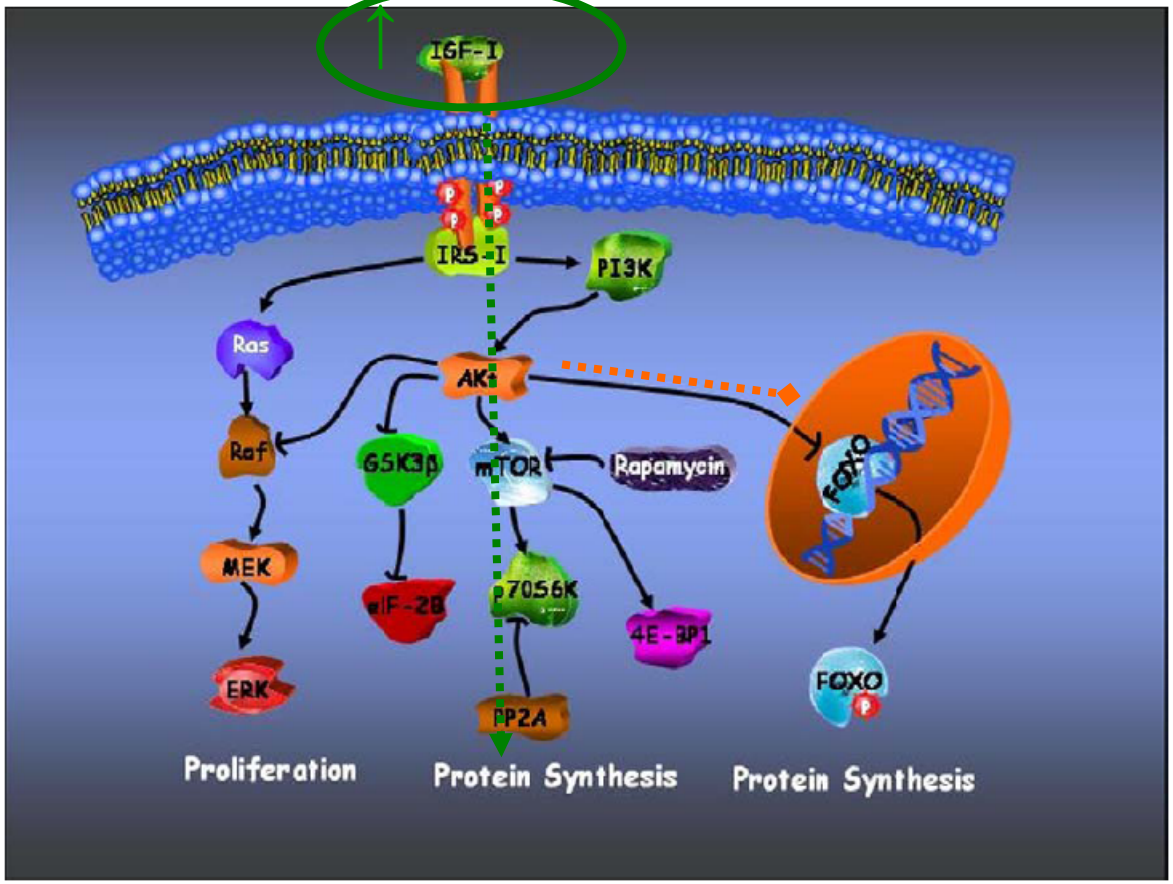
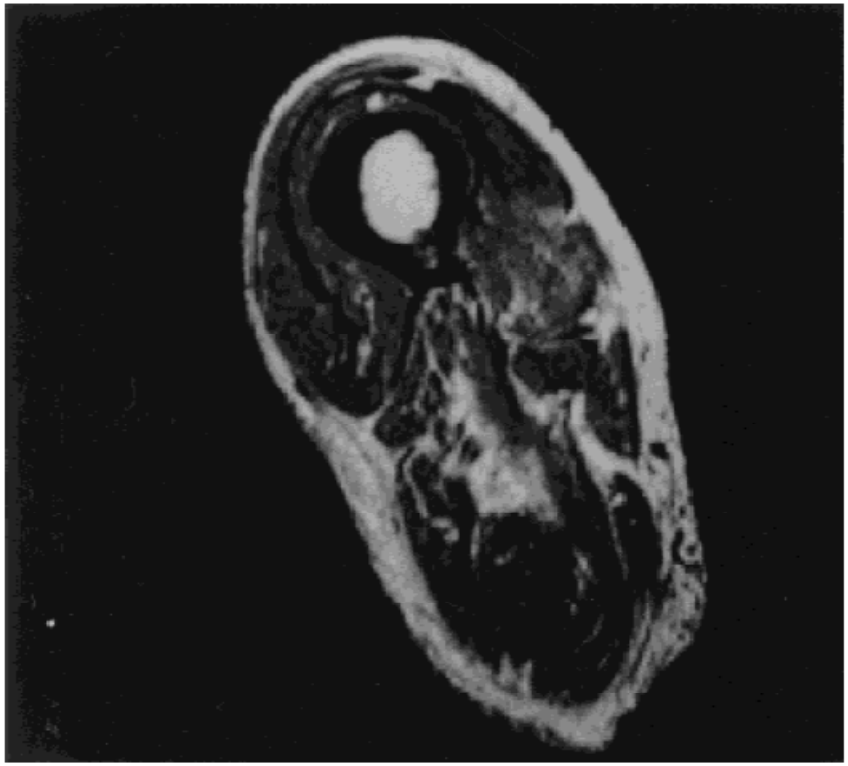


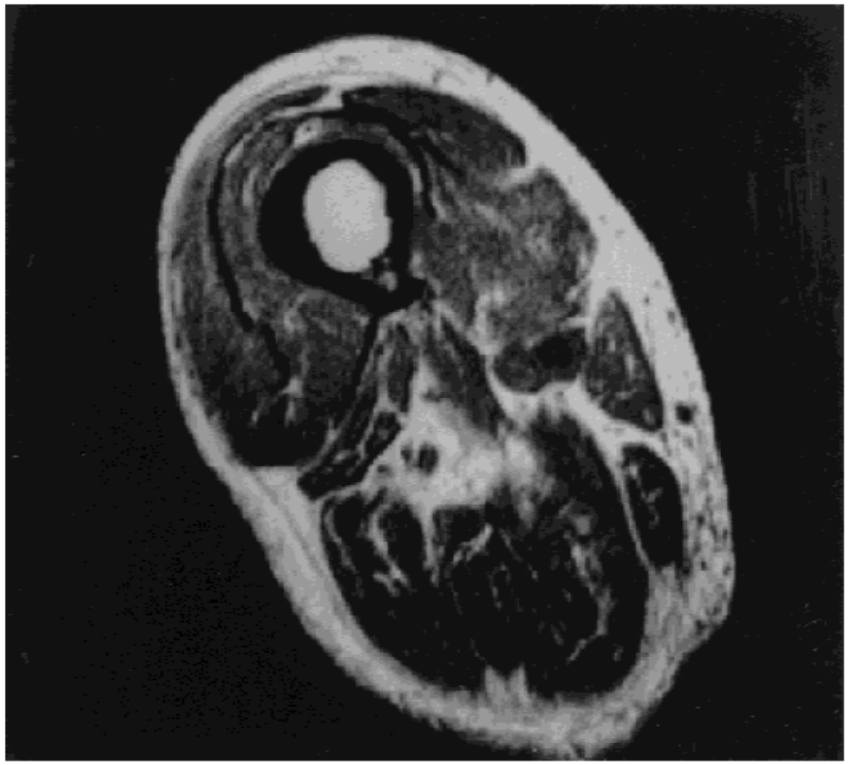
Fig. 4. Signalling pathways involved in hypertrophy. Akt activation leads to the deactivation of FOXO, its release from the DNA strand and exit from the nucleus and binding with the 14-3-3 transport protein to prevent it from becoming active and rebinding to DNA, resulting in a blockade of proteolysis.

Saini ea. *Ageing Research Reviews 2009;8:251–267*

12 weeks strengt training (85-97 j)



Pre

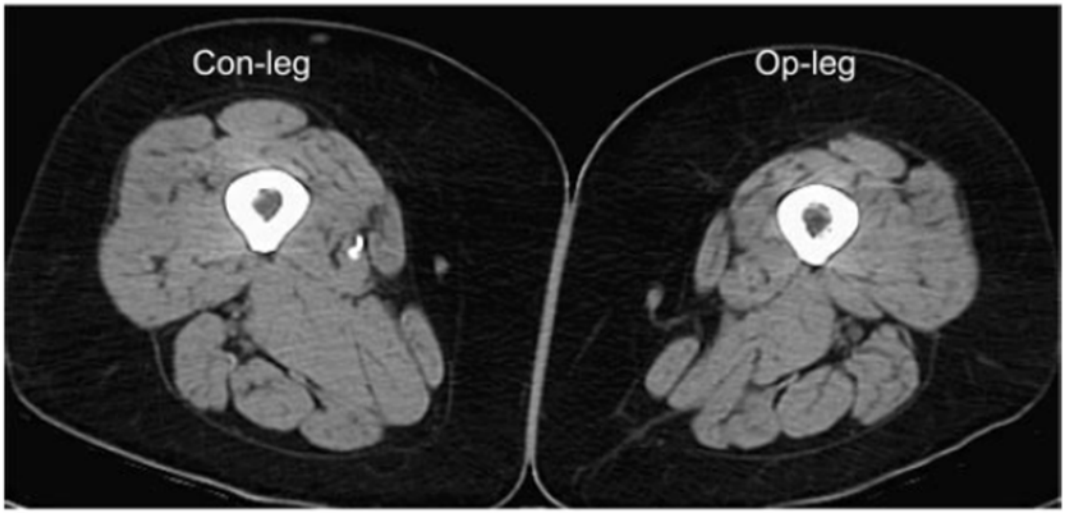


Post

FIGURE 2. MRI images taken at the midthigh region of the male subject CC before (Pre) and after (Post) training (shown to the same scale). Quadriceps LCSA increased by 44% in this subject, who is represented by the triangle symbol with apex upwards in Figures 1, 5, and 6.

Harridge e.a. *Muscle Nerve 1999; 22: 831-839*

Pre-training



Post-training

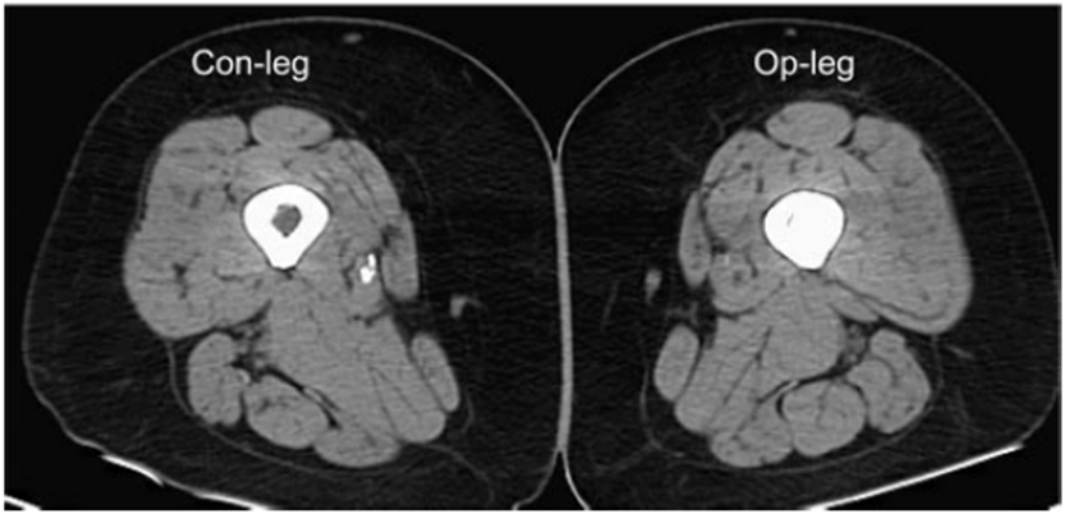


Fig. 1. Computer tomography images taken from the midthigh region of a female subject in the strength training (ST) group before and after training. The 2 images are shown at the same scale. Quadriceps muscle cross-sectional area of the operated side (op-leg) increased 32% in this subject; the nonoperated side (con-leg) did not change from pretraining to posttraining.

Suetta et al. J Appl Physiol 2004; 97: 1954-62

Non-frail elderly:

Strength training in fitness

Frail elderly:

supervised exercise

+ home-based program

Frail or ill Elderly

3.1. Gangrevalidatie ("F"-lijst).

De situaties die gangrevalidatie behoeven worden als volgt gedefinieerd:
"…rechthebbenden vanaf hun 65ste verjaardag, die al eens gevallen zijn met risico op herhaling, te objectiveren door de behandelend geneesheer en kinesitherapeut aan de hand van:
1) de "Timed up & go" test, met een score hoger dan 20 seconden;
en
2) een positief resultaat op ten minste één van twee volgende testen, die allebei moeten worden verricht :
(01) - de "Tinetti" test, met een score kleiner dan 20/28;
(02) - de "Timed chair stands" test, met een score hoger dan 14 seconden."

- → **individually with Physical Therapist**

Rehabilitation for older people in long-term care

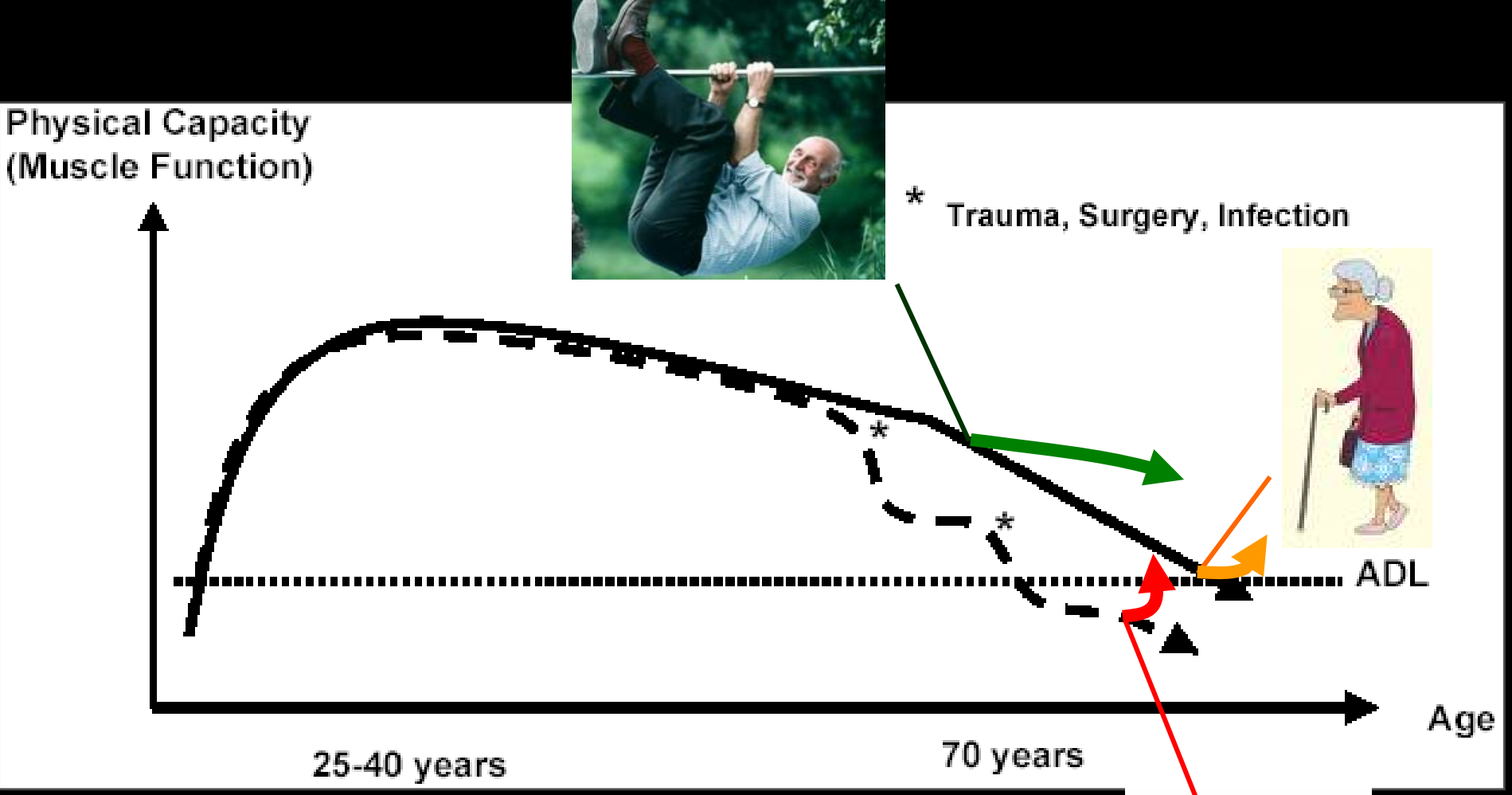
Forster ea *Cochrane review 2010, Age&Ageing 2010*

- 49 trials involving 3611 participants
- overall mean age = 82 yrs (69-89)
- 30 to 45-minute sessions, 3x per week
- physical rehabilitation
  - worthwhile and safe,
  - reducing disability,
  - few adverse events
- no recommendations for best intervention scheme

Organisation

- Supervised EXERCISE sessions
- Home-based EXERCISE program
- Frequency
  - Week 1&2 3 /week 6 sessions
  - Week 3&4 2 /week 4 sessions
  - Week 5-52 1 /week 48 sessions

  1 year 58 sessions



Bautmans ea. *Acta Clinica Belgica, 2009; 64-4*

Thank you.

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www.vub.ac.be/FRIA