Fall Brain
Biological and Cognitive Perspectives

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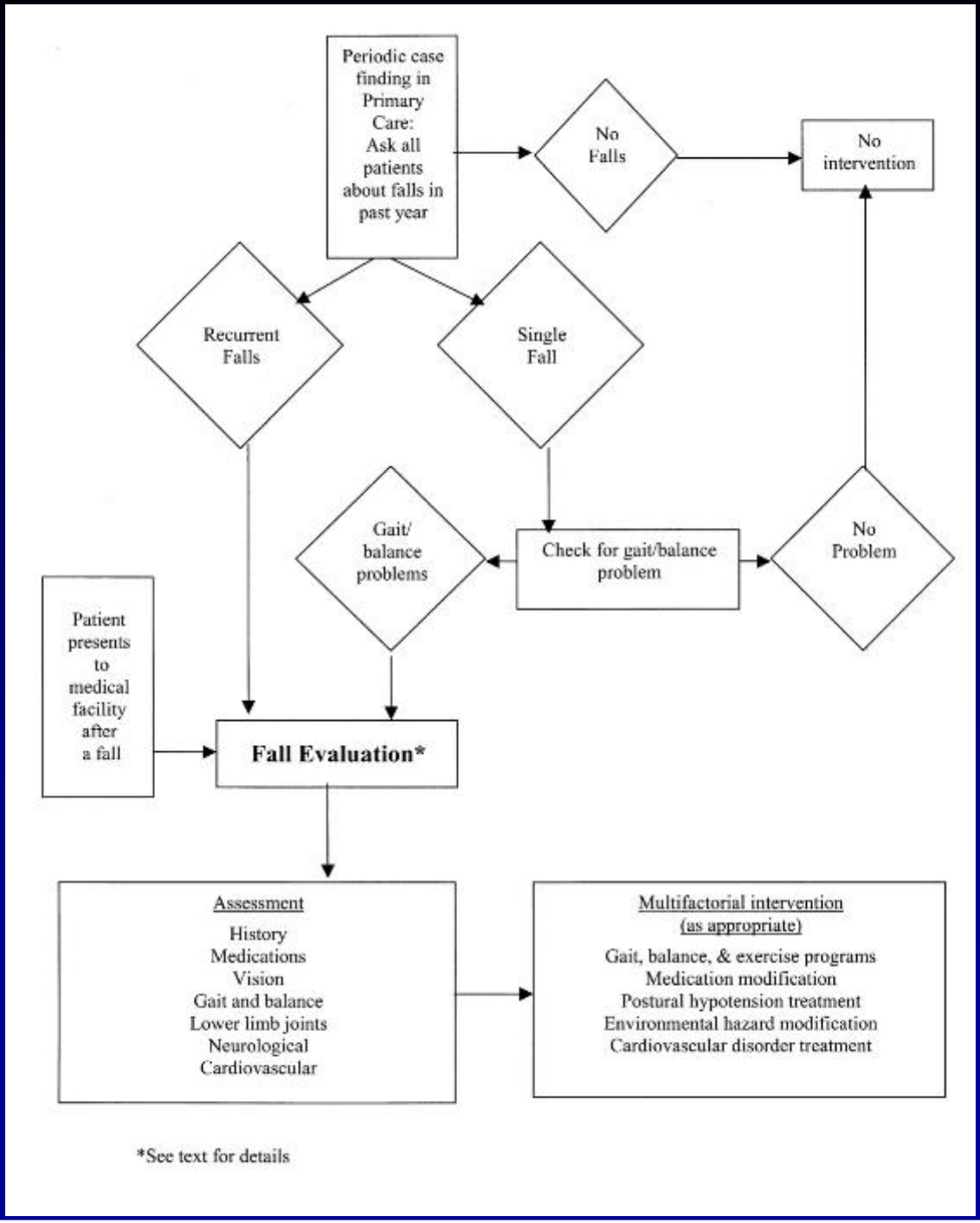
Saint Care Corporation, Japan

Outline

- Clinical predictors of falls
  - Clinical and quantitative gait
  - Motoric Cognitive risk syndrome
- Biology of falls
- Brain substrates
- Cognitive interventions



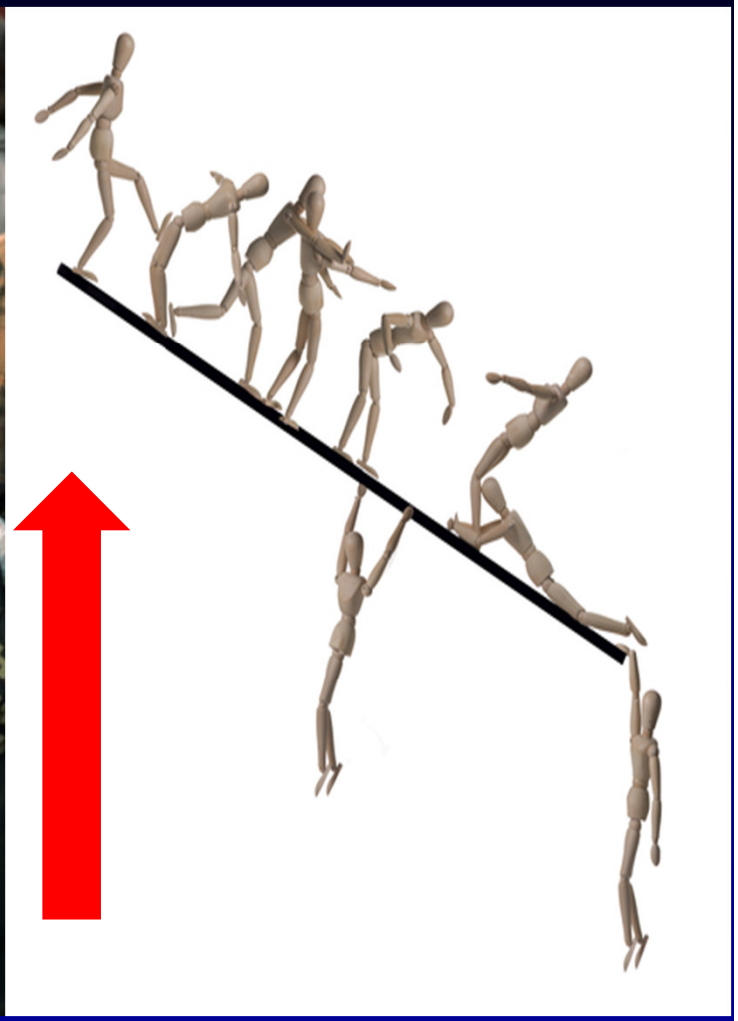
American Geriatrics Society fall guidelines, 2001

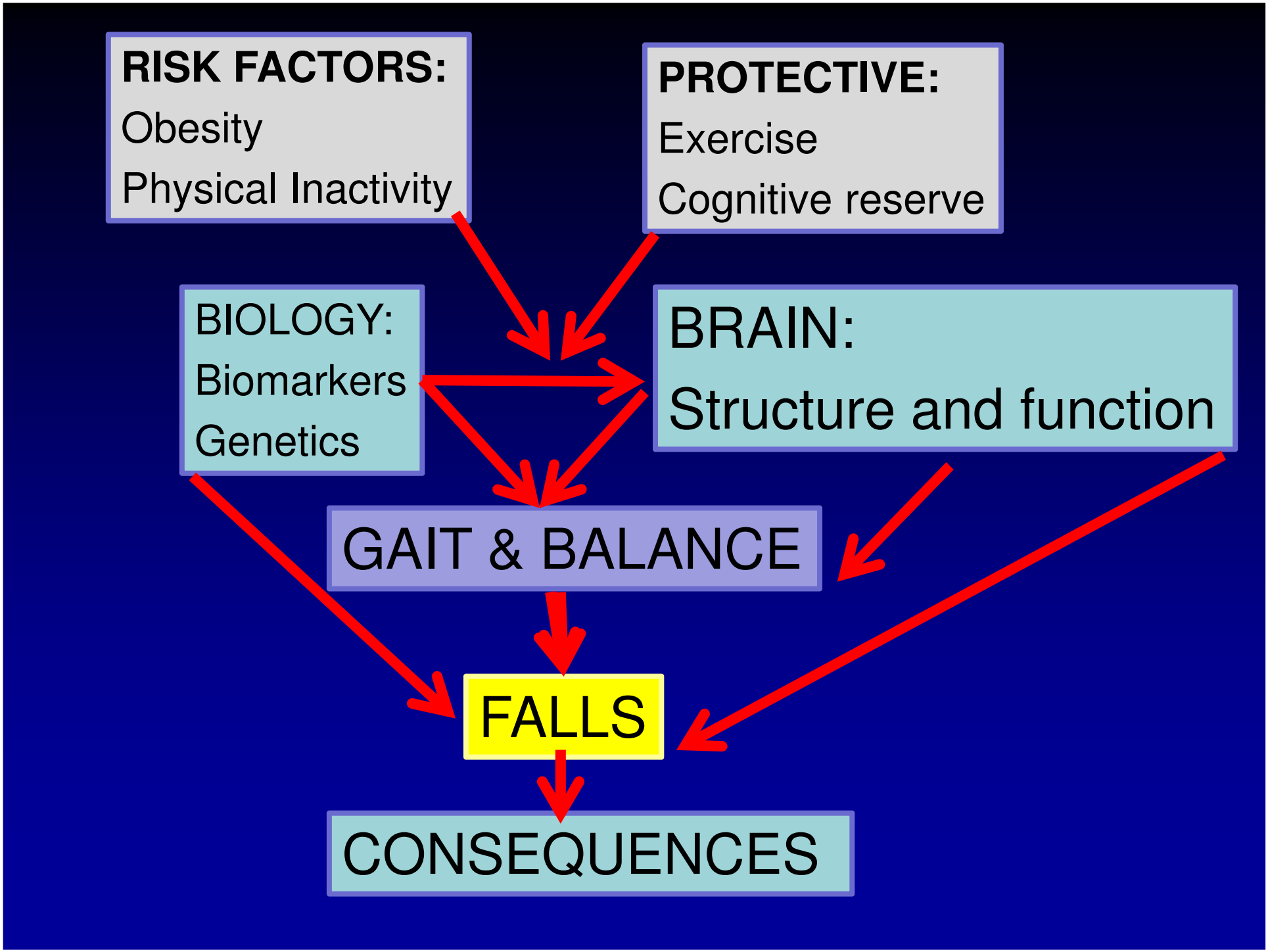
Gait (and balance) is central to fall risk assessment

AGS Panel on Fall Prevention: JAGS, 2001

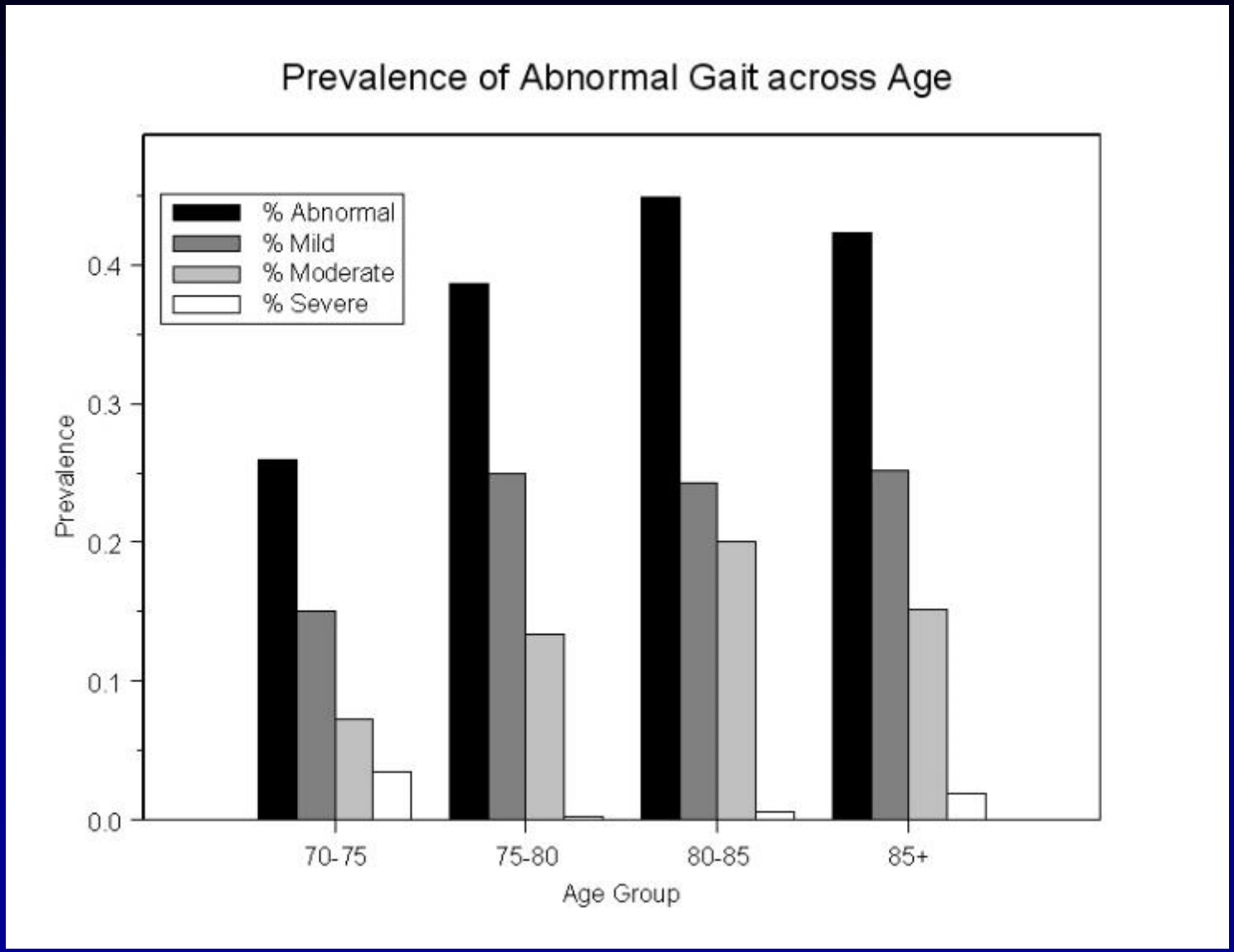
Risk factor	Significant	Mean RR-OR	95% CI
Muscle weakness	10/11	4.4	1.1 – 10.3
Previous falls	12/13	3.0	1.7 – 7.0
Gait deficit	10/12	2.9	1.3 – 5.6
Balance deficit	8/11	2.9	1.6 – 5.4
Use assist device	8/8	2.6	1.2 – 4.6
Visual	6/12	2.5	1.6 – 3.5
Arthritis	3/7	2.4	1.4 – 2.9
Depression	3/6	2.2	1.7 – 2.5
Cognitive impaired	4/11	1.8	1.0 – 2.3
Age >80	5/8	1.7	1.1 – 2.5

Gait and balance should remain mainstay of fall screening. JAMA 2007




RISK FACTORS:
Obesity
Physical Inactivity
PROTECTIVE:
Exercise
Cognitive reserve
BIOLOGY:
Biomarkers
Genetics
BRAIN:
Structure and function
GAIT & BALANCE
FALLS
CONSEQUENCES


Falls predictors:
Clinical gait
Quantitative gait
WWT



Verghese et al. J Am Geriatr Soc 2006

CLINICAL GAIT ABNORMALITIES

Neurological:

- Hempiaretic
- Parkinsonian
- Frontal
- Ataxic
- Neuropathic
- Unsteady

Non-neurological

- Arthritis
- Joint deformities
- Cardiac
- Respiratory

Verghese, New Engl J Med 2002

Neurological gaits & Falls

Gait subtypes	N = 632	Risk ratio (95% CI) *	p-value
Neurological gait	**120**	**1.49 (1.11 – 2.00)**	**0.007**
Hemiparetic	15	0.92 (0.47 – 1.80)	0.81
Frontal	9	1.59 (0.72 – 3.50)	0.25
Parkinsonian	10	0.90 (0.36 – 2.22)	0.82
Unsteady	42	1.52 (1.04 – 2.22)	0.03
Spastic	12	1.20 (0.47 – 3.11)	0.69
Neuropathic	23	1.94 (1.07 – 3.52)	0.03

Verghese et al. J Neurol 2010

Neurological gaits & Falls

Gait subtypes	N	Risk ratio (95% CI) *	p-value
Neurological (overall)	120	1.49 (1.11 – 2.00)	0.007
Hemiparetic	15	0.92 (0.47 – 1.80)	0.81
Frontal	9	1.59 (0.72 – 3.50)	0.25
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Verghese et al. J Neurol 2010

Neuropathic gait

Unsteady gait

QUANTITATIVE GAIT AND FALLS

Adjusted for age, sex, and education, previous falls, illness index, medications, disability scores, Blessed test scores, clinical gait abnormalities, and unipedal stance time.

Variables	Median	Unit change	Risk ratio (95% CI)	p-value
Speed	**95.10**	**10 cm/sec decrease**	**1.07 (1.01 – 1.14)**	**0.046**
Cadence	101.80	10 step decrease	1.01 (0.98 – 1.18)	0.11
Stride length	112.50 cm	10 cm decrease	1.07 (0.98 – 1.16)	0.118
Swing phase	**36.60 %**	**10% decrease**	**1.41 (1.03 – 1.93)**	**0.034**
Double support phase	26.60 %	10% increase	**1.17 (1.03 – 1.32)**	**0.018**
Stride length variability	**0.04**	**One unit increase**	**2.09 (1.52 – 2.87)**	**<0.001**
Swing time variability	**0.05**	**One unit increase**	**1.07 (1.04 – 1.10)**	**<0.001**

Verghese et al. J Gerontol Med Sci 2009

VARIABILITY: SHOULD I CARE?

Variables	Median	Unit change	Risk ratio (95% CI)	p-value
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Treadmill walking improved velocity, stride length and double support time. **But not variability**

Oh-Park et al. J Geriatr Phys Therapy 2011

He's a nice guy, but he played too much football with his helmet off.

…. so dumb he can't walk and chew gum at the same time.

Walking While Talking Test

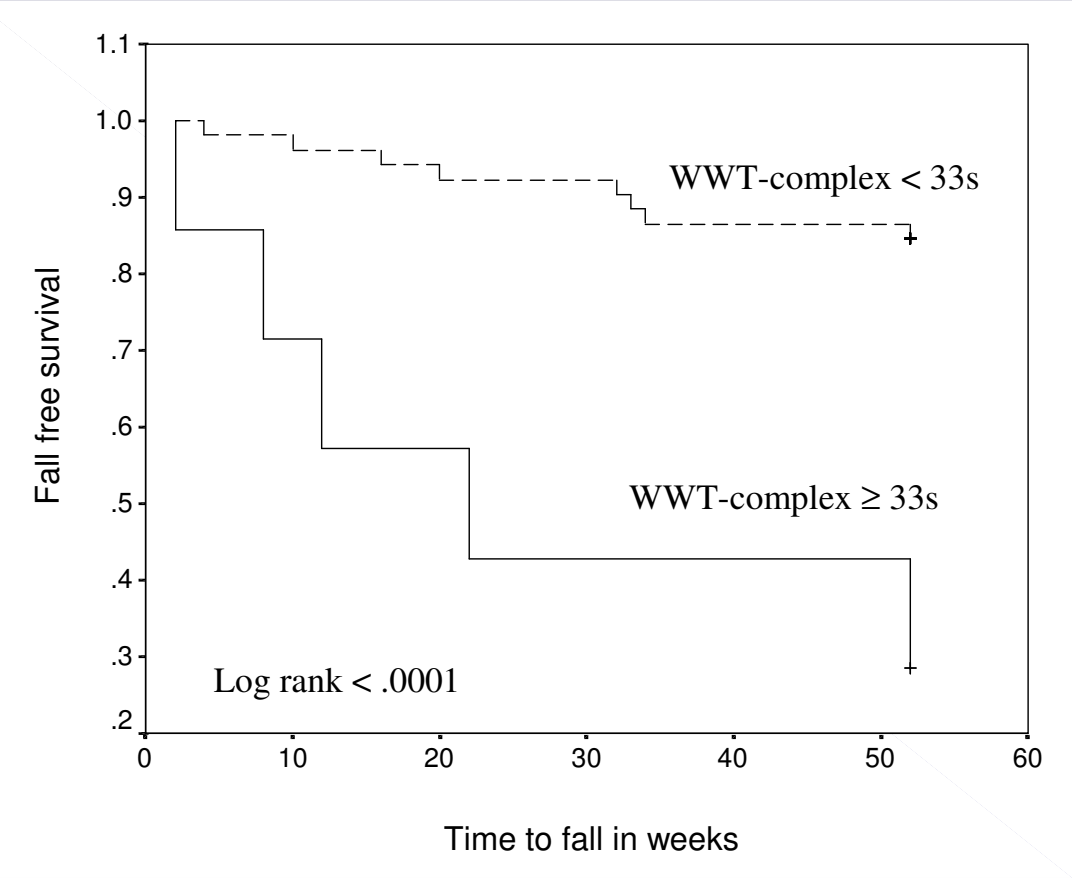
Verghese et al. J Am Geriatr Soc 2002

40 feet: sec

A, C, E…

Complex

Older adults who had difficulty walking while talking were 13 times more likely to fall over the next year.



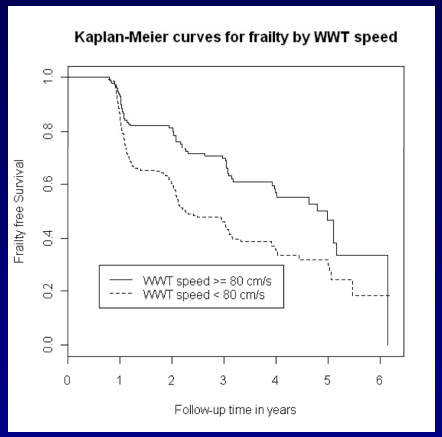
N = 60

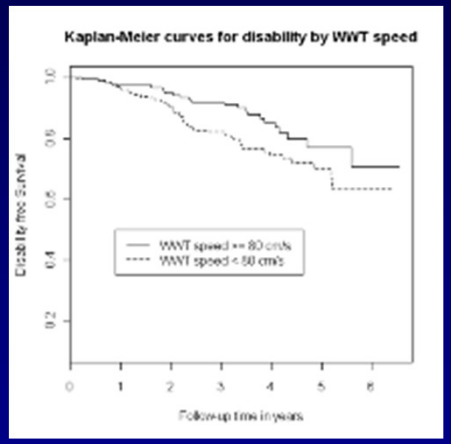
Verghese, J Am Geriatr Soc 2002
Ayers, Gerontology 2014

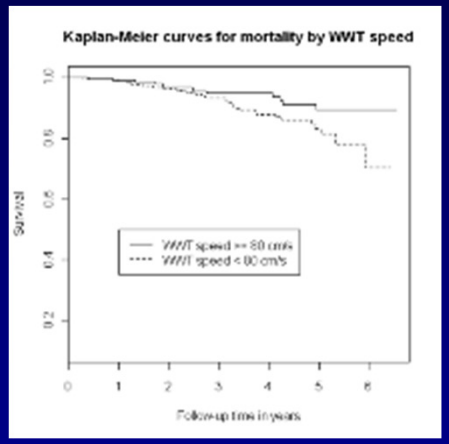
EAS: Mobility Stress Test Approach to Predicting Frailty, Disability, and Mortality in High Functioning Older Adults

Einstein Aging Study

Verghese et al. JAGS 2012







WWT predicts vascular dementia

Ceïde. J Geriatr Psych Neurology 2018

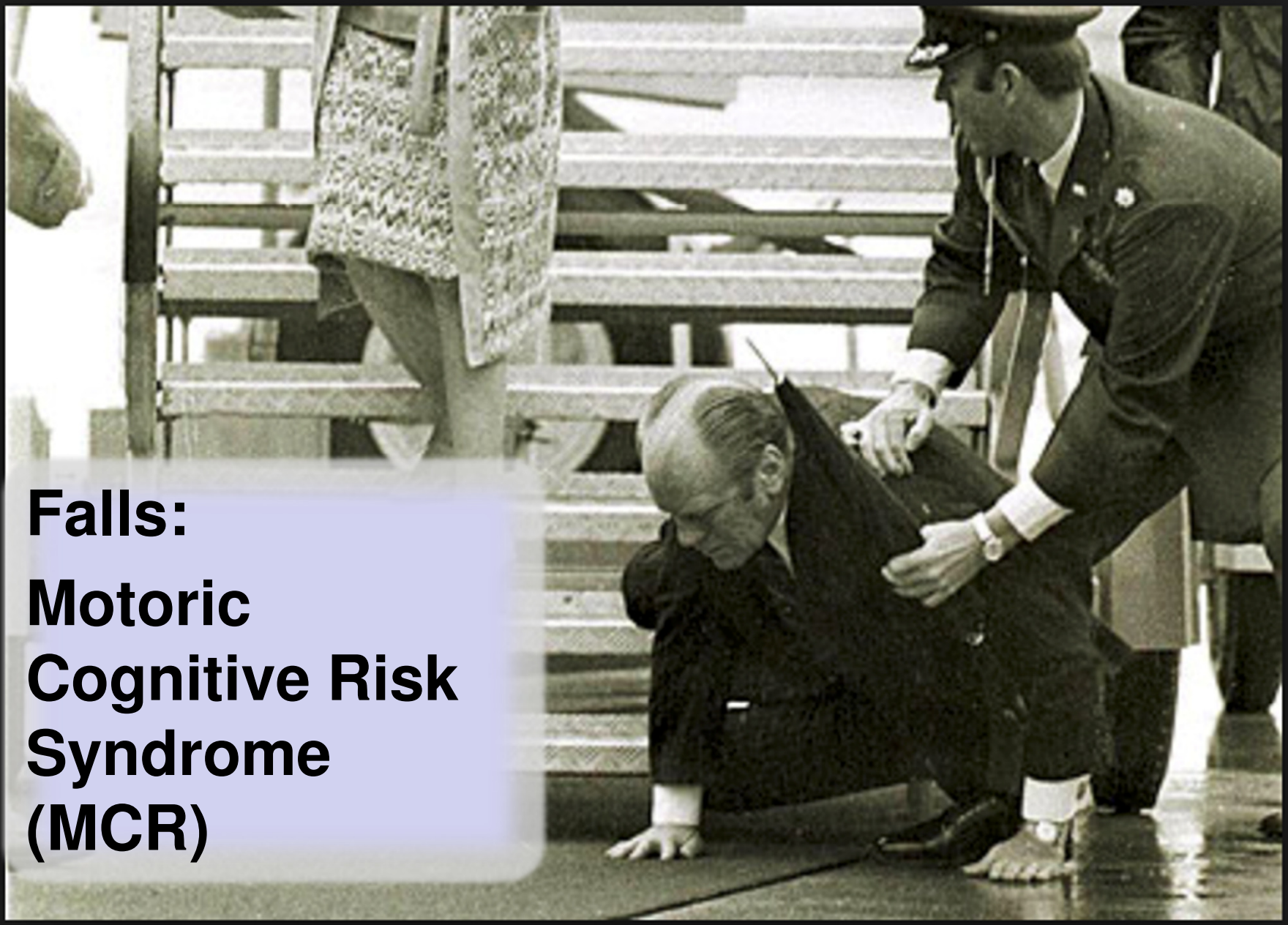
Walking While Talking and Falls

Ayers et al. Gerontology 2013

Factor	Model 1		Model 2	
	HR	p value	HR	p value
Rhythm	0.917 (0.81–1.04)	0.161	0.960 (0.84–1.09)	0.540
Variability	1.041 (0.92–1.18)	0.539	1.044 (0.91–1.19)	0.537
Pace	1.174 (1.04–1.33)	0.011	1.312 (1.11–1.55)	0.002

Values in parentheses represent 95% confidence intervals. Model 1 was adjusted for gender, age and education. Model 2 was adjusted for gender, age, education, illness index, prescription medicines, GDS, Blessed score, chair rise test, clinical gait abnormalities, falls in last year, normal velocity and normal stride length variability

646 older adults. 52% falls, median 2.6y



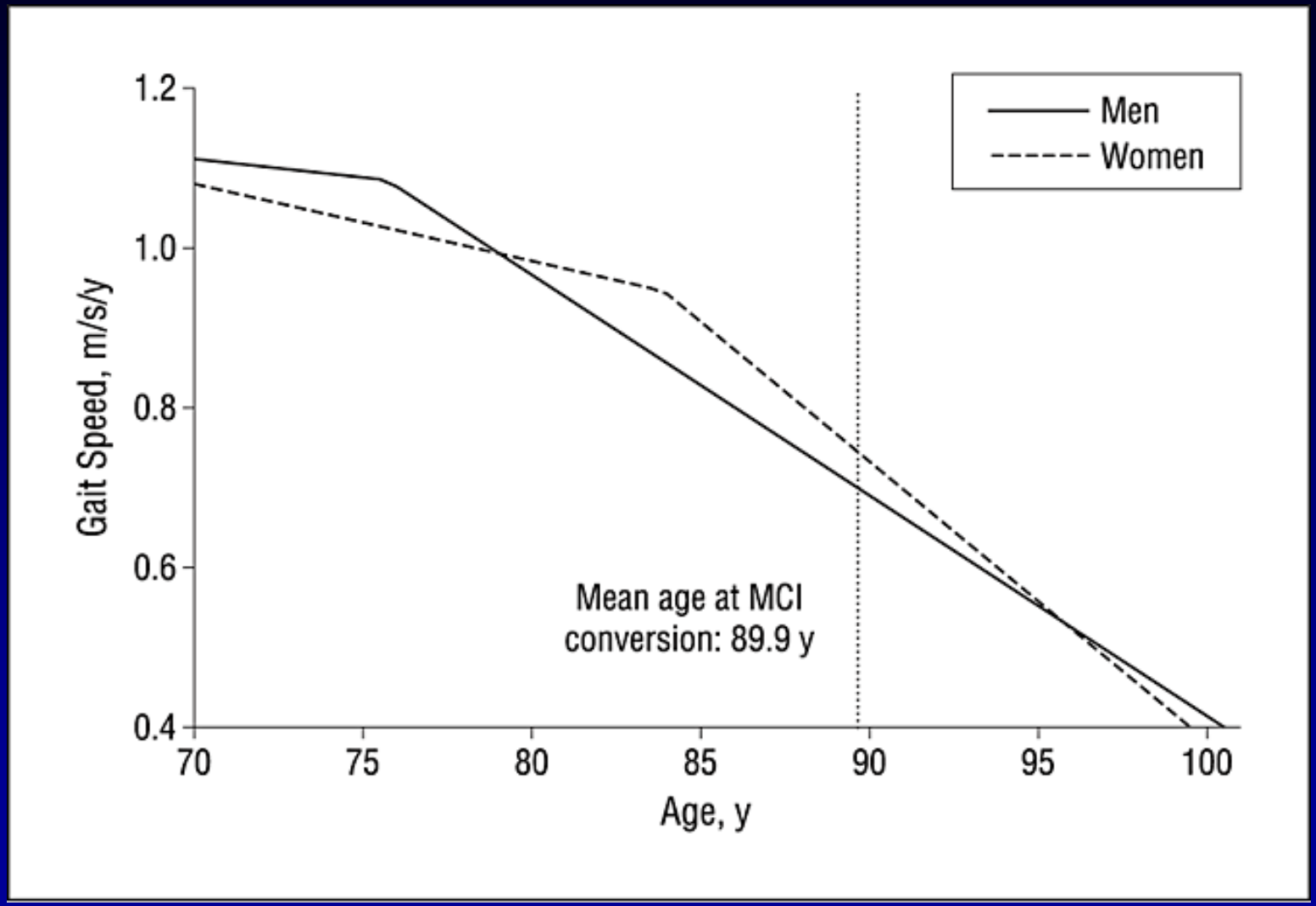
Falls:

Motoric Cognitive Risk Syndrome (MCR)

Mild Cognitive Impairment (MCI) syndrome

- Subjective cognitive complaints
- Objective cognitive
- Preserved ADL
- Absence of dementia

Gait speed declines early in the course of cognitive decline



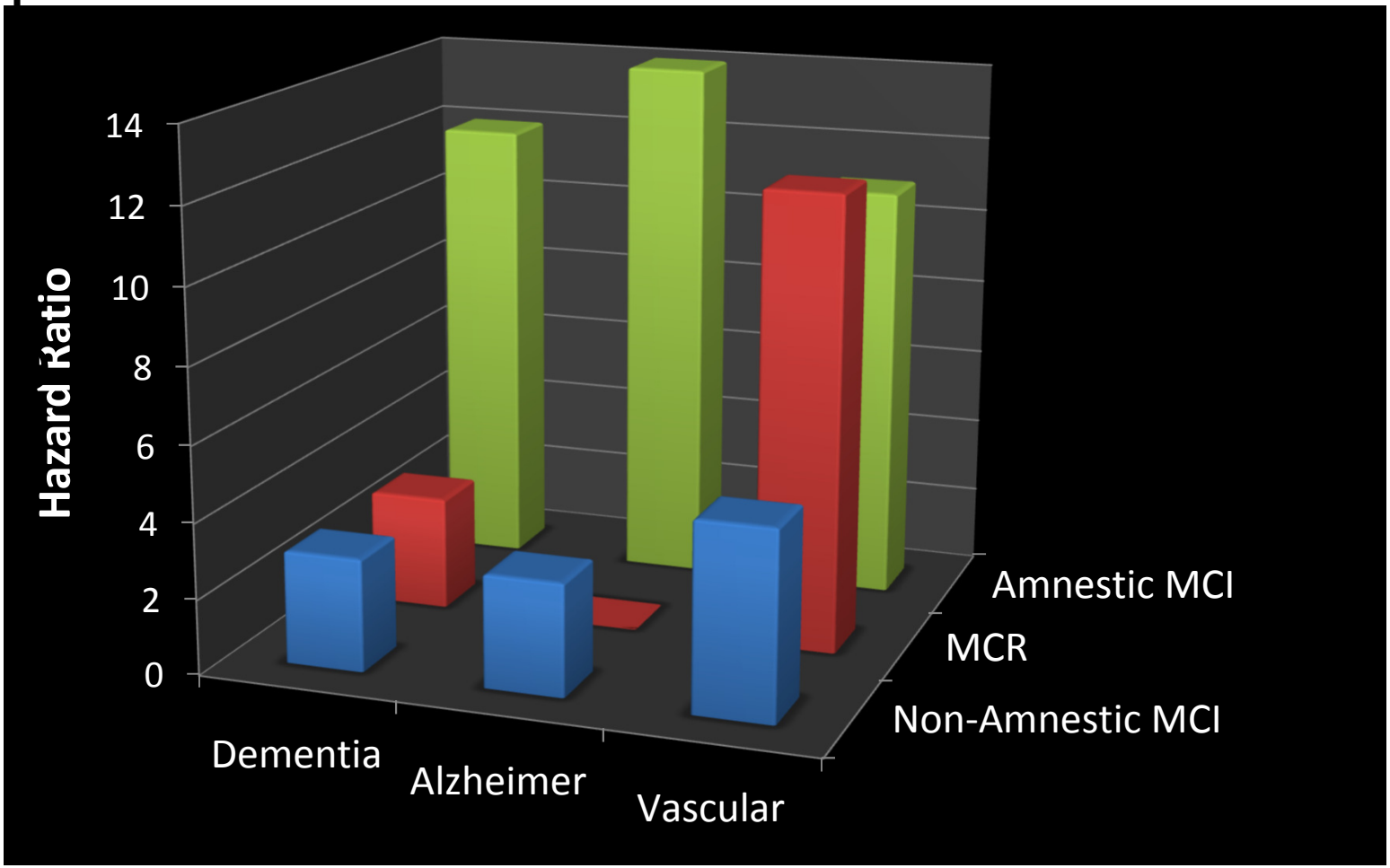
Buracchio, T. et al. Arch Neurol 2010;67:980-986.

Motoric Cognitive Risk (MCR) syndrome

- Subjective cognitive complaints
- Objective motoric: slow gait
  (1 SD below age and sex adjusted means)
- Preserved ADL
- Absence of dementia

J Gerontol Med Sci 2013

E



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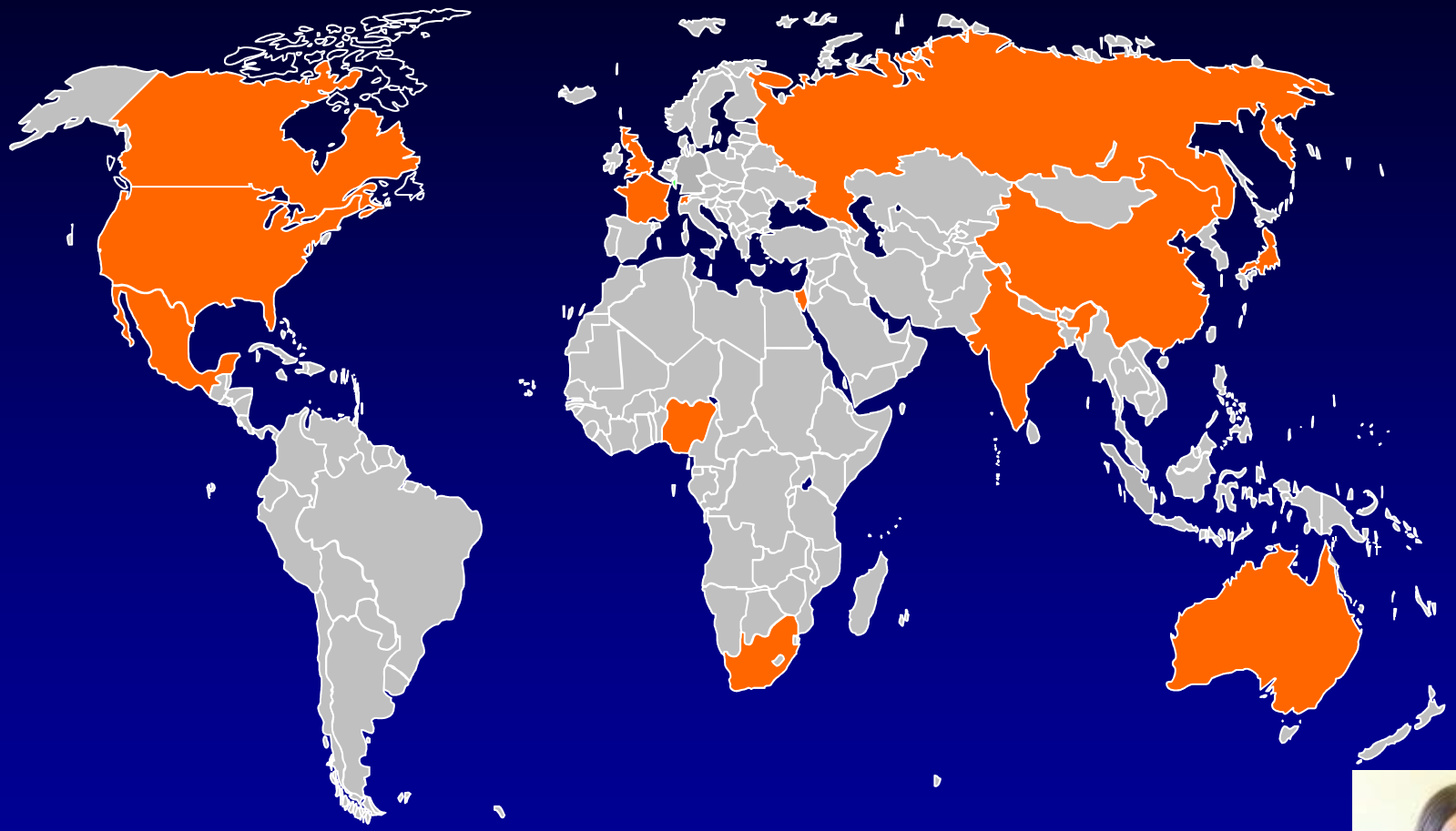
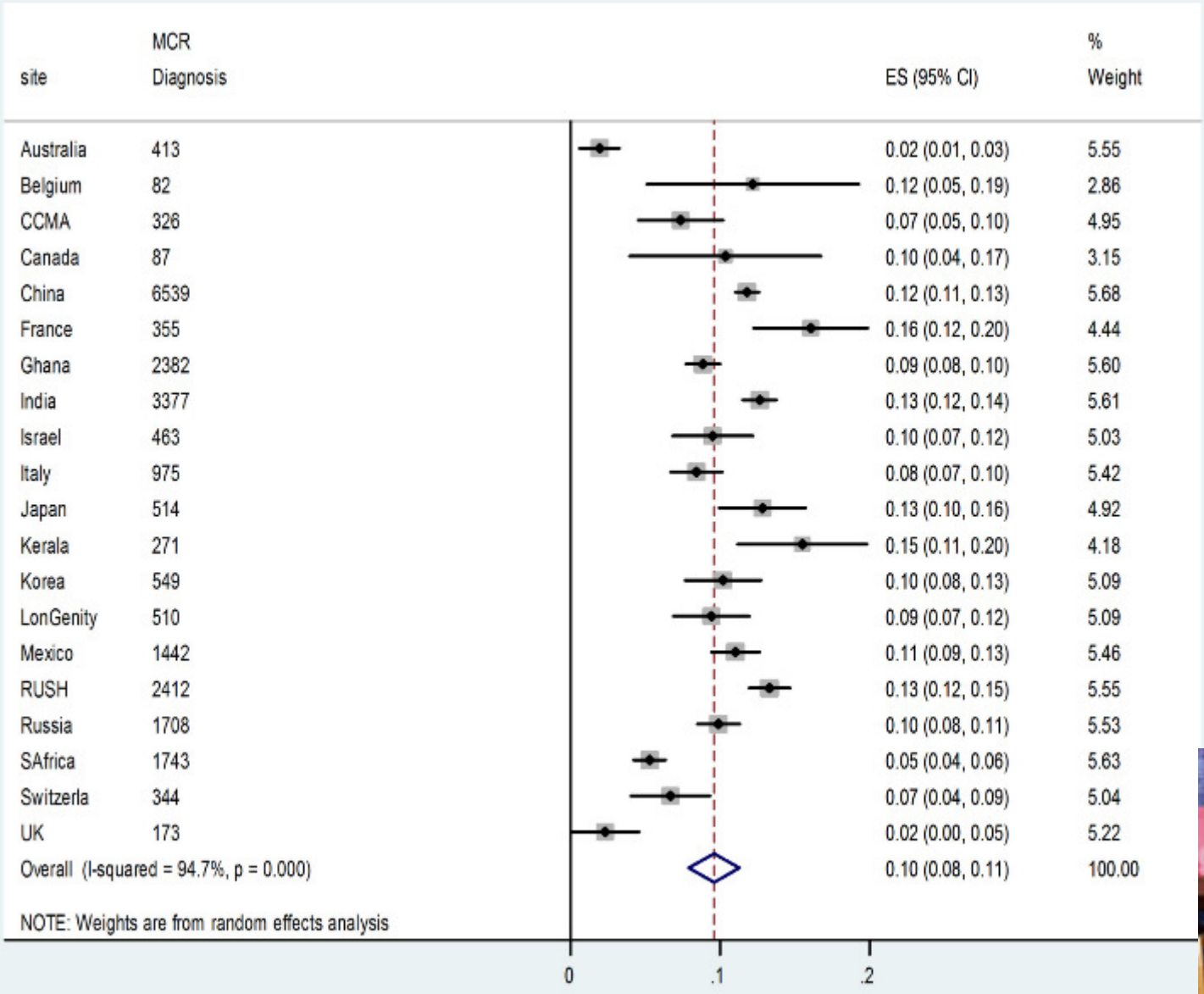
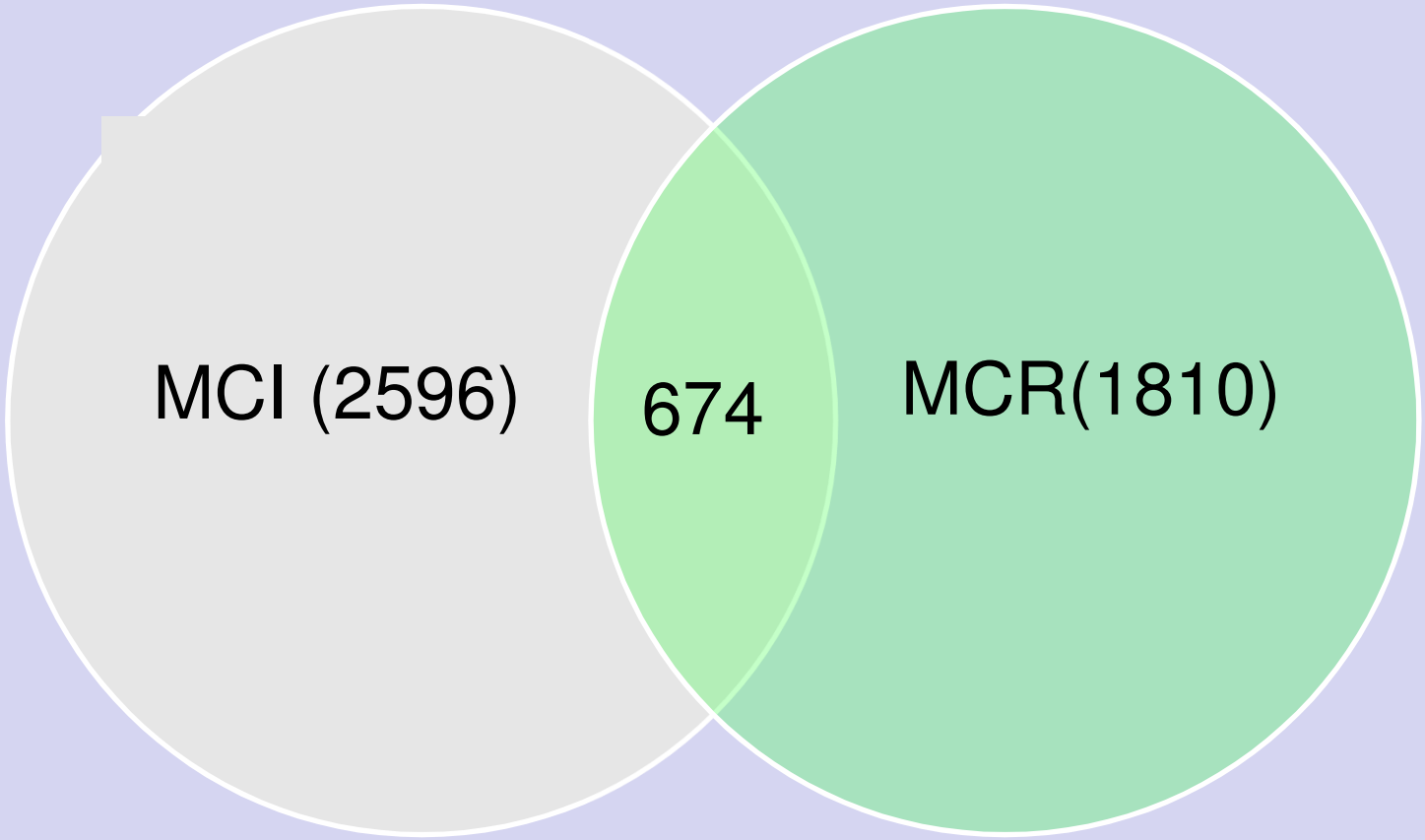
J Gerontol Med Sci 2013

MCR project: global prevalence study



22 sites worldwide. 26,802 participants


site
MCR Diagnosis
ES (95% CI)
% Weight
Australia 413 0.02 (0.01, 0.03) 5.55
Belgium 82 0.12 (0.05, 0.19) 2.86
CCMA 326 0.07 (0.05, 0.10) 4.95
Canada 87 0.10 (0.04, 0.17) 3.15
China 6539 0.12 (0.11, 0.13) 5.68
France 355 0.16 (0.12, 0.20) 4.44
Ghana 2382 0.09 (0.08, 0.10) 5.60
India 3377 0.13 (0.12, 0.14) 5.61
Israel 463 0.10 (0.07, 0.12) 5.03
Italy 975 0.08 (0.07, 0.10) 5.42
Japan 514 0.13 (0.10, 0.16) 4.92
Kerala 271 0.15 (0.11, 0.20) 4.18
Korea 549 0.10 (0.08, 0.13) 5.09
LonGenity 510 0.09 (0.07, 0.12) 5.09
Mexico 1442 0.11 (0.09, 0.13) 5.46
RUSH 2412 0.13 (0.12, 0.15) 5.55
Russia 1708 0.10 (0.08, 0.11) 5.53
SAfrica 1743 0.05 (0.04, 0.06) 5.63
Switzerla 344 0.07 (0.04, 0.09) 5.04
UK 173 0.02 (0.00, 0.05) 5.22
Overall (I-squared = 94.7%, p = 0.000) 0.10 (0.08, 0.11) 100.00
NOTE: Weights are from random effects analysis
0
.1
.2



	Healthy	MCR	Total
Healthy	17932	1810	19742
MCI	2596	674	3270
Total	20528	2484	23012

Neurology 2014

MCR patients are at high risk of developing cognitive decline, dementia and AD

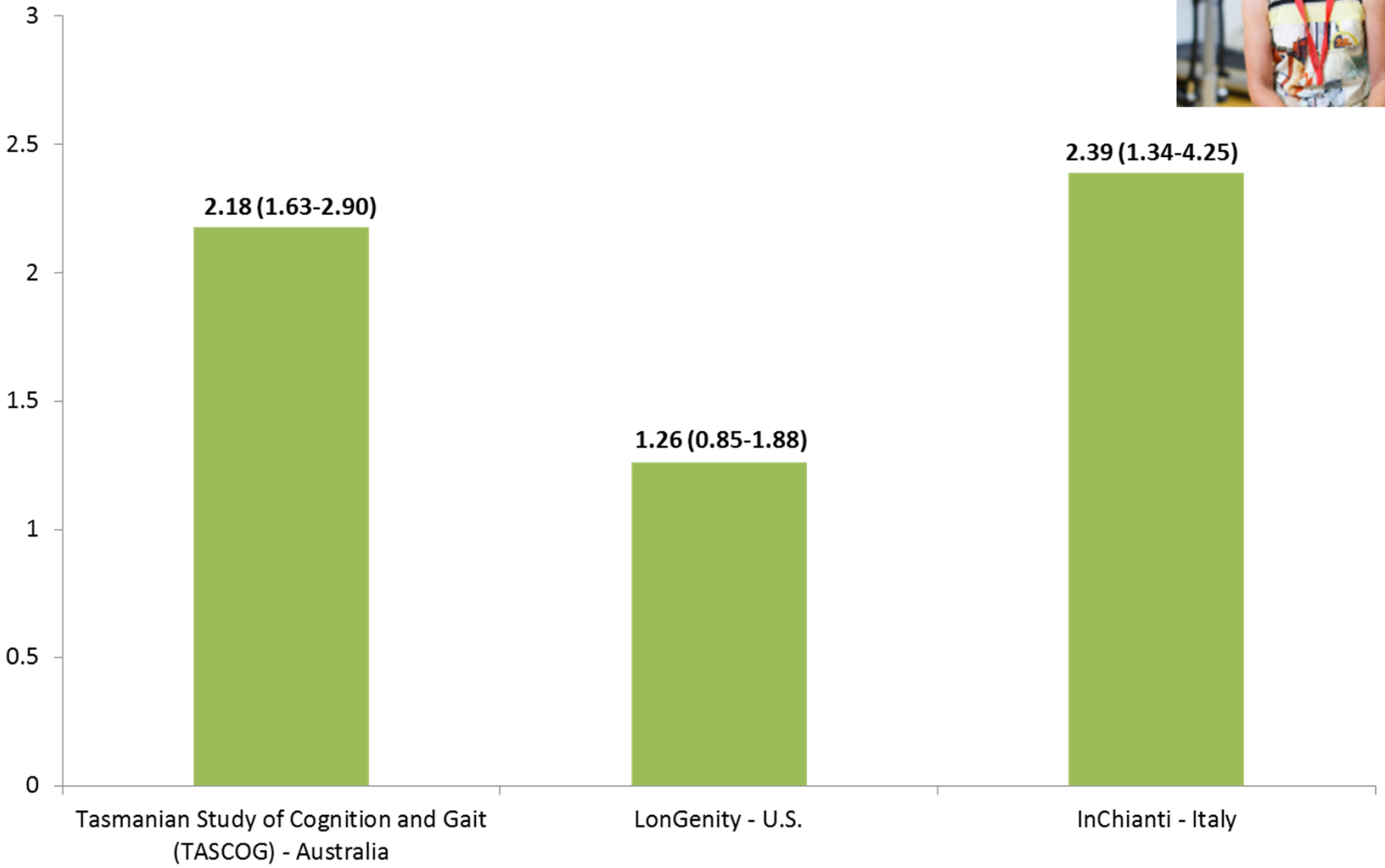
Study	N	Cognitive impairment (MMSE ≥5 points)*	Dementia*
Memory & Aging Project, USA	1280	1.49 (1.08-2.07)	2.10 (1.43-2.09)
Religious Orders Study, USA	1013	1.90 (1.44-2.51)	1.98 (1.44-2.74)
Hispanic EPESE, USA	1562	1.48 (1.16-1.88)	1.79 (1.31-2.44)
InCHIANTI, Italy	700	2.74 (1.54-4.86)	
NCGG-SGS Japan	4235		2.49 (1.52-2.02)

*Hazard ratios with 95% CI adjusted for age, sex, education, presence of vascular disease and MMSE scores

Neurology 2014, JAD 2017

MCR and risk of incident falls.

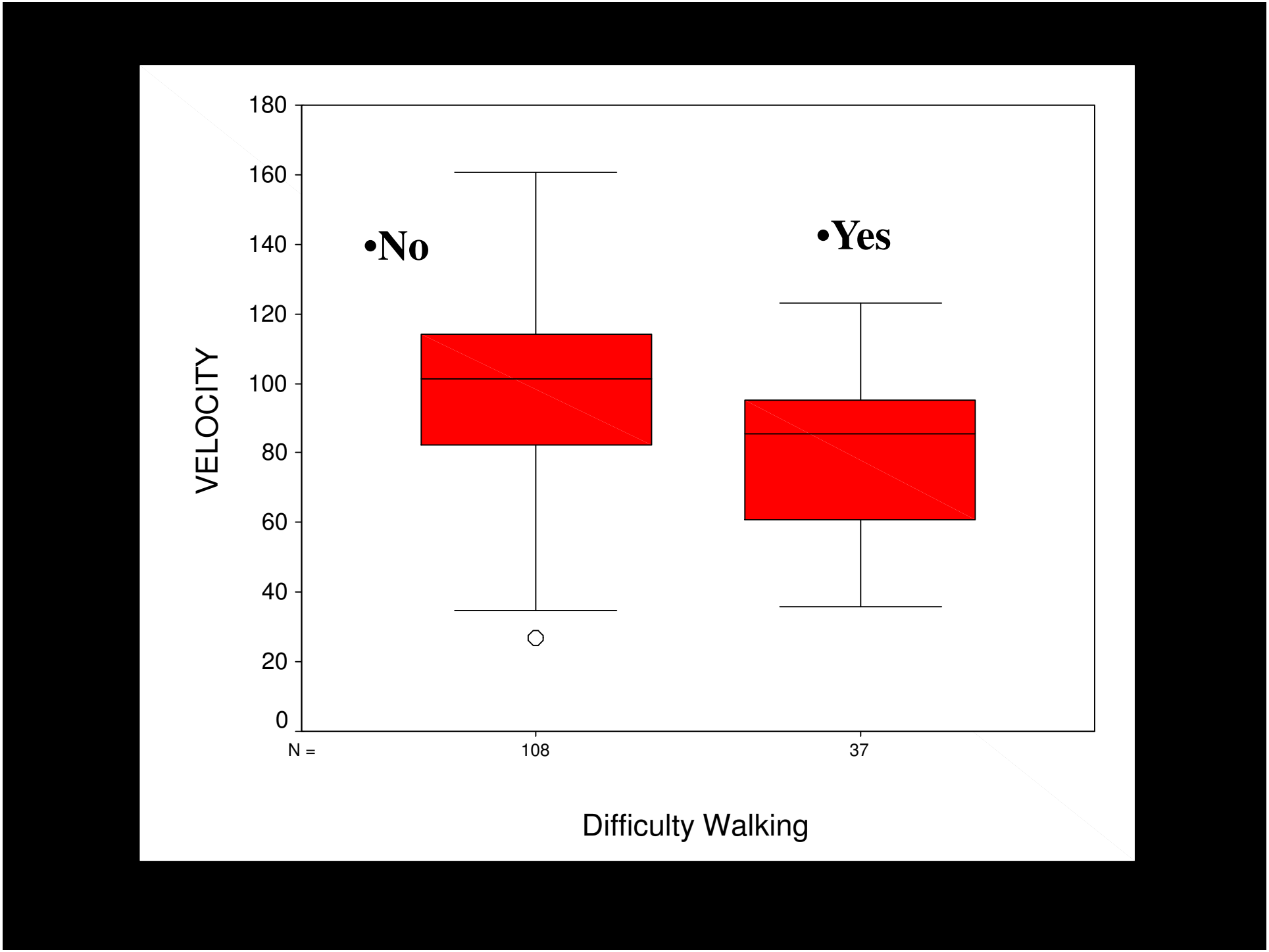
Results adjusted for age and sex.



Callisaya et al. J Alz Disease 2016

Falls:

How do you measure risk?


180
160
140
120
100
80
60
40
20
0
VELOCITY
•No
•Yes
N =
108
37
Difficulty Walking

The 3 dimensions of gait assessment

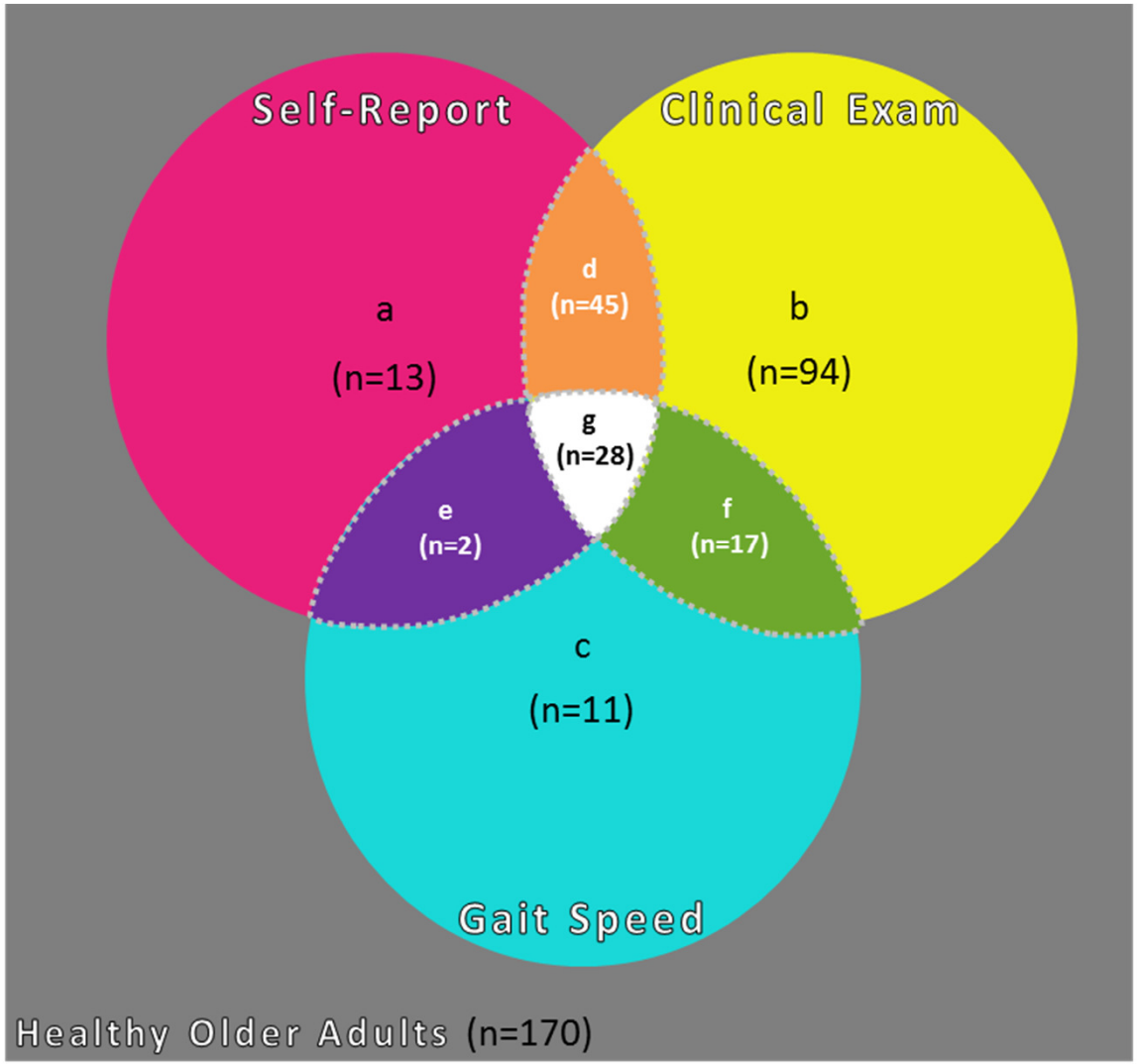
1. Asking ?

2. Looking

3. Measuring

Allali et al. Archives of Gerontology and Geriatrics 2015

Gait assessment from 380 non-demented healthy older adults from the Central Control of Mobility in Aging study



Allali et al. Archives of Gerontology and Geriatrics 2015

Falls and diagnostic groups adjusted for age, gender and education level

	N	OR	95% CI	P-value
Ref Group (Healthy older adults)	170			
Group a (only self)	13	0.54	0.07-4.42	0.369
Group b (only clinical)	94	1.38	0.68-2.80	0.381
Group c (only slow gait)	11	0.66	0.08-5.50	0.703
Group d (self + clinical)	45	1.36	0.55-3.36	0.509
Group f (clinical + slow gait)	17	1.96	0.58-6.61	0.277
Group g (self + clinical + slow gait)	28	5.42	2.24-13.14	**<0.001**

Allali et al. Archives of Gerontology and Geriatrics 2015

SUMMARY 1

- Clinical gait abnormalities increase risk for falls. Look for unsteady gait patterns.
- Speed is an useful indicator of fall risk but maybe not the best.
- Walking while talking as a mobility stress test
- Motoric Cognitive Risk (MCR) syndrome not only predicts risk of dementia but also is a strong fall predictor.
- Multiple view points


Falls biology

RISK FACTORS:
Obesity
Physical Inactivity

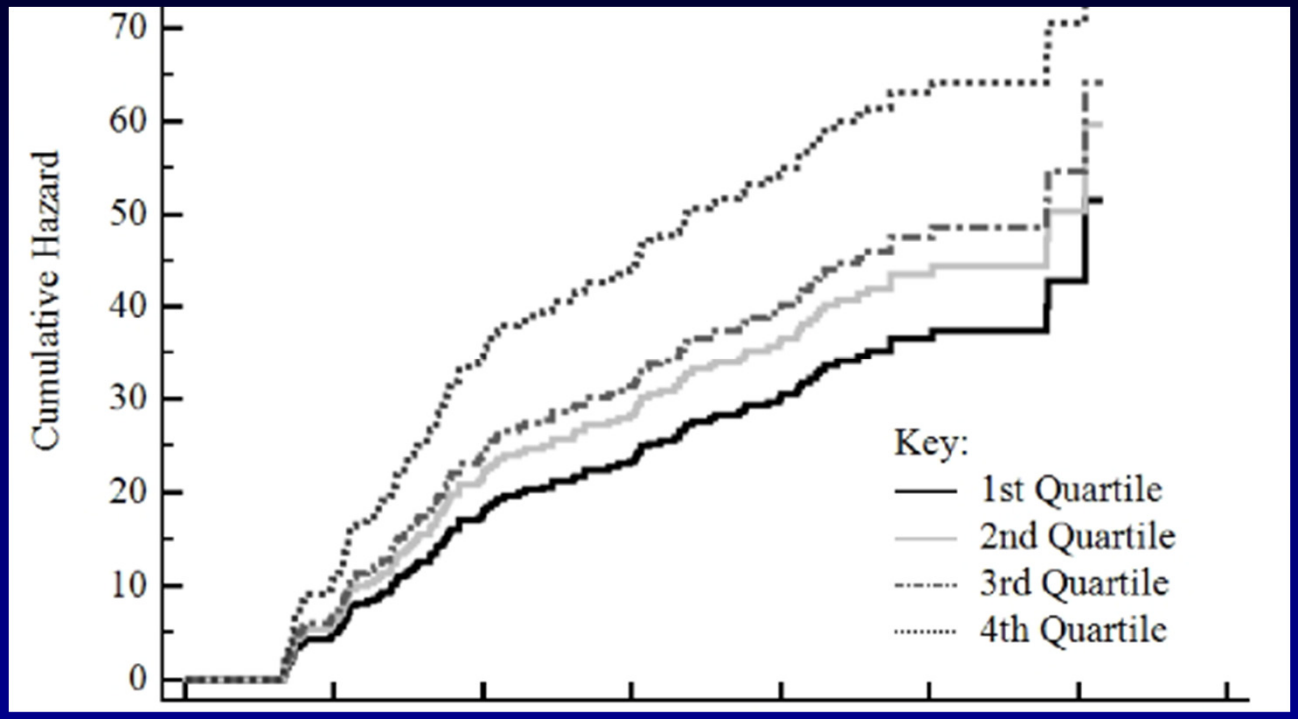
BIOLOGY:

FALLS

Obesity was associated with risk of falls in 10,775 Health and Retirement Study subjects. Compared with normal-weight subjects (BMI 18.5 -29.9), odds ratios for falls was 1.12 for obesity Class 1 (30-34.9), 1.26 for obesity Class 2 (35-39.9), and 1.50 for obesity Class 3 (≥40) in the HRS.

Himes et al. JAGS 2012

Oxidative stress and falls



266 older adults

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Verghese JAGS 2016

Oxidative stress and falls

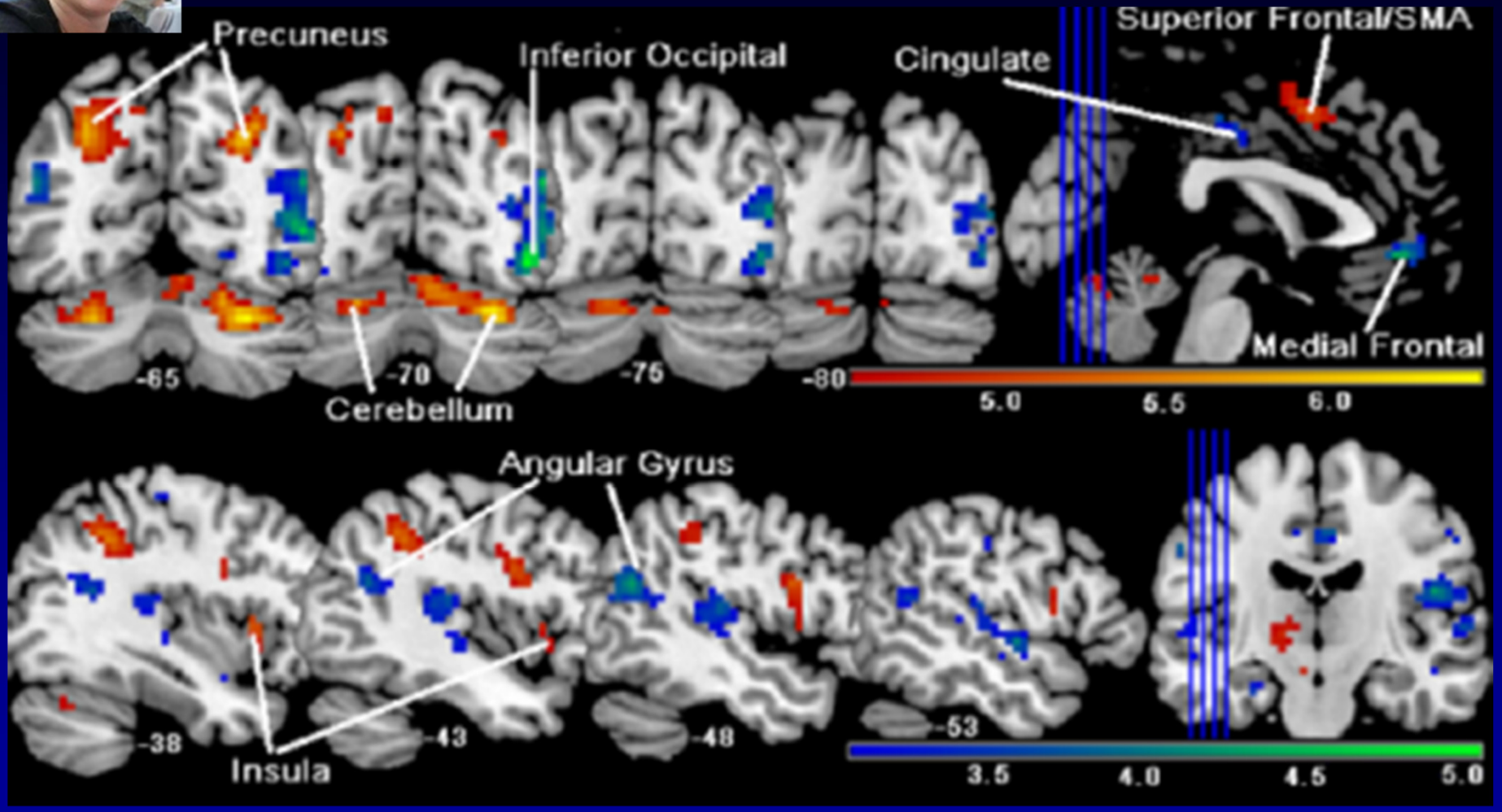
Verghese JAGS 2016

Table 2. Oxidative stress concentration and risk of falls. See Methods for explanation of models.

Risk Factors	Model 1 (n = 266) HR (95% CI), p	Model 2 (n = 257) HR (95% CI), p
Malondialdehyde concentration (log-units)	1.47 (1.10-1.98), 0.010	1.53 (1.11-2.16), 0.010
Age (years)	1.03 (1.00-1.05), 0.054	1.02 (0.99-1.06), 0.227
Female	1.20 (0.82-1.75), 0.343	0.98 (0.65-1.47), 0.923
Education (years)	0.98 (0.93-1.04), 0.497	0.97 (0.91-1.03), 0.278
Comorbidity count (0-9)	1.20 (1.00-1.43), 0.050	1.15 (0.95-1.40), 0.159
Interleukin-6 (log-units)		0.82 (0.61-1.10), 0.192
Medications		1.01 (0.93-1.08), 0.884
Fall in past year		2.28 (1.45-3.59), <0.001
Geriatric Depression Score (0-30)		1.03 (0.97-1.08), 0.345
RBANS* Total Score		1.00 (0.98-1.02), 0.988
Normal walking velocity (cm/sec)		1.00 (0.99-1.01), 0.702
Unipedal stance time (sec)		1.00 (0.98-1.02), 0.824

Falls: brain substrates

fMRI activation patterns during imagined WWT

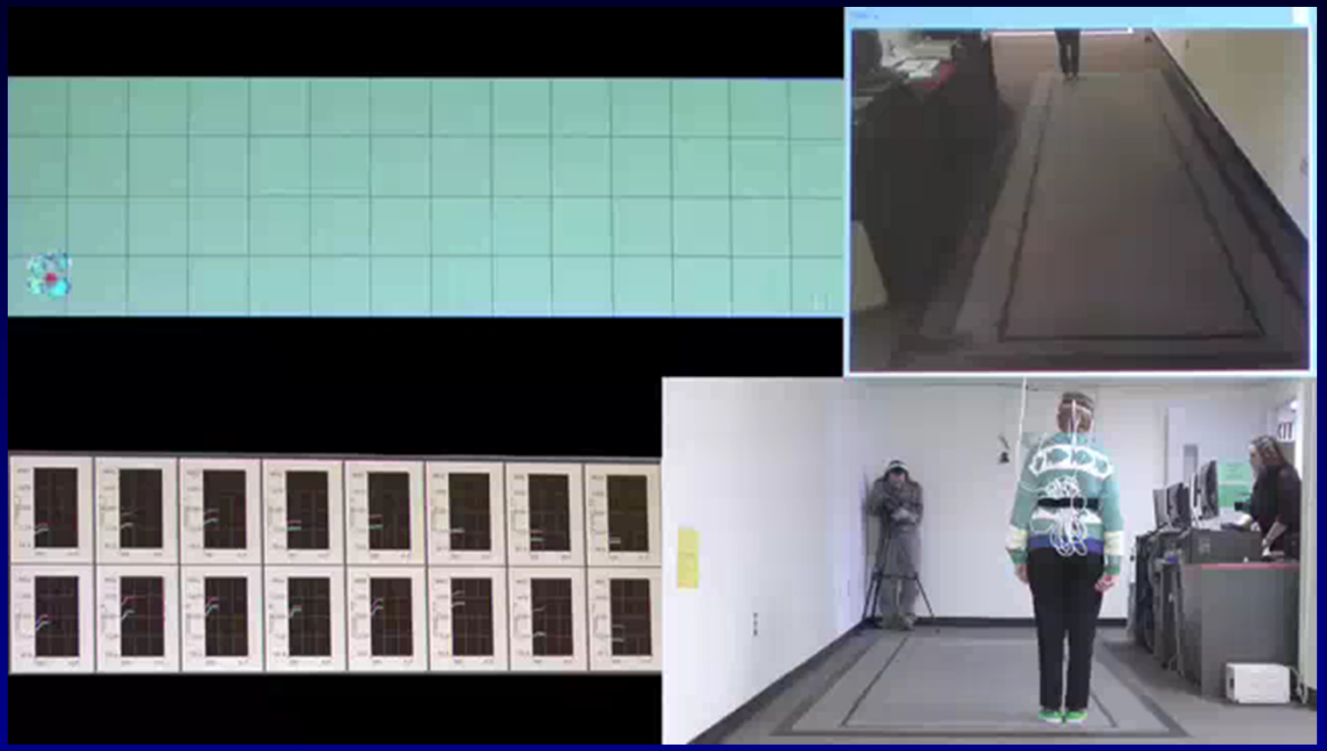


H Blumen et al. Human Brain Mapp 2014

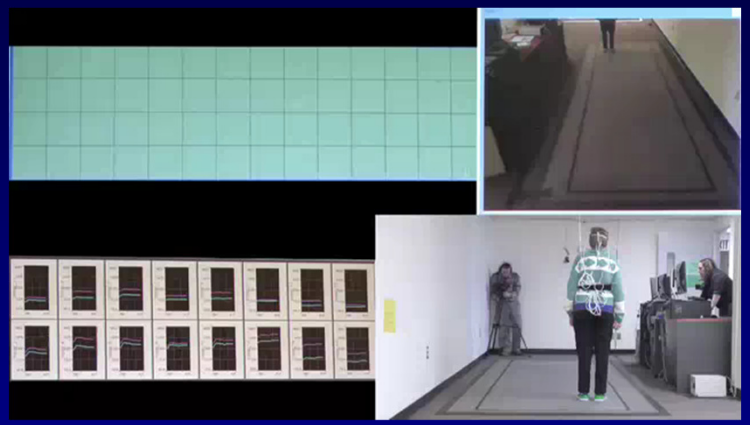
Imaging Motion:
Functional Near Infra-red Spectroscopy (fNIRS)

Holtzer et al. J Gerontol Med Sci 2012, Neuroimage 2015

Walking at normal pace without talking

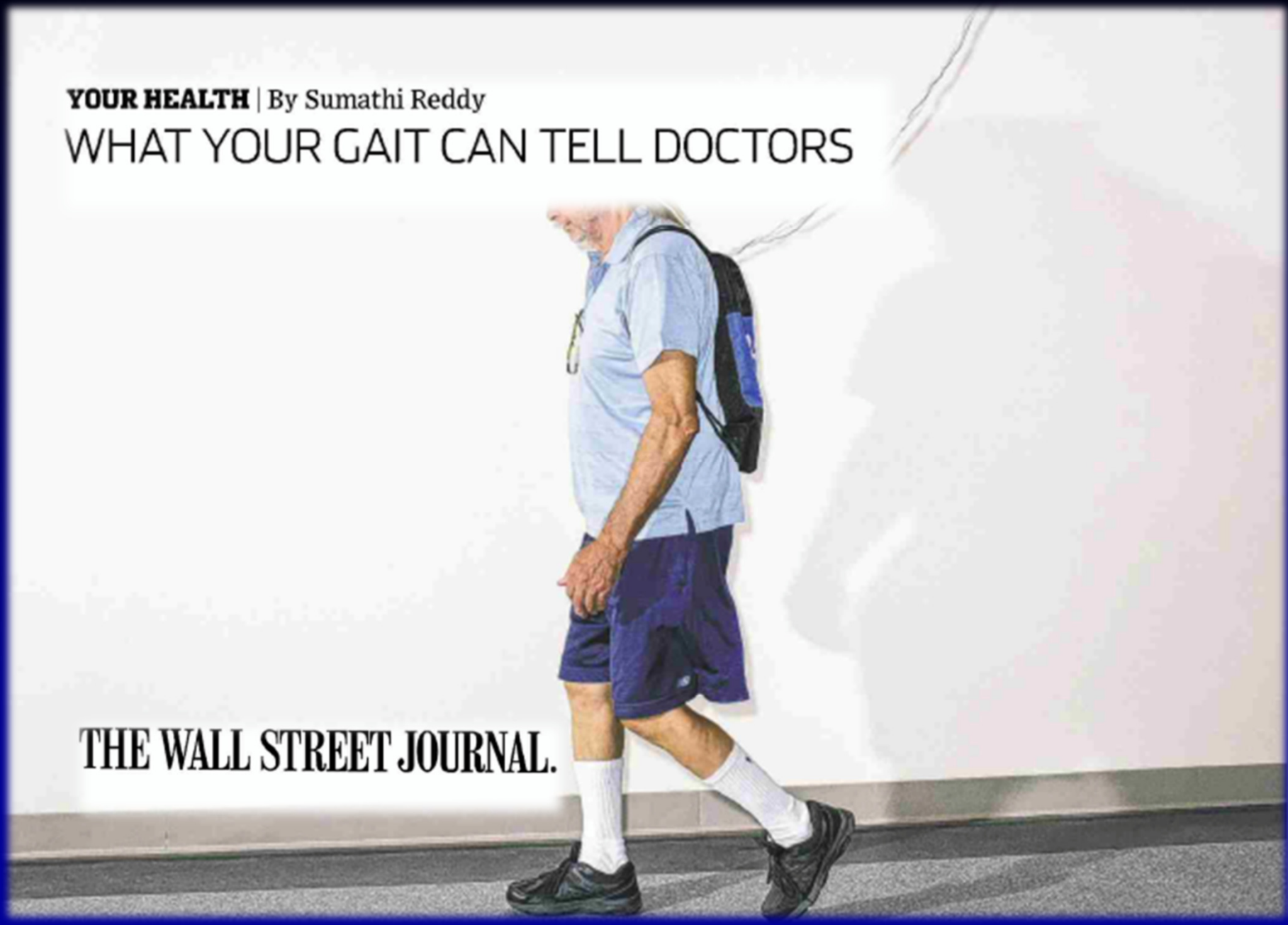


Walking while talking



YOUR HEALTH | By Sumathi Reddy

WHAT YOUR GAIT CAN TELL DOCTORS



THE WALL STREET JOURNAL.

Prefrontal activation on fNIRS during WWT predicts falls in high functioning older adults

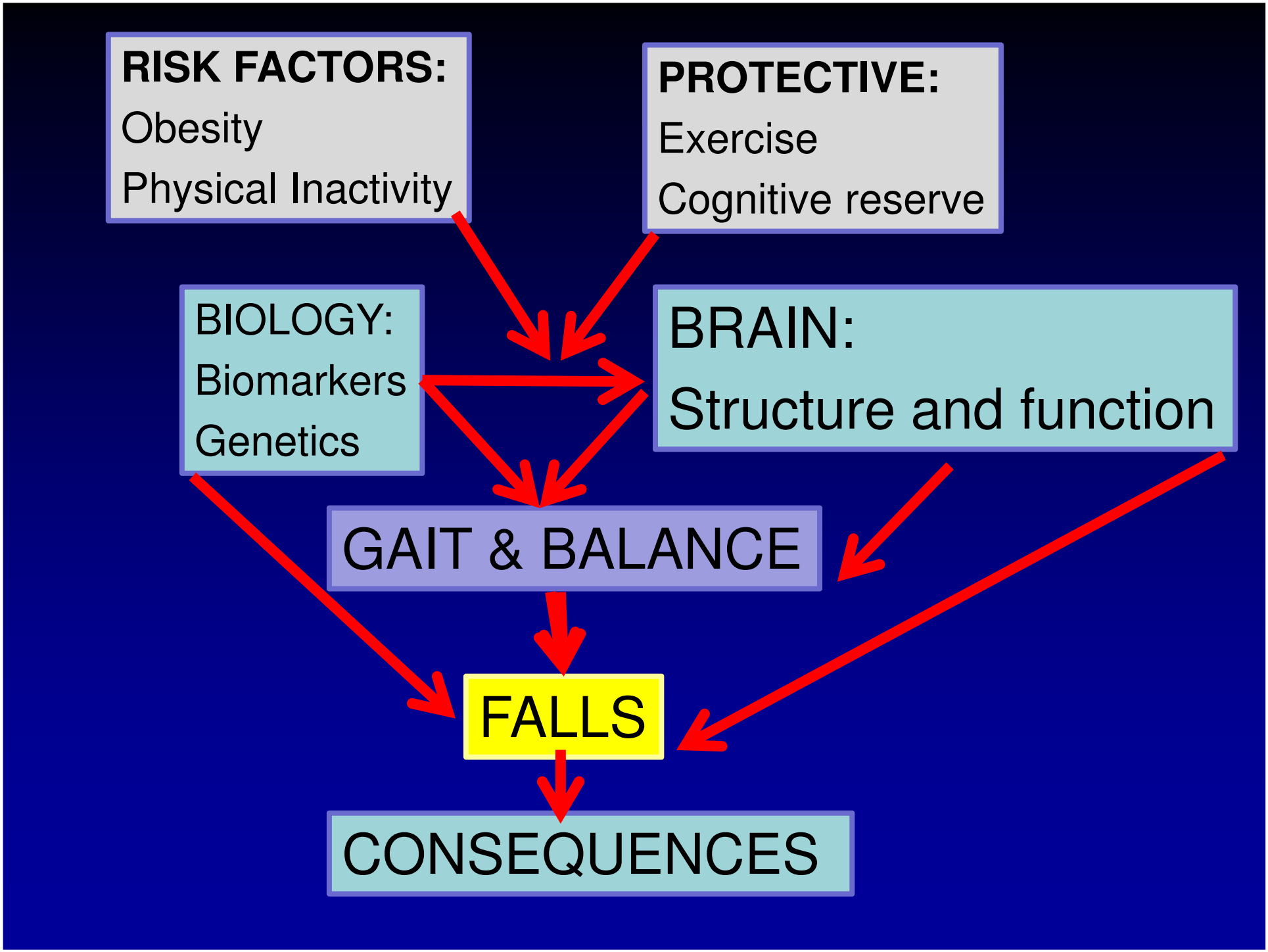
Model adjustments	Fall risk : HR per SD unit, 95% CI
Age, gender, education, illness, cognition	1.32, 1.01 – 1.71
+ fNIRS activation during normal walk and talk alone	1.30, 1.00 – 1.45
+ Digit symbol substitution test	1.32, 1.02 – 1.69
+ WWT velocity	1.37, 1.05 – 1.79

166 high functioning older persons

Mean age 75, 51% women

No dementia and disability, normal gait

Neurology 2017


RISK FACTORS:
Obesity
Physical Inactivity
PROTECTIVE:
Exercise
Cognitive reserve
BIOLOGY:
Biomarkers
Genetics
BRAIN:
Structure and function
GAIT & BALANCE
FALLS
CONSEQUENCES

Cognitive interventions: Falls

Older adults are poor at estimating fall risk

316 community adults

1. Do you think you are likely to have a fall in next 12 months?
 17%

2. Do you think you are at personal risk of having a fall in next 12 months?
 32%

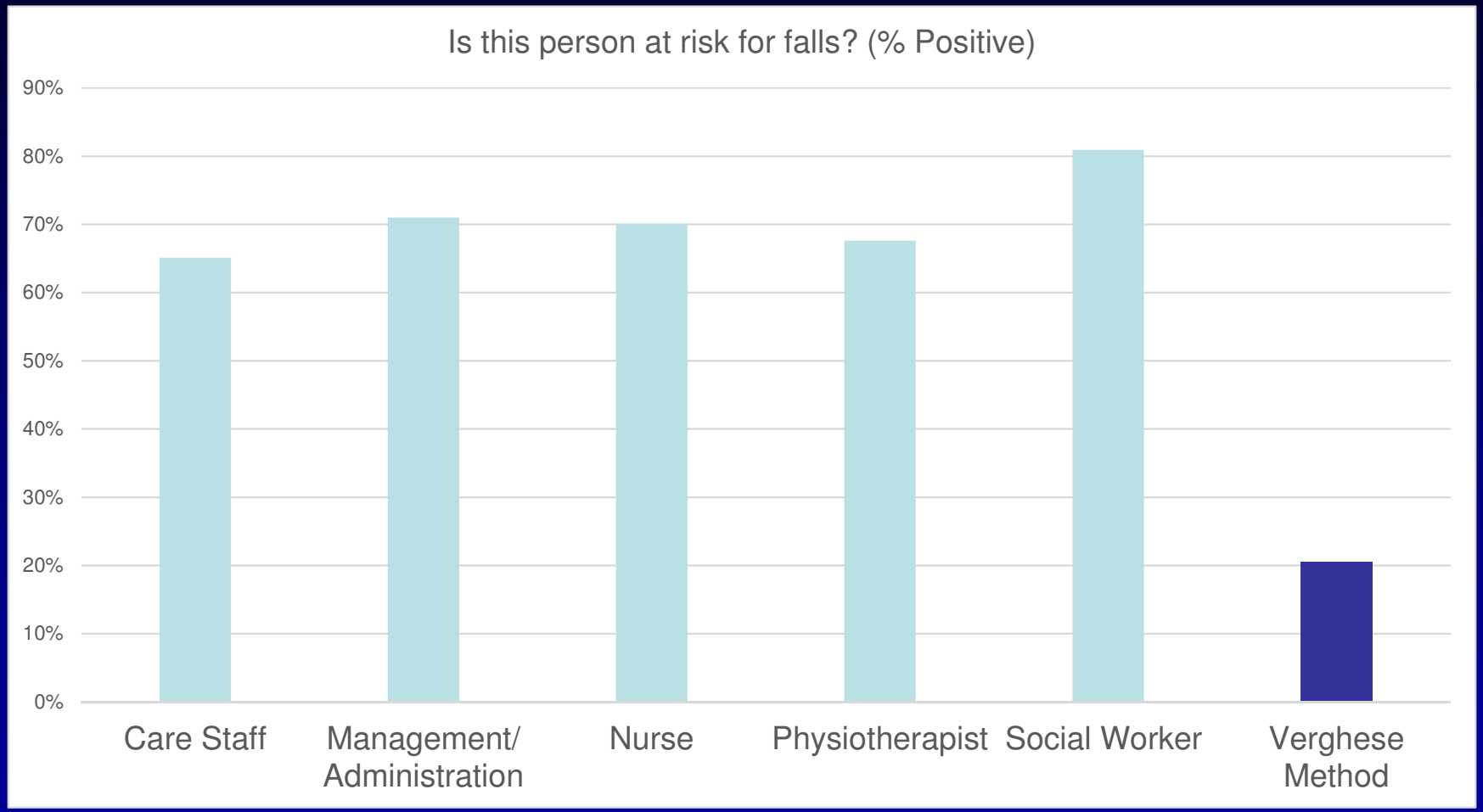
	Q1	Q2
Subjective	Balance 30% Old age 11% Fall 9% Good balance 74%	No reason 33% Old age 20% Fall 18% Careful 47% Healthy 20% No fall 19%
Objective	Fall Depression	Fall Depression Balance

Other risk factors: Age, sex, education, comorbid illness, anxiety, RBANS (cognition), ABC scale, gait speed, Unipedal stance

Verghese. JAGS 2016

Hughes et al. Am J Public Health 2008

Is this person at risk for falls?



400 interviews about 127 patients (90 dementia) in 8 daycare facilities in Sendai city, Japan.

Unpublished data

Dancing and risk of dementia
Adjusted Hazard Ratio 0.24 (0.06-0.99)

Verghese J, New England Journal of Medicine 2003

R21 AG057586-01A1: Social Dancing Intervention for older adults at high risk of Alzheimer's disease and other dementias: A pilot study

Normal

Executive attention
Memory
Verbal IQ

WWT

Executive attention
Memory

Falls

Executive attention

Holtzer, Neuropsychology 2006
Holtzer, Neuropsychology, 2007

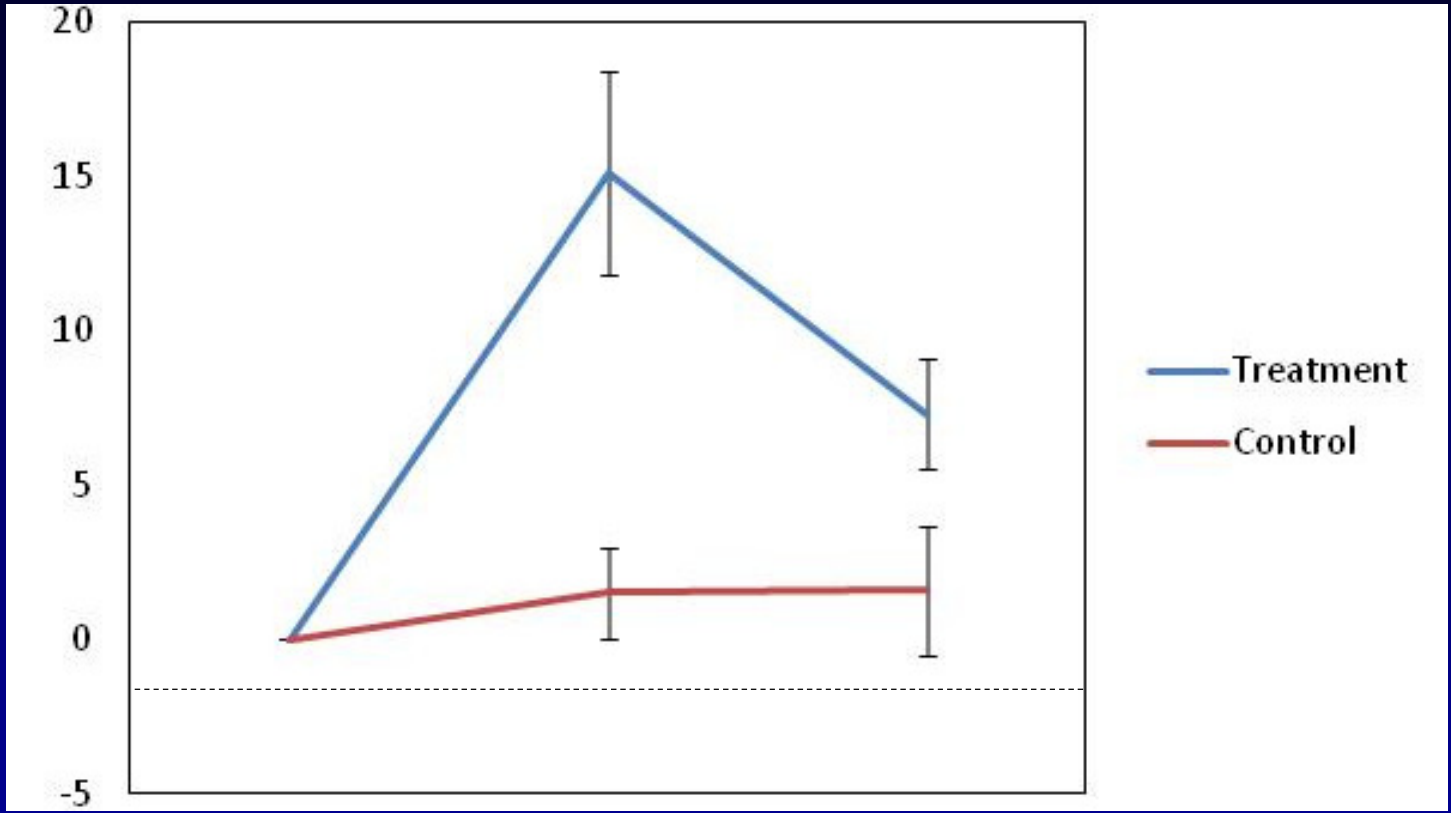
Brain games and mobility in frail seniors

Journal of Gerontology: Medical Sciences 2010

Effect on Gait Velocity

Percent change in gait velocity

Mean ± SEM



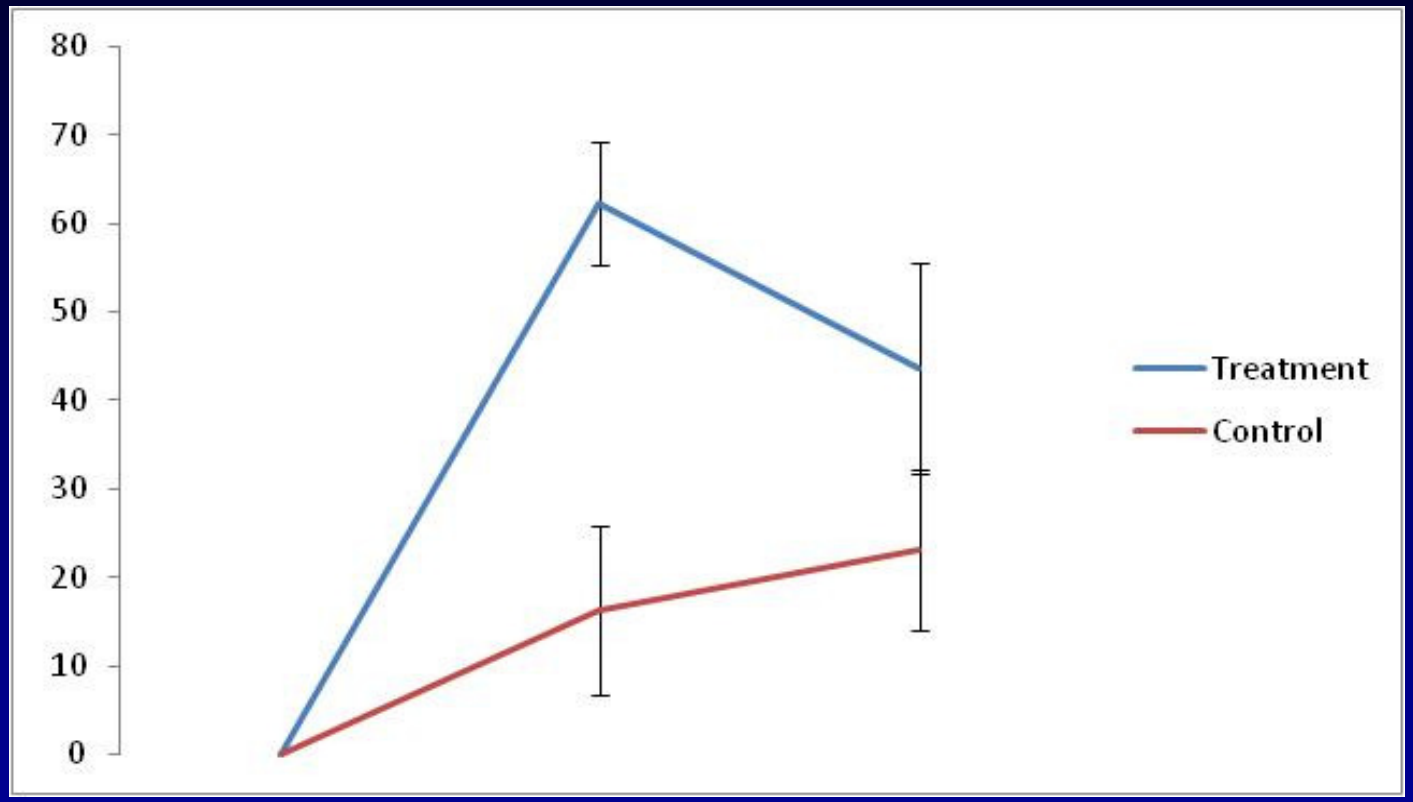
	Time: 0 (baseline)	3 months (Post-trial)	6 months (3-month follow-up)
N	12/12	10/10	9/9

J Gerontol Med Sci 2010

WWT: Walking while reciting alternate alphabets

Percent change gait velocity

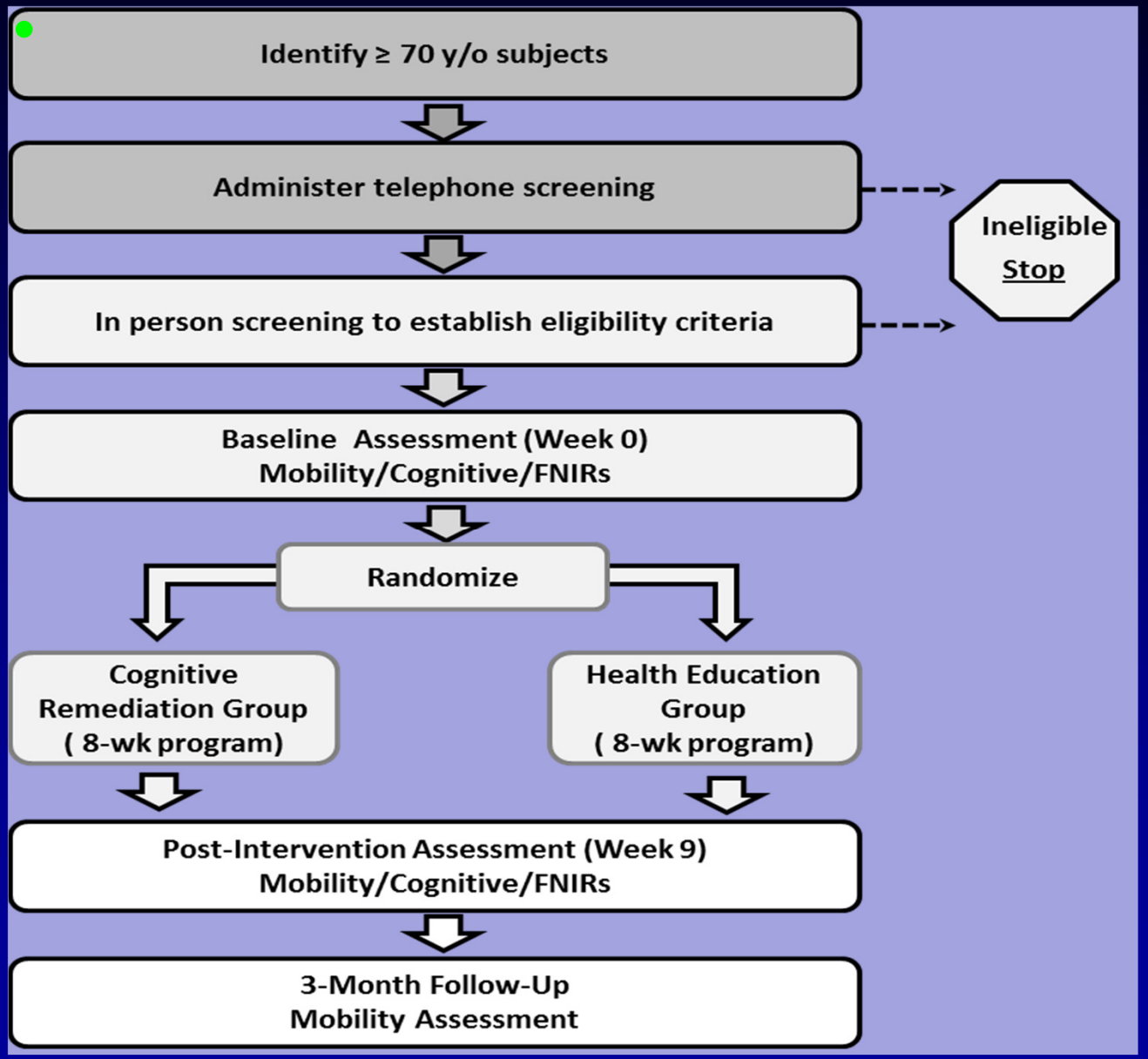
Mean ± SEM



Time: 0 (baseline) **3 months (Post-trial)** **6 months (3-month follow-up)**

J Gerontol Med Sci 2010

R01 AG050448-01 (Verghese/Holtzer): **Cognitive intervention to improve simple and complex walking**



420 sedentary seniors

Far transfer challenge

Neurodegener Dis Manag, 2016

85: Fencing
100: Bicycling
110: Nursing home
117: Stooped smoking
119: Wheelchair. 45 lb
120: Time's mistress
122: mentally intact

<u>Diet</u>
Olive oil
Port wine
Chocolate 1lb/week