Aspetti innovativi nella prevenzione della disabilità

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Outline of today's talk

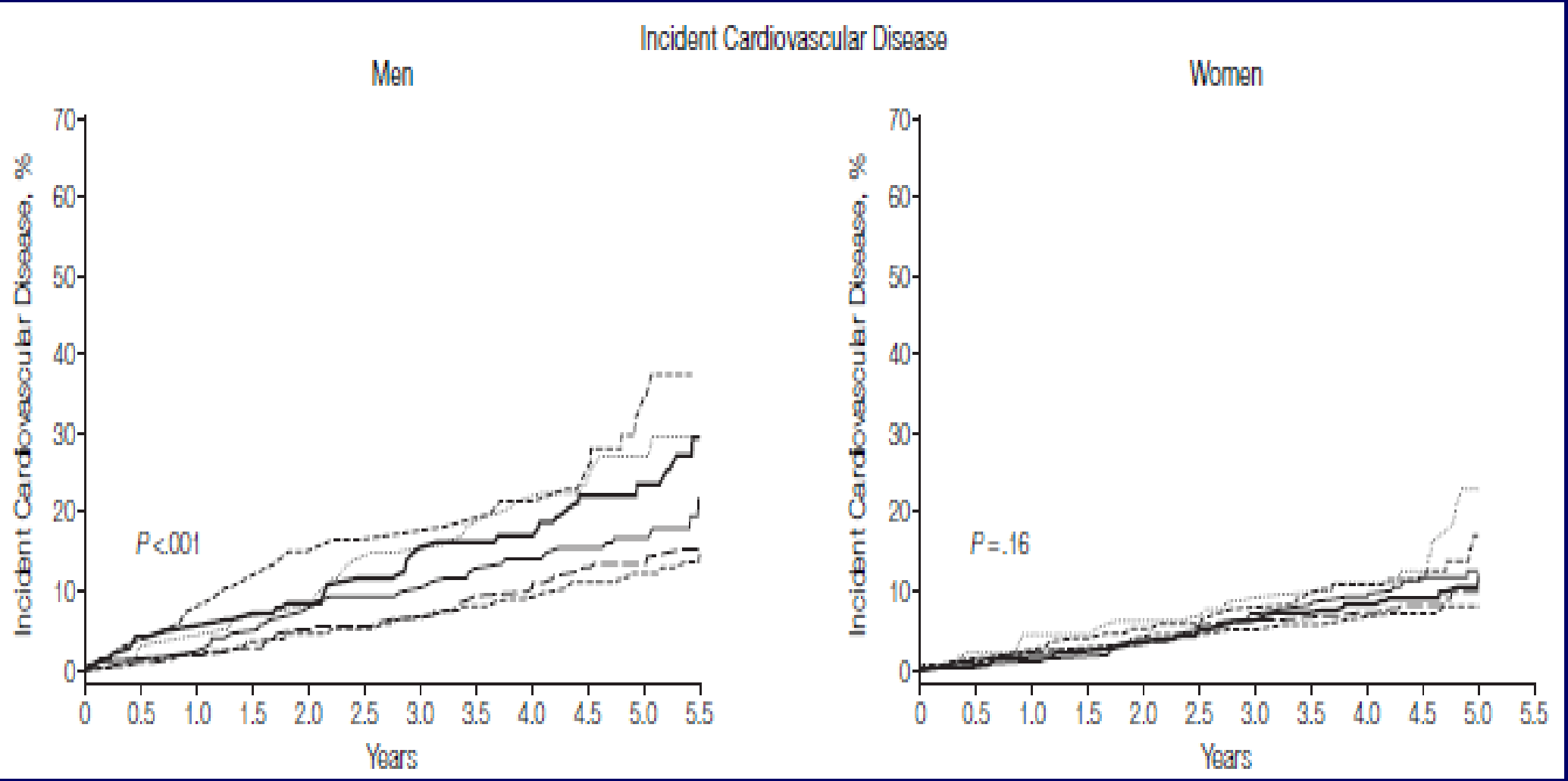
- Relevance of mobility in older adults
- Interventions to avert mobility loss
- The LIFE Study
- The Testosterone Trial
- The ENRGISE Pilot study
- TAME
- Conclusions

Mobility disability in the US in 2010

- About 23.9 million people living in the community had difficulty walking a quarter of a mile or 400 m, including 13.1 million who could not perform this activity
- Among individuals aged 65 and older living in the community, about 15.2 million people (39.4 percent) had difficulty with ambulatory activities, of which 11.2 million had severe difficulty

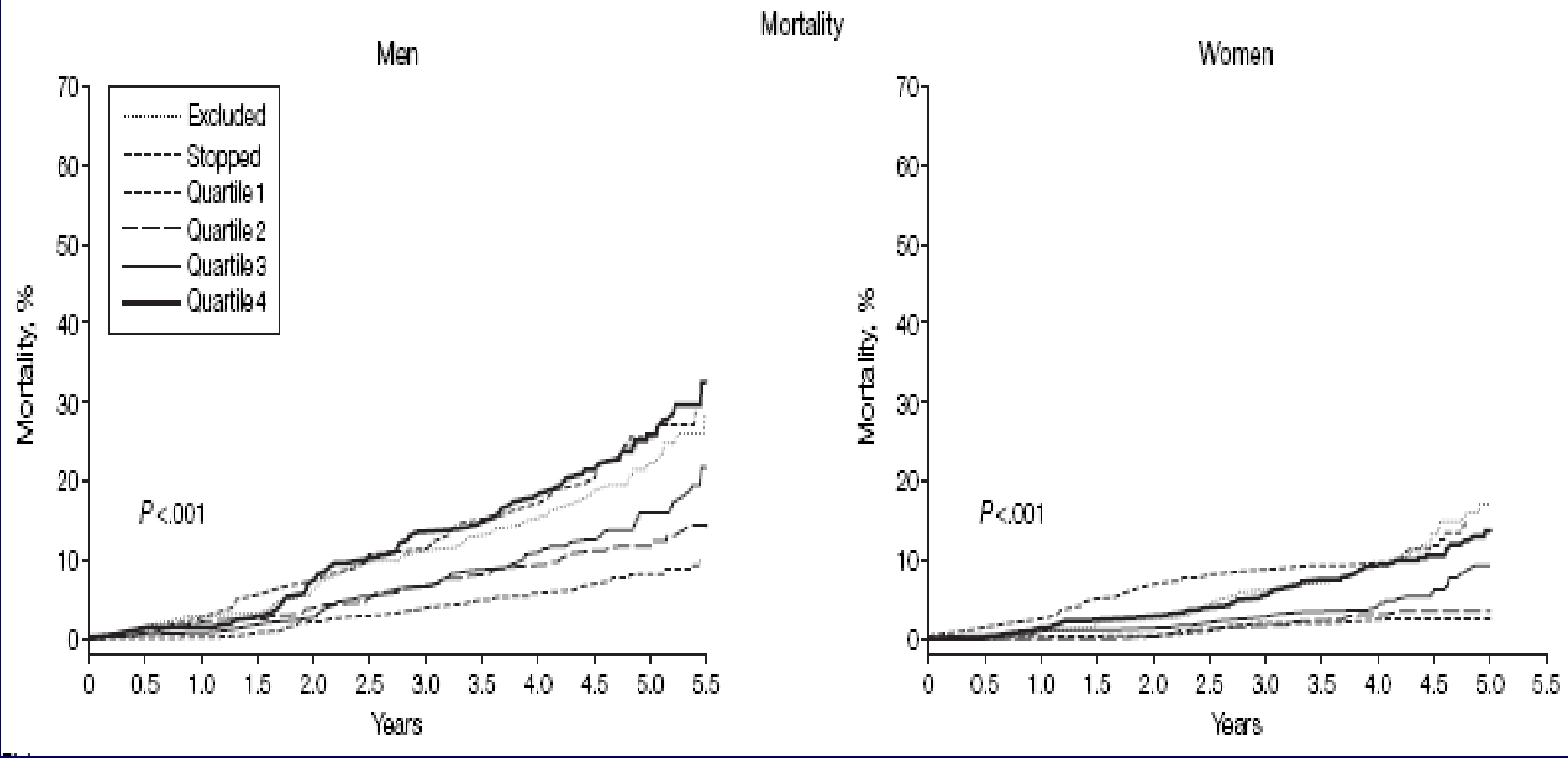
US Census Bureau, Current Population Reports,
MW Brault, July 2012, P70-131

HABC – 400 m walk performance and incident cardiovascular disease



Newman et al. *JAMA; 2006;295:2018*

HABC – 400 m walk performance and mortality



Newman et al. *JAMA; 2006;295:2018*

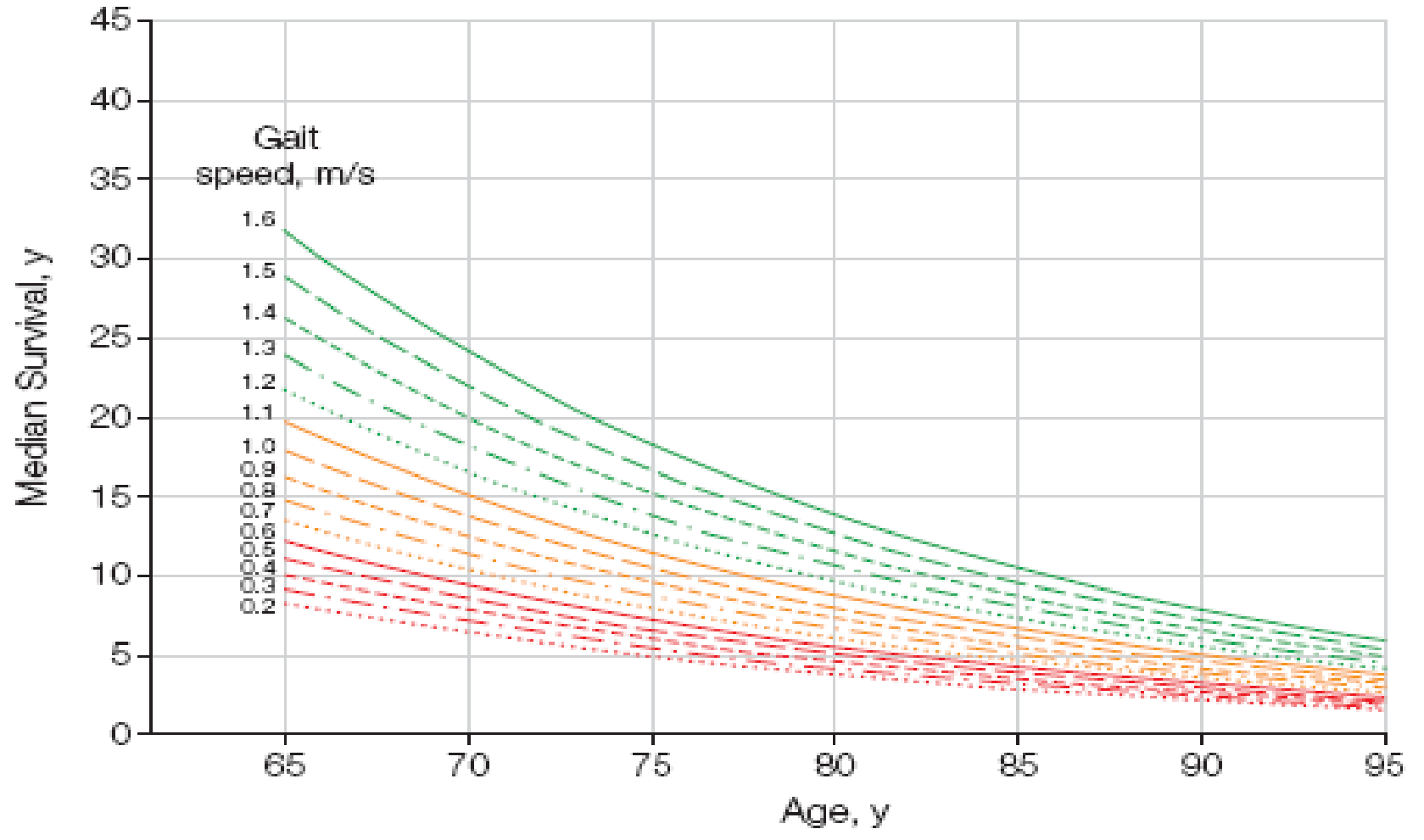
Medicare Current Beneficiary Survey Ability to walk ¼ mile, health care cost and hospitalization rates

Table 4. Adjusted 2004 Health Care Costs and Hospitalization Rates for Community-Dwelling Medicare Beneficiaries Aged 65 or Older by Self-Reported Ability to Walk 1/4 Mile (N=5493)*

	Ability to Walk 1/4 Mile		
	No Difficulty	Difficulty	Unable
Mean annual cost, in $1000 s†			
Total	9.51 (8.80-10.21)	12.28 (11.17-13.39)	13.42 (11.73-15.12)
Out-of-pocket	1.75 (1.60-1.91)	2.03 (1.79-2.26)	1.85 (1.61-2.10)
Hospitalizations per 100 persons‡	25.1 (21.8-28.4)	39.2 (34.0-44.3)	47.3 (40.6-54.0)

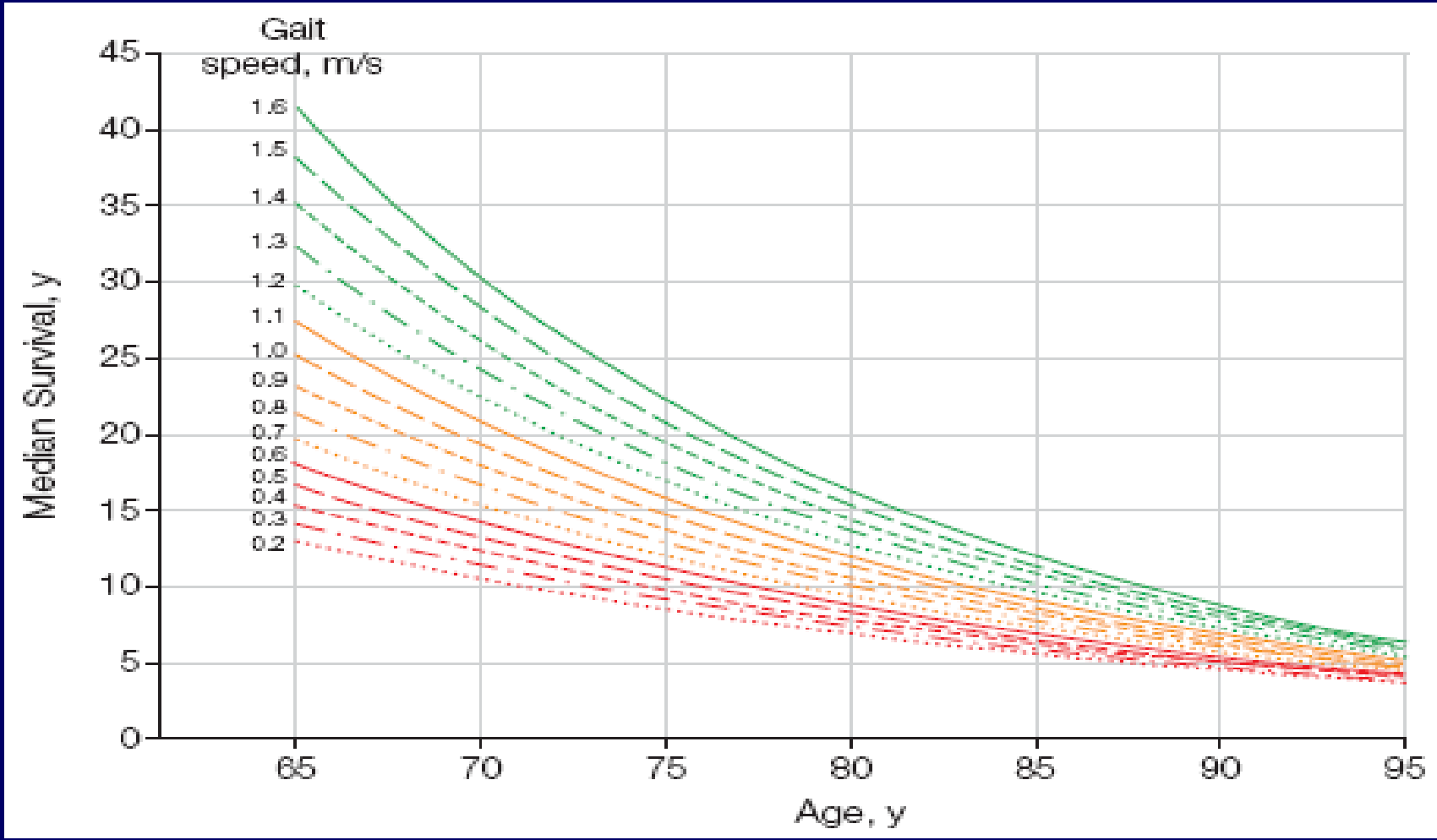
Hardy et al. *J Gen Intern Med Online; 2010:Oct 23*

Predicted life expectancy by age and walking speed in men

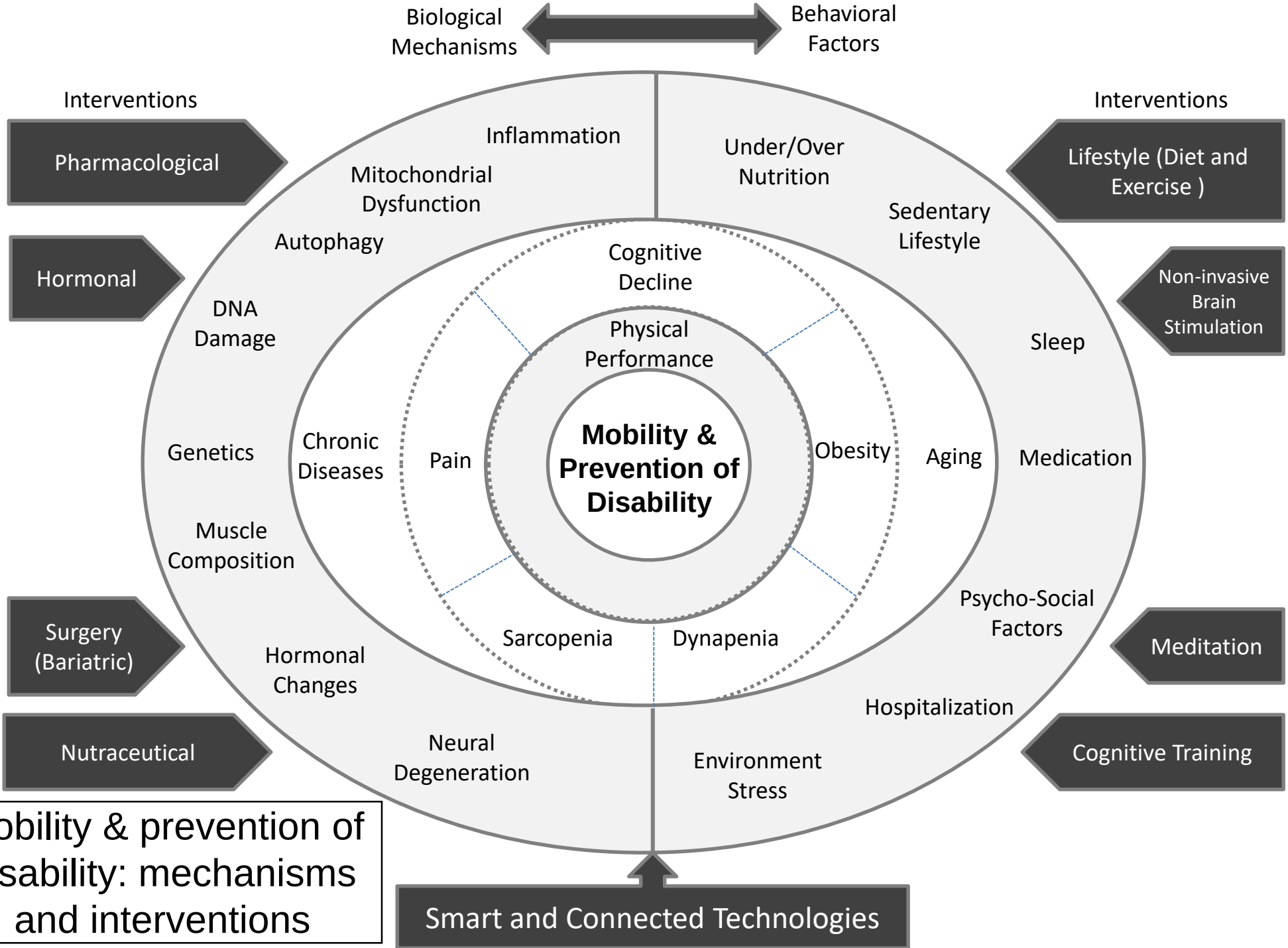


Studenski et al. *JAMA; 2011;305:50*

Predicted life expectancy by age and walking speed in women



Studenski et al. *JAMA; 2011;305:50*



Mobility & prevention of disability: mechanisms and interventions

Criteria for prioritizing the interventions in RCTs

Safety, tolerability and acceptability are key criteria. Vulnerable older persons use multiple drugs and have multiple comorbidities, and thus, are at high risk of adverse drug reactions. Newer drugs are often tested in younger or middle age adults for the treatment of a single condition and therefore, their safety and tolerability in older persons is not fully known. Furthermore, for the prevention of mobility limitations, vulnerable or frail older persons may not be willing to take, and their providers may not be willing to prescribe drugs that bear a risk of severe adverse events.
Benefit on physical performance and/or skeletal muscle
Biological mechanisms are considered to prioritize interventions that target different mechanisms or may have synergistic effects. We exclude interventions that may negatively affect skeletal muscle metabolism.
Practical and affordable for implementation in the US health care system. **Cost** is a major factor for this criterion to maximize the public health impact of the trial

Interventions to maintain mobility Pharmacological

- Acarbose
- ACE inhibitors
- Albuterol
- Angiotensin Receptor Blockers
- Aspirin
- Anti-TNF-alpha, -IL6,-IL1
- Chloroquine, Colchicine
- Cox-2 inhibitors
- Metformin
- Methotrexate
- Myostatin inhibitors
- NSAIDs
- Rapamycin
- Pentoxyphylline
- Salsalate
- Statins
- Thalidomide

Interventions to maintain mobility Hormonal

- DHEA
- Erythropoietin
- Estrogens
- Growth hormone
- GH secretagogues
- Ghrelin
- Oxytocin
- Selective Androgen Receptor Modulators - SARMs
- Testosterone

Interventions to maintain mobility
Nutrition supplements and vitamins

- Carnitine
- CoQ10
- Creatine
- Curcuma
- Lactoferrin
- Linolenic acid
- Omega 3 polyunsaturated fatty acids
  - Fish oil
  - Krill oil
  - Flax
- Nicotinamide Adenine Dinucleotide (NAD+)
- Probiotics
- Resveratrol
- Vitamin C
- Vitamin D
- Vitamin E

Interventions to maintain mobility Behavioral – Physical - Surgical

- Bariatric Surgery
- Cognitive training
- Diet
  - High protein
  - Low calorie
  - Mediterranean
- Health education
- Meditation
- Physical activity
  - Resistance
  - Aerobic
  - Tai Chi
- Smart and connected technologies
- Transcranial direct electrical stimulation
- Yoga

Lifestyle Interventions and Independence for Elders

The LIFE Study

Is a structured physical activity or a health education program more effective in reducing the risk of major mobility disability in older persons?

Pahor et al. JAMA 2014;311:2387

- Multicenter, single-blinded, parallel randomized trial
- 8 field centers across the US
- Coordinating Center: University of Florida
- Data Management Quality Control: Wake Forest University
- Duration: February 2010 – December 2013

ClinicalsTrials.gov NCT01072500

Primary outcome: Major Mobility Disability

Inability to walk 400 m at usual pace on a 20 m course - 10 laps (40 m per lap)

- Within 15 min without sitting
- Without help of a person or walker
- Use of a cane and stop for up to 1 min was acceptable

Pahor et al. JAMA 2014;311:2387

Other outcomes

- Secondary outcomes:
  - Cognitive function
  - Injurious falls
  - Cost-effectiveness
- Tertiary outcomes:
  - Cardiovascular and pulmonary events
  - Dementia/MCI

Major mobility disability events

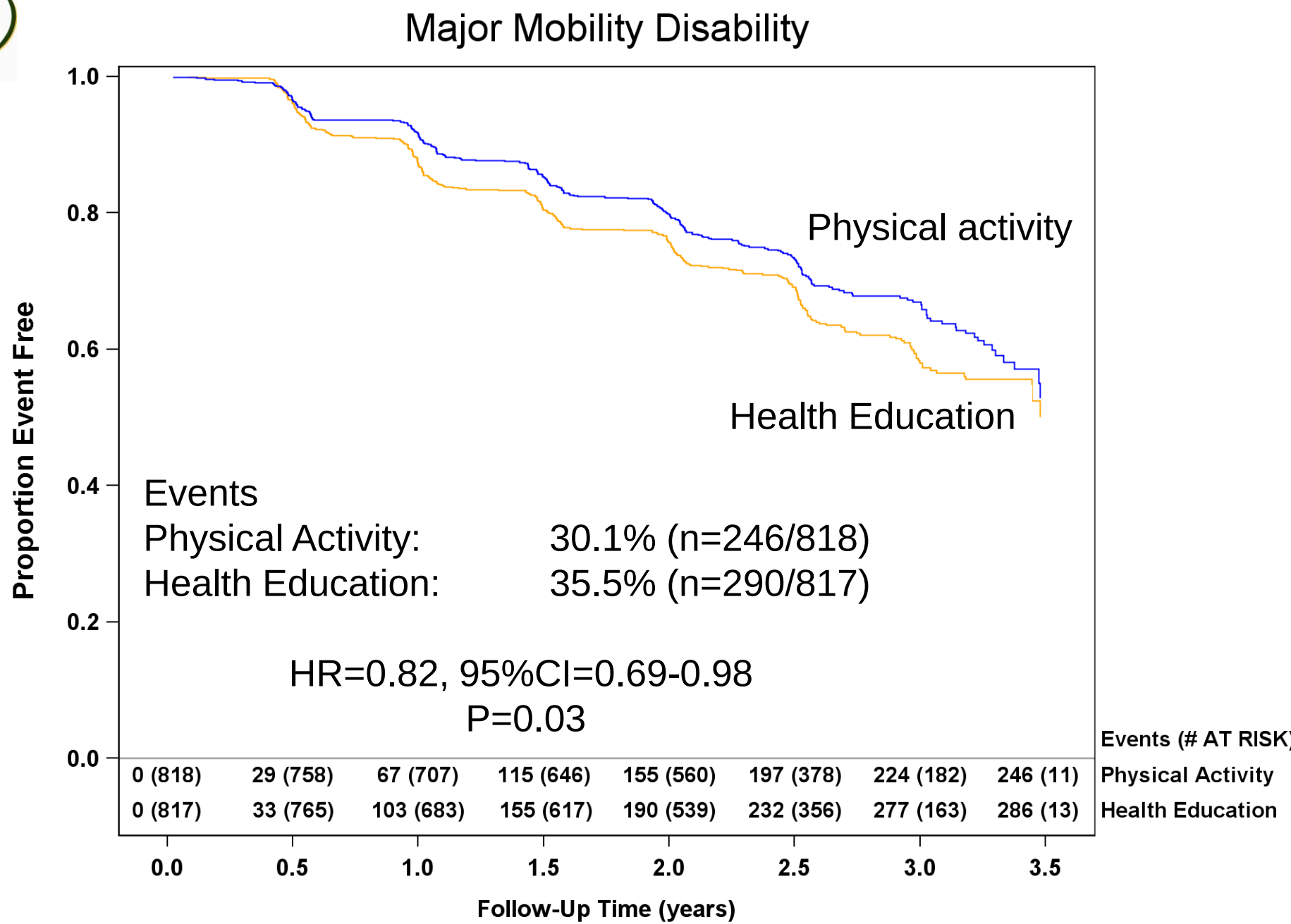
- 32.5% (532/1635) participants

Persistent mobility disability events

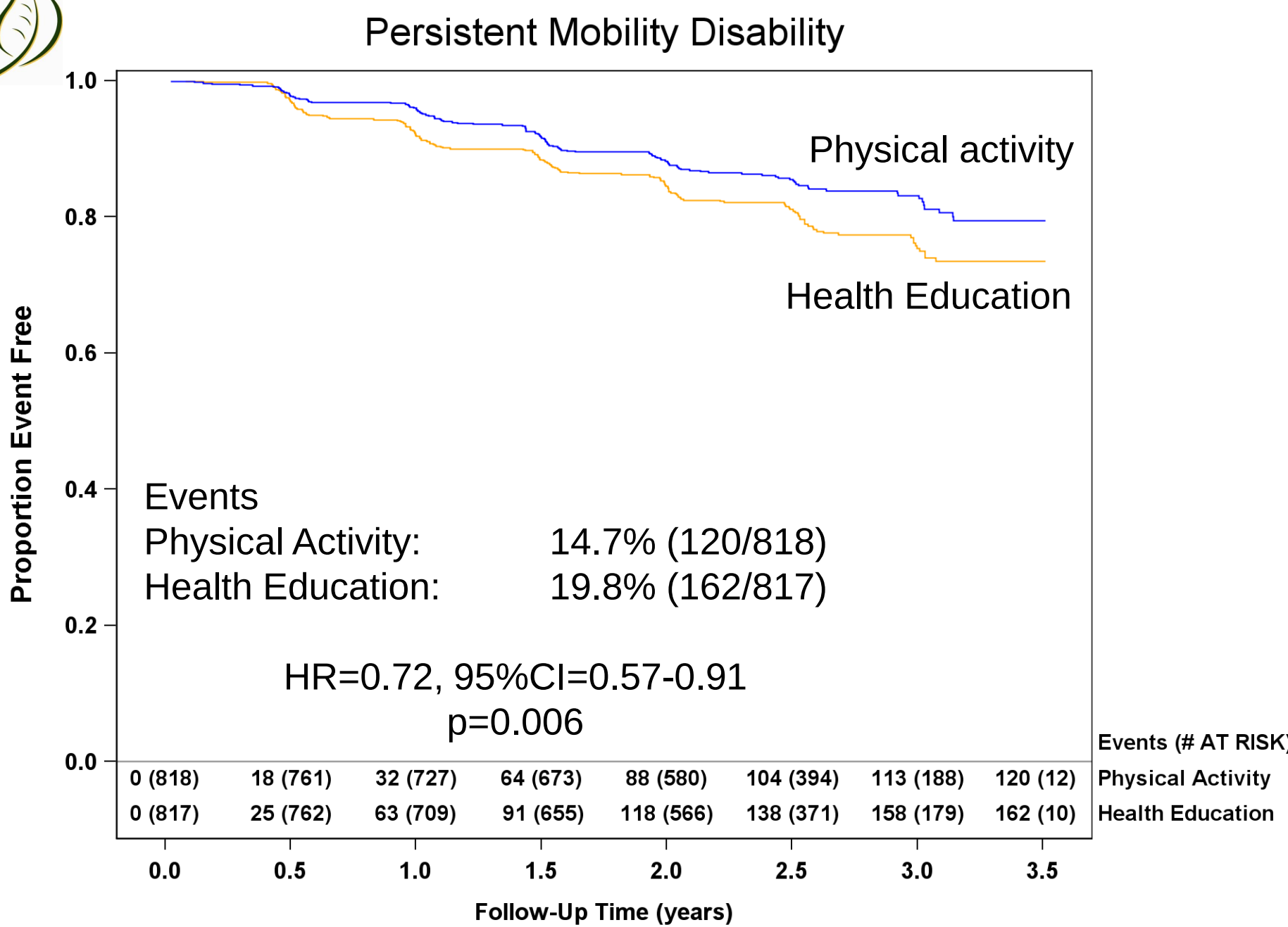
- 17.2% (282/1635) participants

Over an average of 2.6 years of follow-up

Pahor et al. JAMA 2014;311:2387



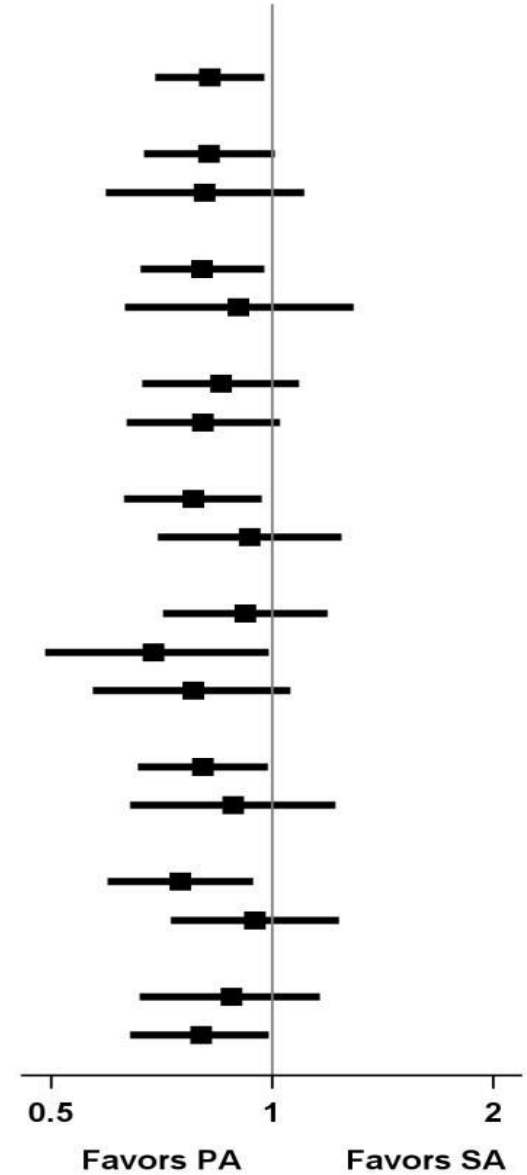
Pahor et al JAMA 2014;311:2387



Pahor et al JAMA 2014;311:2387

Major Mobility Disability – Subgroup Analysis

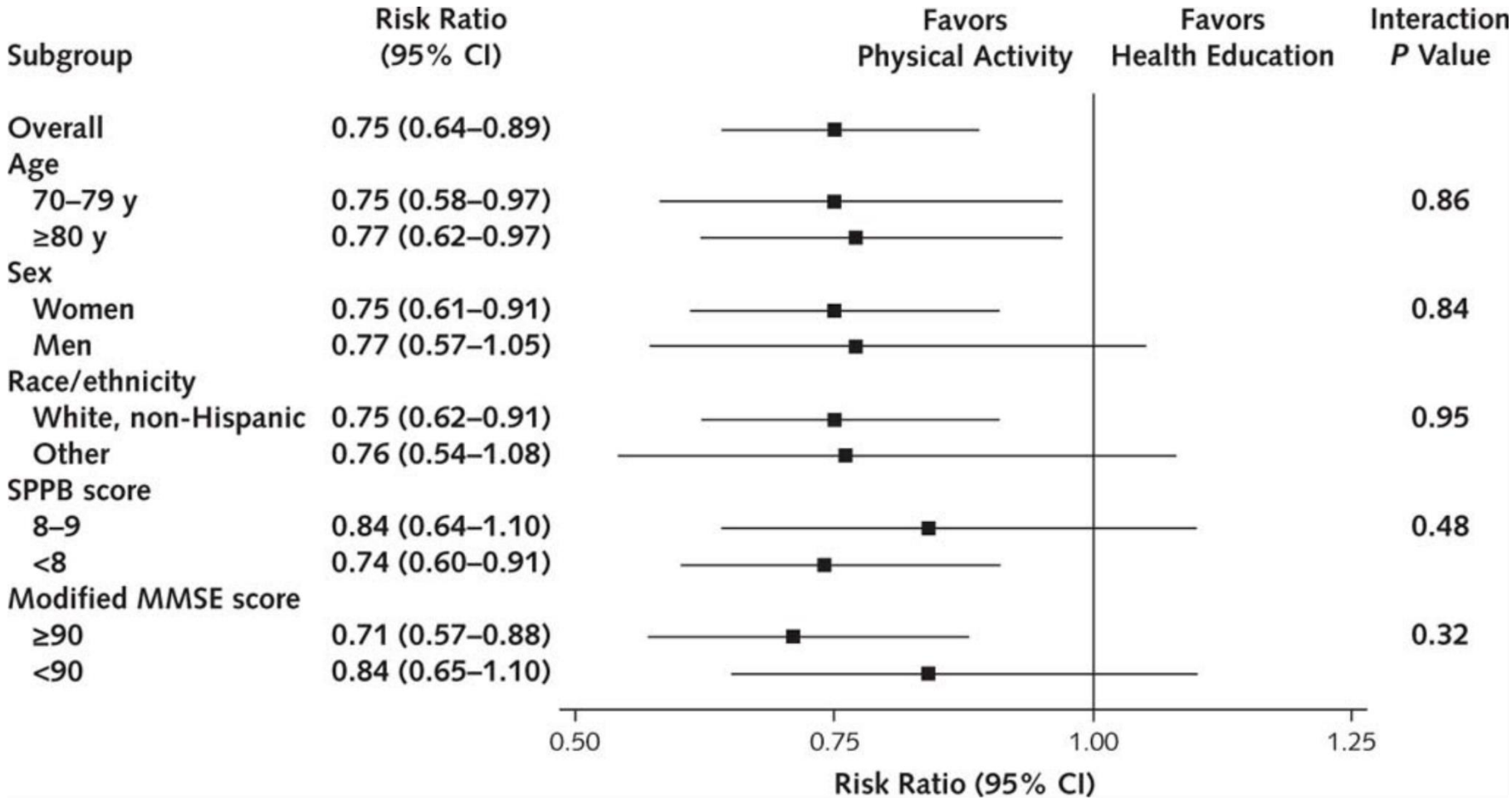
Subgroup	PA (Events / N)	SA (Events / N)	Hazard Ratio (95% CI)	Interaction P-Value
Overall	246 / 818	290 / 817	0.82 (0.69, 0.98)	
Gender				
Female	171 / 547	204 / 551	0.82 (0.67, 1.01)	0.95
Male	75 / 271	86 / 266	0.81 (0.59, 1.11)	
Ethnicity/Race				
Non-Hispanic White	182 / 604	234 / 635	0.80 (0.66, 0.98)	0.58
Other	64 / 211	56 / 180	0.90 (0.63, 1.29)	
Age				
70-79	123 / 477	138 / 455	0.85 (0.67, 1.09)	0.76
80+	123 / 341	152 / 362	0.81 (0.63, 1.03)	
History of CVD				
No CVD	155 / 582	187 / 563	0.78 (0.63, 0.97)	0.34
CVD	91 / 236	103 / 254	0.93 (0.70, 1.24)	
History of Diabetes				
None	114 / 406	126 / 414	0.92 (0.71, 1.19)	0.41
Impaired FG	59 / 192	68 / 165	0.69 (0.49, 0.99)	
Diabetes	73 / 220	96 / 238	0.78 (0.57, 1.06)	
Gait Speed				
<0.8 m/s	173 / 485	210 / 508	0.81 (0.66, 0.99)	0.63
0.8+ m/s	73 / 333	80 / 309	0.88 (0.64, 1.22)	
SPPB				
<8	135 / 353	177 / 378	0.75 (0.60, 0.94)	0.19
8 or 9	111 / 465	113 / 439	0.95 (0.73, 1.23)	
3MSE (post-hoc)				
<90	95 / 261	108 / 261	0.88 (0.66, 1.16)	0.58
90+	151 / 557	182 / 556	0.80 (0.64, 0.99)	



Pahor et al JAMA 2014;311:2387

Physical Activity: Overall Burden and Transitions Between States of Major Mobility Disability

Gill et al. Ann Intern Med. Published online September 27, 2016. doi:10.7326/M16-0529



Risk ratios denoting the burden of major mobility disability over time for physical activity versus health education according to subgroups.

MMSE = Mini-Mental State Examination; SPPB = Short Physical Performance Battery.

Cost-effectiveness of the LIFE Physical Activity Intervention for Older Adults at Increased Risk for Mobility Disability

Erik J. Groessl,[1,2] Robert M. Kaplan,[3] Cynthia M. Castro Sweet,[4] Timothy Church,[5] Mark A. Espeland,[6] Thomas M. Gill,[7] Nancy W. Glynn,[8] Abby C. King,[9] Stephen Kritchevsky,[10] Todd Manini,[11] Mary M. McDermott,[12] Kieran F. Reid,[13] Julia Rushing,[6] and Marco Pahor, MD,[11]; for the LIFE Study Group

Table 3. Incremental Cost per Disability Prevented

	Total Costs US$/ Participant	Proportion Becoming Disabled	Incremental Cost	Incremental Reduced Disability	Incremental Cost-effectiveness
Health education	1,001	290/817 (35.5%)	—	—	
Physical activity	3,302	246/818 (30.1%)	2,301	5.43%	US$42,376/ disability prevented

Table 4. Incremental Cost per Quality-Adjusted Life-Year (QALY)

	Total Costs US$/ Participant	QALYs	Incremental Cost	Incremental QALYs	Incremental Cost-effectiveness
Health education	1,001	−0.1302	—	—	
Physical activity	3,302	−0.0834	2,301	0.0468	US$49,167/QALY

LIFE – Cognitive outcomes Sink et al; JAMA;2015;314:781

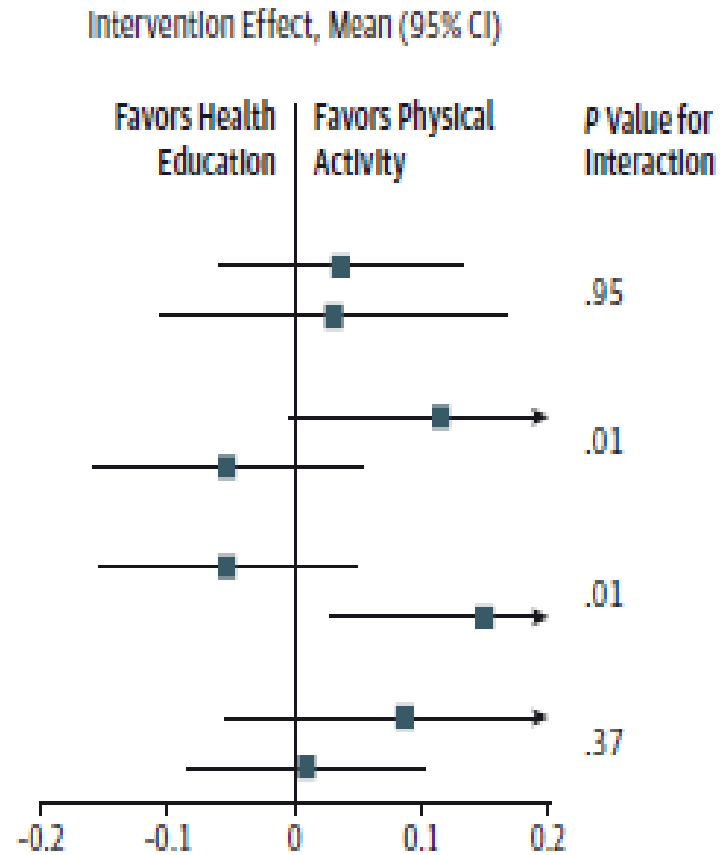
Table 2. Adjusted Raw and z-Transformed Follow-up Cognitive Function Scores

	Mean (95% CI)			
	Physical Activity (n = 735)[a]	Health Education (n = 741)[a]	Difference Between Groups	*P* Value
Digit Symbol Coding task				
Raw score	46.26 (45.75 to 46.82)	46.28 (45.72 to 46.83)	−0.01 (−0.80 to 0.77)	.97
z Score	−0.003 (−0.046 to 0.040)	−0.002 (−0.045 to 0.041)	−0.001 (−0.063 to 0.060)	
Revised Hopkins Verbal Learning Test				
Immediate word recall				
Raw score	22.83 (22.52 to 23.14)	22.97 (22.67 to 23.28)	−0.14 (−0.58 to 0.29)	.52
z Score	−0.073 (−0.132 to −0.014)	−0.046 (−0.105 to 0.013)	−0.027 (−0.110 to 0.055)	
Delayed word recall				
Raw score	7.22 (7.03 to 7.41)	7.25 (7.06 to 7.44)	−0.03 (−0.29 to 0.24)	.84
z Score	−0.167 (−0.234 to −0.100)	−0.157 (−0.224 to −0.090)	−0.010 (−0.103 to 0.084)	
Composite *z* score[b]	−0.130 (−0.187 to −0.073)	−0.106 (−0.163 to −0.049)	−0.024 (−0.105 to 0.057)	.56
Executive function				
Percentage correct on n-back task				
1-back	83.7 (82.5 to 84.9)	82.9 (81.8 to 84.1)	0.7 (−0.9 to 2.4)	.39
2-back	53.2 (51.6 to 54.8)	51.9 (50.4 to 53.5)	1.3 (−0.9 to 3.5)	.26
Reaction time on task switching, s				
No	1.47 (1.42 to 1.51)	1.46 (1.42 to 1.51)	0.01 (−0.06 to 0.07)	.86
Yes	2.43 (2.37 to 2.49)	2.39 (2.33 to 2.45)	0.04 (−0.05 to 0.13)	.37
Reaction time on Flanker task, s				
Congruent	0.65 (0.64 to 0.67)	0.67 (0.66 to 0.68)	−0.02 (−0.03 to −0.01)	.04
Incongruent	0.73 (0.72 to 0.74)	0.75 (0.73 to 0.76)	−0.02 (−0.04 to 0)	.07
Composite *z* score[b]	−0.003 (−0.060 to 0.054)	−0.025 (−0.080 to 0.030)	0.022 (−0.057 to 0.101)	.59
Mean global composite *z* score[b,c]	−0.052 (−0.099 to −0.005)	−0.081 (−0.128 to −0.034)	0.029 (−0.038 to 0.095)	.40

LIFE – Cognitive outcomes: Executive function

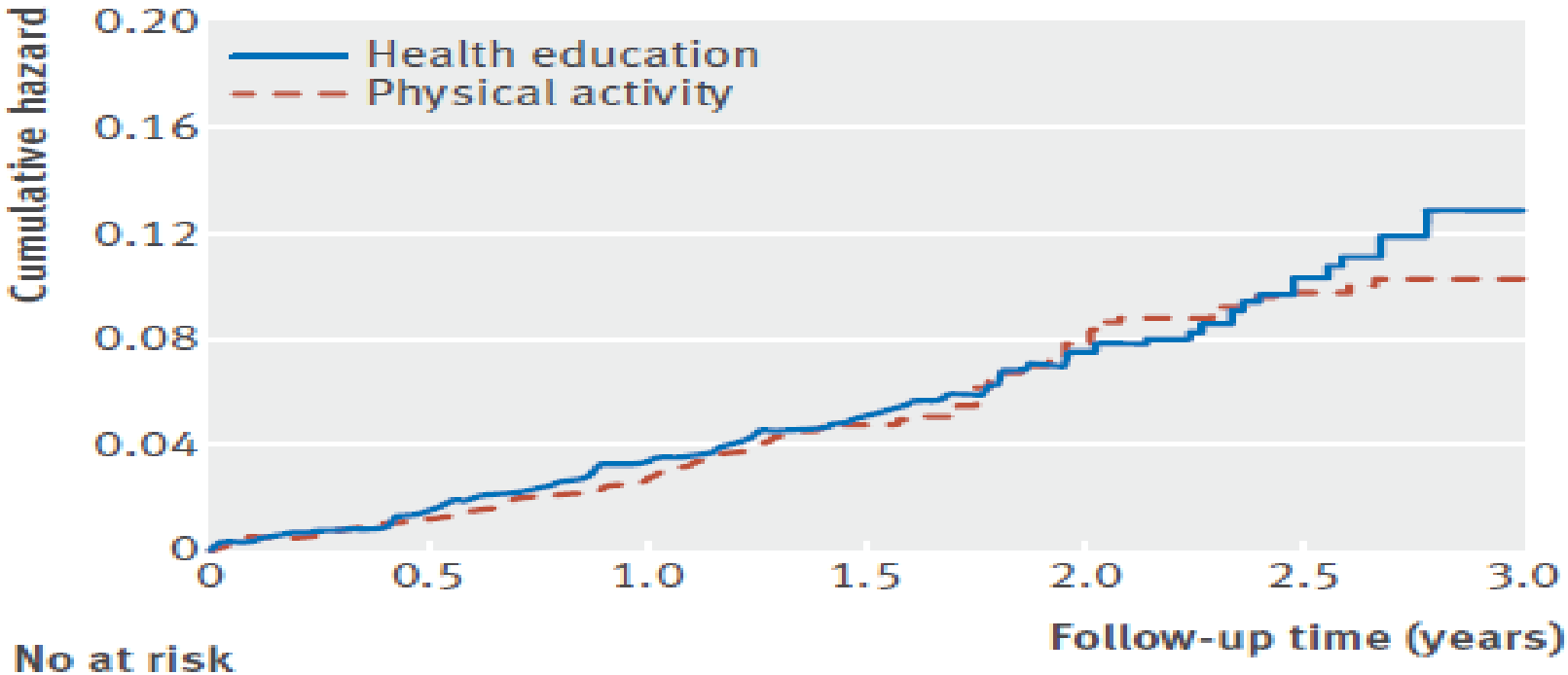
C Executive function composite

	Mean z-Transformed Score (95% CI)		Intervention Effect, Mean (95% CI)
	Physical Activity	Health Education	
Sex			
Female	0.037 (-0.031 to 0.106)	0.001 (-0.066 to 0.068)	0.037 (-0.059 to 0.132)
Male	-0.017 (-0.113 to 0.080)	-0.048 (-0.145 to 0.049)	0.031 (-0.105 to 0.167)
Short Physical Performance Battery score			
<8	0.026 (-0.061 to 0.113)	-0.090 (-0.173 to -0.007)	0.116 (-0.004 to 0.236)
8-9	-0.023 (-0.098 to 0.051)	0.030 (-0.046 to 0.105)	-0.053 (-0.159 to 0.053)
Age group, y			
70-79	0.020 (-0.051 to 0.091)	0.073 (-0.000 to 0.146)	-0.053 (-0.155 to 0.049)
80-89	0.019 (-0.069 to 0.107)	-0.131 (-0.215 to -0.047)	0.150 (0.029 to 0.271)
Modified Mini-Mental State Examination score			
<90	-0.059 (-0.164 to 0.045)	-0.146 (-0.247 to -0.045)	0.087 (-0.054 to 0.228)
90-100	0.054 (-0.014 to 0.120)	0.044 (-0.023 to 0.111)	0.010 (-0.084 to 0.103)



Sink et al. JAMA;2015;314:781

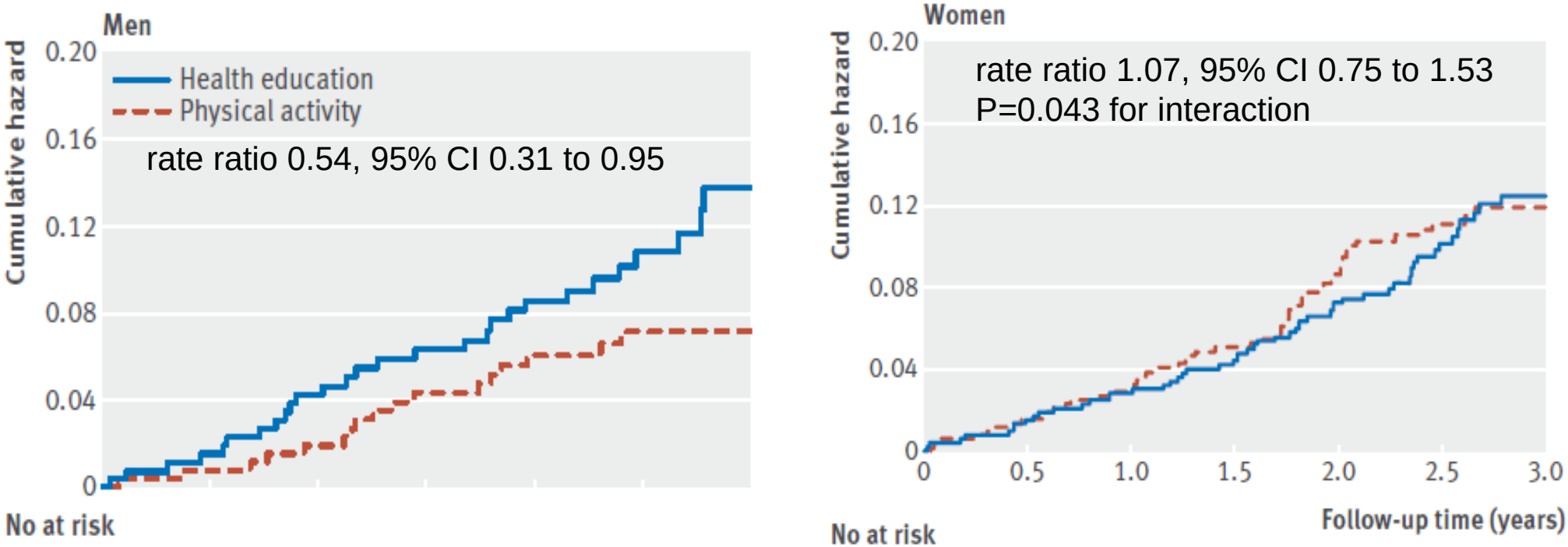
LIFE – Serious fall injuries



No at risk						
Physical activity						
818	787	763	731	651	452	227
Health education						
817	796	768	739	670	457	224
Outcomes						
Physical activity						
0	10	21	37	58	70	72
Health education						
0	12	27	39	58	73	82

Gill et al. BMJ;2016;352:i245

LIFE – Serious fall injuries in men and women



No at risk

Physical activity	271	262	254	240	214	150	69
Health education	266	259	245	233	213	143	70

Outcomes

Physical activity	0	2	5	11	15	17	17
Health education	0	4	11	16	21	25	28

No at risk

Physical activity	547	525	509	491	437	302	158
Health education	551	537	523	506	457	314	154

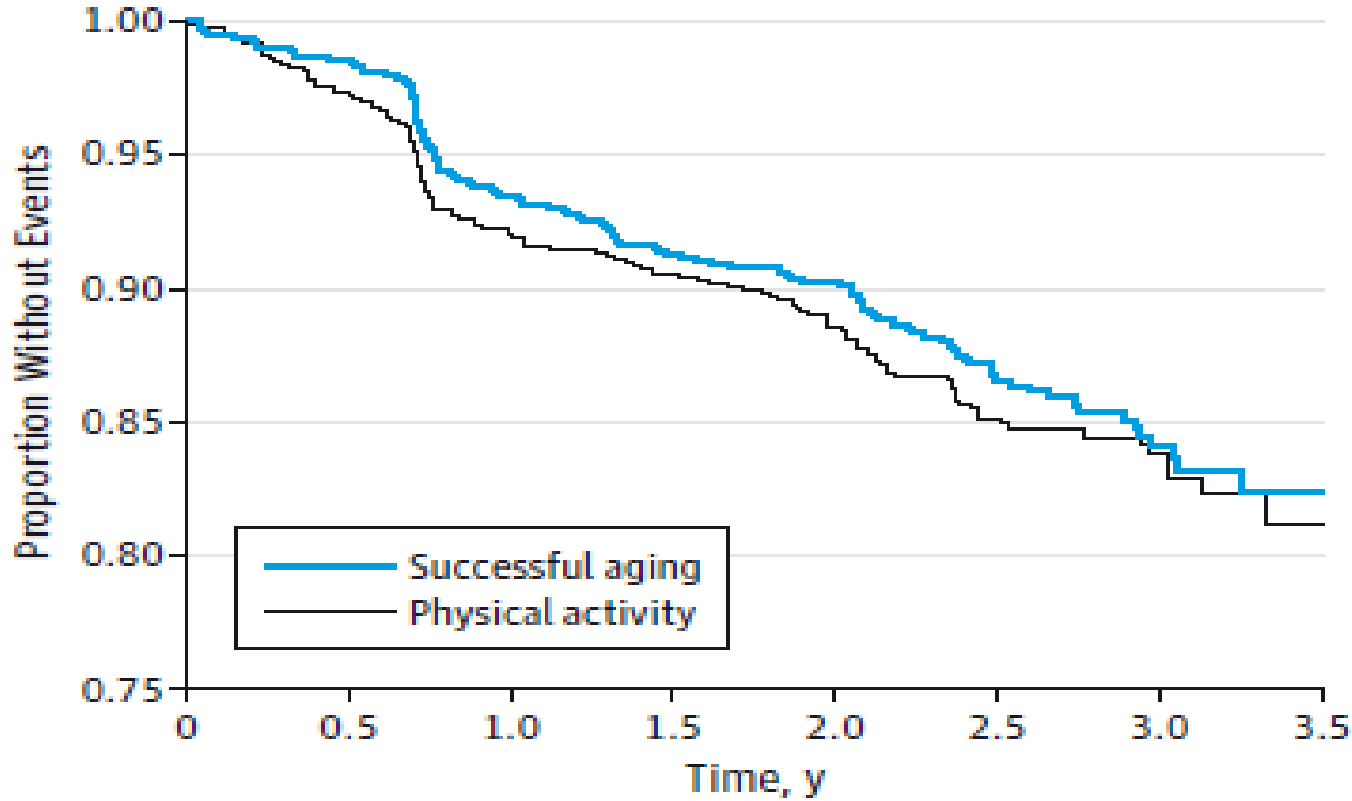
Outcomes

Physical activity	0	8	16	26	43	53	55
Health education	0	8	16	23	37	48	54

Gill et al. BMJ;2016;352:i245

LIFE – Cardiovascular disease events

Figure 1. Total Cardiovascular Disease Event Rates by Intervention Group



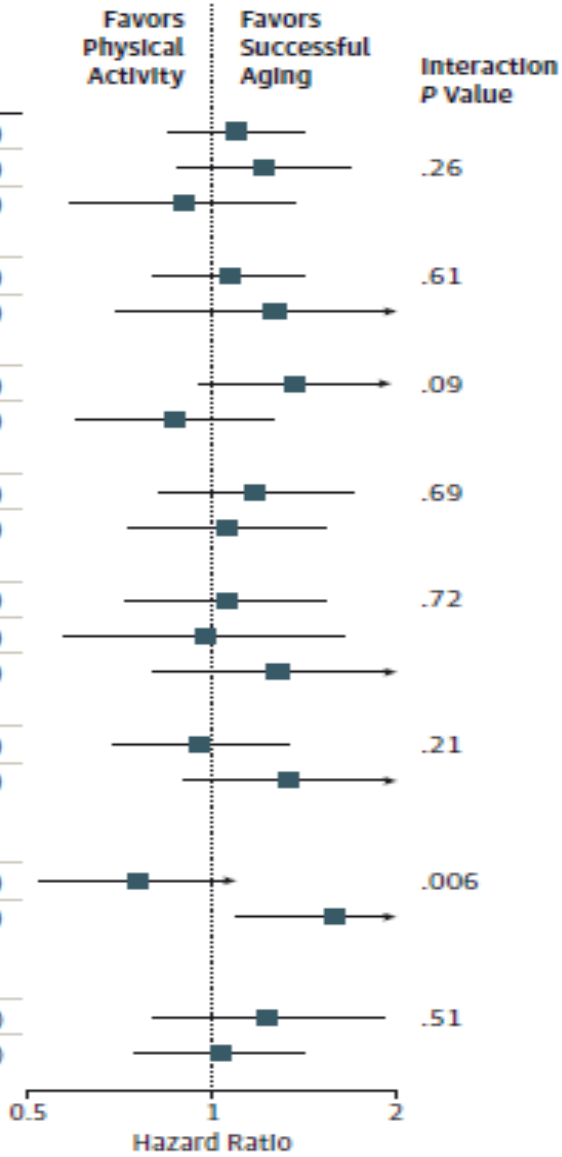
No. at risk								
Successful aging	817	797	745	715	654	447	217	17
Physical activity	818	780	728	701	633	426	207	11

Cumulative hazards plot.

Newman et al. JAMA Cardiol 2016;1:568

LIFE – Cardiovascular disease events

Subgroup	Physical Activity: No. of Events/ No. of Participants	Successful Aging: No. of Events/ No. of Participants	Hazard Ratio (95% CI)	Interaction *P* Value
Overall sex	121/818	113/817	1.10 (0.85-1.42)	
Female	79/547	68/551	1.21 (0.88-1.68)	.26
Male	42/271	45/266	0.90 (0.59-1.36)	
Ethnicity/race				
Non-Hispanic white	93/604	94/635	1.07 (0.80-1.42)	.61
Other	28/211	19/180	1.26 (0.70-2.28)	
Age				
70-79 y	67/477	52/455	1.36 (0.95-1.96)	.09
≥80 y	54/341	61/362	0.87 (0.60-1.26)	
History of cardiovascular disease				
No cardiovascular disease	62/582	53/563	1.18 (0.81-1.70)	.69
Cardiovascular disease	59/236	60/254	1.06 (0.73-1.53)	
History of diabetes				
None	54/406	53/414	1.05 (0.72-1.54)	.72
Impaired FG	28/192	28/165	0.97 (0.57-1.65)	
Diabetes	39/220	32/238	1.28 (0.80-2.06)	
Gait speed				
<0.8 m/s	67/485	72/508	0.96 (0.68-1.33)	.21
≥0.8 m/s	54/333	41/309	1.34 (0.89-2.02)	
Short physical performance battery score				
<8	50/353	67/378	0.76 (0.52-1.10)	.006
8 or 9	71/465	46/439	1.59 (1.09-2.30)	
Modified Mini-Mental State Examination				
<90	56/261	38/261	1.23 (0.80-1.90)	.51
≥90	75/557	75/556	1.03 (0.75-1.42)	



Newman et al. JAMA Cardiol 2016;1:568

Effects of Testosterone Treatment in Older Men

BACKGROUND

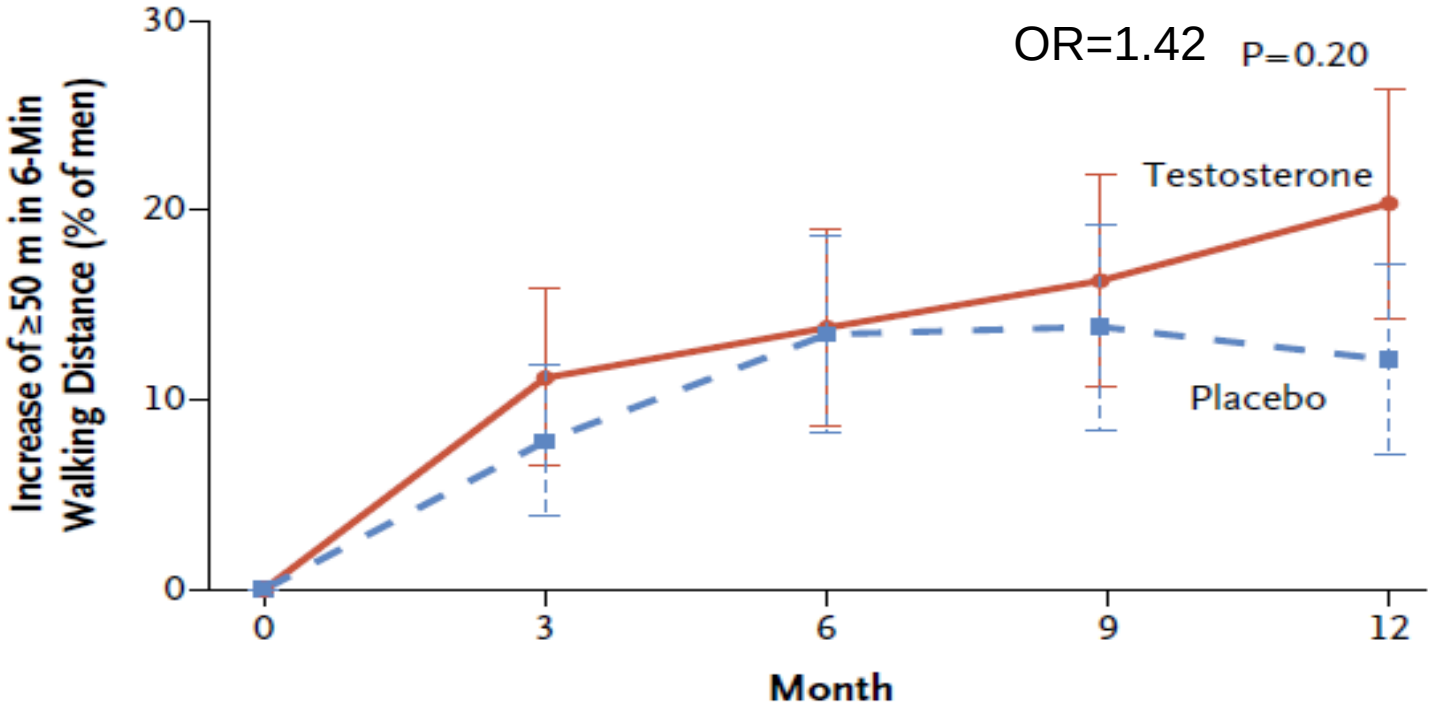
Serum testosterone concentrations decrease as men age, but benefits of raising testosterone levels in older men have not been established.

METHODS

We assigned 790 men 65 years of age or older with a serum testosterone concentration of less than 275 ng per deciliter and symptoms suggesting hypoandrogenism to receive either testosterone gel or placebo gel for 1 year. Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial. The primary outcome of each of the individual trials was also evaluated in all participants.

Snyder et al; NEJM;2016;347:611

TTrial – Walking ability: Increase >= 50 m in the 6 min walk test

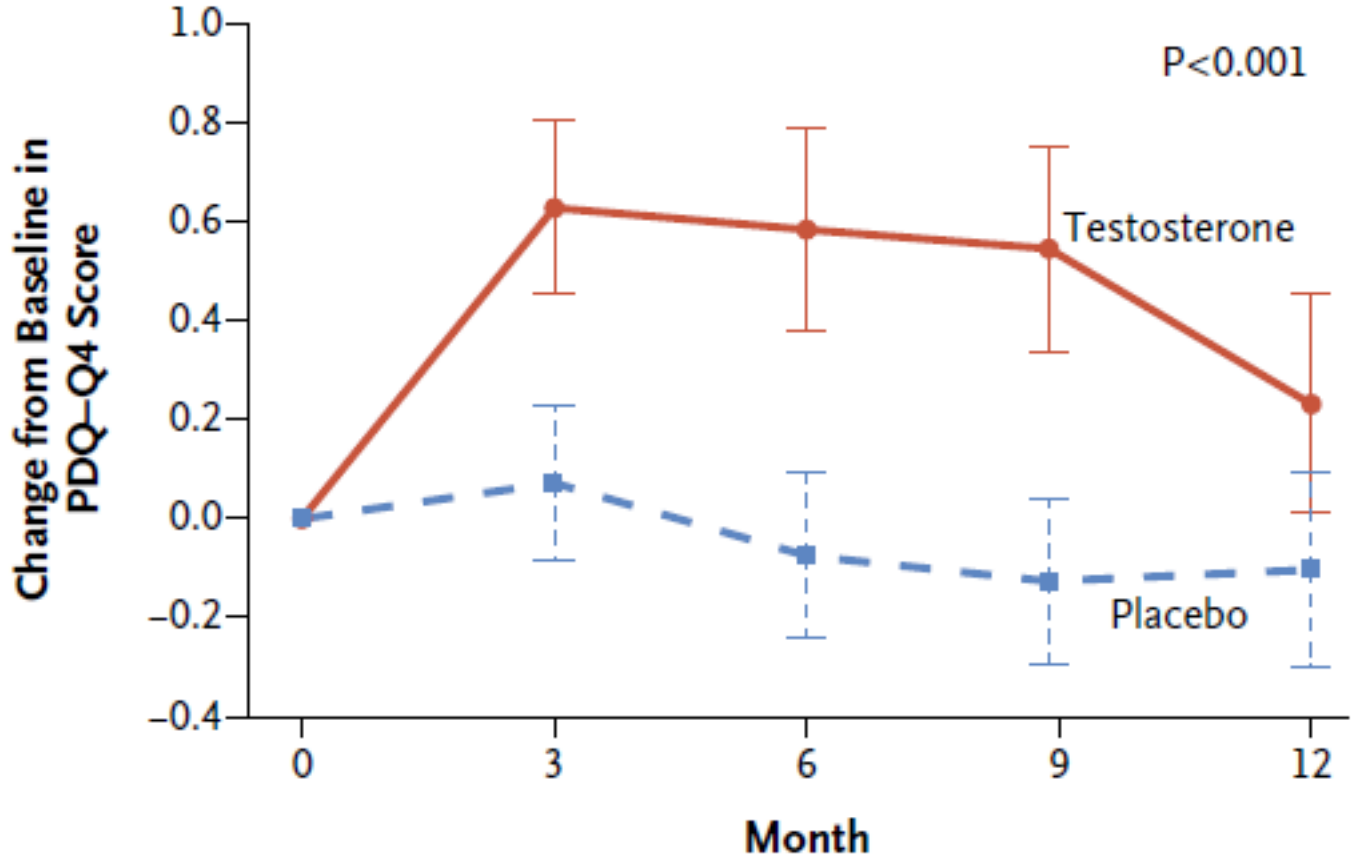


No. at Risk					
Testosterone	193	179	174	172	172
Placebo	197	179	171	159	165

Physical function participants n=390 OR=1.42 p=0.20
All TTrial participants n=790 OR=1.76 p=0.003

Snyder et al; NEJM;2016;347:611

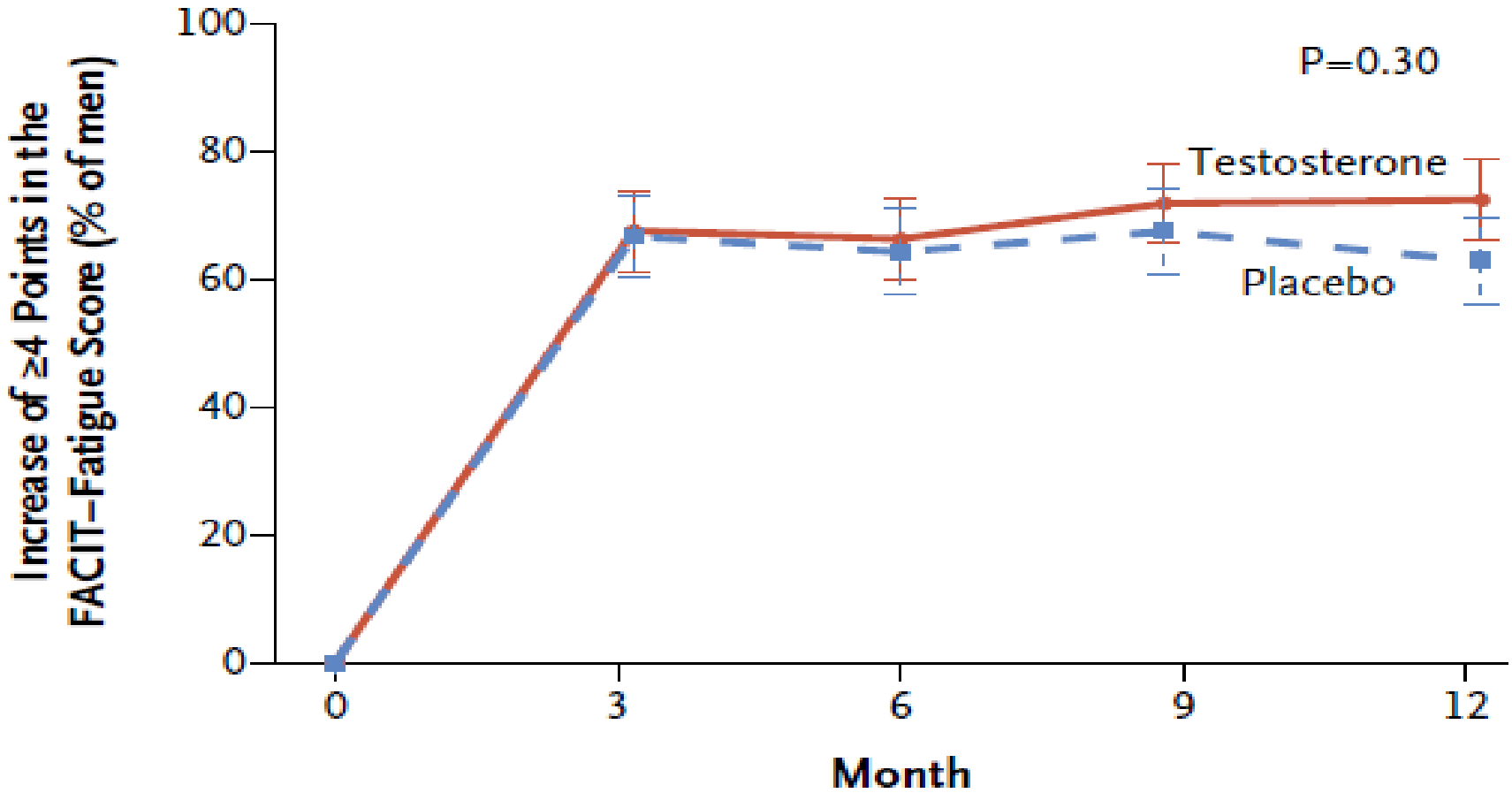
TTrial – Sexual function: Psychosexual Daily Questionnaire



No. at Risk					
Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

Snyder et al; NEJM;2016;347:611

TTrial – Vitality:
Functional Assessment of Chronic Illness Therapy (FACIT)



No. at Risk					
Testosterone	236	219	217	206	203
Placebo	238	207	196	188	191

Snyder et al; NEJM;2016;347:611

enrgise

ENabling Reduction of low-Grade Inflammation in Seniors - Pilot Study

Funding: NIA U01AG050499

Abbott grant for study drug – the company has no other involvement with the study

- Double-blinded, 2x2 factorial randomized pilot trial
- 5 field centers
- Coordinating Center: University of Florida
- Data Management Quality Control: Wake Forest University
- n=300 – follow-up duration 12 months

ClinicalsTrials.gov NCT02676466

Selection of the Interventions

Criteria / Interventions	1. Safe, tolerable, acceptable	2. IL-6 redu-ction	3. Physical performance	4. Inno-vation	5. Mecha-nism	6. Practical, affordable
ACEIs, ARBs	+	+	+	+	+	+
ω-3	+	+	+	+	+	+
Mediterranean diet	+	+	+	+	+	-
Physical activity, weight loss	+	+	+	-	+	+?
Vitamin D	+	+	+	-	+	+
Anti-TNF-α, -IL6,-IL1; methotrexate thiazolidinediones	-	+	?	+	+	?
Statins, chloroquine, colchicine	-	+	- ?	+	-	+
Corticosteroids, aspirin, NSAIDs, cox-2 inhibitors	-	+	?	+	+	+
Fosinopril, ghrelin, lactoferrin, oxytocin, salsalate, curcuma, creatine, probiotics, resveratrol	+	- ?	- ?	+	+ ?	+

+ positive evidence, - negative evidence, ? evidence lacking

Specific Aims

Conduct a pilot RCT in 300 older persons at risk of mobility decline to assess:

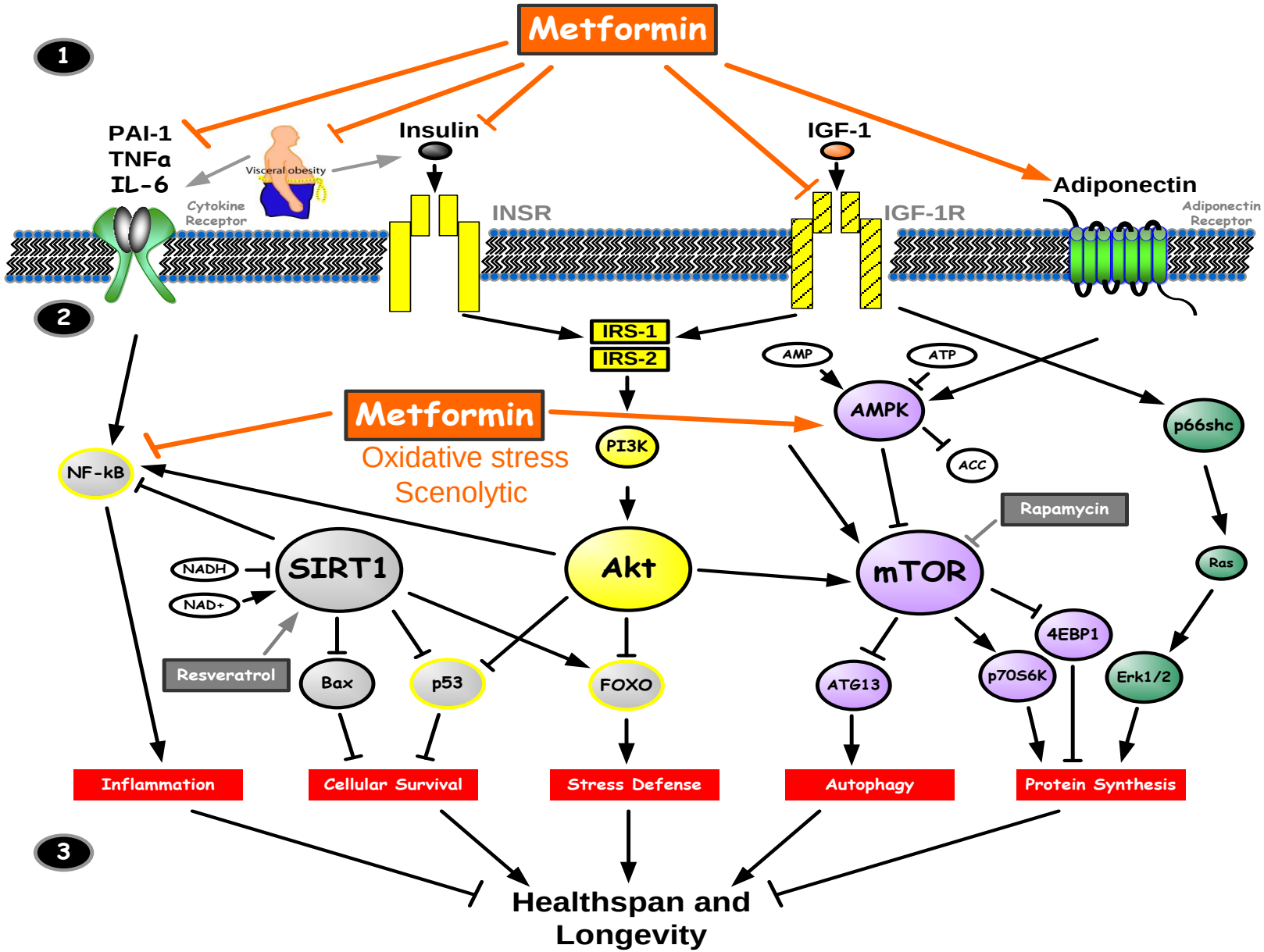
- Compared with placebo, the effects of losartan, ω-3, and losartan+ω-3 on IL-6 and walking speed;
- The recruitment yields, the target population, adherence, retention, tolerability of the interventions
- The primary outcome, sample-size, design, and cost for the main trial;
- The intra-subject variability of IL-6,
- The dosage and safety of the interventions

Outcomes

- Primary Outcomes
  - IL-6
  - Walking speed during 400 m walk test
- Secondary outcomes
  - SPPB
  - Frailty
  - Grip strength
  - Isokinetic knee extension strength
  - Inability to walk 400m (planned primary outcome for the main trial)
  - Biomarkers of inflammation

enrgise

Metformin targets multiple pathways of aging



Barzilai N et al Metformin as a Tool to Target Aging. Cell Metab. 2016 Jun 14;23(6):1060

TAME (Targeting Aging with MEtformin)

- To show that multiple morbidities of aging can be targeted by metformin
- (FDA) To obtain a new indication for the delay of age-related morbidities
- To apply the discoveries of geroscience as a powerful new tool for achieving primary prevention of multiple diseases

TAME: Targeting Aging with METformin

Stratum 1: High Risk

Slow gait speed OR obesity plus hypertension and/or dyslipidemia (no CVD, cancer, or MCI/Dementia)

Stratum 2: Positive History

1 or 2 of CVD, Cancer, MCI present at baseline

Inclusion Criteria

3000 subjects

65-79 years

Double blind placebo control study

Primary outcome

Time to new diagnosis of a composite component: CVD (MI, stroke, CHF, revascularization, PAD), cancer, MCI or dementia, death.

Secondary outcomes

Time to occurrence of composite functional outcome: Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, developing ADL limitation, transition to MCI/dementia

Primary Composite + Type 2 diabetes mellitus (T2DM)

Tertiary outcomes

Accumulation rate of 14 age-related chronic health conditions (e.g. depression, osteoporosis, osteoarthritis)**, rate of acute events** (e.g. falls, pneumonia)**, change in measures of function** (gait speed, etc.)**, and quality of life measures** (pain, sleep quality, fatigue)

Main findings

- LIFE involves the most vulnerable older adults who are understudied and who are typically not included in large clinical trials
- LIFE demonstrates mobility benefit of a physical activity program in vulnerable older adults
- Those at highest risk, benefited the most on a broad range of health outcomes
- The physical activity intervention is cost effective

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Exercise as Medicine ONLINE FIRST

Patricia P. Katz, PhD; and Russell Pate, PhD

Prescribing exercise may be just as important as prescribing medication—perhaps even more important in some cases. However, clinicians need training, tools, and support for this effort. It is time for medical schools to start preparing students to prescribe exercise as effectively as they prescribe statins, and for health systems to support physicians in addressing inactivity just as they provide support in addressing other health risks.