Prevention of Cognitive Decline and Dementia: Fiction or Reality?

Pr Bruno Vellas M.D, Ph.D

Chair Gerontopole

UMR INSERM 1027, University of Toulouse, France

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Hôpitaux de Toulouse

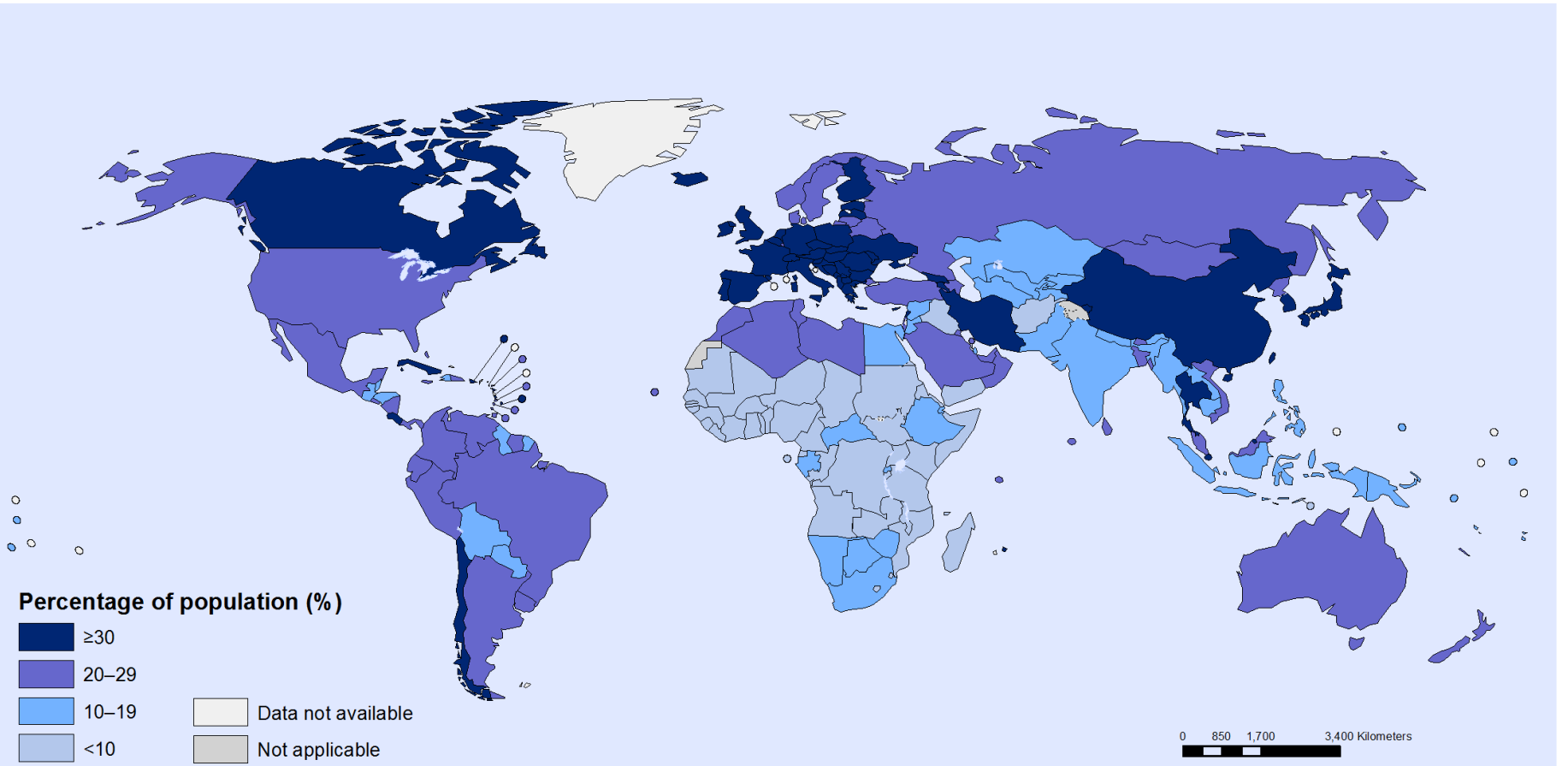
Toulouse GÉRONTOPÔLE

WHO - Collaborative Centre for Frailty, Clinical Research and Geriatric Training

Conflicts of Interest

- *The Gerontopole have the mission to work, on Alzheimer's drug development and have to work with any companies with potential interesting drug development (list available: Merck, Lilly, Biogen, Roche, Genentech, Avanir, Nestle, Astra..); However B Vellas have no stock options in any of these companies*

Estimated population aged 60 years or older (2050)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization

Dependence

Prevalence of dependence/disability: 350 to 600 million

Region	Year	Total population (millions)	Number of dependent people (millions)	Prevalence of dependence (%)	Increase in numbers (compared to numbers in 2000, %)	Dependency ratio* (%)
Established Market Economies	2010	885	42	4.7	10	7.8
	2030	925	48	5.2	28	9.7
	2050	928	49	5.3	31	10.4
Former Socialist Economies of Europe	2010	322	17	5.3	0	7.9
	2030	290	17	5.8	-1	9.7
	2050	252	16	6.2	-8	12.5
India	2010	1164	64	5.5	23	8.8
	2030	1409	90	6.4	74	10.0
	2050	1572	113	7.2	119	12.1
China	2010	1366	76	5.6	18	8.3
	2030	1485	102	6.9	57	11.6
	2050	1462	111	7.6	70	14.0
Middle-East Crescent	2010	755	35	4.7	29	7.8
	2030	1044	55	5.2	100	8.5
	2050	1283	77	6.0	180	9.8
Other Asia and Islands	2010	918	46	5.0	24	7.9
	2030	1131	66	5.8	78	9.3
	2050	1274	84	6.6	126	11.1
Latin America and Caribbean	2010	594	28	4.7	23	7.5
	2030	723	40	5.5	73	8.9
	2050	806	49	6.1	115	10.6
Sub-Saharan Africa	2010	829	42	5.0	29	9.6
	2030	1279	70	5.5	118	9.6
	2050	1760	115	6.5	257	10.5
Worldwide	**2010**	**6833**	**350**	**5.1**	**20**	
	2030	**8286**	**488**	**5.9**	**68**	
	2050	**9337**	**614**	**6.6**	**110**	

World Alzheimer Report 2013. **ADI 2013**

The Freedom of *Healthy Ageing*

Dr John Beard

Director, Ageing and Life Course

World Health Organization

World Report on Ageing and Health

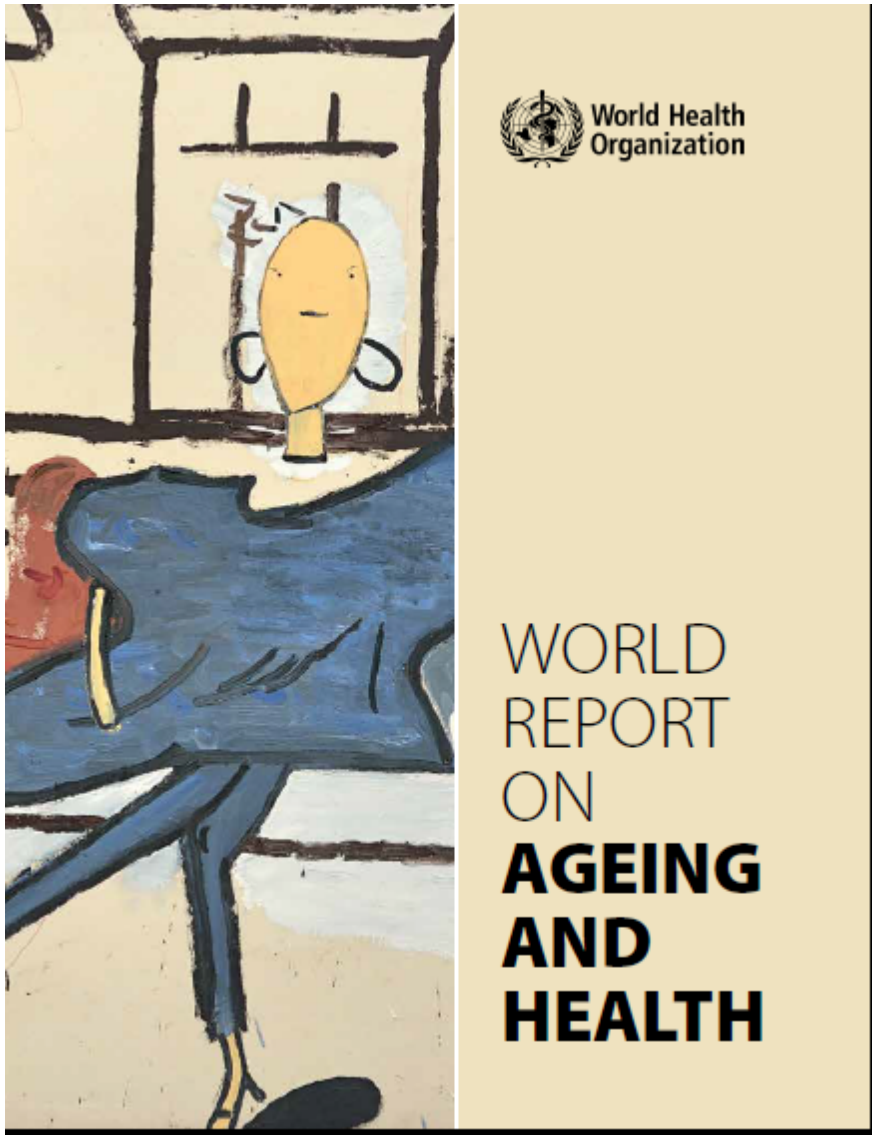
"Healthy Ageing - the process of developing and maintaining the functional ability that enables wellbeing in older age."

“To shift the focus from disease to capacity”

Hôpitaux de Toulouse

Toulouse GÉRONTOPÔLE

WHO - Collaborative Centre for Frailty, Clinical Research and Geriatric Training



Prevention of Cognitive Decline and Dementia: Fiction or Reality?

- **I. Cognitive decline in older adults using precision medicine**
- **II. How can we prevent cognitive decline part of our clinical practice now and in the near future**

I. Cognitive Decline in Older Adults

- Subjective Memory Complaints
- Vascular Cognitive Decline
- Cognitive Decline Related to Alzheimer's Disease
- Cognitive Decline Related to Frailty

  - To be effective intervention: targeted, strong and sustained
  - Precision medicine, personalized therapy

Subjective Memory Complaints

- **Definition:** Subjective memory complaints, 60% normal cognitive functions (CDR 0), 40% objective cognitive decline, CDR 0.5,early M.C.I
- **Advantages**: observance, frequent population
- **Disadvantages**: some of them will have no cognitive decline, some more likely to decline if recent (less than 5 years) and progressive complaint
- **Prevalence**: 60 % (MAPT), cultural influence
- **Intervention Studies**: GuidAge, MAPT

M.A.P.T: Multi-domain Alzheimer Preventive Trial

- Randomized, placebo control study
- 1680 subjects; 70yrs +, living in the community
- Inclusion criteria :
  - Subjective memory complaint, slow gait speed
- Three years Intervention + 2 years observation
  - Multi-domain Intervention plus placebo
  - Omega 3 (800 mg DHA)
  - M.I plus Omega 3
  - Placebo
- Primary End Point: Cognitive decline
- Secondary: SPPB, Frailty
- Brain MRI(500), Florbetapir PET (271), FDG (68)

(Andrieu S et al: Lancet Neurology 2016)

Toulouse GÉRONTOPÔLE

MAPT Multi-Domain Intervention

- Yearly Alzheimer Preventive Clinic Assessment
- Cognitive training:
  - Reasoning: strategies (8 sessions); S Willis (Seattle)
  - Mnemonic strategies (4 sessions); S Belleville (Montreal)
  - one session by month for 36 months
- Physical training
  - 150 minutes of moderately intensive physical activity per week; eg: walking (30 minutes per day).
- Nutrition Education

(Andrieu S, Lancet Neurology, July 23, 2015)

Toulouse GÉRONTOPÔLE

Good Sensibility for Cognitive Composite Score as Primary Criteria

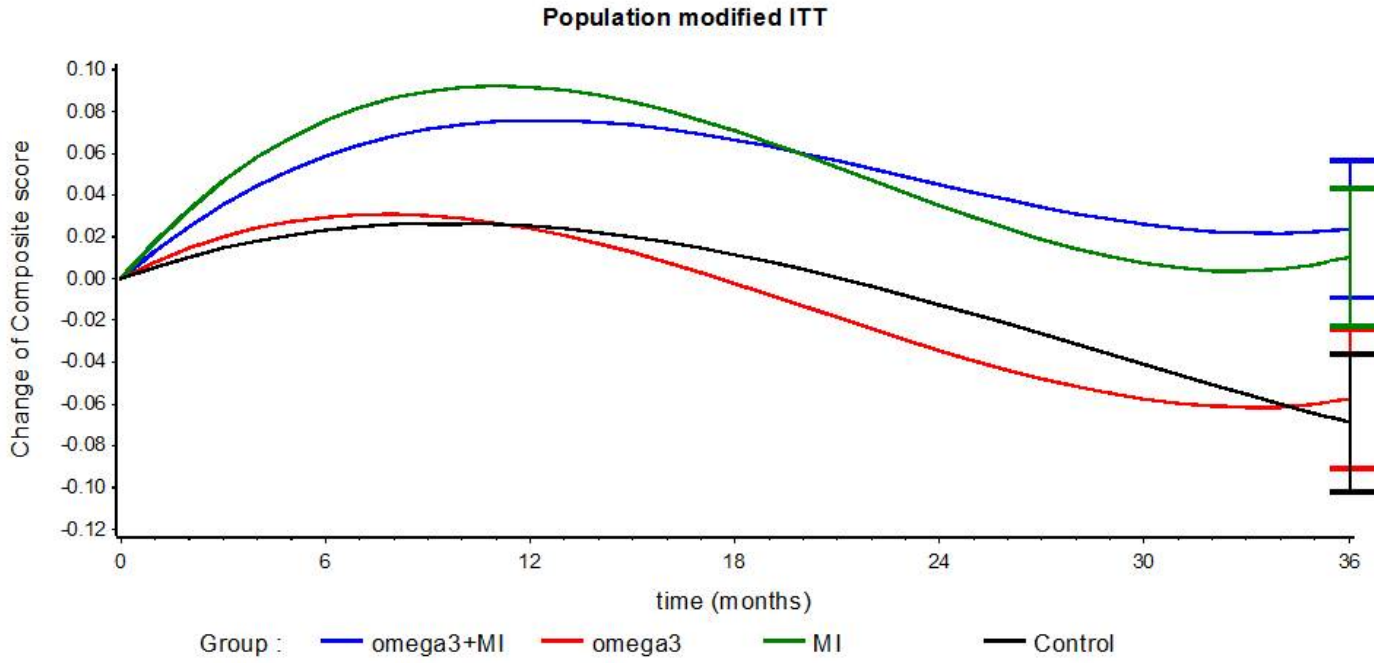
Composite Score:
Episodic memory: FCRST (Free + total recall)
Orientation : 10 items MMSE
Executive Function : WAIS (DSSS)
Verbal Fluency (animals 2 mn)

Donohue et al (adapted, JAMA Neurology 2016)
Coley N , Andreiu S (Alzheimer Dementia 2016)

MAPT Results: Primary Criteria: ITT (N=1525)

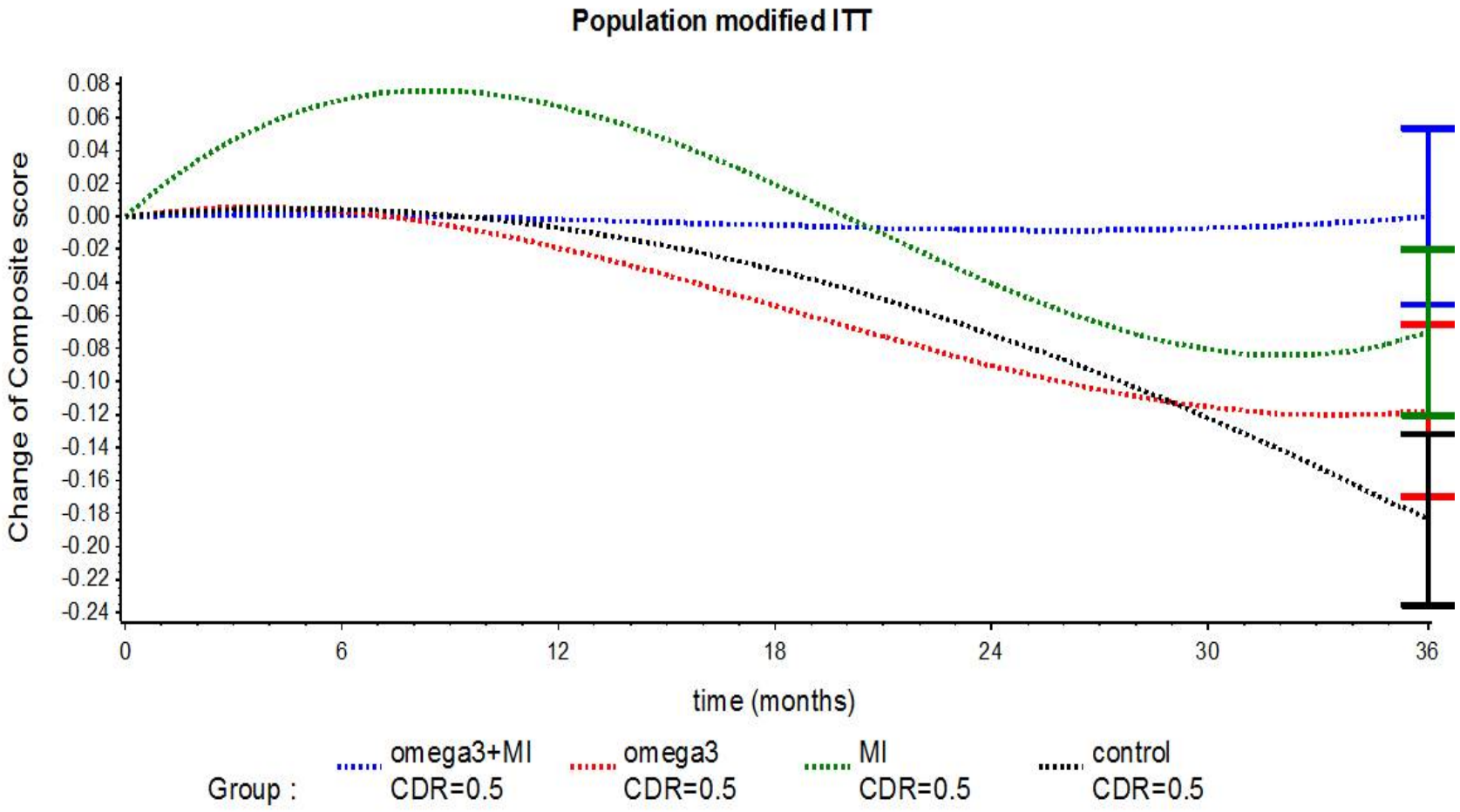
Group	Mean change from baseline to 36 months (95% CI)	Mean difference (95% CI) vs placebo	P value (raw)	P value (Hochberg)
Omega3 + Multid	**0.02 (-0.04 ; 0.09)**	**0.09 (0.00 ; 0.18)**	**0.0473**	**0.1419**
Omega3	-0.06 (-0.12 ; 0.01)	0.01 (-0.08 ; 0.10)	0.8121	0.8121
Multid	0.01 (-0.05 ; 0.07)	0.08 (-0.01 ; 0.17)	0.0896	0.1792

- Composite Score



M0:	n=374	n=381	n=390	n=380
M36:	n=304	n=301	n=301	n=308

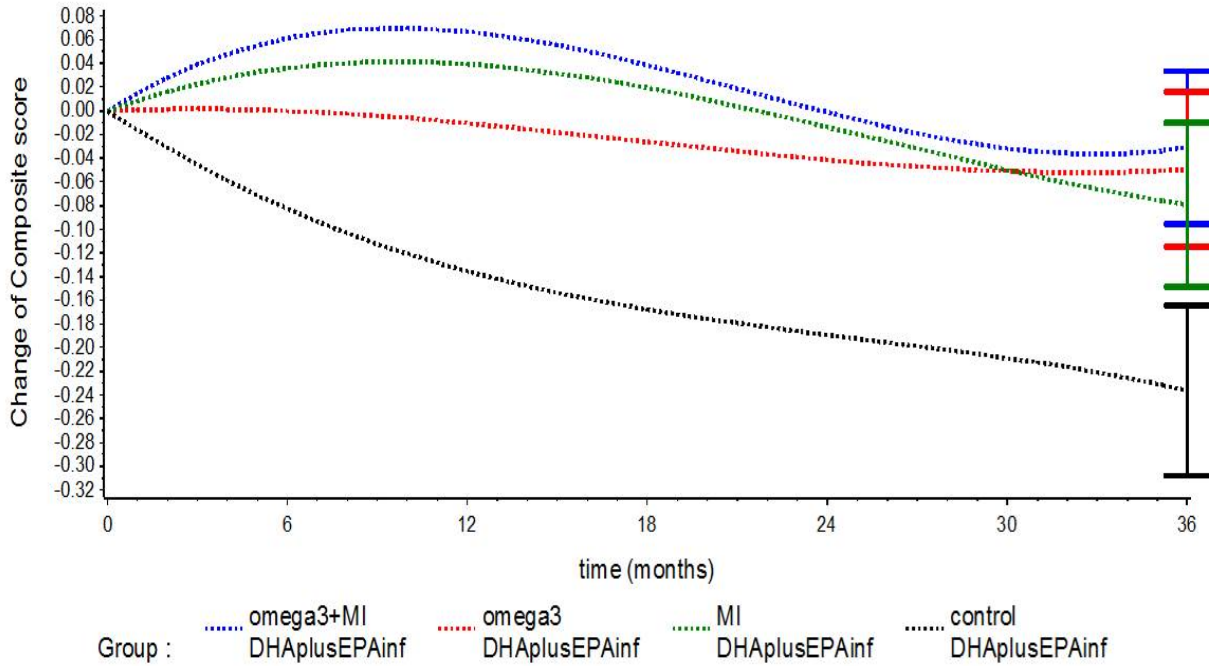
MAPT: Sub-group, Early MCI: CDR 0.5



M0:	n=151	n=160	n=166	n=160
M36:	n=115	n=119	n=129	n=122

Low DHA Results From the MAPT Trial

3-year change from baseline on composite score in intervention and control groups in subjects with low baseline erythrocyte DHA+EPA% (defined as the lowest DHA+EPA% quartile) in the ITT population



Error bars are SE

Intervention group:	Omega-3 + Multidomain	Omega-3 + placebo	Multidomain + placebo
Difference in 3y change from baseline vs. control	0.21	0.19	0.16
95%CI	[0.02; 0.39]	[0.00; 0.38]	[-0.04; 0.35]
P (raw)	0.0339	0.0543	0.1170
P (adjusted for multiple comparisons)	0.1017	0.1086	0.1170

DO-HEALTH

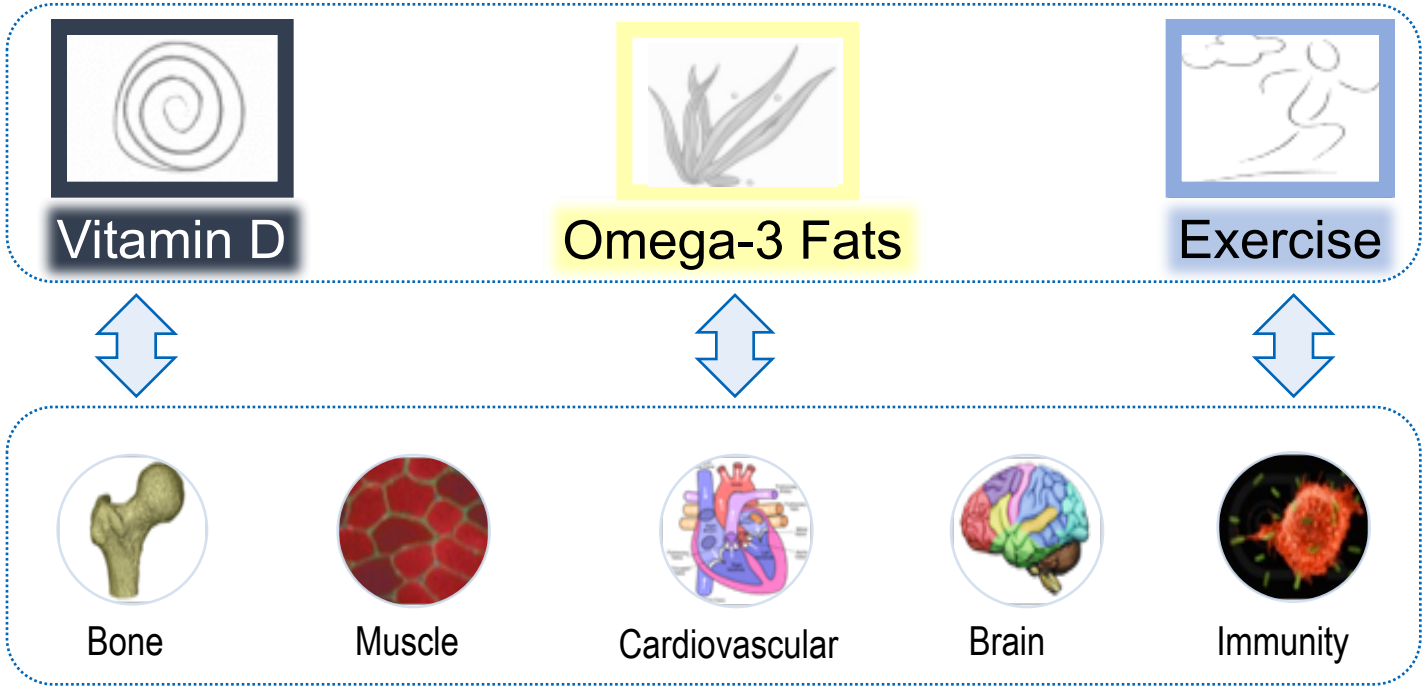
- Vitamin D3 - Omega3 - Home Exercise – HeALTHy Aging and Longevity Trial

  - Funded by the European Commission Framework 7 research programme and the University of Zurich.
  - Europe‘s largest healthy aging study.
  - 2157 healthy seniors recruited at 7 centres in 5 countries.
  - Study to establish whether vitamin D, omega-3 fatty acids and a simple home exercise program will prevent disease at older age

Universität Zürich[UZH]

DO-HEALTH -

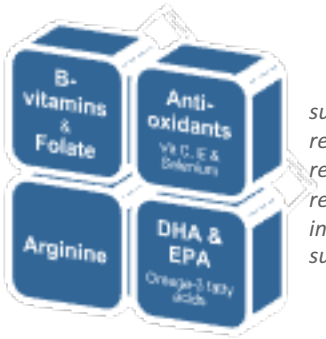
- The 3 most promising interventions to impact on 5 key health endpoints



⇨ Evidence from large clinical trial is missing

Nolan Trial: Brain Protector Blend

The BPB was designed to **target known biological risk factors** for brain aging



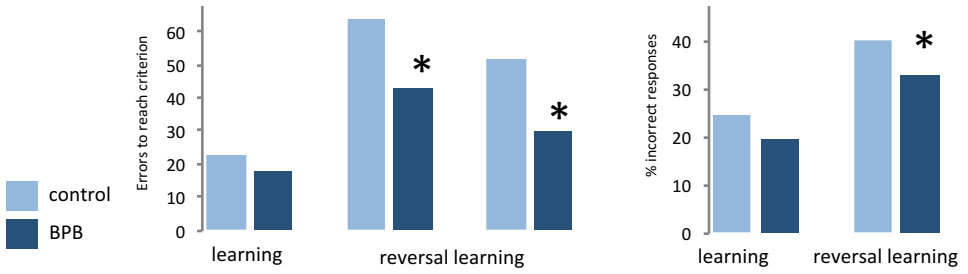
support brain physiology through B-vitamins
reduce homocysteine
reduce inflammation
reduce oxidative stress
increase blood flow
support healthy neuronal structure

Various rodent models

NOLAN Clinical Study to prove effects in humans

2003 **2005** **2010** **2016**

Research shows that the **BPB improves cognition in aged dogs…** **…and aged cats**



Above effects were observed after 8 (dog) and 2.5 (cat) months of intervention in the egocentric reversal learning task * p<0.05

Four Large Type of Cognitive Decline

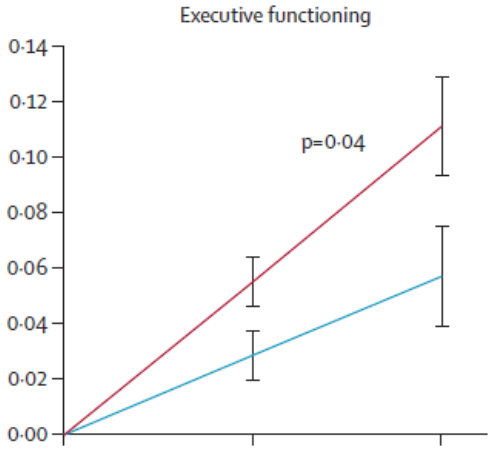
- Subjective Memory Complaints
- Vascular Cognitive Decline
- Cognitive Decline Related to Alzheimer’s Disease
- Cognitive Frailty , in Frail older adults

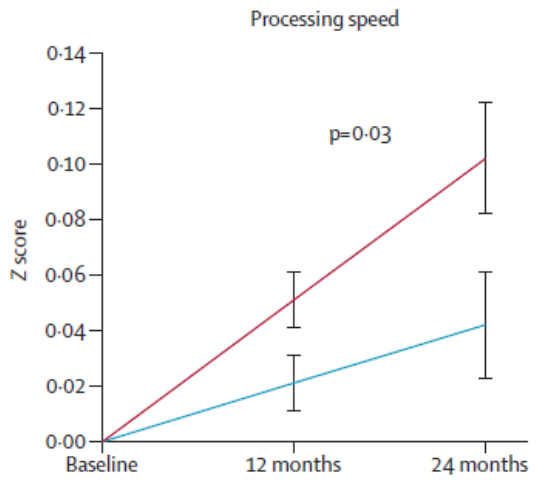
Vascular Cognitive Decline: Finger Trial

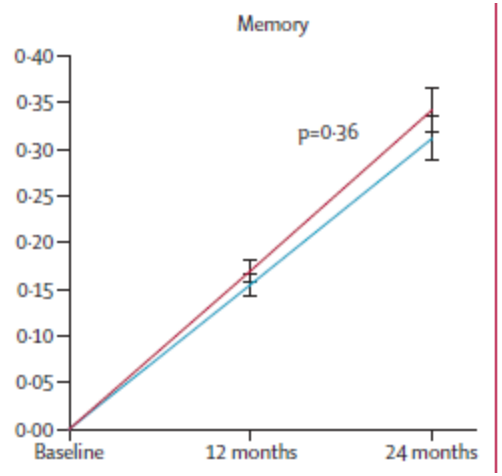
- Target Population: CAIDE:Cardiovascular Risk Factors, Aging and Dementia :
  - Age,
  - Sex,
  - Height and weight,
  - Serum cholesterol,
  - Systolic and diastolic blood pressure,
  - Physical activity status,
  - Years of education .

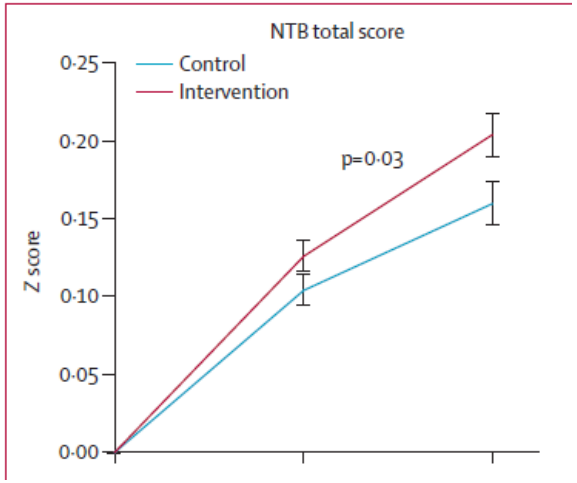
  - Score >= 6 and cognition at mean level or slightly lower than expected for age. (Alz & Dementia 2015)
- **A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial.** (N=1280) (Lancet 2015)

Finger Trial: Effect on Cognition









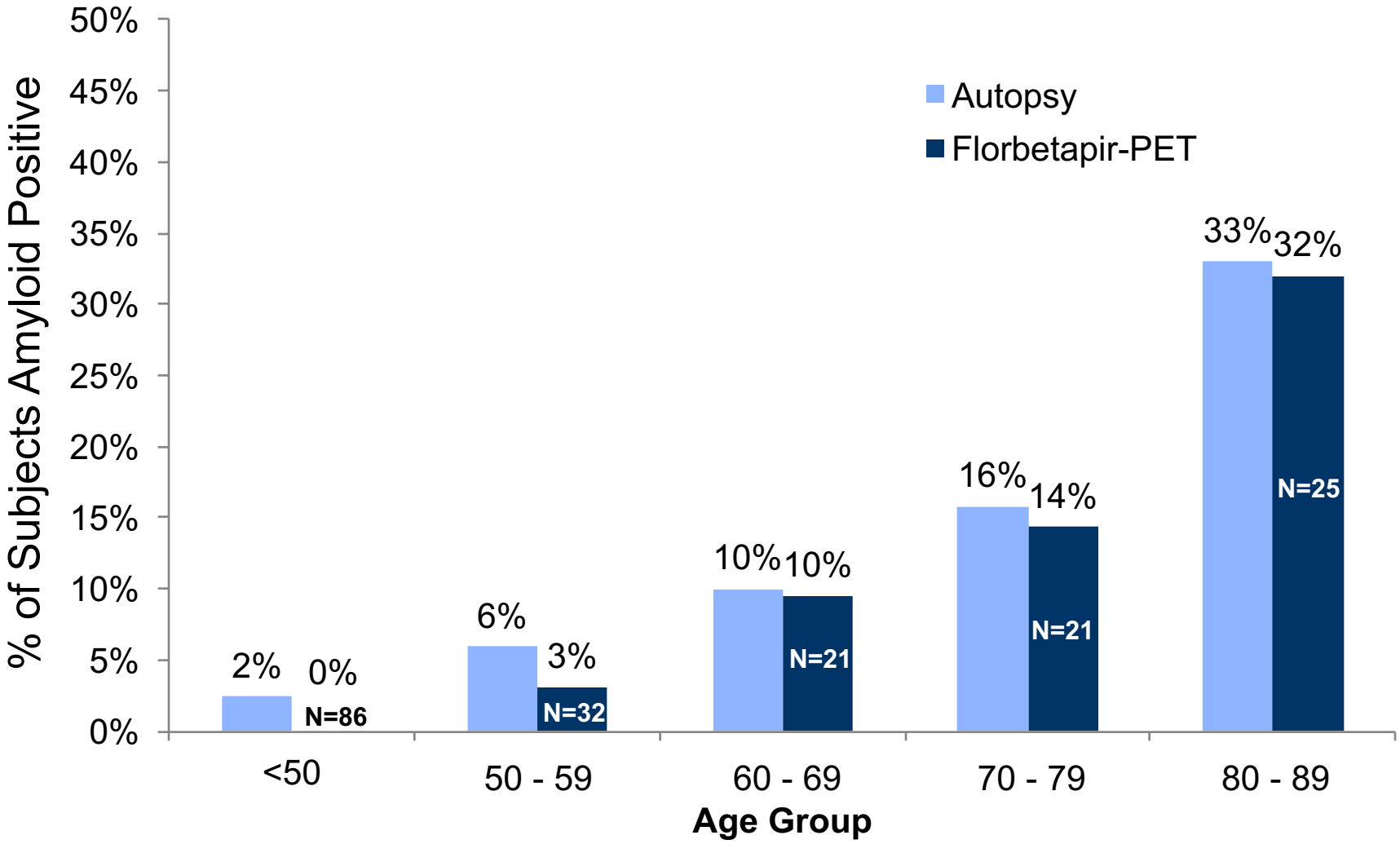
	Odds ratio (95% CI)		p value
	Intervention (n=554)	Control (n=565)	
Overall cognitive decline			
NTB total score	1 (reference)	1·31 (1·01–1·71)	0·04
Cognitive decline per domain			
NTB memory score	1 (reference)	1·23 (0·95–1·60)	0·12
NTB executive functioning score	1 (reference)	1·29 (1·02–1·64)	0·04
NTB processing speed score	1 (reference)	1·35 (1·06–1·71)	0·01

In post-hoc analyses, we defined cognitive decline as decrease in NTB total score (overall decline) and NTB domain scores (decline per domain) between the assessments at baseline and at 24 months. Logistic regression analyses were used to assess risk of cognitive decline in the control group compared with the intervention group. Analyses are based on all participants with data available at both baseline and 24 months. NTB=neuropsychological test battery.

Table 2: **Risk of cognitive decline from baseline to 24 months**

Four Large Type of Cognitive Decline

- Subjective Memory Complaints
- Vascular Cognitive Decline
- Cognitive Decline Related to Alzheimer’s Disease
- Cognitive Frailty , in Frail older adults



Prevalence of Amyloid Phenotype in Normal Elderly Subjects

What We Have Learned from Drug Trials in Alzheimer?

(Jour Prev Alz Dis 2017, No3)

- 1990 – 2000: Dementia stage: too late
- 2000 – 2010: Early AD but no precision medicine, no good target (30% of those classified as mild Alzheimer in the solaneuzumap trial are amyloid negative and don't progress after 4 years of follow up (NEJM 2016)
- 2010 – 2017: Prodromal to mild AD, precision medicine (biomarkers), specific therapy: however maybe not strong enough (doses) (NEJM 2017 in press), too late
- 2017: Same trials with higher dose, anti-tau, regenerative Medicine
- Early preventive trials eg A 3 with β-secretase inhibitors

Pro-dromal Alzheimer or MCI due to AD

- **Definition**
  - Objective cognitive decline: logical memory
  - CDR=0.5
  - Amyloid signature (PET or CSF)
  - spared ADL's
- **Advantages**: conversion, observance
- **Disadvantages**: screening, cost, cut off for pour defining cognitive decline
- **End-Point**: CDR-SB
- **Prevalence**: 5 to 10% (MAPT)

Preclinical Alzheimer

- **Definition**
  - No objective cognitive decline
  - Amyloid or Tau Signature (PET or CSF)
  - Spared ADL
- **Advantages**: large target, early intervention
- **Disadvantages**: conversion, slow cognitive decline, cost
- **End-Point**: composite score, logical memory

- **Prevalence**: 20 to 30% with amyloid signature

Anti-Amyloid Treatment in Asymptomatic AD (A4) Study

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β accumulation on screening PET imaging
- Phase 3 randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 240w
- Trial N=1150 (N=575+ per treatment arm)
- Observational cohort of Aβ negative "screen fails" – LEARN study (funded by Alzheimer's Association)
- Ethics component – Disclosure of amyloid status

EARLY (A5) Trial

- Industry sponsored trial of Janssen oral BACE inhibitor with academic collaboration
- EARLY is a more global study - launched in Europe, Australia, will start in US in fall 2016
- Amyloid eligibility by CSF or PET – same "amyloid positive" normals criteria as in A4
- Broader age range – 60-85 years old
  - Participants age 60-65 must have additional risk factor
- Broader cognitive range than A4
- Longer trial – up to 4.5 years

A3 Study

- A3 will leverage the A4 /A5 screening to identify people with "subthreshold" Aβ levels who are at high risk for continued amyloid accumulation
- Four year Phase IIb/IIIa 4 trial - BACE inhibitor
- Primary outcomes are biomarkers – rate of Aβ accumulation, tau spreading, MR atrophy
- Exploratory sensitive cognitive outcomes (iPAD)
- Public-private-philanthropic partnership (P4)
  - In process of selecting therapeutic agent

Aging & Rejuvenation Therapies

- Adults have a pool of **stem cells** in organs tissue that respond to exercise or injury – pumping out new cells to repair.
- **Aging frailty can be considered as a depletion of endogenous stem cells contributing to a reduced ability to regenerate or repair organs and tissues**.
- Cell-based, regenerative treatment strategy could ameliorate frailty and restore muscle and brain functions

Effect of MSCs on Phenotypes of Frailty

Frailty phenotypes	MSC response	Postulated mechanism of action
Weight loss	Maintains total caloric expenditure	↓ Inflammation which suppresses the onset of sarcopenia
Exhaustion	↑ Pulmonary function, ↓ chronic inflammation	↑ Endothelial function, ↓ markers of inflammation
Weakness	↑ Physical performance	↑ Mitochondrial transfer, ↑endogenous stem cell function
Slow gait speed	↑ 6-minute walk distance	↑ Endothelial function, ↑ cardiac performance, ↑ skeletal muscle performance
Decreased activity level	↓ Chronic inflammation, ↑ quality of life	↓ TNF-α, ↓ IL-1β, ↑ IL-10

Notes**:** MSCs home to sites of injury and to enhance repair of damaged tissue (heart, joints, muscle, and blood vessels) and **exert their regenerative effects via paracrine signaling, mitochondrial transfer, direct cellular contact, and exosome excretion.**

Intravenous Delivery of Allogeneic Mesenchymal Stem Cells Reduces Chronic Inflammation in Frailty and Reverses Immunosenescence

Ana Marie Landin International Conference Sarcopenia Frailty Research, April 2017, Barcelona

- **Intervention**: Administering allo-hMSCs by intravenous infusion in patients with aging frailty
- **Design**: Subjects (N=80) first randomized in a pilot phase that tested the dose effect of (20-, 100- and 200-million) allo-hMSCs. Twelve to 15 months after, subjects received a second infusion with 100-million allo-hMSCs
- **Results**:
  - Well tolerated.
  - TNF-α significantly reduced at 6 months post 1st infusion in all patients.
  - Immune risk phenotype significantly improved at 6 months post 1st infusion and was maintained throughout the study
  - Some clinical preliminary effects on physical and cognitive functions
- **Comments:** systemic effects of stem cells, rejuvenation therapy

Prevention of Cognitive Decline and Dementia: Fiction or Reality

- Part II: How Can We Prevent Cognitive Decline in Clinical Practice:
  - Increase intrinsic capacity reserves in early aging
  - Monitor and Preserve functions in late aging
  - Restore functions as soon as possible

Increase Intrinsic Capacities Reserve in Early Aging

- WHO defines *intrinsic capacity* as the combination of the individual's physical and mental – including psychosocial – capacities, and *functional*

- INSPIRE: INStitute for Prevention of AgIng and REjuvenation

Instituts thématiques

Inserm

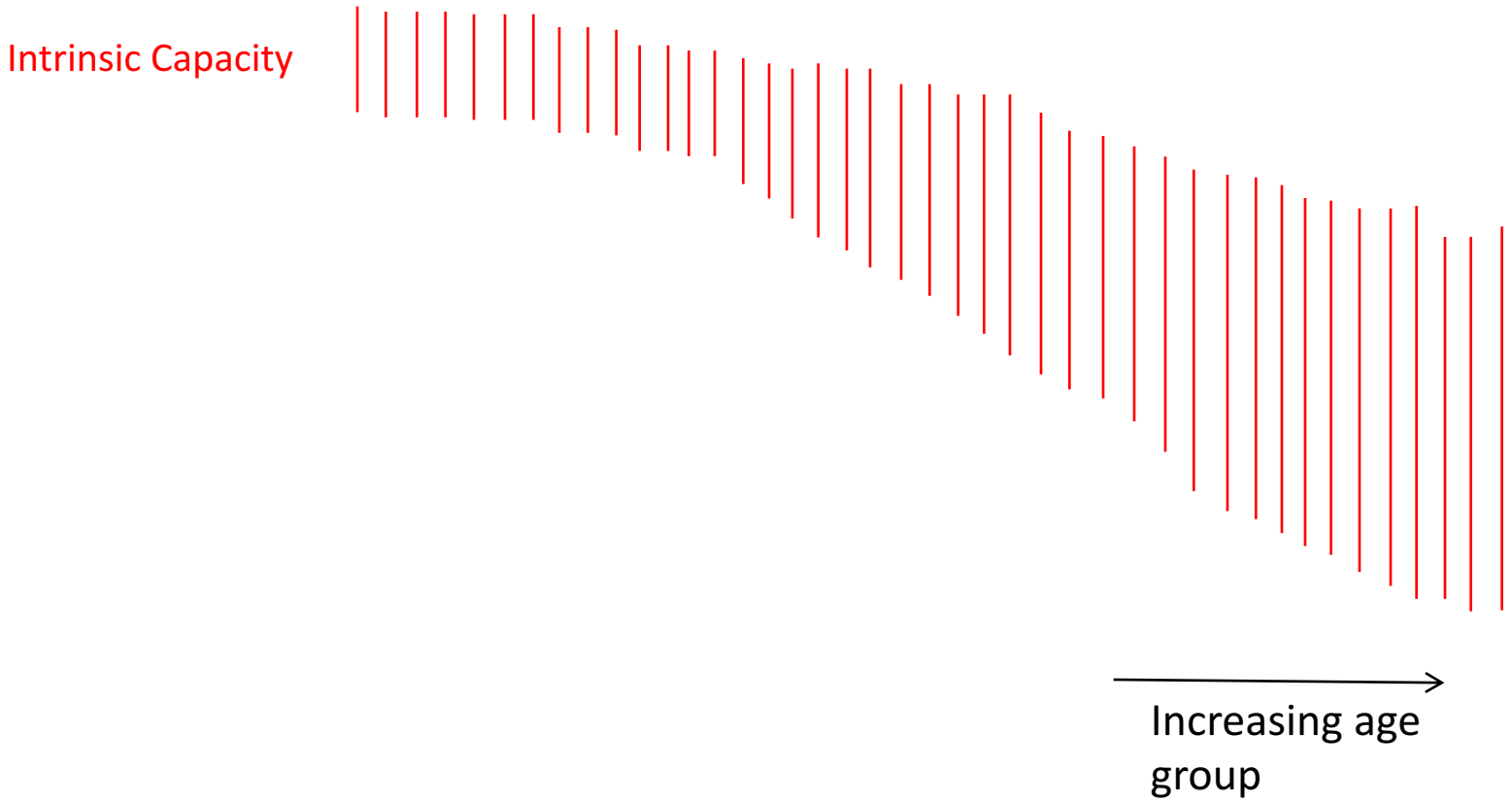
Institut national de la santé et de la recherche médicale

Hôpitaux de Toulouse

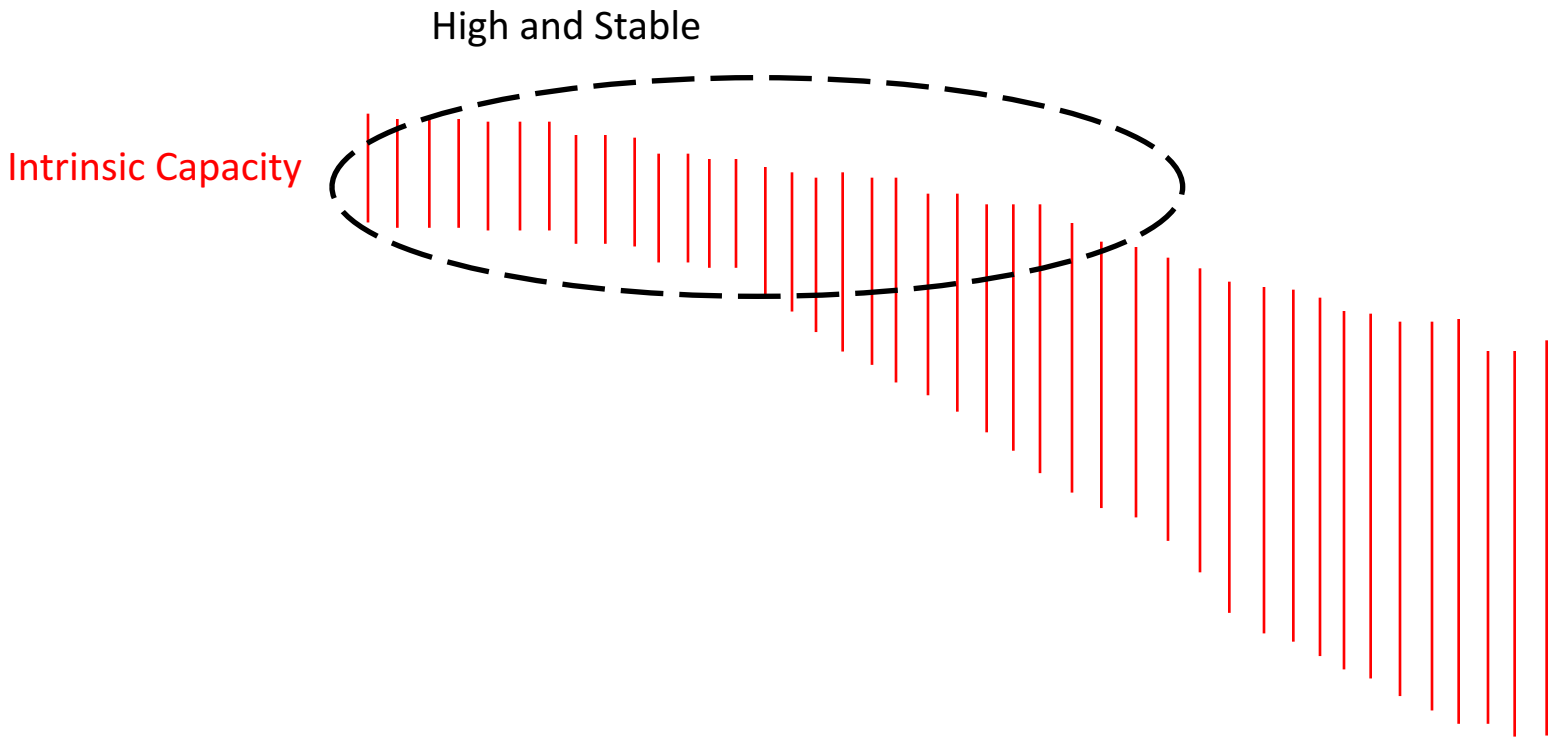
Toulouse GÉRONTOPÔLE

WHO - Collaborative Centre for Frailty, Clinical Research and Geriatric Training

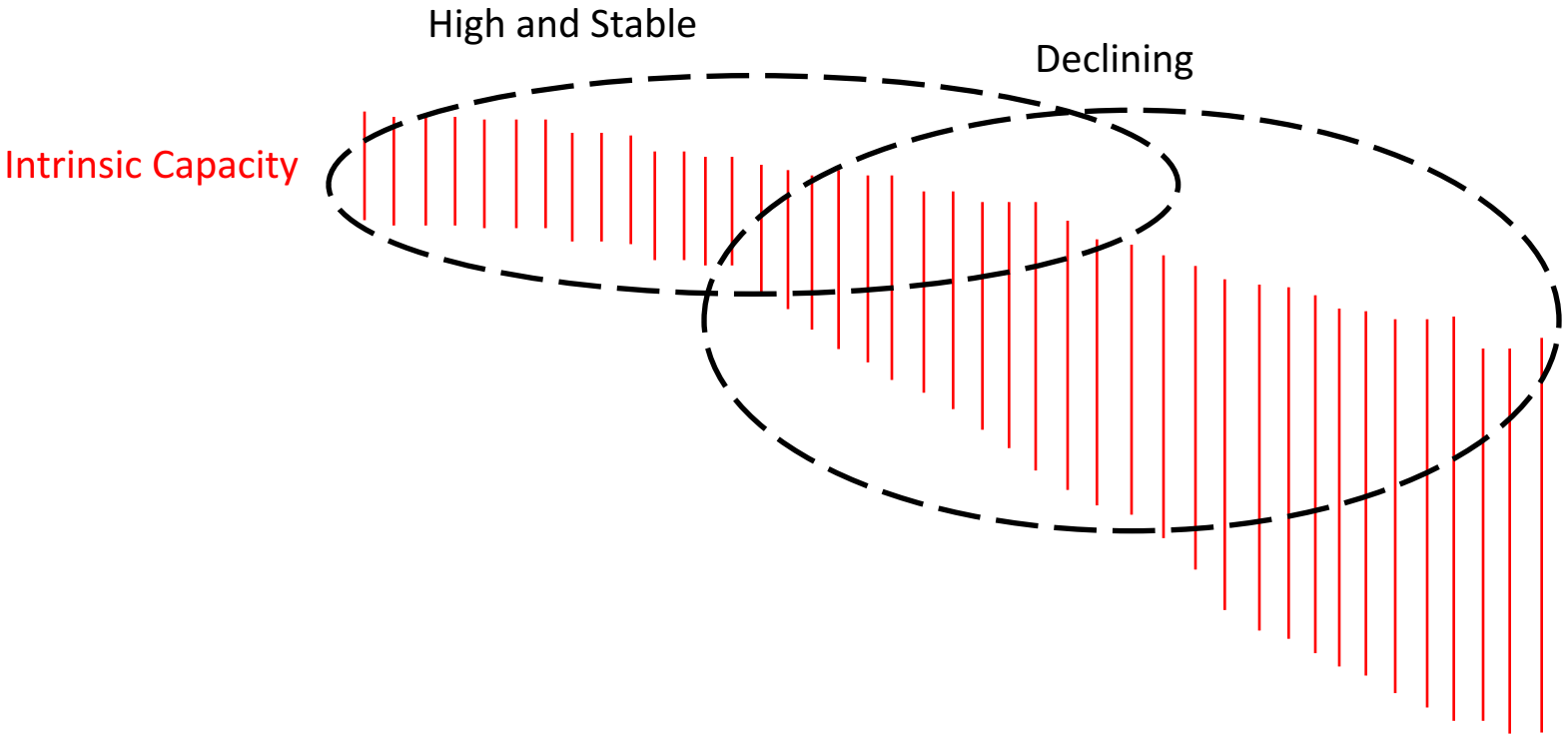
Population in the second half of life



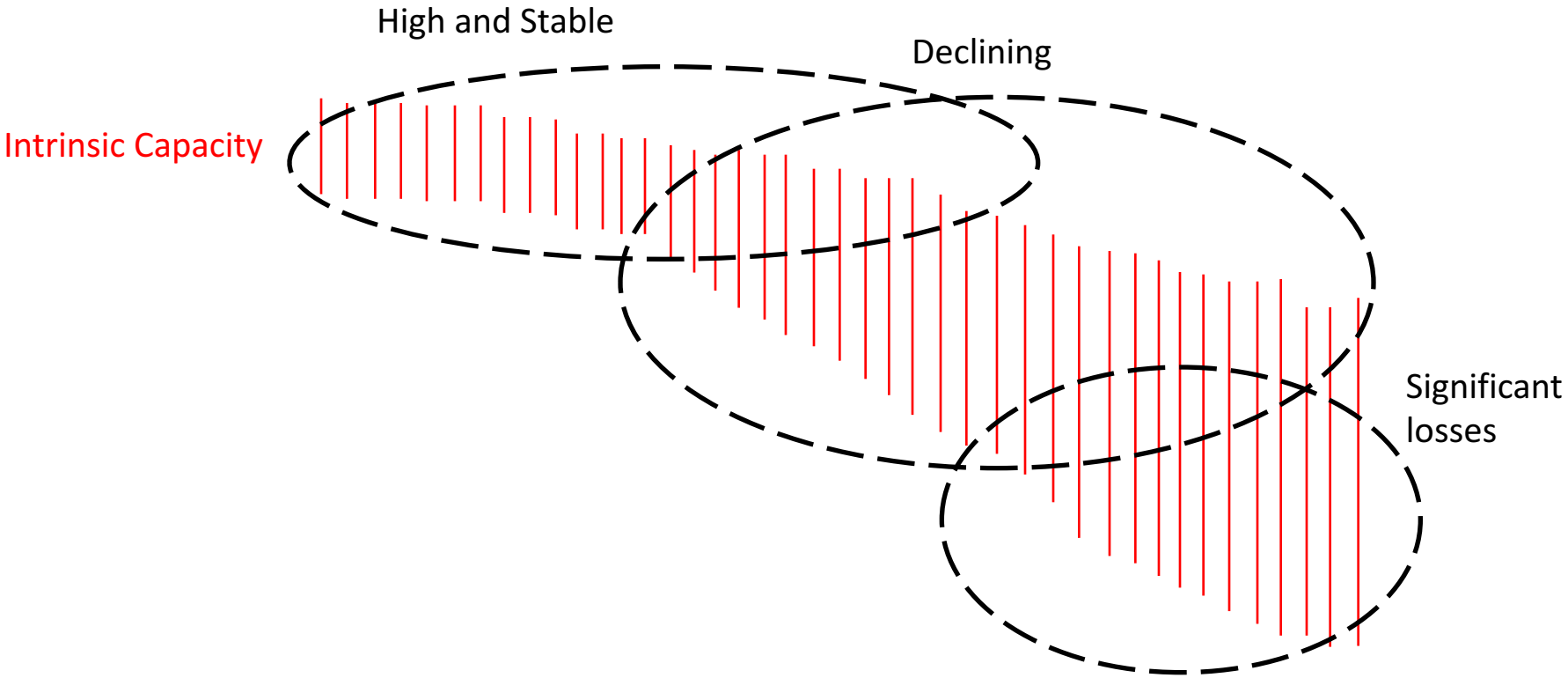
Population in the second half of life



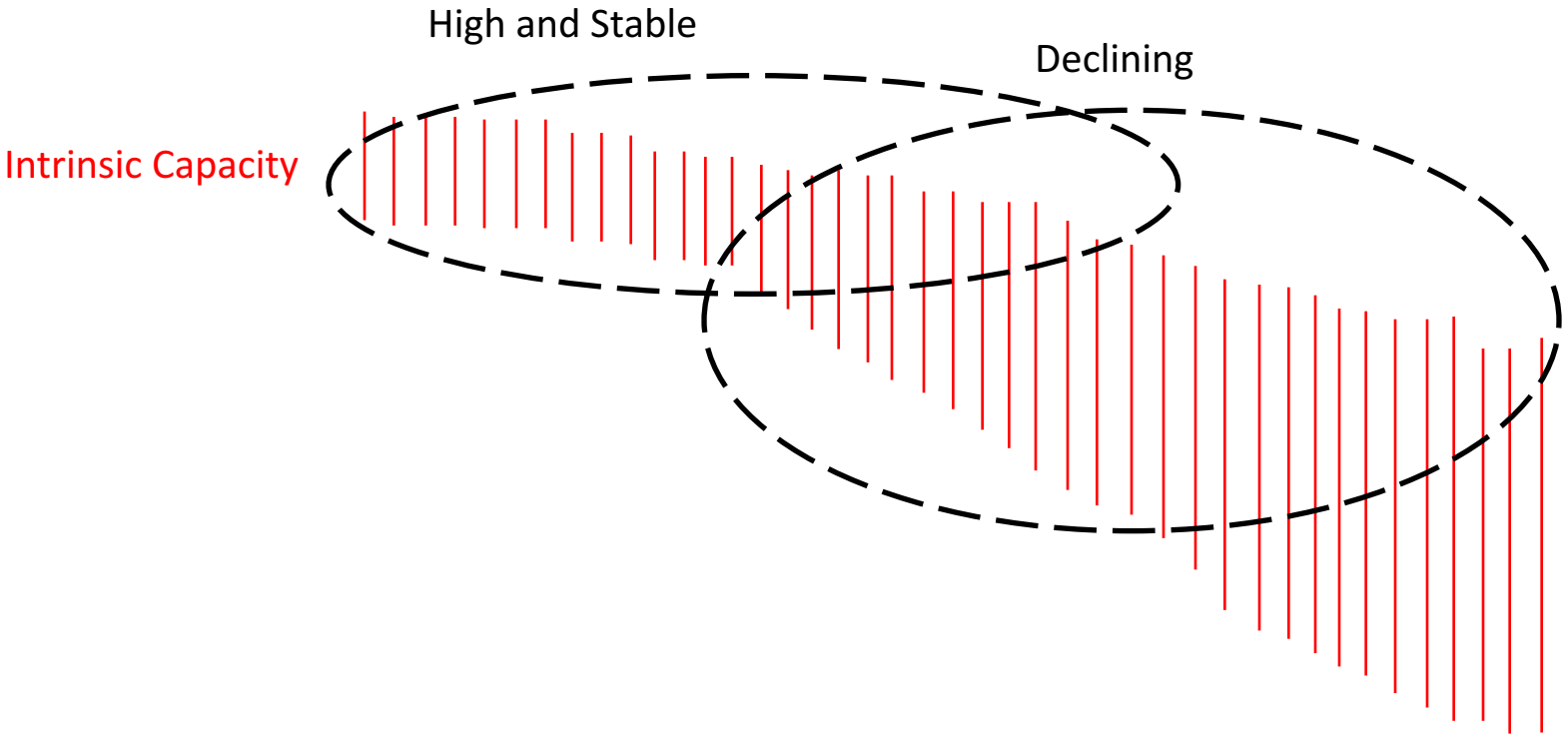
Population in the second half of life



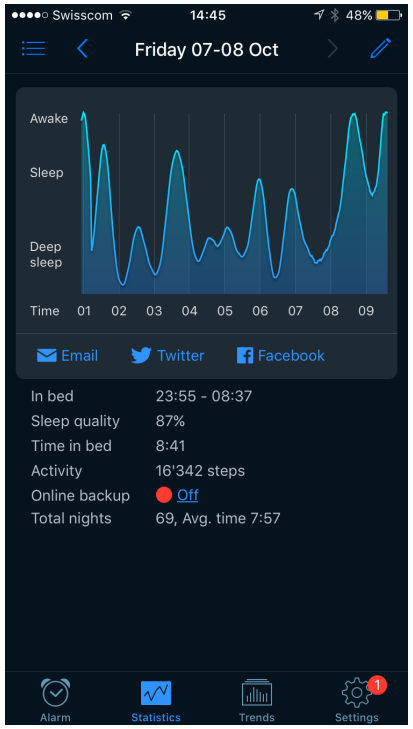
Population in the second half of life

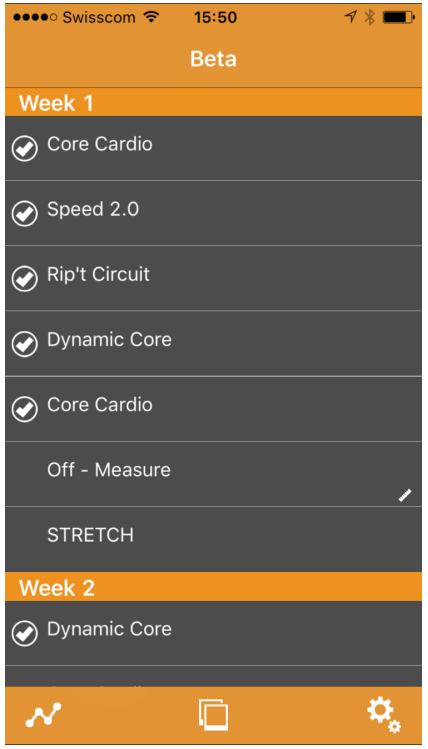


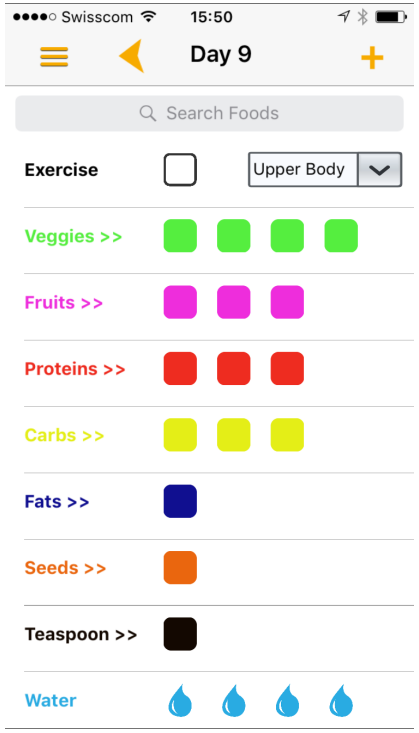
Population in the second half of life



We alredy monitor diet, sleeping patterns, physical exercise







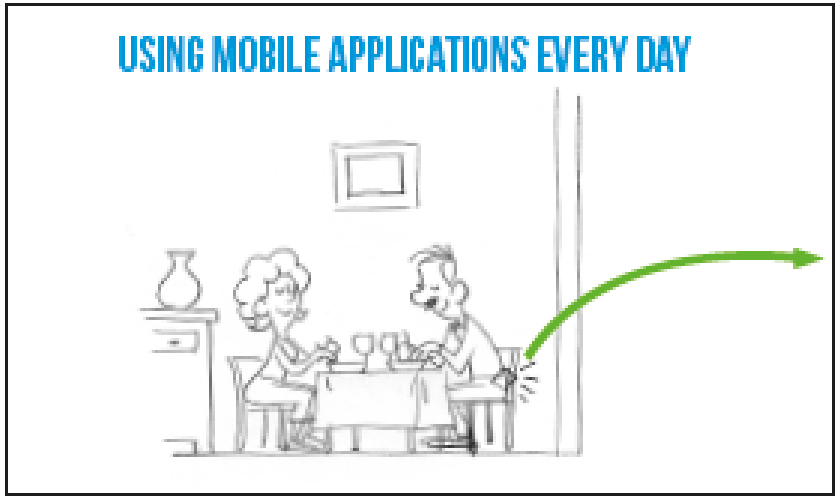
Voice emotion recognition and voice analysis for determining mental states

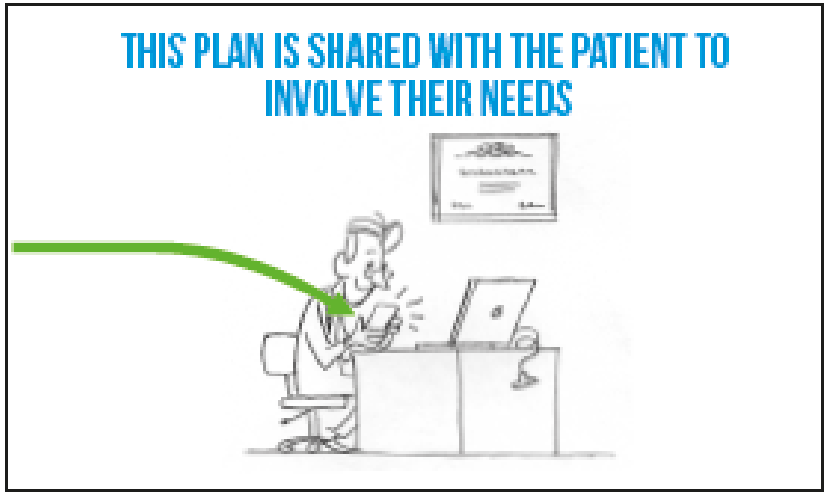
Healthy　　ME-BYO MIMOSYS　　Sick

Stress and brain nerve damage can be monitored.

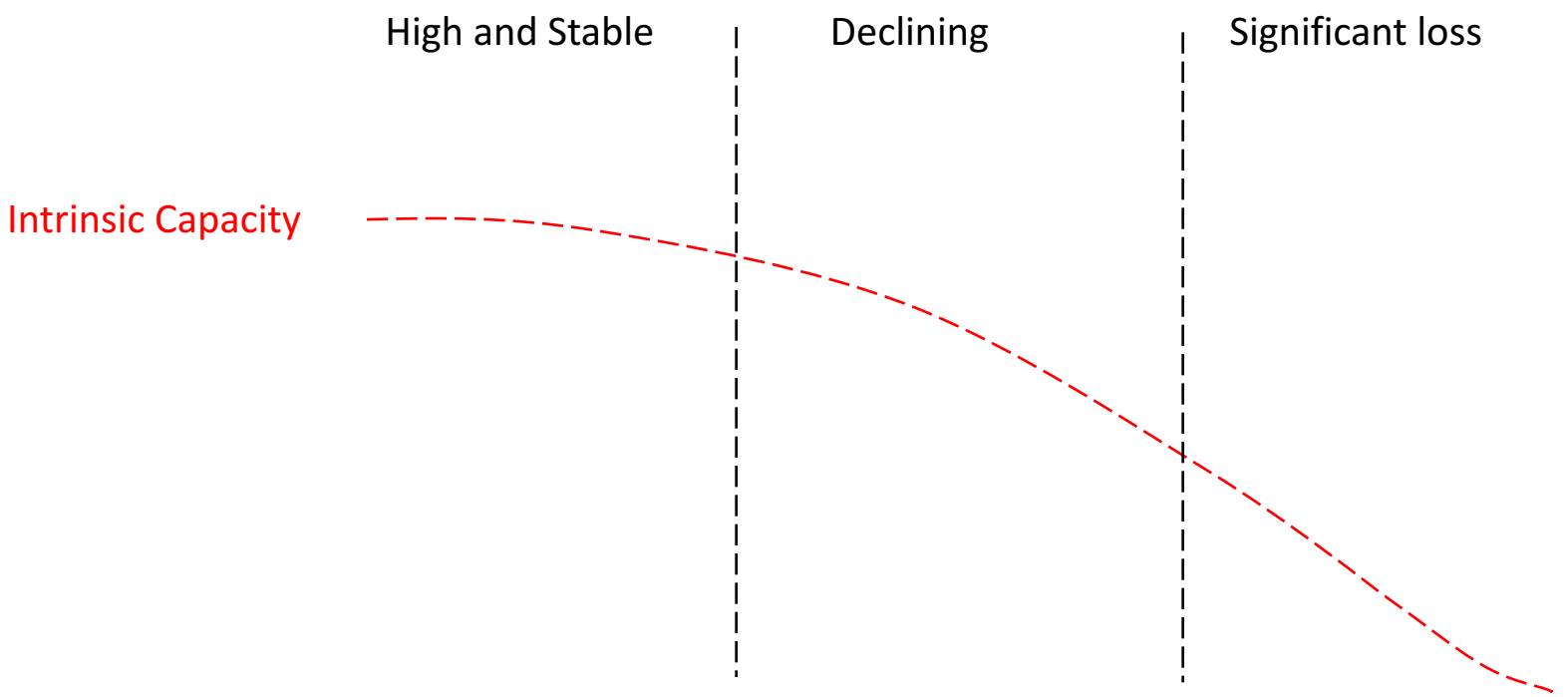
MIMOSYS enables this.

Monitoring intrinsic capacity using self management

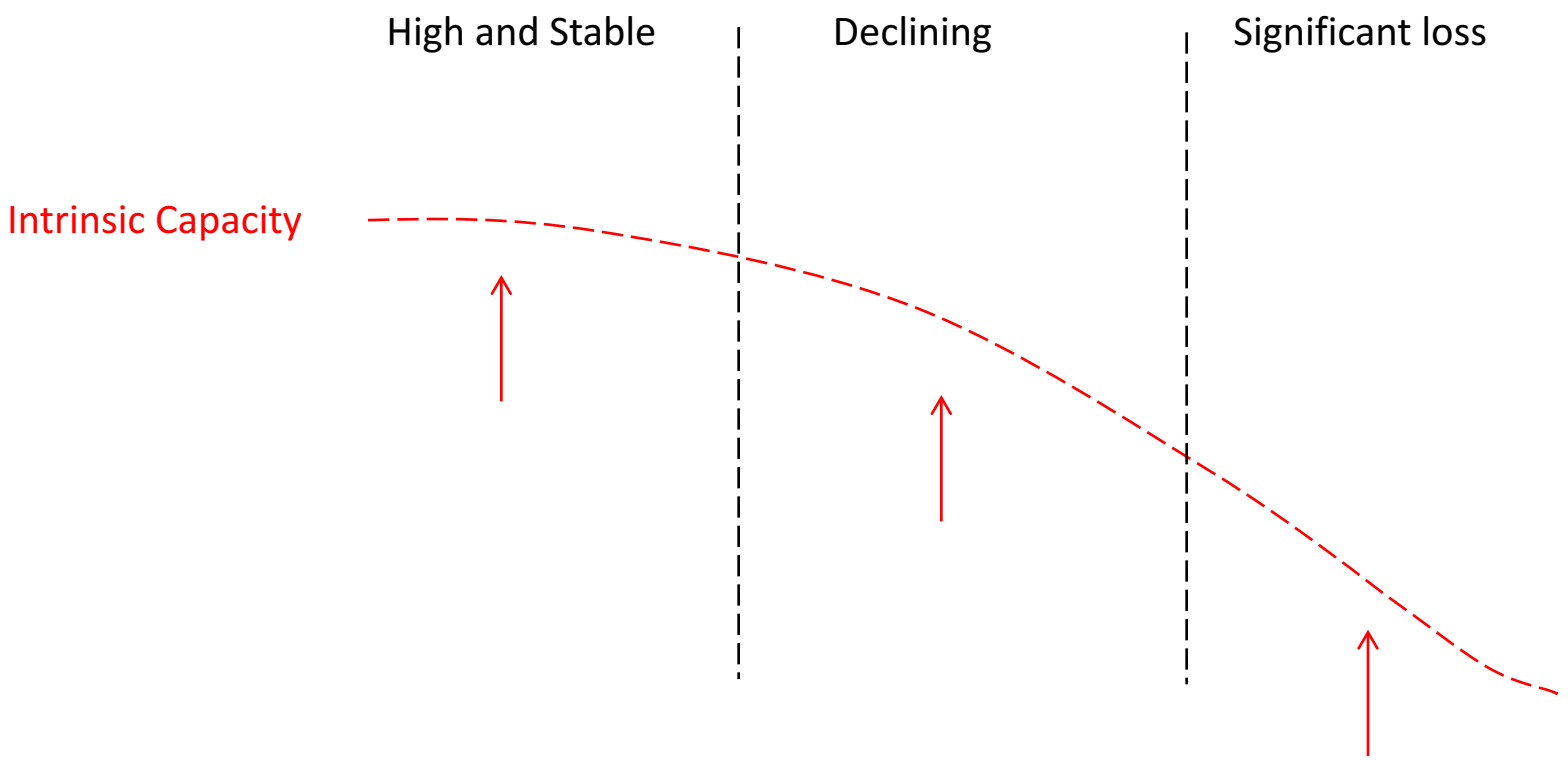




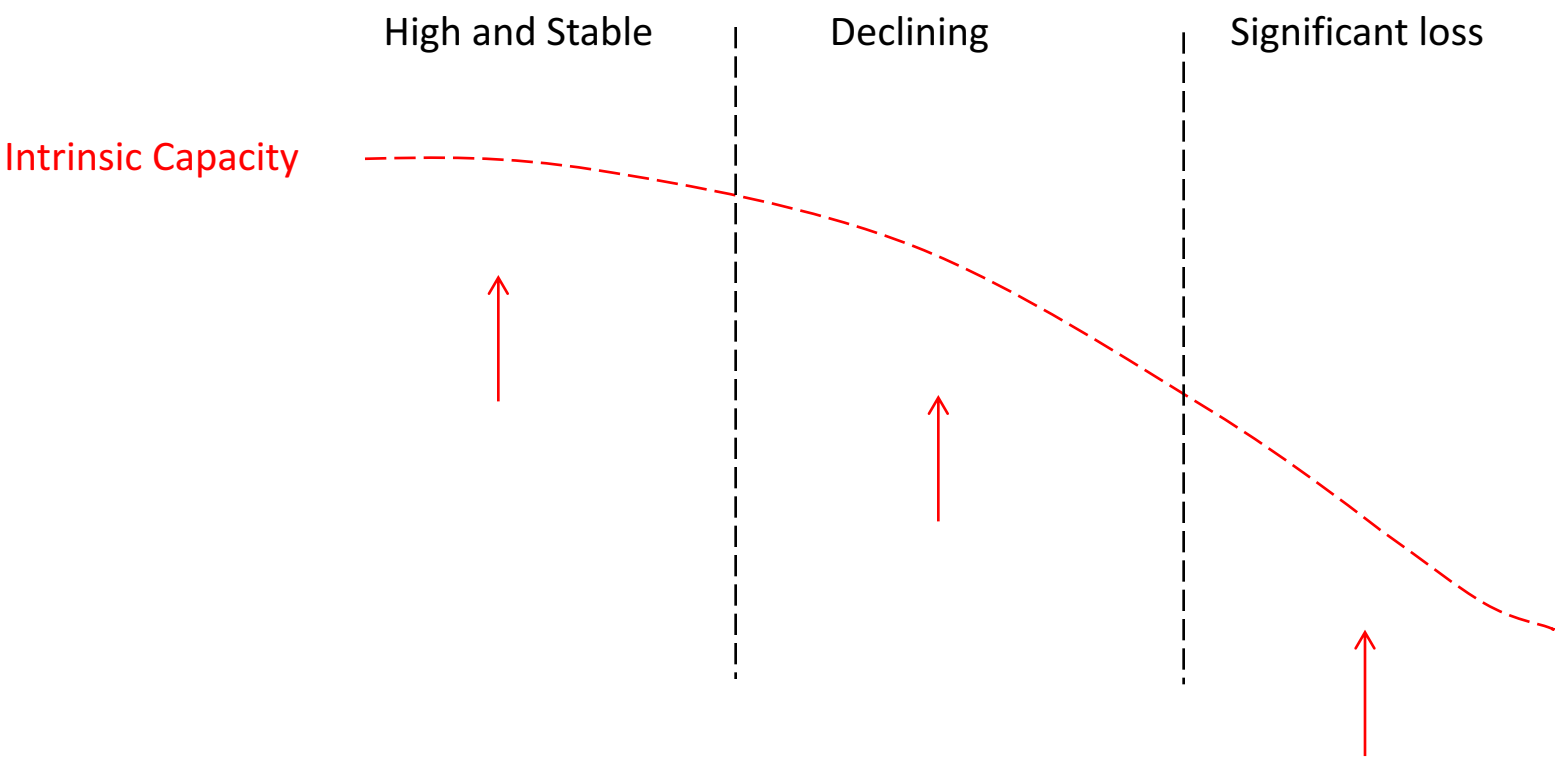
Population in the second half of life



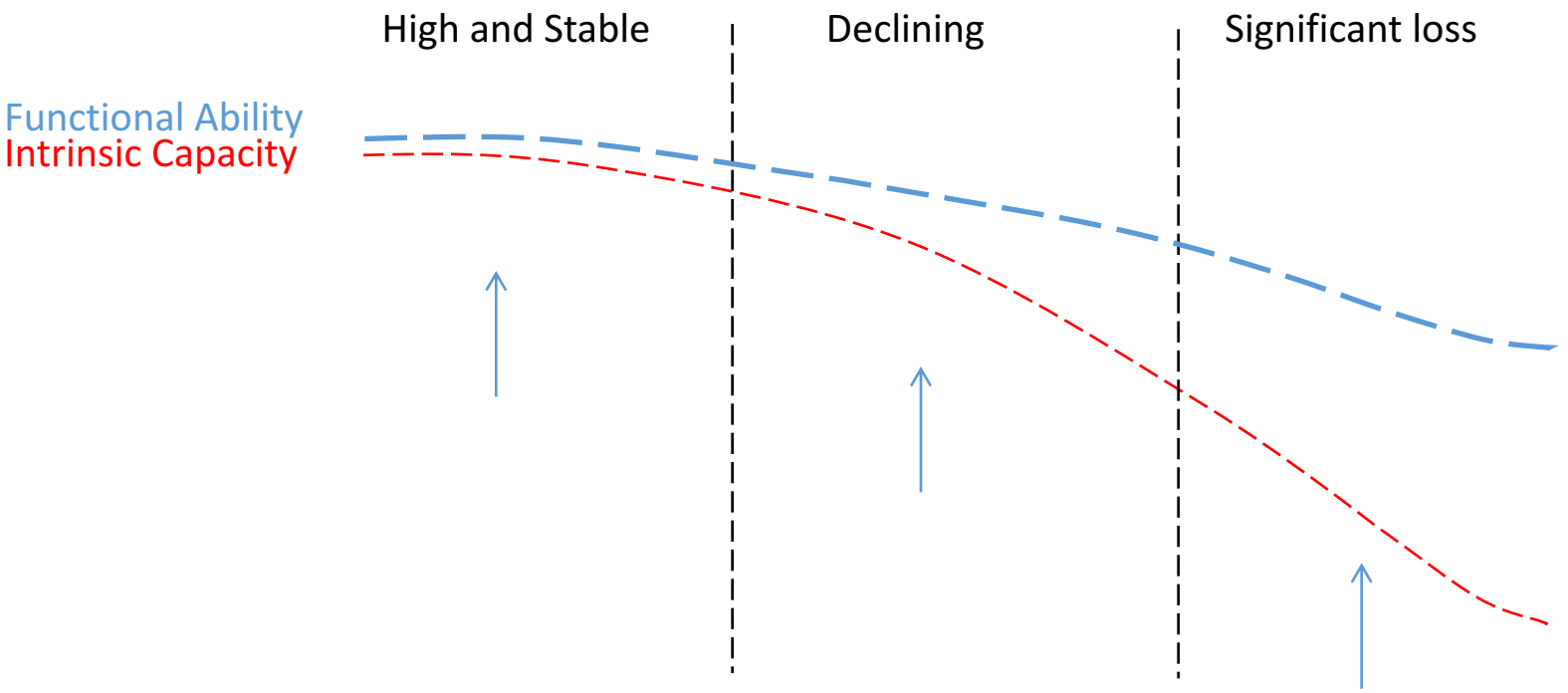
Population in the second half of life



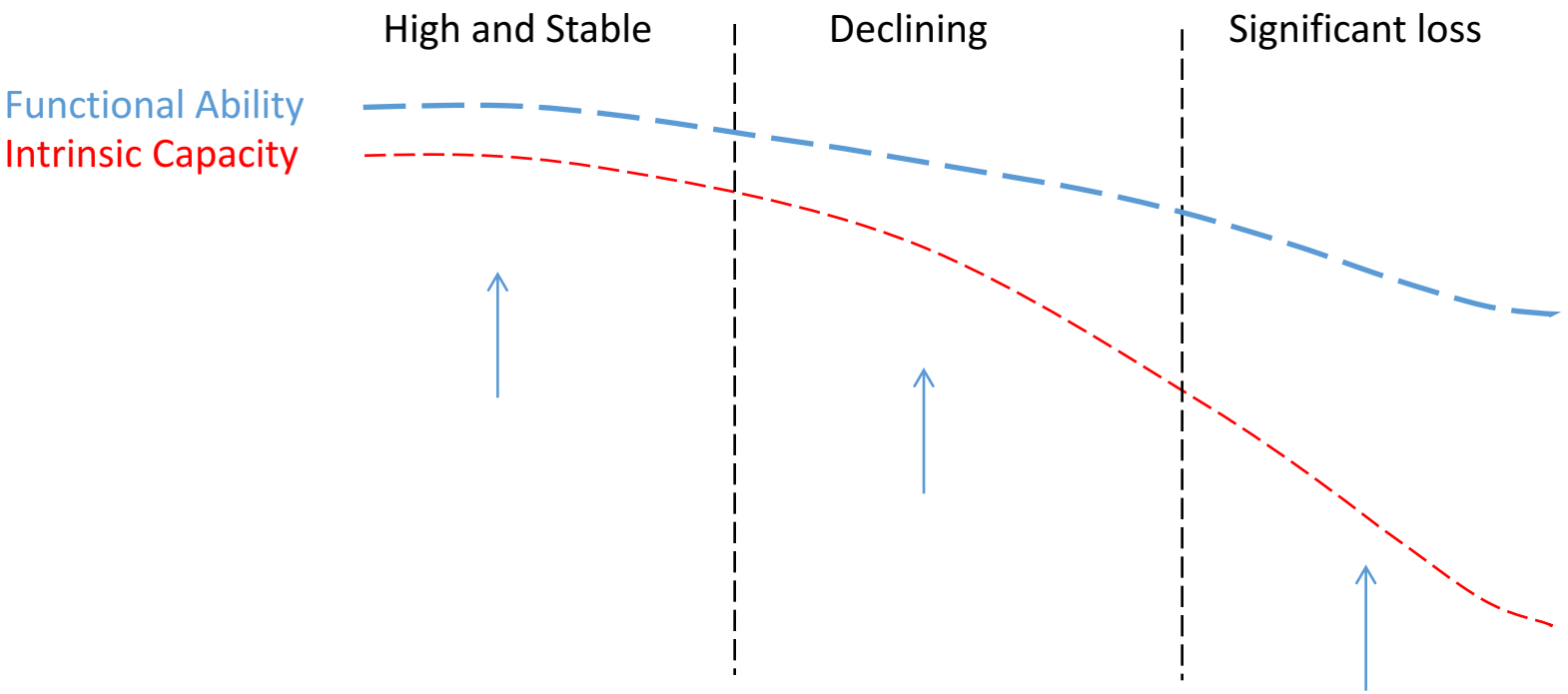
Population in the second half of life



Population in the second half of life



Population in the second half of life

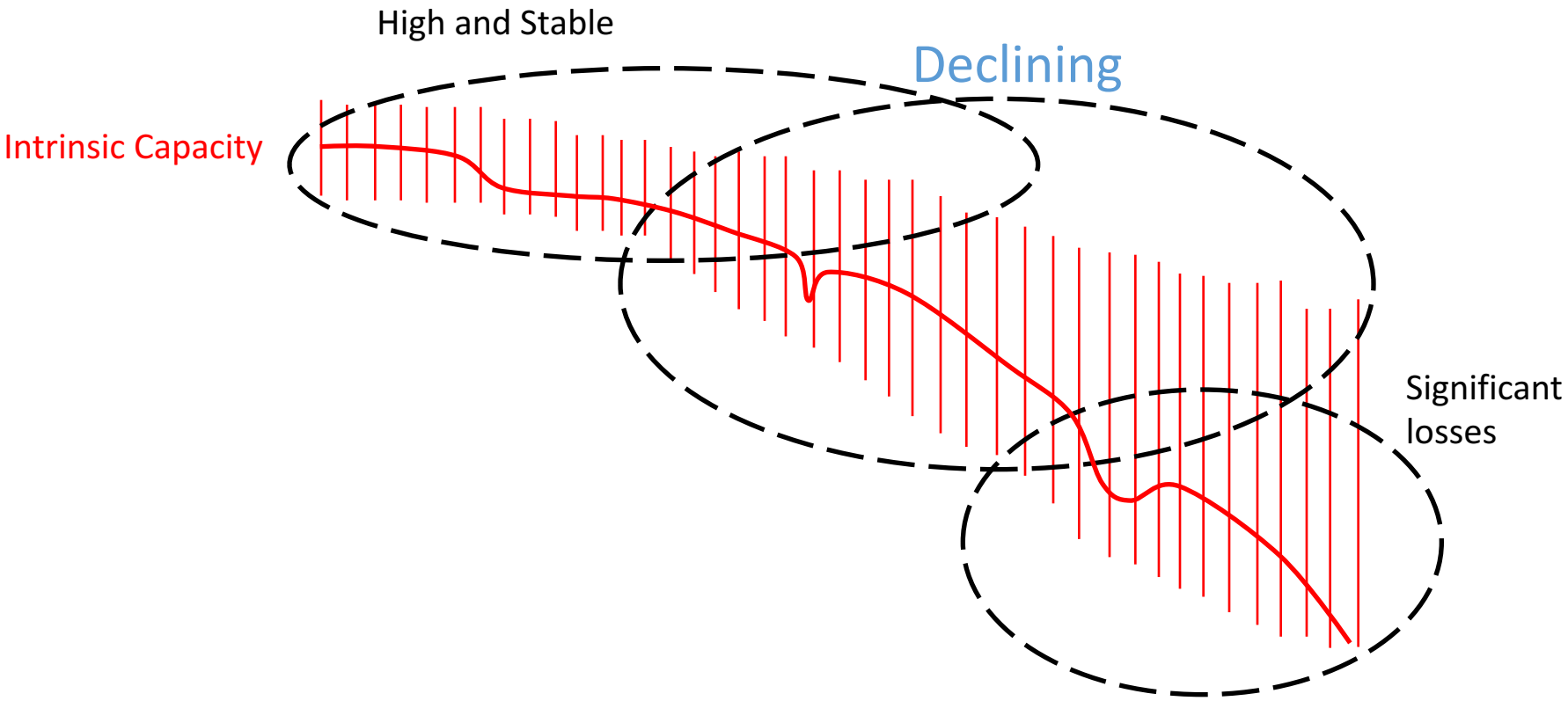


Prevention of Cognitive Decline and Dementia: fiction or reality

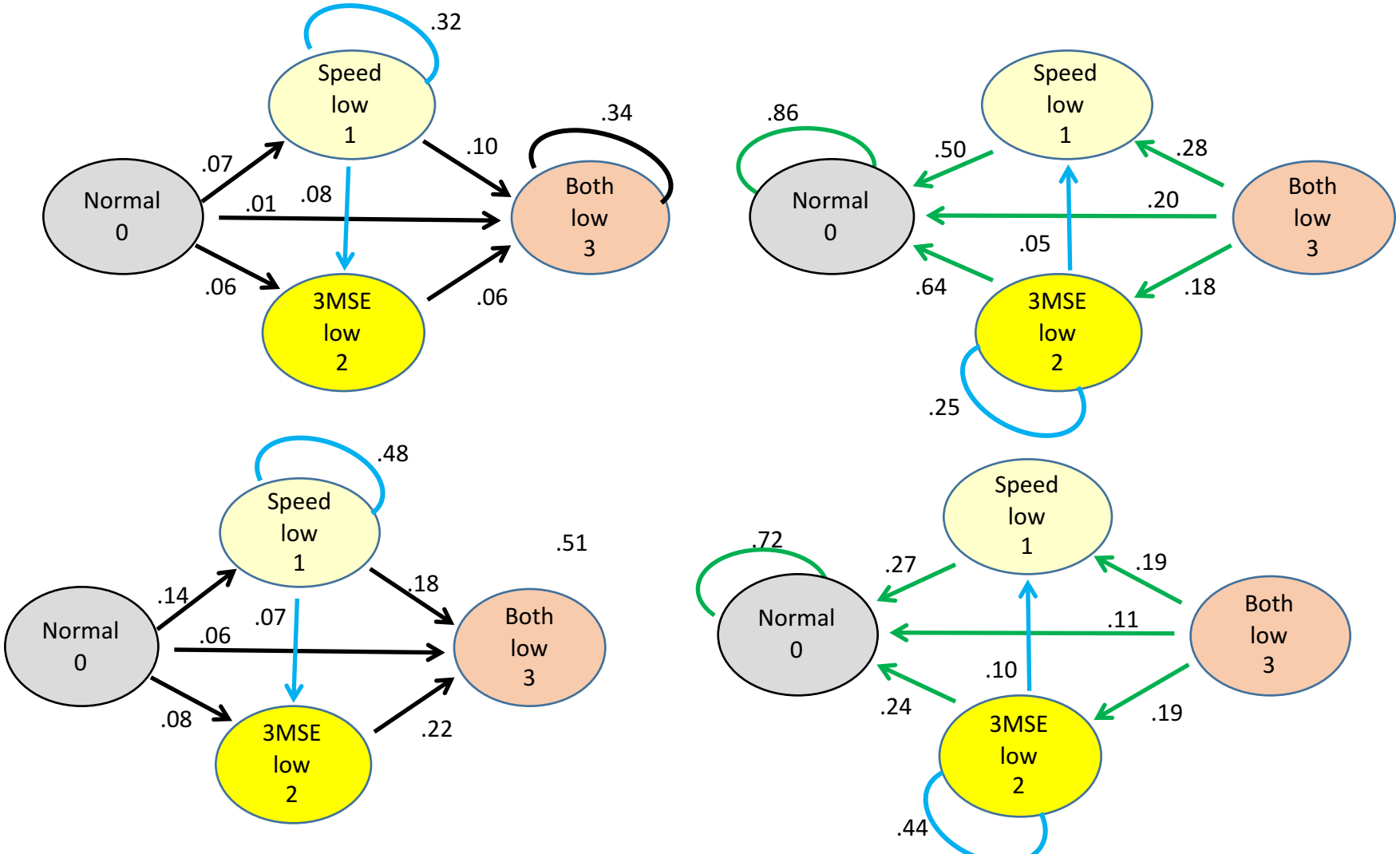
- What are the causes of cognitive decline in older adults

- How can we prevent cognitive decline ?:
  - Increase intrinsic capacity reserves in early aging
  - Monitor and Preserve functions in late aging
  - Restore functions as soon as possible

Monitor and Preserve Functions in Late Aging



NMAPS: Results- Above (Younger transition matrix – 60 ≤ age ≤ 78 years), Below: Older 78 + (JNHA 2017)



COGNIGRAM™ digital cognitive assessment system received positive notification from the FDA

Boston, MA – July 2017:

Self-administered assessment that can be completed both in-clinic and at-home.

For prescription use

Can be used to assess cognition on a single occasion or cognitive change over periodic assessments.

Performance is unaffected by language, education, cultural background, or practice

Intervention to Maintain Functions in Late Aging

- Late Aging stable:
  - Multi-domain Intervention: Nutrition , physical and cognitive exercise
  - Vascular et metabolic risk factors
  - Brain Protector Blend ?

- Decrease of cognitive functions: Precision Therapy
  - Amyloid related cognitive decline: β-secretase inhibitors ?
  - If Amyloid biomarkers negative: Low DHA / EPA: Omega 3 , Vit D , if chronic inflammation ?

Prevention of Cognitive Decline and Dementia: fiction or reality

- What are the causes of cognitive decline in older adults

- How can we prevent cognitive decline ?:
  - Increase intrinsic capacity reserves in early aging
  - Monitor and Preserve functions in late aging
  - Restore functions as soon as possible

Restore Cognitive Functions in Older Adults

- Amyloid Related: Amyloid monoclonal antibody, anti-tau , (Phase III in process), combinations ?

- Regenerative Medicine ? Stems cells ?

Perspective (2): P4 / Contemporary Medicine

P4 Medicine	Contemporary Medicine
Proactive, predictive	Reactive
Precision medicine	Population
Participative: Wellness & diseases	Only diseases
Personalized data clouds	Averaged patient population
Personalized data clouds for clinical trials	Averaged patient population for clinical trials

INITIATIVE EUROPÉENNE

Innovative Medicines Initiative

EPAD

European Prevention of Alzheimer's Dementia Consortium

Coordination Française : Toulouse GÉRONTOPÔLE

Collaboration Centres Académiques/Partenaires Industriels

efpia
European Federation of Pharmaceutical Industries and Associations

Prevalence of dependence/disability: de 350 - 600 M de 2010 à 2040

Region		population (millions)	Number of dependent people (millions)	depe (%)	ease in numbers pared to 2000, %)	Dependency ratio* (%)
Establish Econon	2010	885	42	4.7		7.8
	2030	925	48	5.2		9.7
	2050	928	49	5.3	3	10.4
Fo alist s of	2010	322	17	5.3		7.9
	2030	290	17	5.8		9.7
	2050	252	16	6.2	6	12.5
	2010	1164	64	5.5	23	.8
	2030	1409	90		74	
	2050	1572	113		119	
ina	2010	1366	76	5	18	
	2030	1485	102	6.9	57	
	2050	1462	1	7.6	70	
iddle-East escent	2010	755		4.7	29	
	2030	1044		5.2	100	
	2050	12	77	6.0	180	
er Asia and ds	2010		46	5.0	24	
	2030		66	5.8	78	
	20	274	84	6.6	126	1
erica and		594	28	4.7	23	7.5
		723	40	5.5	73	8.9
	2050	806	49	6.1	115	10.6
Sub-Sa ca	2010	829	42	5.0	29	9.6
	2030	1279	70	5.5	1	9.6
	2050	1760	115	6.5		10.5
Worldwide	**010**	**6833**	**350**	**5.1**		
		8286	**488**	**5.9**	**68**	
			614		**110**	

World Alzheimer Report 2013. **ADI 2013**