# CAN DEMENTIA BE PREVENTED?

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# Conflict of interest statement

- Member of editorial boards of JPAD, Neurotorium
- Member of SAB with Advantage Therapeutics, AmyriAD, Biogen Canada, Cerveau technologies, Eisai Canada, Enigma US, Lundbeck Foundation, Medesis, Roche Canada, TauRx

# Objectives

- Look at the natural history of age-associated cognitive decline sometimes leading into dementia
- Discuss findings in observational research about protective and risk factors
- Study the results of interventions to take advantage of these observations
- Consider population versus individual prevention strategies

# Overview

- Natural history of age-associated cognitive decline and dementia
- Findings in observational studies
- Results in intervention studies
- Population-based prevention vs individual prevention

# Overview

- **Natural history of age-associated cognitive decline and dementia**
- Findings in observational studies
- Results in intervention studies
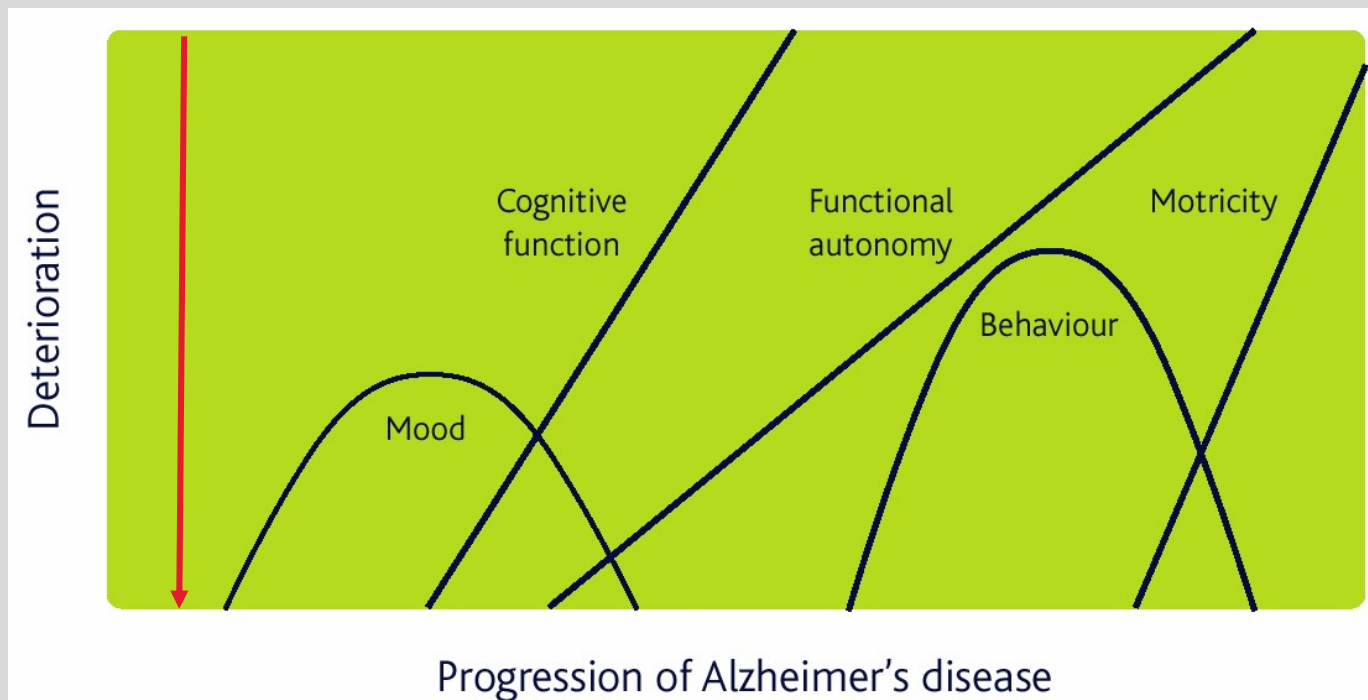- Population-based prevention vs individual prevention

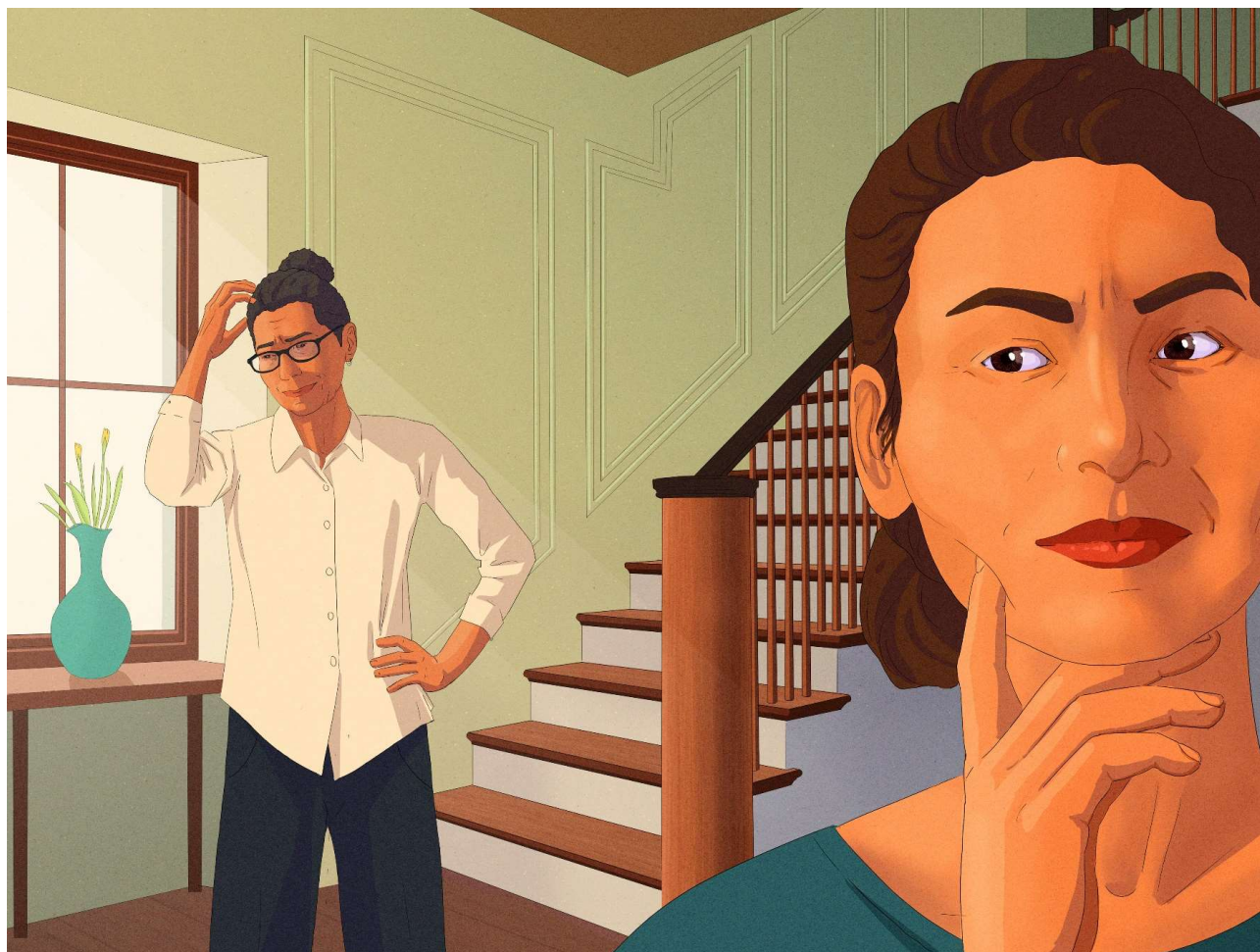# PROGRESSION OF SYMPTOMS IN "TYPICAL"ALZHEIMER'S DISEASE
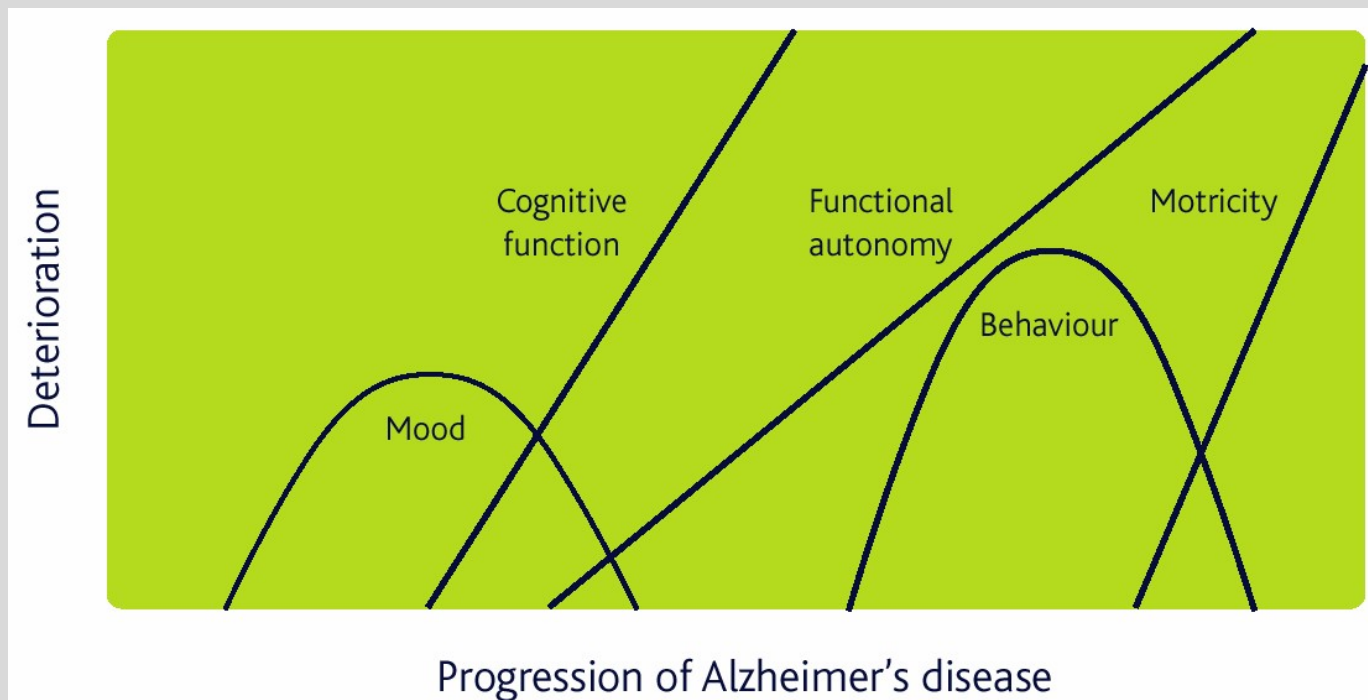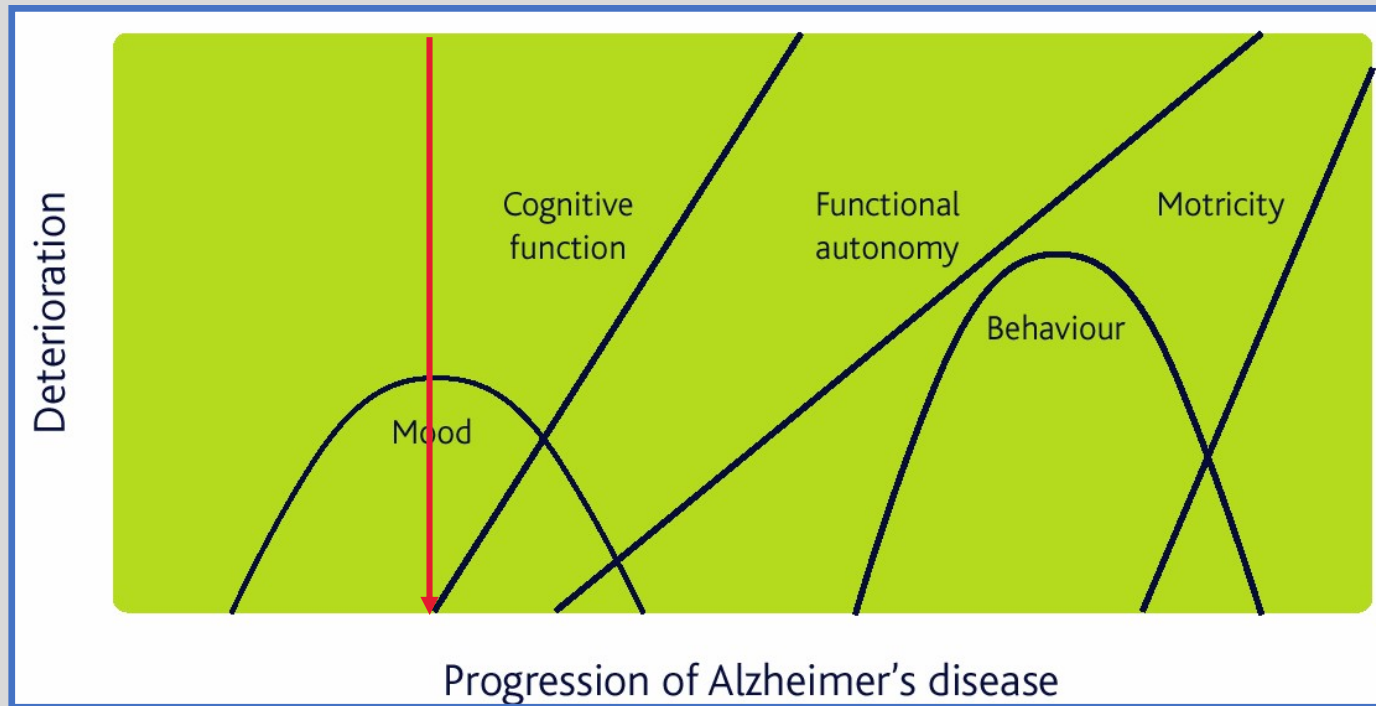


Lovestone & Gauthier 2000

# SUBJECTIVE COGNITIVE DECLINE (SCD)



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# MILD BEHAVIOURAL IMPAIRMENT (MBI)

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# MBI Checklist

**Mild Behavioral Impairment Checklist (MBI-C)**

Date: _____

Rated by: ☐ Clinician  ☐ Informant  ☐ Subject

Location: ☐ Clinic  ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

| | YES | NO | SEVERITY |
|---|---|---|---|
| *This domain describes interest, motivation, and drive* | | | |
| Has the person lost interest in friends, family, or home activities? | Yes | No | 1  2  3 |
| Does the person lack curiosity in topics that would usually have attracted her/his interest? | Yes | No | 1  2  3 |
| Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation? | Yes | No | 1  2  3 |
| Has the person lost motivation to act on her/his obligations or interests? | Yes | No | 1  2  3 |
| Is the person less affectionate and/or lacking in emotions when compared to her/his usual self? | Yes | No | 1  2  3 |
| Does she/he no longer care about anything? | Yes | No | 1  2  3 |
| *This domain describes mood or anxiety symptoms* | | | |
| Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness? | Yes | No | 1  2  3 |
| Has the person become less able to experience pleasure? | Yes | No | 1  2  3 |
| Has the person become discouraged about their future or feel that she/he is a failure? | Yes | No | 1  2  3 |
| Does the person view herself/himself as a burden to family? | Yes | No | 1  2  3 |
| Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)? | Yes | No | 1  2  3 |
| Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic? | Yes | No | 1  2  3 |
| *This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward* | | | |
| Has the person become agitated, aggressive, irritable, or temperamental? | Yes | No | 1  2  3 |
| Has she/he become unreasonably or uncharacteristically argumentative? | Yes | No | 1  2  3 |
| Has the person become more impulsive, seeming to act without considering things? | Yes | No | 1  2  3 |
| Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence? | Yes | No | 1  2  3 |

| | | | |
|---|---|---|---|
| Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn? | Yes | No | 1  2  3 |
| Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)? | Yes | No | 1  2  3 |
| Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views? | Yes | No | 1  2  3 |
| Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)? | Yes | No | 1  2  3 |
| Does the person no longer find food tasteful or enjoyable? Are they eating less? | Yes | No | 1  2  3 |
| Does the person hoard objects when she/he did not do so before? | Yes | No | 1  2  3 |
| Has the person developed simple repetitive behaviors or compulsions? | Yes | No | 1  2  3 |
| Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting? | Yes | No | 1  2  3 |
| *This domain describes following societal norms and having social graces, tact, and empathy* | | | |
| Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings? | Yes | No | 1  2  3 |
| Has the person started talking openly about very personal or private matters not usually discussed in public? | Yes | No | 1  2  3 |
| Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before? | Yes | No | 1  2  3 |
| Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private? | Yes | No | 1  2  3 |
| Does the person now talk to strangers as if familiar, or intrude on their activities? | Yes | No | 1  2  3 |
| *This domain describes strongly held beliefs and sensory experiences* | | | |
| Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings? | Yes | No | 1  2  3 |
| Has the person developed suspiciousness about the intentions or motives of other people? | Yes | No | 1  2  3 |
| Does she/he have unrealistic beliefs about her/his power, wealth or skills? | Yes | No | 1  2  3 |
| Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"? | Yes | No | 1  2  3 |
| Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others? | Yes | No | 1  2  3 |

# MILD COGNITIVE IMPAIRMENT (MCI)
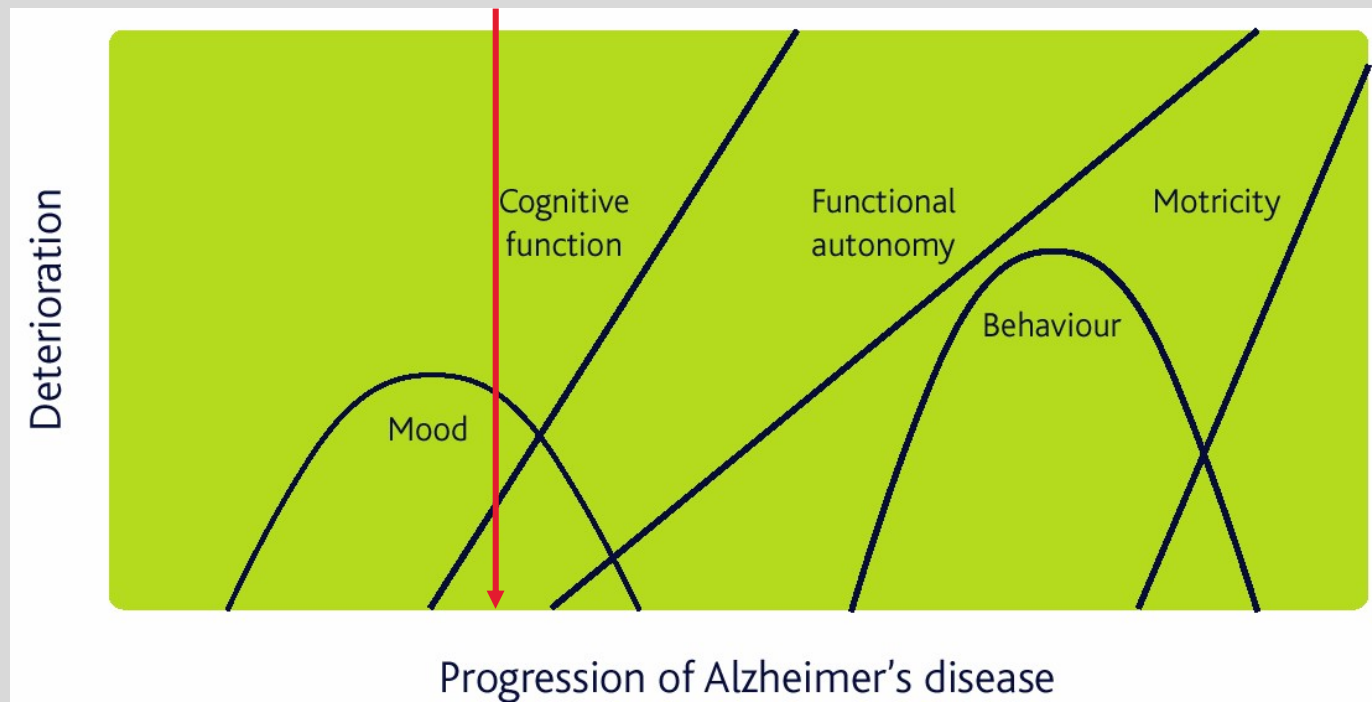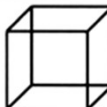


Lovestone & Gauthier 2000

# MoCA

➢ One-page

➢ 30-point scale

➢ 10 minutes to administer

www.mocatest.org

# MoCA COGNITIVE ASSESSMENT XPRESSO

## Self-administered public app
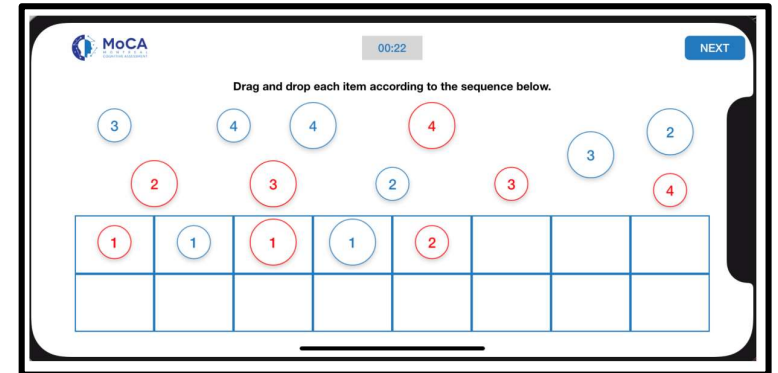
| | |
|---|---|
| Length | 6-10 min |
| Cognitive domains | Short-term visual memory, Executive function, Concentration, Processing speed |
| Device | Mobile, tablet, laptop, desktop |
| Validation | 45 subjects AUC 0.8 with MoCA Standard |

Additional validation ongoing

If interested to help in validation: Contact us at info@mocatest.org

**Diagnosis, Assessment & Disease Monitoring**

**REVIEW ARTICLE**

# Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19

Maiya R. Geddes[1,2,3] | Megan E. O'Connell[4,5] | John D. Fisk[6,7,8] | Serge Gauthier[2] |
Richard Camicioli[9] | Zahinoor Ismail[10,11] | for the Alzheimer Society of Canada Task Force
on Dementia Care Best Practices for COVID-19

# CLINICAL DEFINITION OF MAJOR NEUROCOGNITIVE DISORDER (DEMENTIA)

- Decline in intellectual abilities (memory plus one other cognitive domain)

- Interfering with social or occupational life

- There may be little insight and reporting is done by family

- There may be concomitant anxiety and depression

# MILD DEMENTIA DUE TO AD AND/OR OTHER CAUSES



Progression of Alzheimer's disease
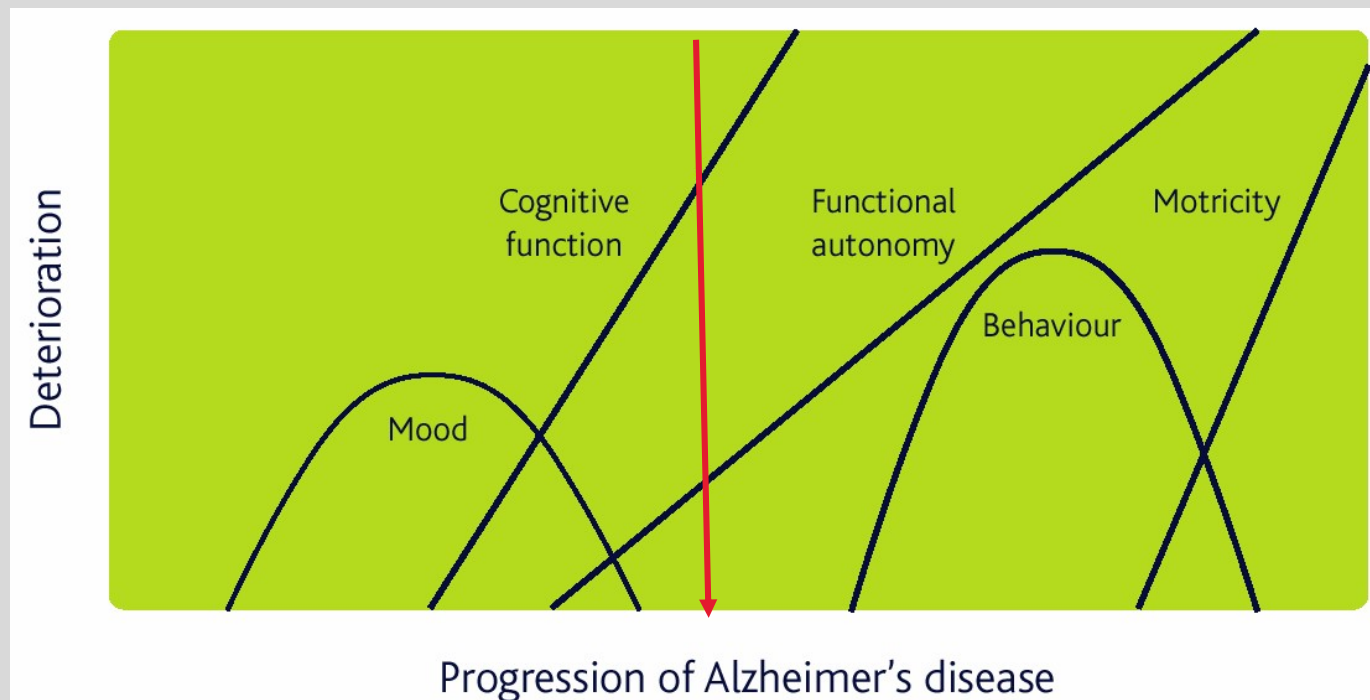
Lovestone & Gauthier 2000

# Summary

- There are `prodromal symptoms` over many years before dementia, some cognitive (SCD, MCI), some mood & behavioral (MBI)

- Not all persons with such symptoms progress to dementia, but they are at higher risk – opportunity for prevention!

- Researchers are fine tuning measurement tools for cognition, mood & behavior, functional autonomy, so they could be used on line for screening and follow-up

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- Natural history of age-associated cognitive decline
- **Findings in observational studies**
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# Overview

- Natural history of age-associated cognitive decline
- **Findings in observational studies**

    * Mise en contexte: biological changes linked to AD

    * Examples of epidemiological and lifestyle studies

- Results in intervention studies
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- Natural history of age-associated cognitive decline
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    - **\* Mise en contexte: biological changes linked to AD**
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# Alzheimer's disease exists on a spectrum from minimal symptoms to dementia

**Increasing Alzheimer's pathology**

No symptoms

Mild cognitive symptoms

Dementia

Time
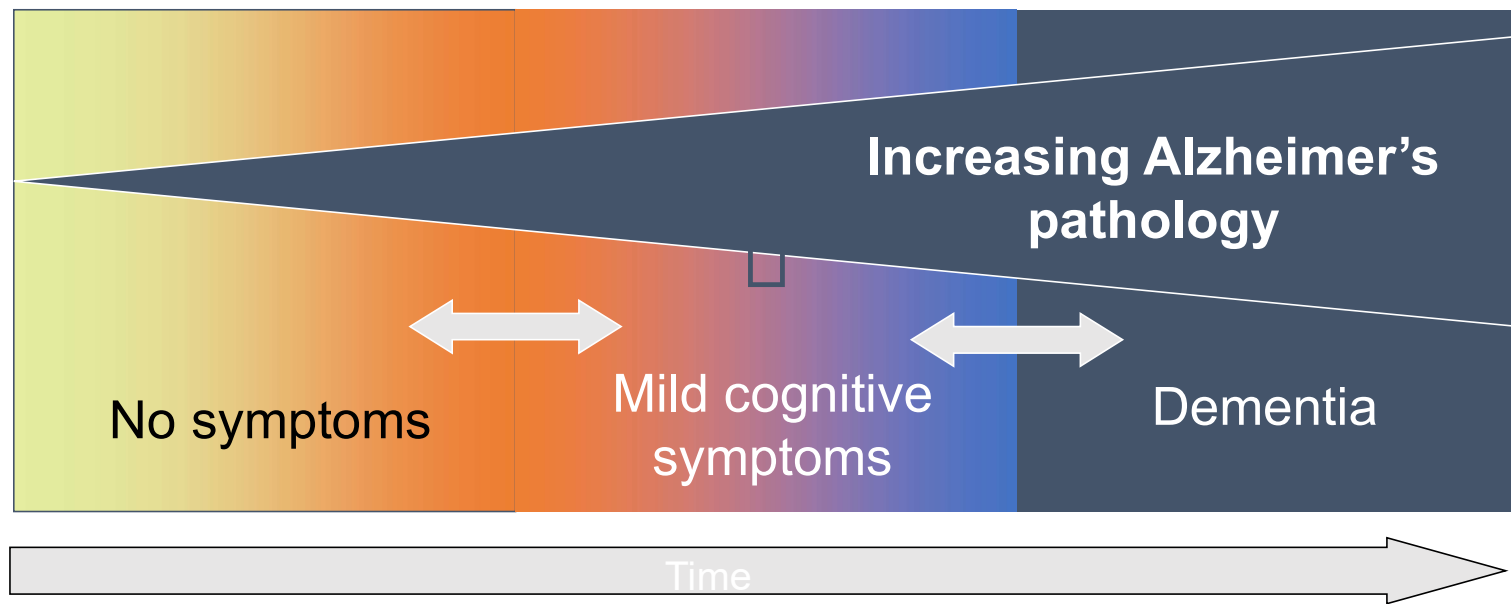
- Increasingly severe phenotype
- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

© JL Cummings, 2008

# PATHOLOGIES ASSOCIATED WITH AD

**AGE**

30

40

**β-amyloid deposition**

50

**Microglial activation**

60

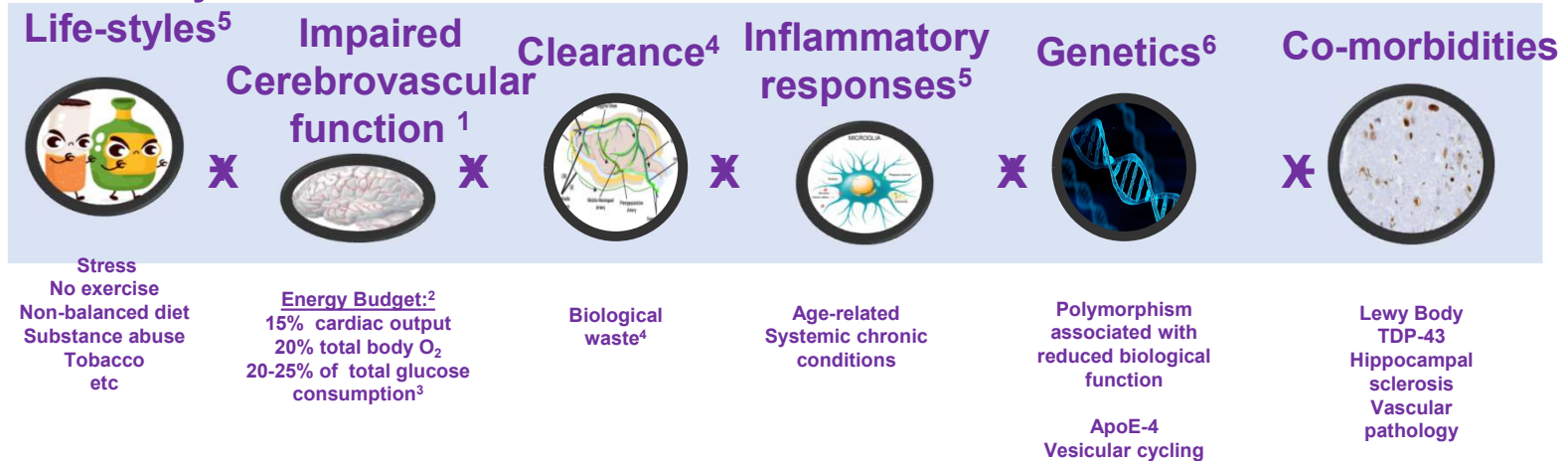**NFTs**

70

**Neuronal loss**

**Symptoms**

80

90

100
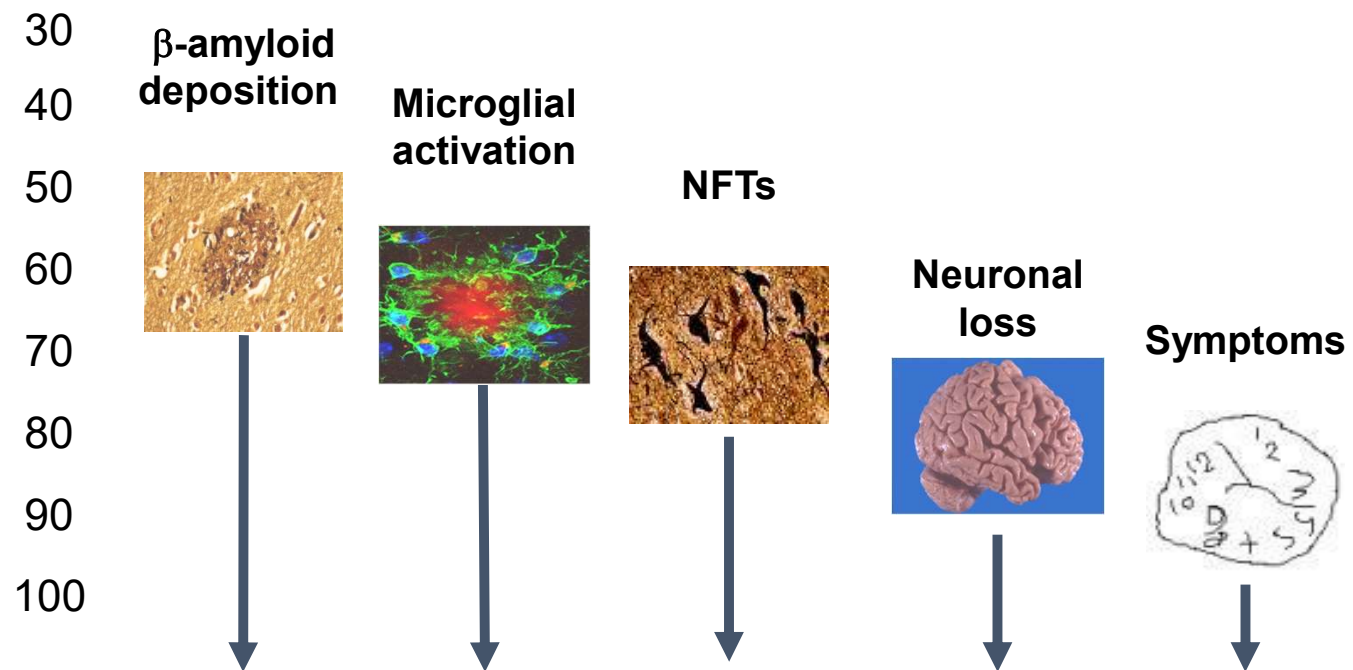
# Dementia risk factors accelerates neurodegeneration in AD

Increment the deleterious effects of AD pathophysiology driving neurodegeneration (additive effect)

Synergize with the deleterious effects of AD pathophysiology driving neurodegeneration
- Their combined effect is higher than the sum of each factor alone)

**Unhealthy Life-styles[5]**

**Impaired Cerebrovascular function [1]**

**Clearance[4]**

**Inflammatory responses[5]**

**Genetics[6]**

**Co-morbidities**

**Stress**
**No exercise**
**Non-balanced diet**
**Substance abuse**
**Tobacco**
**etc**

**Energy Budget:[2]**
**15% cardiac output**
**20% total body $O_2$**
**20-25% of total glucose consumption[3]**

**Biological waste[4]**

**Age-related Systemic chronic conditions**

**Polymorphism associated with reduced biological function**

**ApoE-4**
**Vesicular cycling**

**Lewy Body**
**TDP-43**
**Hippocampal sclerosis**
**Vascular pathology**

$O_2$, oxygen.
1. Jack C, et al. Alzheimers Dement 2018;14:535–62; 2. Willie CK, Smith KJ. J Physiol 2011;589:779–80; 3. Goyal M and Raichle M. J Pediatr Gastroenterol Nutr 2018;66:S46–S49; 4.Kaur J, et al. Front Neuroanat 2021;15:665803; 5. Madore C, et al. Immunity 2020;52:222–40; 6. Przedborski S, et al. J Clin Invest 2003;111:3–10.
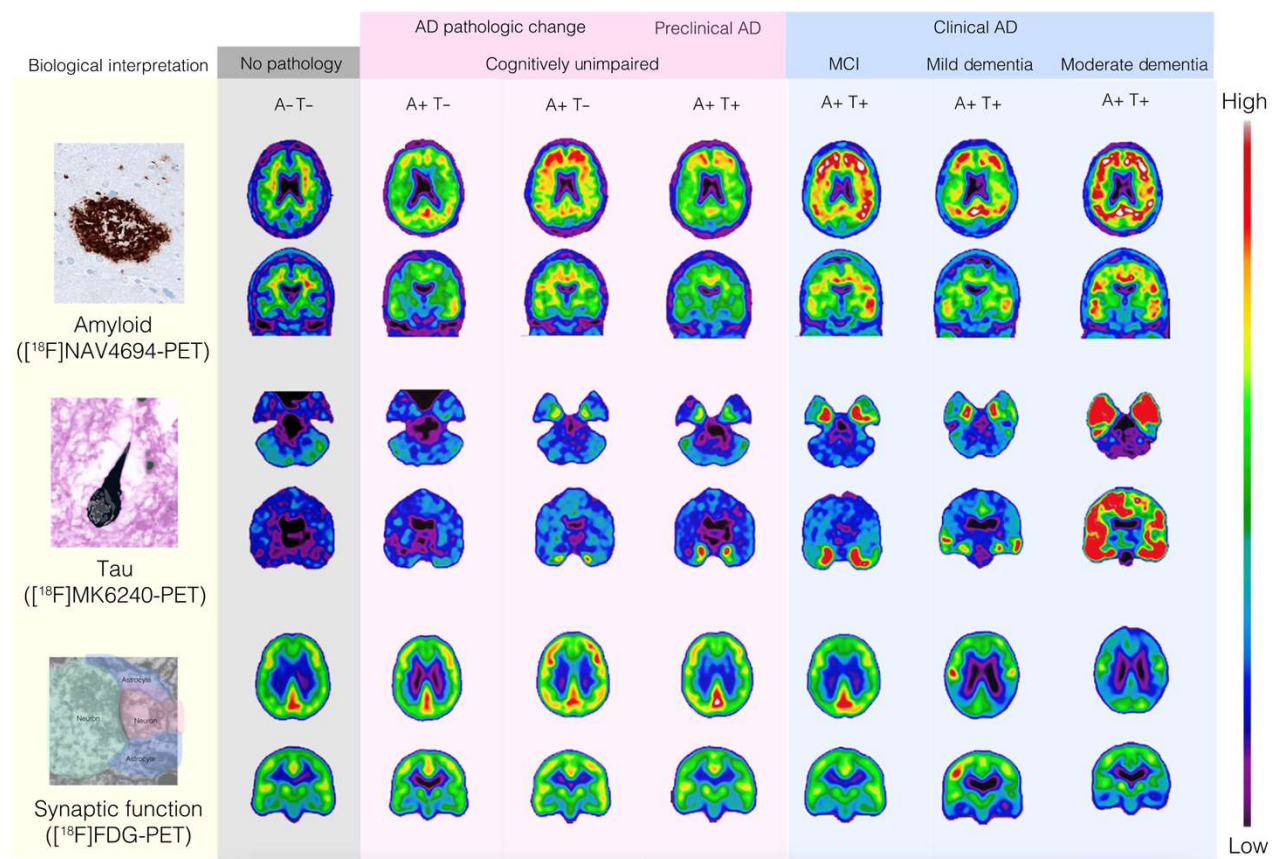
# Biologic observational study at McGill: TRIAD

- TRIAD stands for `Translational Biomarkers of Aging and Dementia`, en français *BIOVIE* pour `*Biomarqueurs de vieilissement et de démence*`

- Look up triad.tni-mcgill.com/participate/ for more info, or video made by participants https://www.youtube.com/watch?v=5vmP_4zErVo&t=4s

- Cognitively healthy individuals

- Mild cognitive impairment

- Mild dementia due to Alzheimer or atypical (including early onset)

# AT(N) biologic definition of AD
(Jack et al, LN 2022:21:866-869)

- Amyloid (A)                        PET, CSF, blood
- Tau (T)                            PET, CSF, blood
- Neurodegeneration (N)     MRI, PET, CSF, blood

| Biological interpretation | No pathology | AD pathologic change | | Preclinical AD | Clinical AD | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | Cognitively unimpaired | | | MCI | Mild dementia | Moderate dementia |
| | A− T− | A+ T− | A+ T− | A+ T+ | A+ T+ | A+ T+ | A+ T+ |

Amyloid
([¹⁸F]NAV4694-PET)

Tau
([¹⁸F]MK6240-PET)

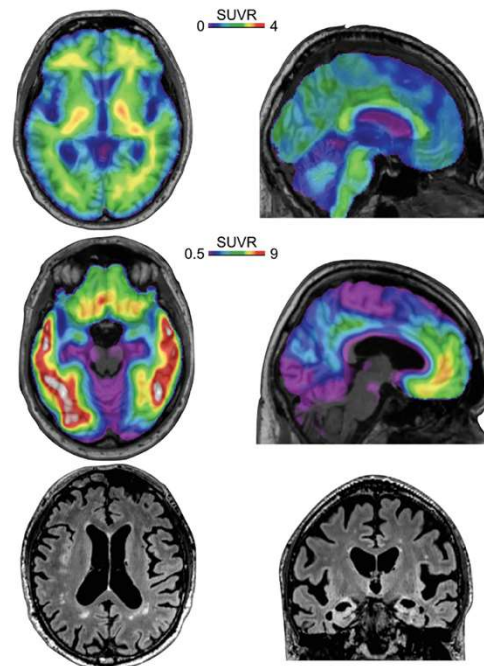Synaptic function
([¹⁸F]FDG-PET)

High

Low

Figure. Amyloid positron emission tomography (PET), tau PET, and MRI from a man, age 80, with mild dementia (CDR 1) after a gradual cognitive decline over 5 years and clinical diagnosis of probable AD. The amyloid PET is read as negative, the tau PET positive on the temporal lobe, precuneus, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak V). The MRI shows mild general and hippocampal atrophy (Scheltens 4-5), White matter hyperintensities (WMH) are limited to the periventricular regions (Fazekas 1). This individual has a neurofibrillary tangle predominant dementia.
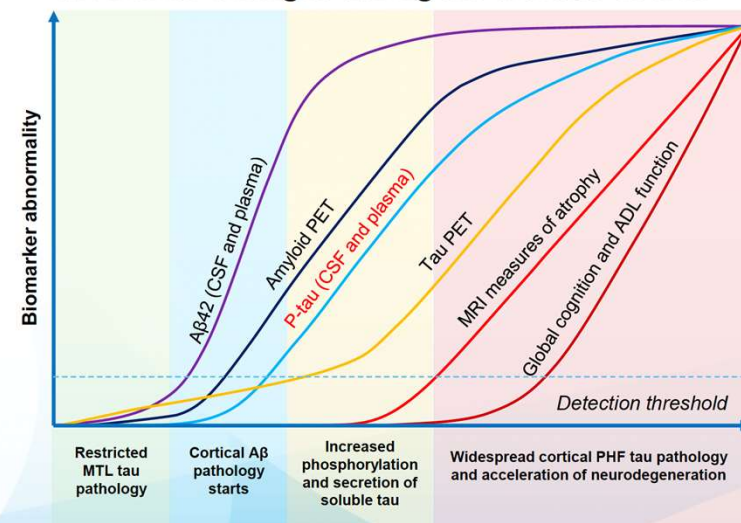
Gauthier & Rosa-Neto. Practical Neurology 2019; 18(5): 60-63

# Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer's disease

## Plasma p-tau levels are increased in AD



Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]
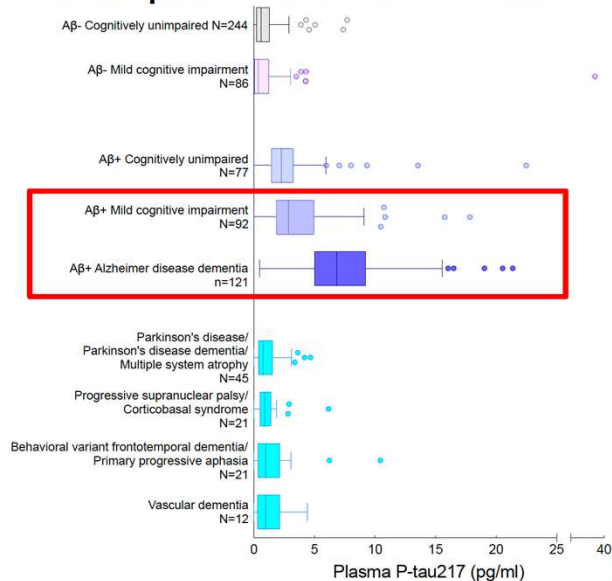
## Approximative ordering of Alzheimer's disease biomarker changes during the disease course



Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

# Overview

- Natural history of age-associated cognitive decline
- **Findings in observational studies**

    * Mise en contexte: biological changes linked to AD

    * **Examples of epidemiological and lifestyle studies**

- Results in intervention studies
- Population-based prevention vs individual prevention

# Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

**Prevention potential ≈ 40%
12 modifiable risk factors**

1. Diabetes
2. High blood pressure at midlife
3. Obesity at midlife
4. Physical inactivity
5. Depression
6. Smoking
7. Low education
8. Hearing loss
9. Traumatic Brain Injury
10. High alcohol consumption
11. Social isolation
12. Air pollution

**Protective factors**
- Healthy diet
- Education
- Physical activity
- Mental activity
- Social activity

## 'Novel' risk factors

- Loneliness
- Hopelessness
- Stress
- Sleep disturbances
- Impaired oral health
- Infections?  Covid-19?

Lisko, Kivipelto et al., J Intern Med. 2021

# Epidemiologic observational study in USA looking at modifiable dementia risk factors (MDRF)

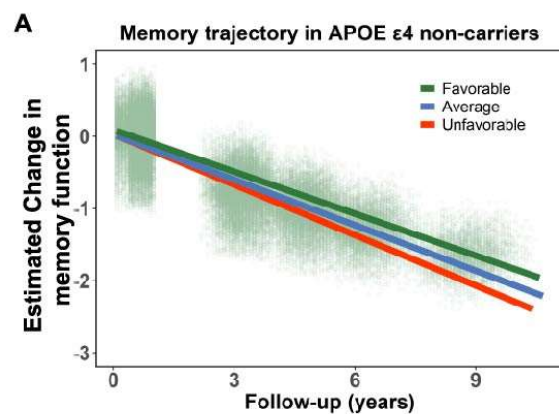- In the Framingham Study Cox models were used to examine each potential MDRF and incipient dementia, ages 33-80, N=4,015
- Diabetes HR1.62
- Physical inactivity HR 1.57
- Obesity HR 1.76
- Having multiple MDRF increase dementia risk

# Epidemiologic observational study in China looking at healthy lifestyle factors and impact on age-associated memory decline
(Jia et al. BMJ, 2023;380:e072691)

- Over 10 years in 60+ Chinese population N=29,072

- Reduction in memory decline using an Auditory Verbal Learning Test for those with 4+ of healthy diet, regular physical exercises (150 min/week), active social contact (2+/week), active cognitive activity (2+/week), no smoking, no alcohol

- Protective effect seen also in persons at increased genetic risk (ApoE4 carriers)

**A** Memory trajectory in APOE ε4 non-carriers
**B**
**C** Memory trajectory in APOE ε4 carriers
**D**

# Epidemiologic observational study in China looking at healthy lifestyle factors and impact on age-associated memory decline

- Over 10 years in 60+ Chinese population N=29,072

- Reduction in memory decline using an Auditory Verbal Learning Test for those with <u>healthy diet</u>: 7+ of 12 food items including fruits, vegetables, fish, meat, dairy products, salt, oil, eggs, careals, `legumes`, nuts, tea.

# Summary

- The new biological definition of AD facilitates research but is currently limited to A and T. Other factors are at play such as vascular factors, neuroinflammation, α-synuclein, TDP-43.

- TRIAD and similar cohorts have led to rapid progress in blood biomarkers, expected to be used clinically very soon for persions with mild symptoms.

- Observational studies show different types of risk or protective factors towards age-associated cognitive decline and dementia for populations. They may differ between countries.

# Overview

- Natural history of age-associated cognitive decline
- Findings in observational studies
- **Results in intervention studies**
- Population-based prevention vs individual prevention

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

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto
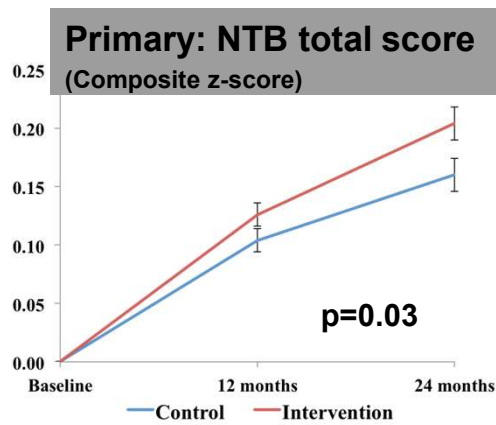
**MULTIDOMAIN INTERVENTION**

Nutrition

Exercise

Cognitive training

**Social activities**

Vascular risk monitoring

**Dementia Risk Score (midlife)**

CAIDE

N = 1260
Age 60-77 years
At risk general population

2 years

**REGULAR HEALTH ADVICE**

*Kivipelto et al., Lancet Neurology 2006
Alzheimer's and Dementia 2011*
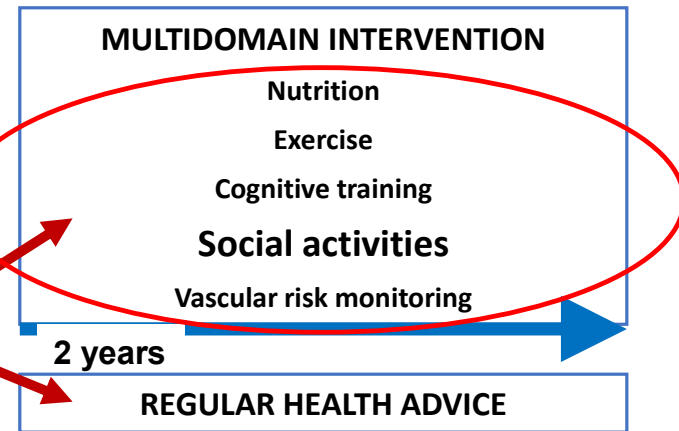
**Extended 5- & 7-year follow-up finished
11-year follow-up**

# FINGER Trial: summary of primary findings



**Primary: NTB total score**
(Composite z-score)

p=0.03

Control    Intervention

**25% higher improvement**

**Executive functioning**

p=0.04

**83% higher improvement**

**Processing speed**

p=0.03

**150% higher improvement**

**Memory (complex tasks)**

p=0.04
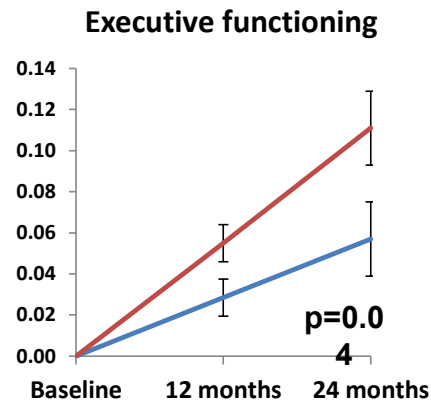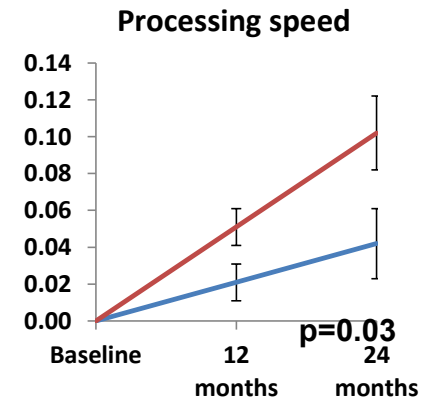
**40% higher improvement**
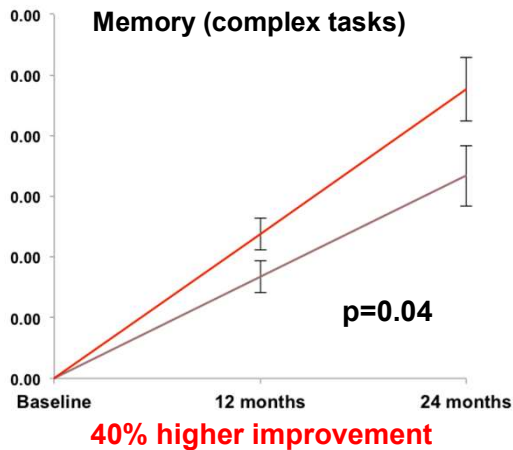
*Red - intervention*
*Blue - control*

*Lines = estimates for change from baseline to 1 & 2 years*
*Error bars = standard errors*
*P-values = difference in trajectories over time between groups*

*Ngandu, Kivipelto et al. Lancet 2015*

# Beneficial effects of the intervention: cognition

FINGER

| COGNITION | % Improvement vs control *(p value)* | |
|---|---|---|
| **Global Cognition** | **+ 25%** | *(0.03)* |
| **Executive function** | **+ 83%** | *(0.04)* |
| **Processing Speed** | **+ 150%** | *(0.03)* |
| **Memory** | **+ 40%** | *(0.04)* |

Global cognition and specific cognitive domains assessed with the Neuropsychological Test Battery

*Lancet 2015*

# The FINGER model

FINGER

**N = 1260**
**Age 60-77 years**

MULTIDOMAIN INTERVENTION

**Nutrition**

**Exercise**

**Cognitive training**

## Social activities

**Vascular risk monitoring**

**2 years**

REGULAR HEALTH ADVICE

**Extended 5- & 7-year follow-up completed**
**11-years follow-up in 2022**

CAIDE
Dementia risk score
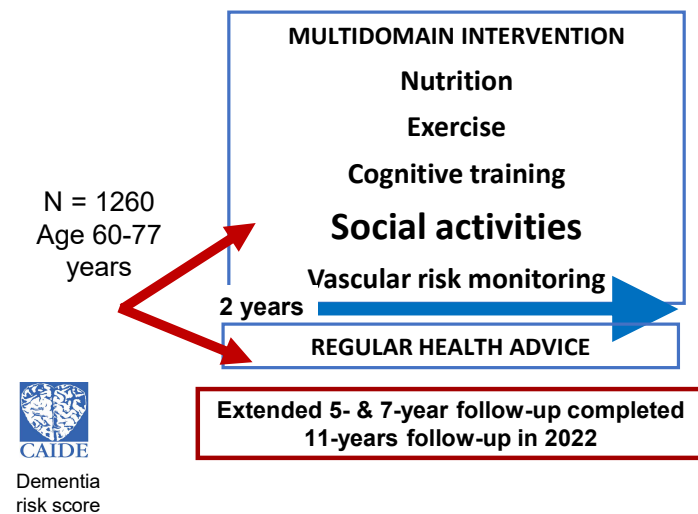
- Cognitive benefits
- 20% lower risk cardiovascular events
- 30% lower risk for functional decline
- 60% lower risk of chronic diseases
- Better health related quality of life
- Health-economical benefits

*Lancet 2015; JAMA Neurology 2018, Eur Ger Med 2017, JAMDA 2017, JAGS 2019; Alzheimer's Dementia 2021; European J Cardiology 2022, Alzheimer's Dementia 2022*

# FINGER

# APOE4 carriers - clear beneficial effects

## Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention
### A Subgroup Analysis of a Randomized Clinical Trial

Alina Solomon, MD, PhD; Heidi Turunen, BM; Tiia Ngandu, MD, PhD; Markku Peltonen, PhD; Esko Levälahti, MSc; Seppo Helisalmi, PhD; Riitta Antikainen, MD, PhD; Lars Bäckman, PhD; Tuomo Hänninen, PhD; Antti Jula, MD, PhD; Tiina Laatikainen, MD, PhD; Jenni Lehtisalo, MSc; Jaana Lindström, PhD; Teemu Paajanen, MA, Psy; Satu Pajala, PhD; Anna Stigsdotter-Neely, PhD; Timo Strandberg, MD, PhD; Jaakko Tuomilehto, MD, PhD; Hilkka Soininen, MD, PhD; Miia Kivipelto, MD, PhD

**Telomere length:** FINGER intervention counteracts shortening of telomeres among the ApoE4 carriers *(Sindi, Solomon, Kivipelto et al.,* Gerontol A Biol Sci Med Sci *2021)*
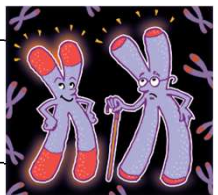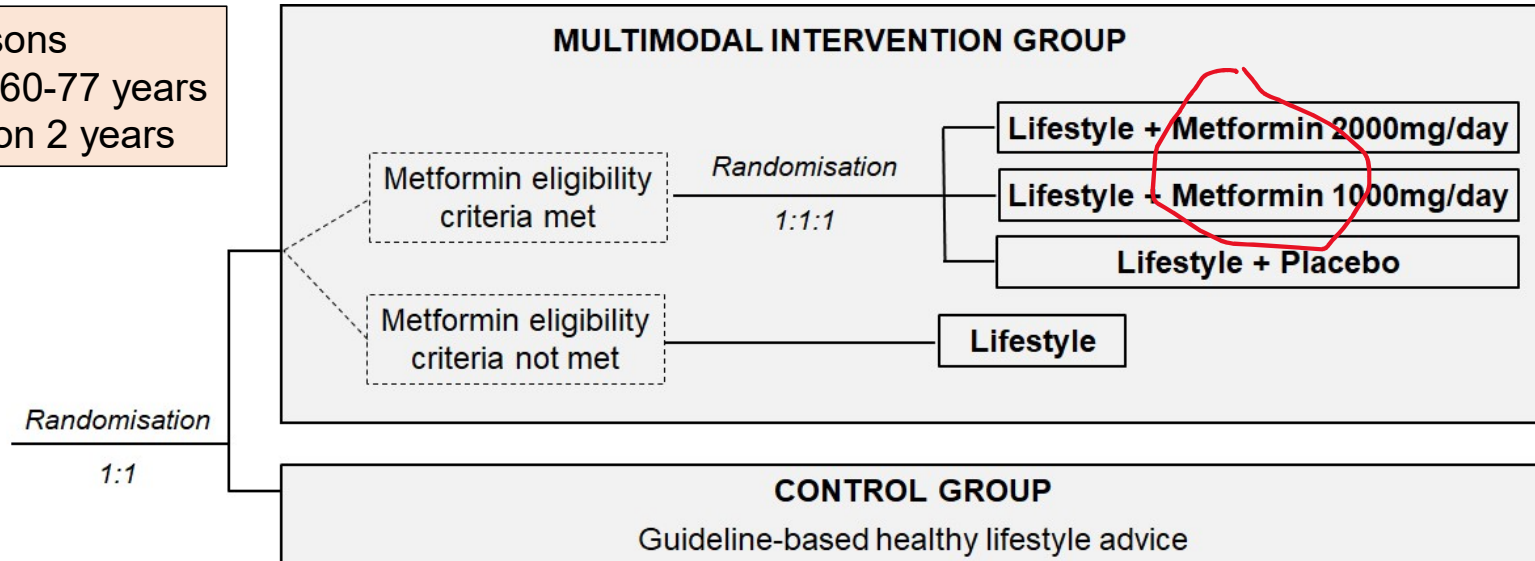
**FINGER 2.0**

Next generation of clinical trials:

Combine updated FINGER lifestyle model

with pharmacological intervention

# MET-FINGER study diagram

## Phase 2b proof of concept trial

Diabetes medicine metformin
Repurposed drug approach

At risk persons
Age range 60-77 years
Trial duration 2 years

**MULTIMODAL INTERVENTION GROUP**

Metformin eligibility
criteria met

*Randomisation*

*1:1:1*

Lifestyle + Metformin 2000mg/day

Lifestyle + Metformin 1000mg/day

Lifestyle + Placebo

Metformin eligibility
criteria not met

Lifestyle

*Randomisation*

*1:1*

**CONTROL GROUP**
Guideline-based healthy lifestyle advice

**Outcomes:**
memory and
cognition
Brain scans
Alzheimer related
biomarkers

**Lifestyle domains:** *nutrition, exercise, cognitive and social activities, cardiovascular / metabolic risk factors*

**BMC Geriatrics**

CrossMark

# SYNERGIC TRIAL (SYNchronizing Exercises, Remedies in Gait and Cognition) a multi-Centre randomized controlled double blind trial to improve gait and cognition in mild cognitive impairment

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# SYNERGIC Trial
# Design and sample

- 20-week multicenter phase II double-blind RCT + 6 months of follow-up

- Sample size n=200

- MCI - Age 60-85

- Baseline, week 22-24 (6 months), and week 52-54 (12 months)

- Investigating **efficacy** of multimodal aerobic and resistance training, with potential synergistic effects of cognitive training and vitamin D

- **Primary Outcome:** ADAS Cog 13 and plus

- **Secondary Outcomes**: Other cognitive domains, MRI, gait and mobility & blood biomarkers

# SYNERGIC Trial Interventions

**3** interventions… in individuals with MCI

Cognitive training + Physical exercises + Vitamin D



### Vitamin D

- 10,000 IU of Vitamin D3 or matching placebo 3 x/week (daily dose: 4,258 IU)

- Maximum daily dose approved by Health Canada as a supplementation is 10,000 IU

# SYNERGIC Trial Results: Primary outcome

ANCOVA comparing ADAS-Cog 13 at T6, controlling for baseline values, age and sex for 3 different interventions. The lower the scores, the less impaired participants are.

| | Total n=176 | Exercise + Cognitive (Arm 1+2) n= 70 | Exercise (Arm 3+4) n= 70 | Control (Arm 5) n= 36 | p-value |
|---|---|---|---|---|---|
| ADAS-Cog 13, mean (SD) | 13.99 (6.28) | 12.45 (5.77) | 14.37 (5.96) | 16.19 (7.52) | 0.024 |
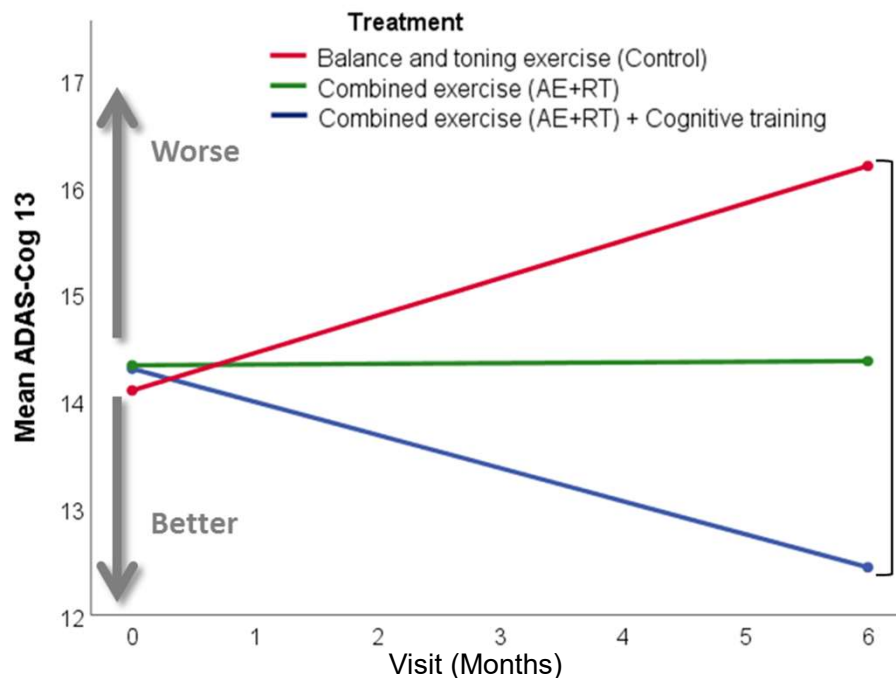


For the **main** intervention:

Absolute 1.85 points improvement in ADAS-Cog

Relative 3.75 points improvement in ADAS-Cog

**Effect size of 0.56**

# Conclusions from SYNERGIC Trial

- Combining exercise + cognitive training has synergistic effect to improve cognition and mobility that the single modalities

- Multi-domain, personalized combination of progressive aerobic + resistance training coupled with cognitive training is feasible to do in older adults with cognitive impairment (MCI)

- Adding Vitamin D did not enhance cognition or mobility

**MM1**      pone lo que dijo Roanld Peterson en neurology today

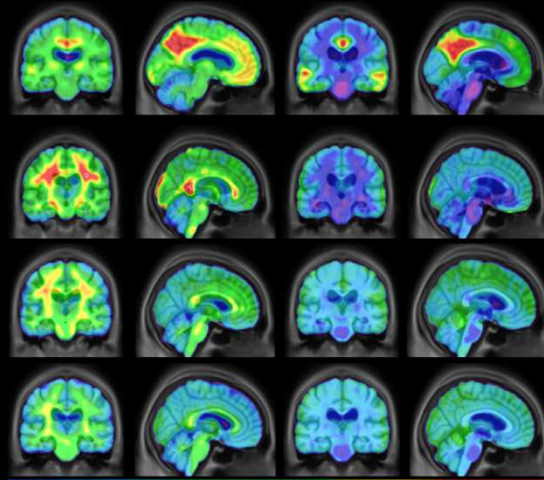          Manuel MonteroOdasso, 2022-11-08

# Overview

- Natural history of age-associated cognitive decline
- Findings in observational studies
- Results in intervention studies
- **Population-based prevention vs individual prevention**

World Alzheimer Report 2021
Journey through the diagnosis of dementia



World Alzheimer Report 2022
Life after diagnosis:
Navigating treatment, care and support

# ADI World Alzheimer Report 2022

(alzint.org)

### Chapter 23: Strategies towards dementia risk reduction

- Is there a pre-symptomatic stage of AD leading possibly to prevention? W. Jagust

- Strategies for risk reduction. M Kivipelto et al.

- Population-based approaches to prevention. S Walsh et al

- Communicating personal risk profiles. I Choi

- Prevetion and management of atrial fibrillation. J. Coza

# Summary

- Population-based prevention is currently the most realistic way to decrease dementia prevalence

- In addition, a personalized approach based on genetic and biological risk may be possible, as with other chronic conditions such as diabetes – DISCUSS THIS WITH YOUR FAMILY DOCTOR!

- Sign up as volunteer for observational and therapeutic studies

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