

Frailty and risk in Mild Cognitive Impairment

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Disclosures

Through Dalhousie University's Industry Liaison Office, I have asserted copyright of the **Clinical Frailty Scale**, the **Pictorial Fit Frail Scale**, a **Comprehensive Geriatric Assessment**, and the **Hierarchic Assessment of Mobility and Balance**. Each is **free for use**. We ask users not to change, commercialize, or charge for them.

I co-founded Ardea Outcomes. We contract with pharma, device manufacturers, academic groups, and charities for individualized outcome measurement, but not in frailty.

I edit *Brocklehurst's Textbook of Geriatric Medicine & Gerontology*.

Let's review some key terms

MCI = Mild cognitive impairment = cognitive impairment that does not meet criteria for dementia

aMCI = amnestic MCI = memory dominant

naMCI = non-amnestic MCI = other than memory dominant

MBI = Mild Behavioural Impairment

Let's review a few more key terms

Dementia = Cognitive impairment in more than one domain that is sufficiently severe to interfere with social or occupational function.

NCI = No cognitive impairment

SCI = Subjective cognitive impairment

Let's mention some other terms and move on

Cognitive Impairment, Not Dementia

(MMI = Mild Motor Impairment)

(MCI of Parkinson's, of Lewy Body Disease, etc)

(Vascular Cognitive Impairment)

(Cognitive Frailty)

A comfortably understandable story about age, MCI, and dementia

As people age, they can develop memory / cognitive complaints.

Such complaints merit investigation, beginning by risk stratification and cognitive testing. Risk is higher **if function is suspect**: e.g. missed appointments, motor vehicle crashes, family reports.

Common risk factors are a **positive family history**, problems with vascular health (especially **hypertension**) and **delirium**.

A comfortably understandable story about age, MCI, and dementia (2).

Cognitive screening tests (e.g. **MMSE**, **MoCA**, FreeCog) can indicate potentially important problems.

If these are negative, consider SCI “subjective cognitive impairment”, encourage diet, exercise, and social engagement, and re-evaluate annually. Treat **vascular risk factors**, especially **hypertension**.

If there is no clear evidence of functional impairment, but an objective deficit is found, **this indicates MCI**.

MCI increases the risk of dementia, might indeed be the prodrome, and merits more detailed review. (Up next.)

Approach to MCI

Fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD5)

Be vigilant for potential symptoms of cognitive disorders.

Self- or informant-reported cognitive symptoms.

Decline in instrumental activities of living – note lack of effective performance, especially poor initiative and planning. (“Mom just sits and stares”.)

Missed appointments, difficulty with instructions or taking medications.

Approach to MCI

CCCDTD5 guidelines

Decrease in self-care. (Foot care, umbilicus, breasts / skin folds)

Being victimized by financial scams.

New onset, later-life behavioural changes (mood, anxiety).

Uncharacteristic irritability.

Clinical concern for a cognitive disorder (not always shared by the patient) suggests “validated assessments of cognition, activities of daily living, and neuropsychiatric symptoms”.

Diagnosis of MCI – cognitive testing with rapid screening tools

Memory Impairment Screen (MIS) + clock drawing test (CDT),

Mini-Cog

Ascertain Dementia 8 (AD8; an Informant Questionnaire)

MoCA- four item version (Clock-drawing, Tap-at-letter-A, Orientation, and Delayed-recall)

GP Assessment of Cognition (GPCOG).(93%)

Diagnosis of MCI – cognitive testing with more detailed screening tools

Mini-Mental State Examination

Montreal Cognitive Assessment (+/- Memory Index)

Rowland Universal dementia assessment scale.

Combining screening tools with function questionnaires is best if time allows.

Diagnosis of MCI/Neuroimaging

“Even in older subjects, anatomical neuroimaging is recommended, IF:”

New cognitive signs/symptoms – i.e. within the past 2 years;

Unexpected/unexplained decline in cognition and/or function in a patient with known dementia;

Recent and significant head trauma;

Unexplained neurological symptoms or signs, at onset or during evolution (includes gait disturbances)

History of cancer, risk for intracranial bleeding;

?Normal Pressure hydrocephalus

Significant vascular risk factors.

Diagnosis of MCI / Neuroimaging Modality

Magnetic resonance imaging (MRI) is recommended over computed tomography (CT), 3T MRI should be favoured over 1.5 T.

If MRI is performed, use a dementia protocol ...

If CT is performed, we recommend a non-contrast CT with coronal reconstructions to better assess hippocampal atrophy. 1C (100%)

Treatment of MCI / prevention of dementia

Wait for it

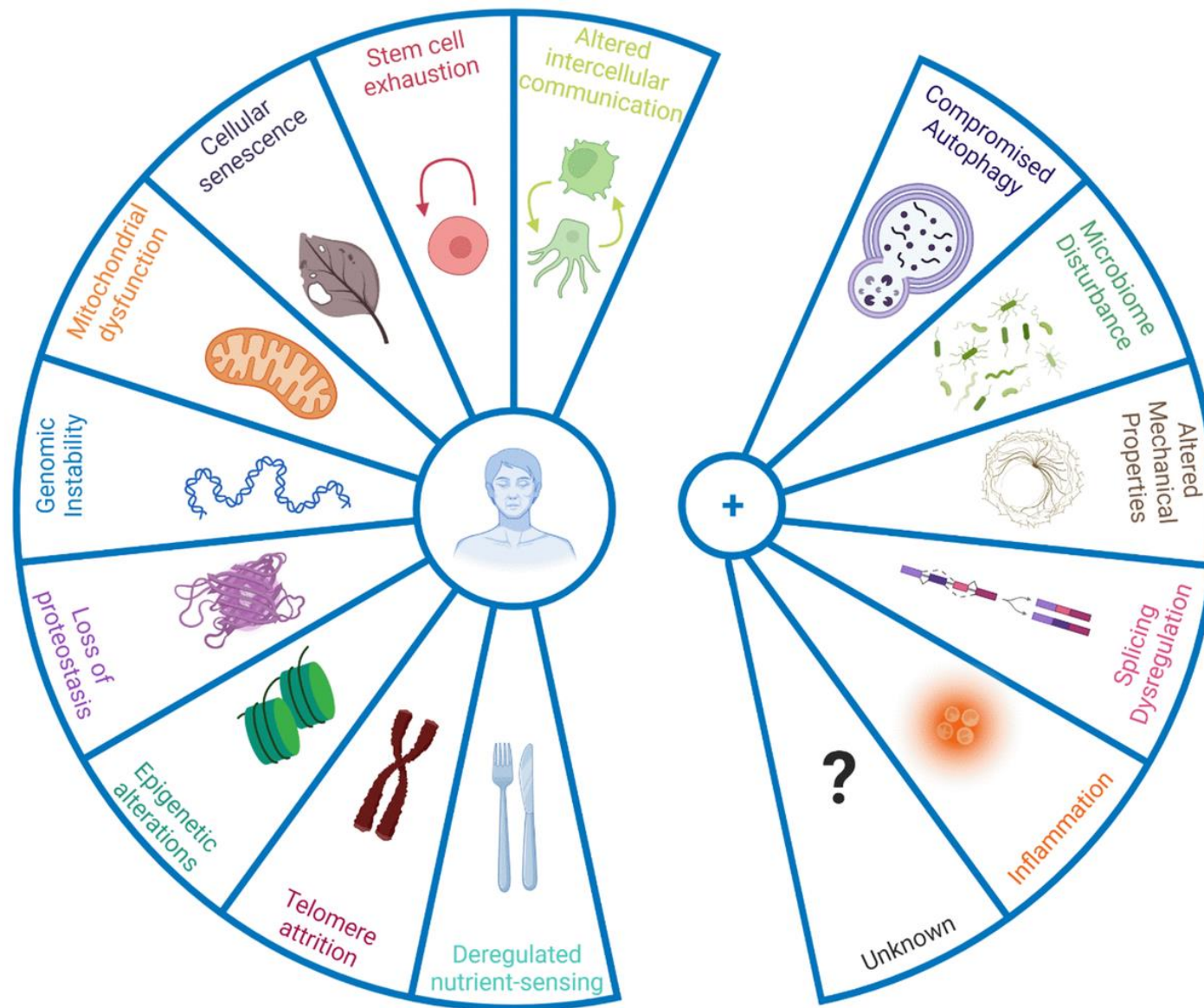
Treatment of MCI / prevention of dementia

Now we leave the comfortable
story ...

Our population is aging, with predictable consequences for population health.

Population aging means more people have more age-related illnesses.

Much of age-related damage is *intrinsic*.
“... imperfect fidelity” in normal processes.



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Age-related illnesses often **occur in the same people**, on a background of age-associated molecular and cellular damage.

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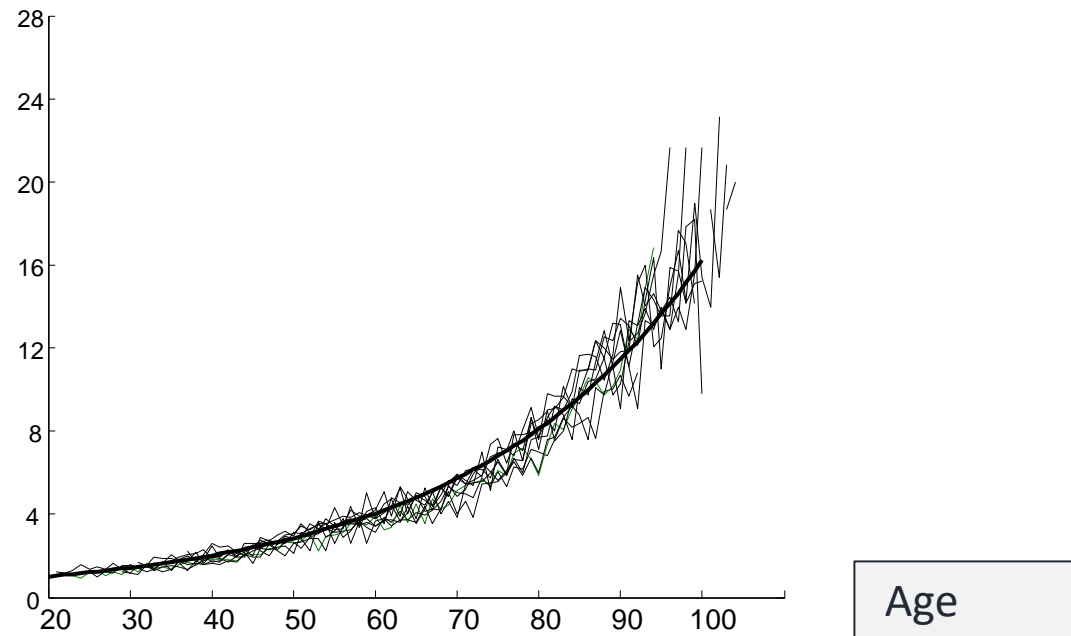
Age-related molecular and cellular damage scale up to become **clinically visible health deficits**.

Frailty manifests stereotypically, and changes as the *degree of frailty* increases.



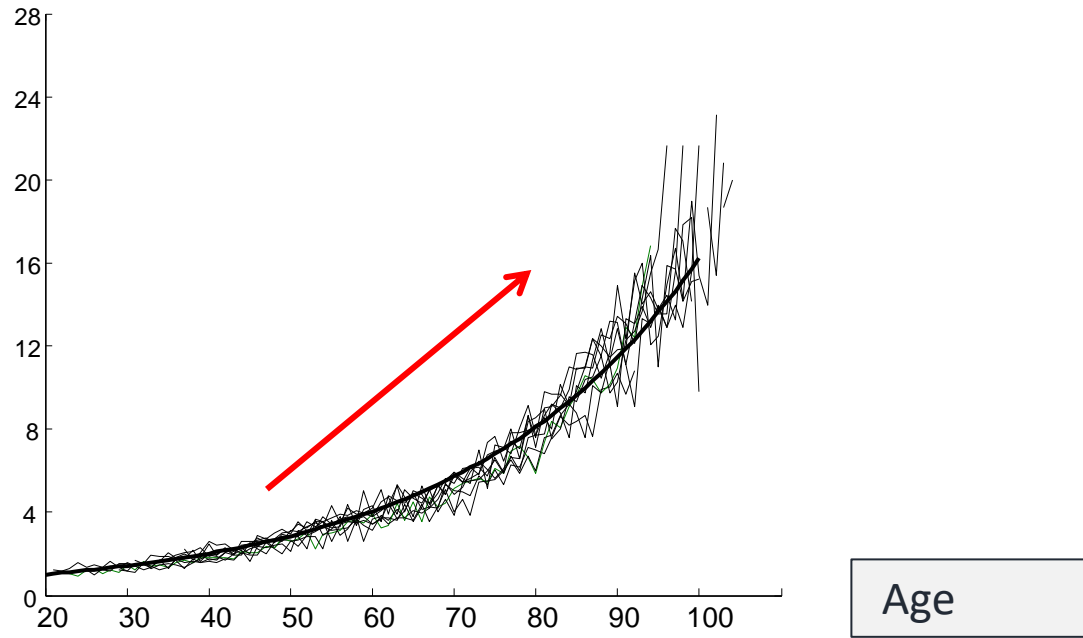
The rate of deficit accumulation (ageing) increases at $\sim 4.5\%/year$ – *on average* (8 successive 2-year waves NPHS)

Degree
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frailty /
deficit
accumulation



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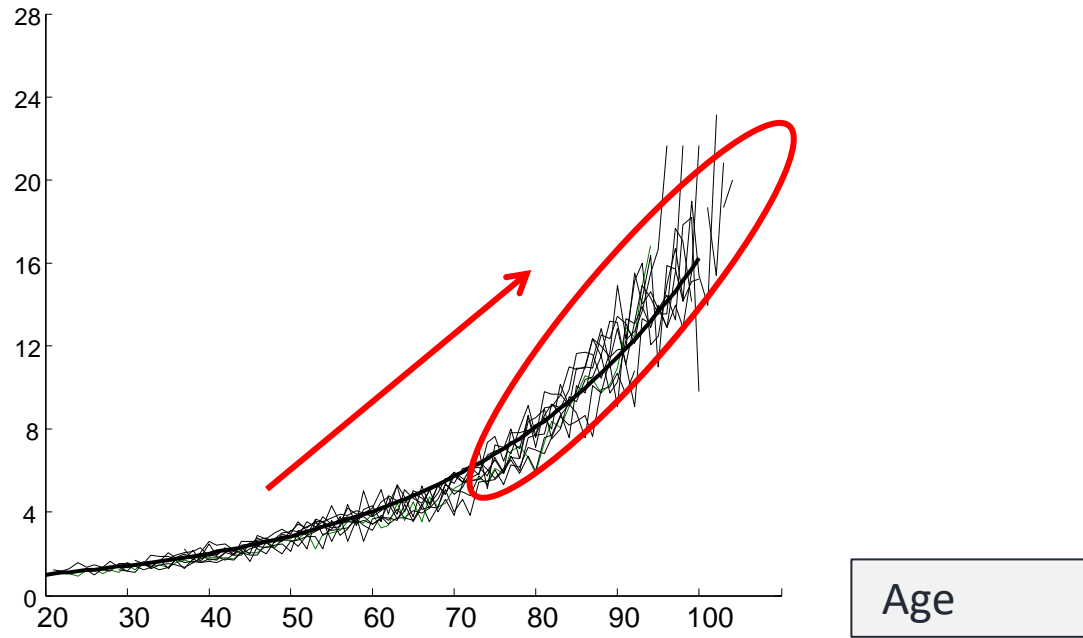
Degree of frailty / deficit accumulation



Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

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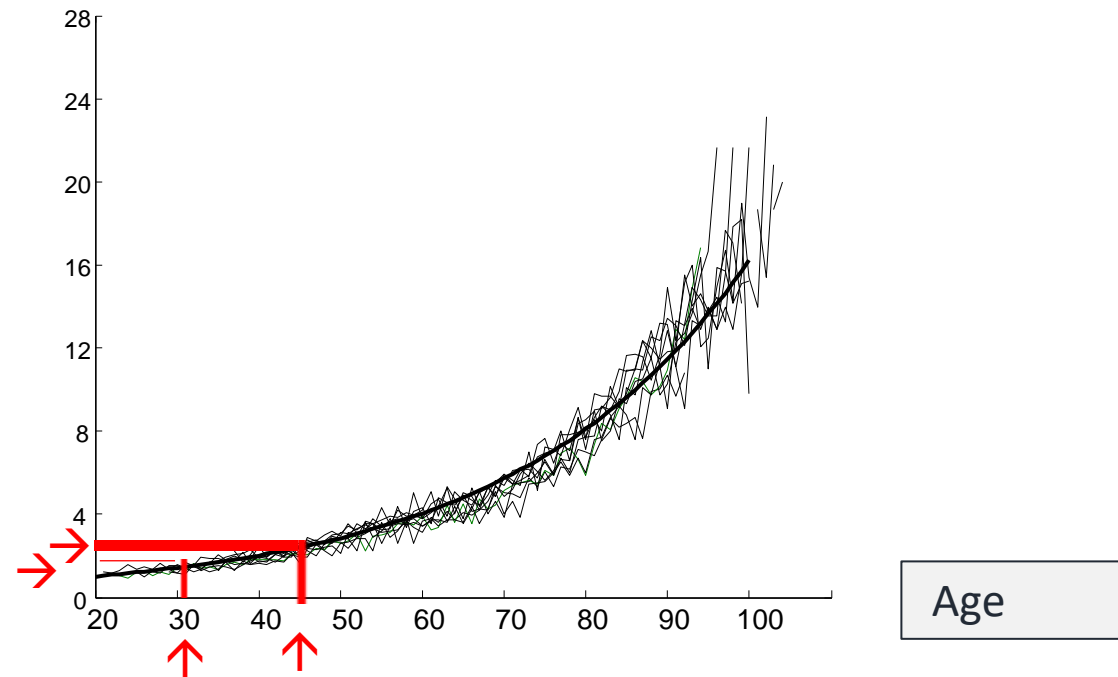


Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%$ /year rate of deficit accumulation translates into a 15-year doubling time.

Degree of frailty / deficit accumulation

Just as with compound interest, it's not the first couple of doubling times where we see the big impact ...

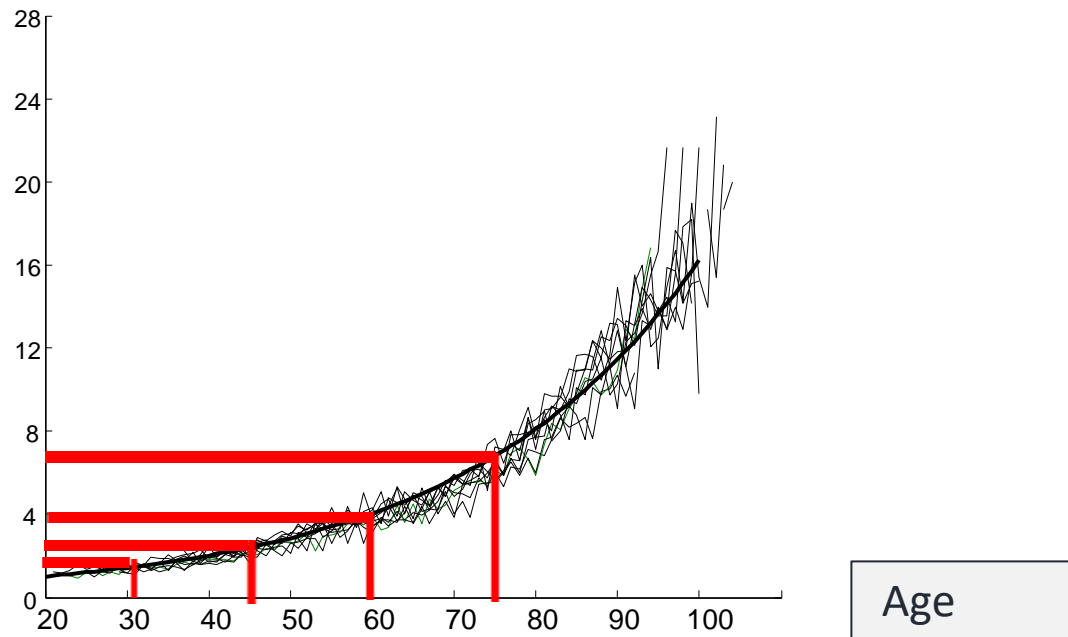


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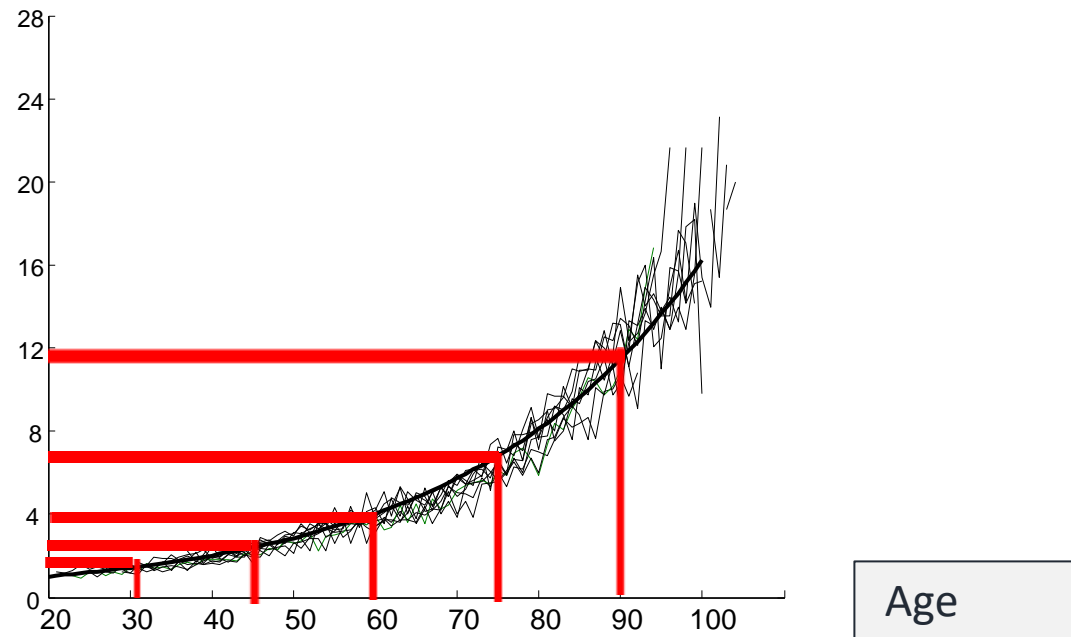


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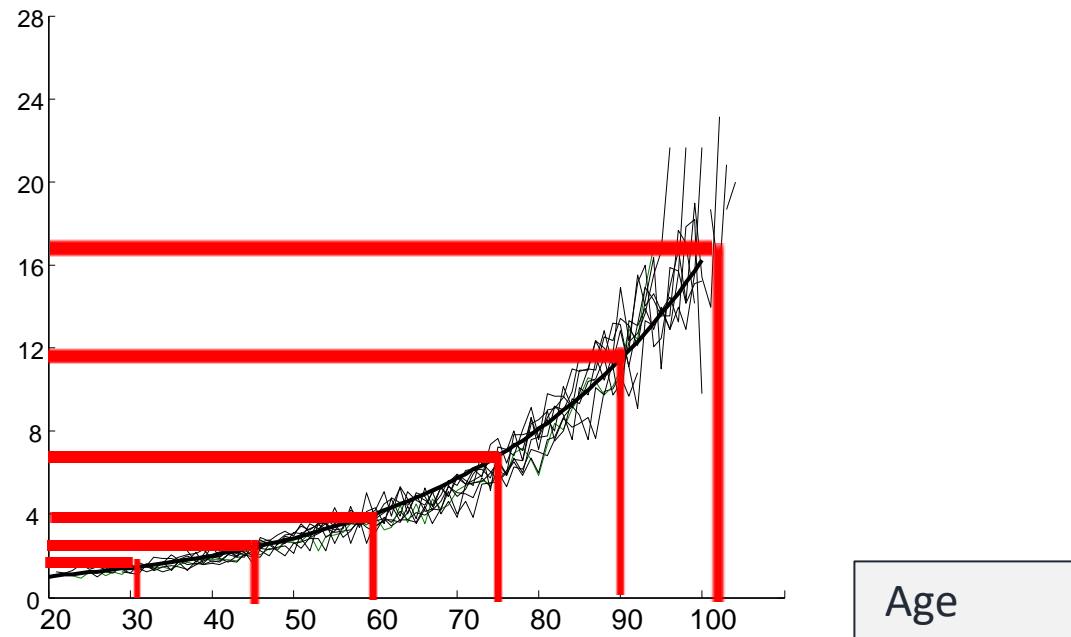


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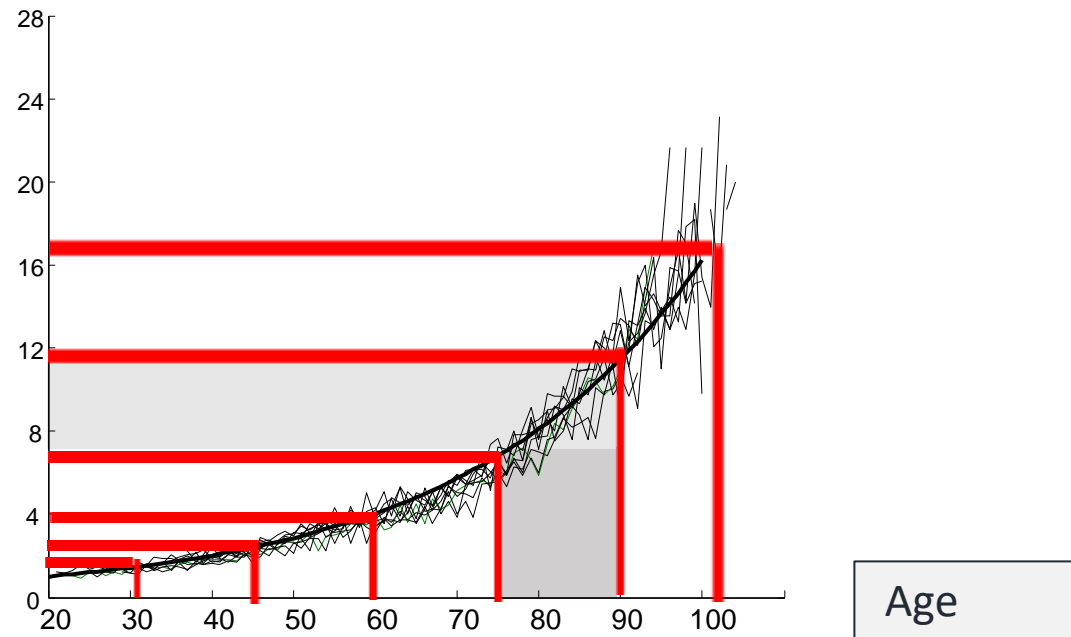
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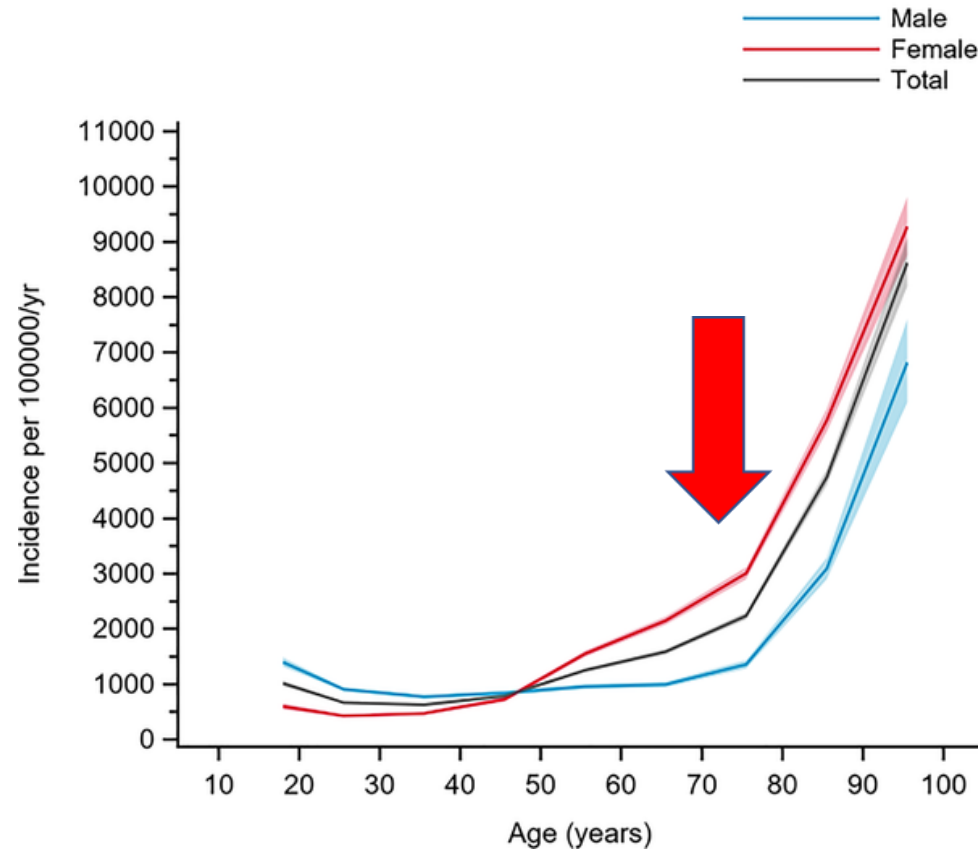
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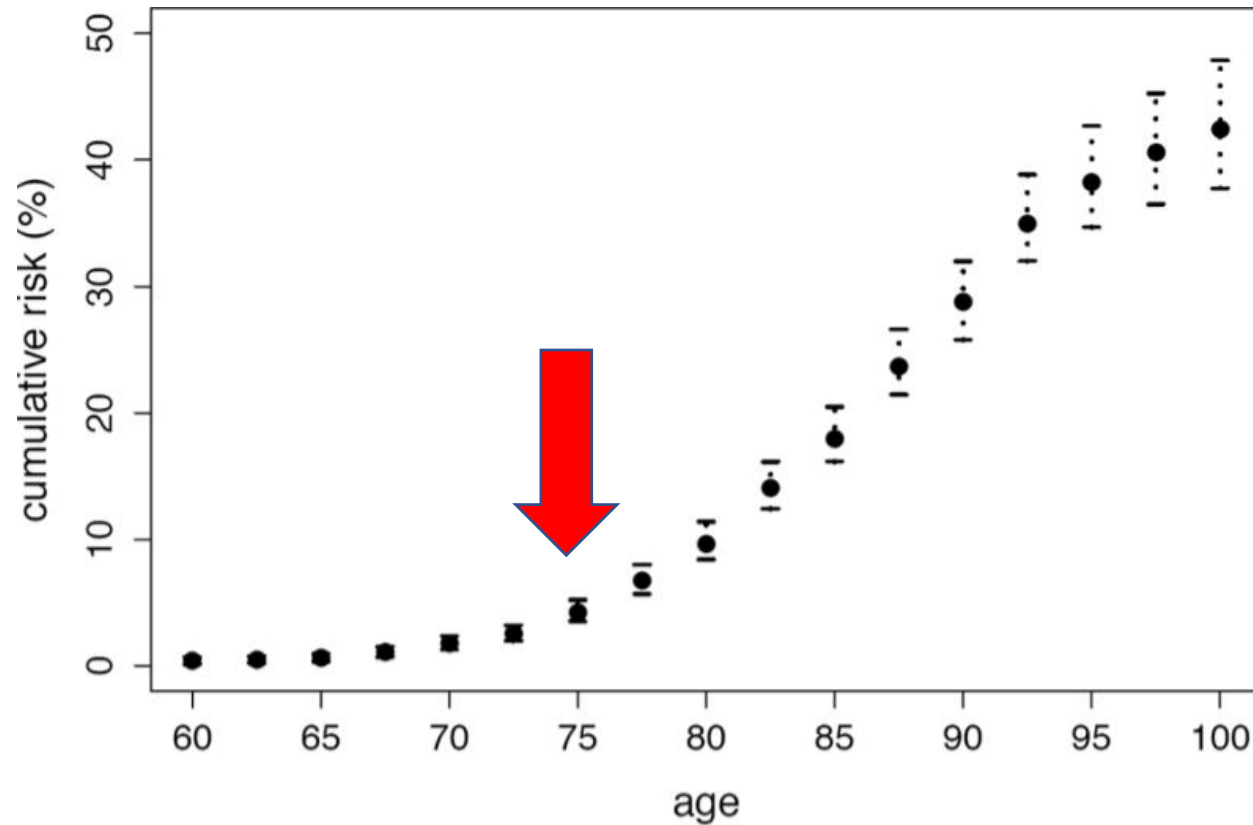
Four-year Age- & gender-specific incidence (95% CIs) of fractures (Swedish Fracture Registry), 2015–2018.



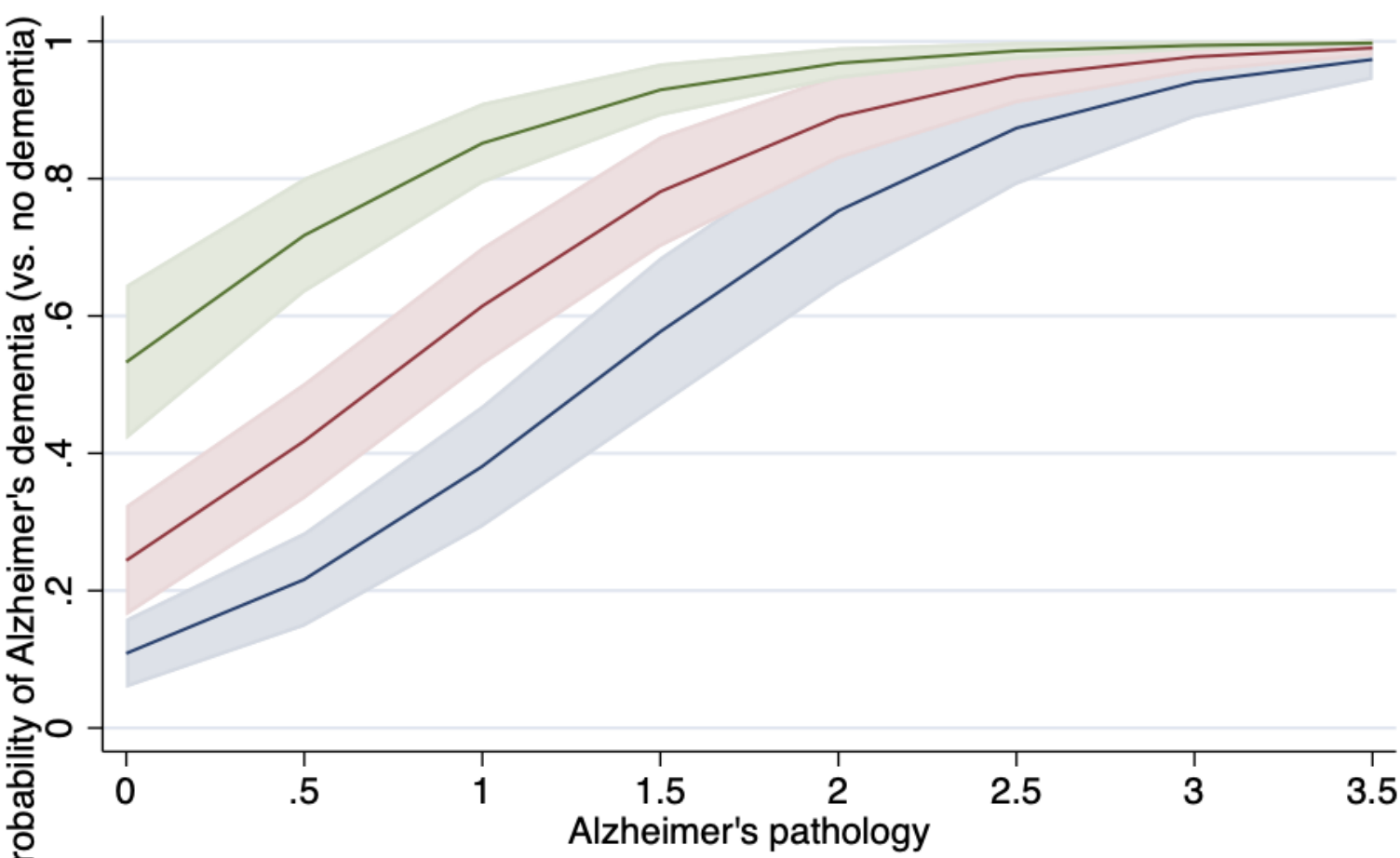
Bergh C, et al. PLOS ONE 2020 15(12): e0244291. DOI: /10.1371/journal.pone.0244291

Estimated lifetime risk of dementia in older Canadians

Cumulative risk of dementia

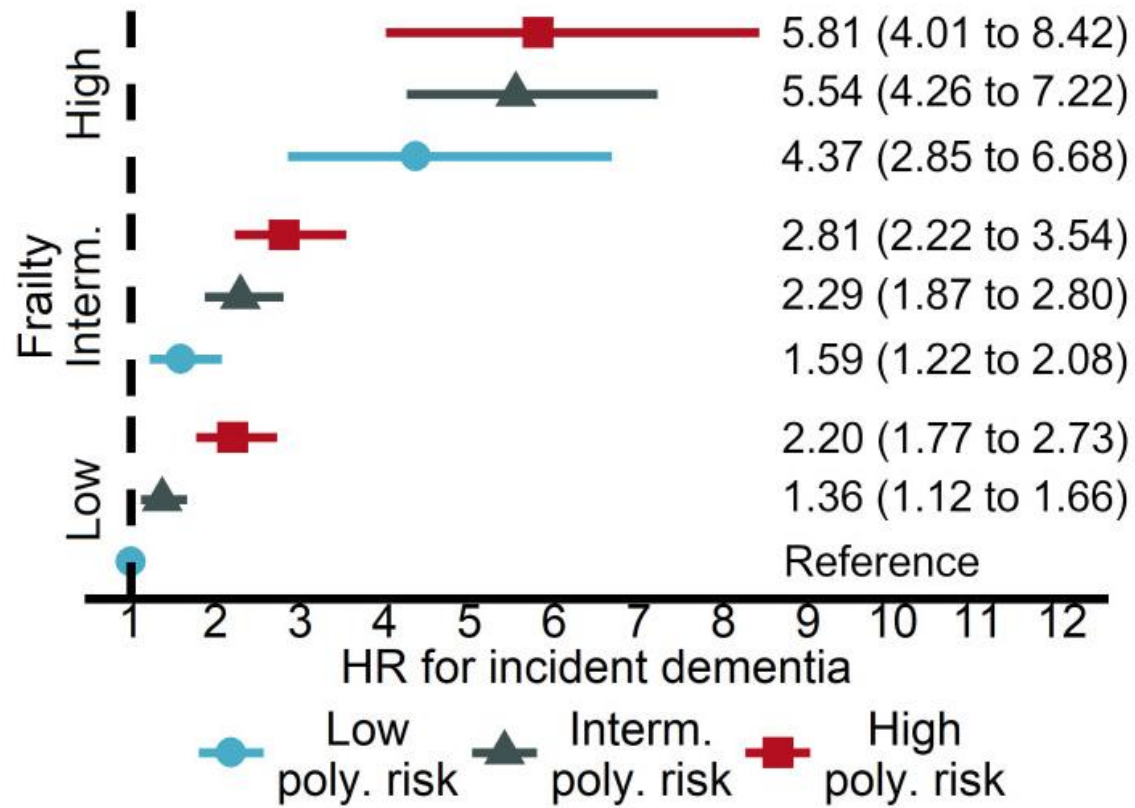


We need to know how frail someone is to understand whether and how they might develop dementia.

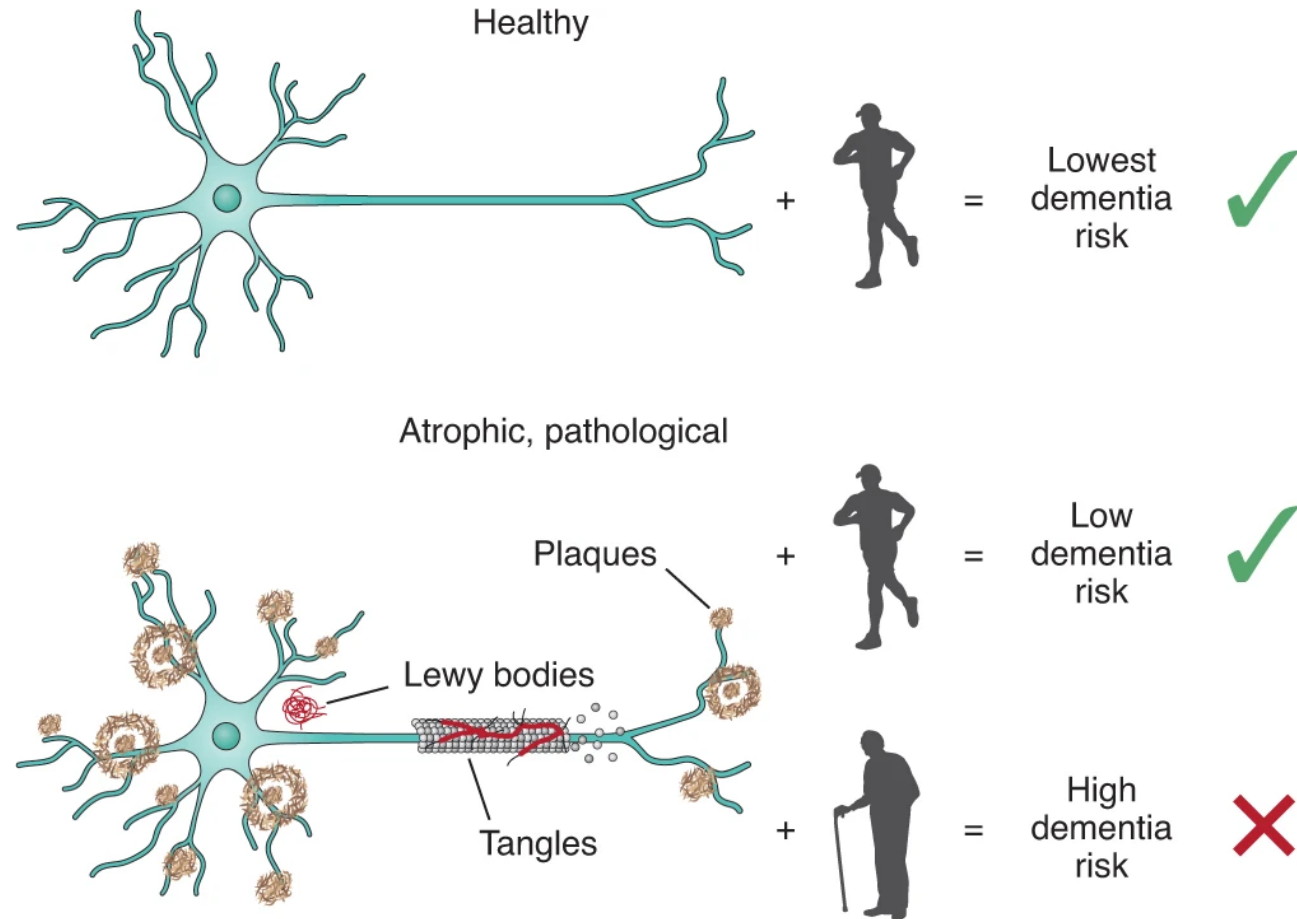


Higher frailty was associated with higher odds of dementia, especially in people with low Alzheimer's pathology.

Frailty moderates polygenic risk in late life dementia

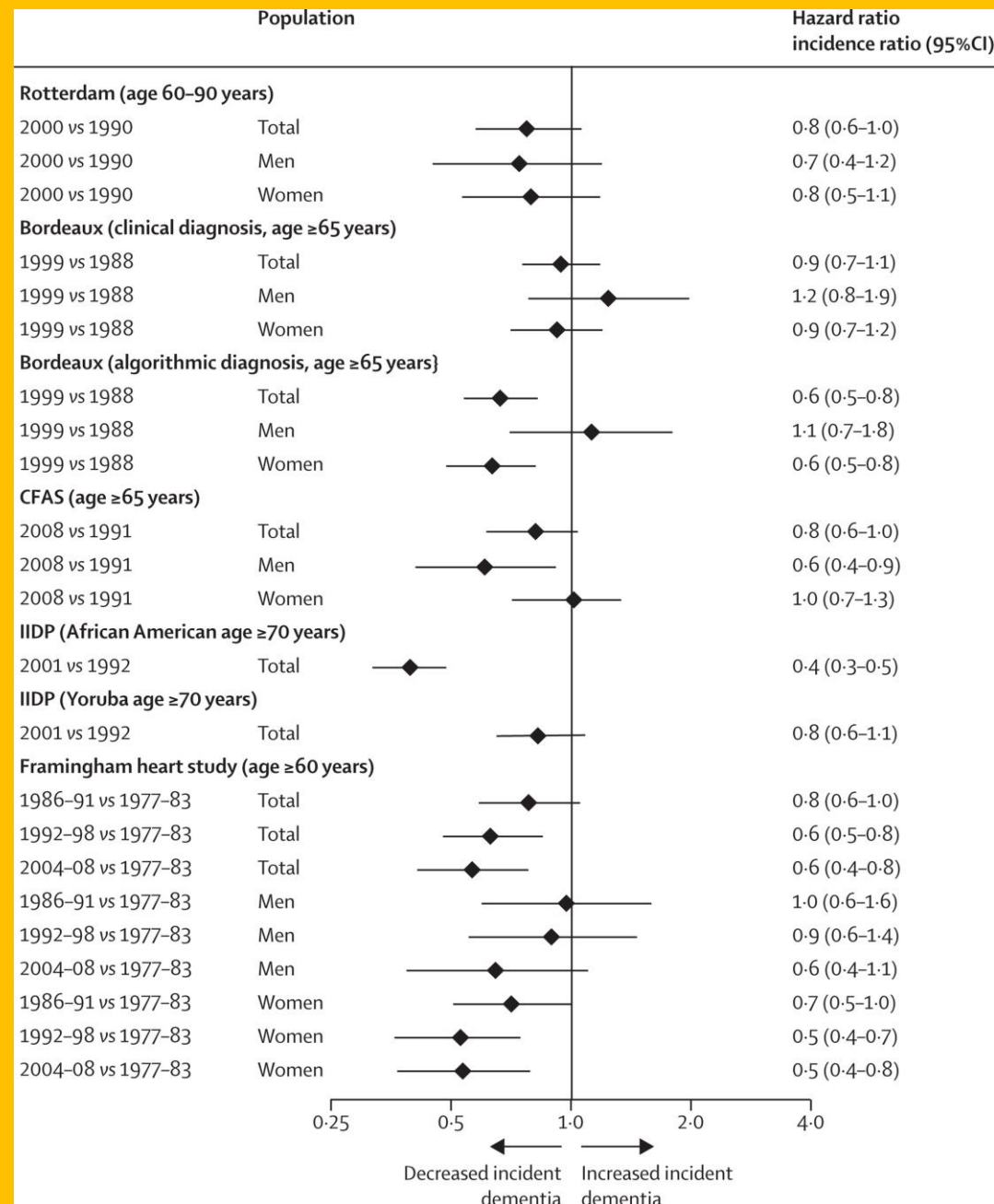


Frailty is not a disease, but it profoundly influences disease expression.



Song X et al. *Neurology* 2011;77:227-234.
 Rockwood K et al., *Nat Med* 2019;25:1331-1332.
 Wallace LMK et al., *Lancet Neurol* 2019;.
 Wallace LMK et al., *Neurology* 2020; 95:e3269-e3279
 Wallace LMK et al., *Int Psychogeriatr* 2021;33:1035-43.
 Ward DD et al., *Ann Neurol* 2021; 89:1221-1225
 Ward DD et al., *J Neurol, Neurosurg, Psychiatry* 2021;92:136-142.
 Ward DD et al., *J Neurol, Neurosurg, Psychiatry* 2022;93:343-350.

Dementia incidence appears to be falling worldwide, despite there being “no pharmacological disease-modifying treatment”.



Livingston G, et al., Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446. Erratum in: *ibid.* 2023;402:1132. PMID: 32738937



Effect of Antihypertensives on Incident Dementia: An individual participant data meta-analysis

Analysis	HR (95% CI)
Main analysis	
Treated HTN	1.13 (0.99-1.28)
Untreated HTN	1.42 (1.15-1.76)
Fully adjusted	
Treated HTN	1.04 (0.88-1.22)
Untreated HTN	1.37 (1.04-1.81)
>5 y follow-up	
Treated HTN	1.14 (0.97-1.35)
Untreated HTN	1.30 (0.97-1.76)



N= 34,519 community-dwelling adults aged 60+ years, from 17 studies.

How to prevent dementia.

Eat well.

Learn well (including maintaining hearing and eyesight).

Exercise.

Do it all in groups.

To prevent dementia, we must tackle frailty.

Intervention

Diet (more fruits & vegetables; fewer highly processed foods)

Diet Mediterranean

Physical Activity (higher vs none)

Social Prescribing

Treat Hypertension

Meta-analysis

Kojima et al., *J Frailty Aging* 2022;11:45-50.
Moderate certainty

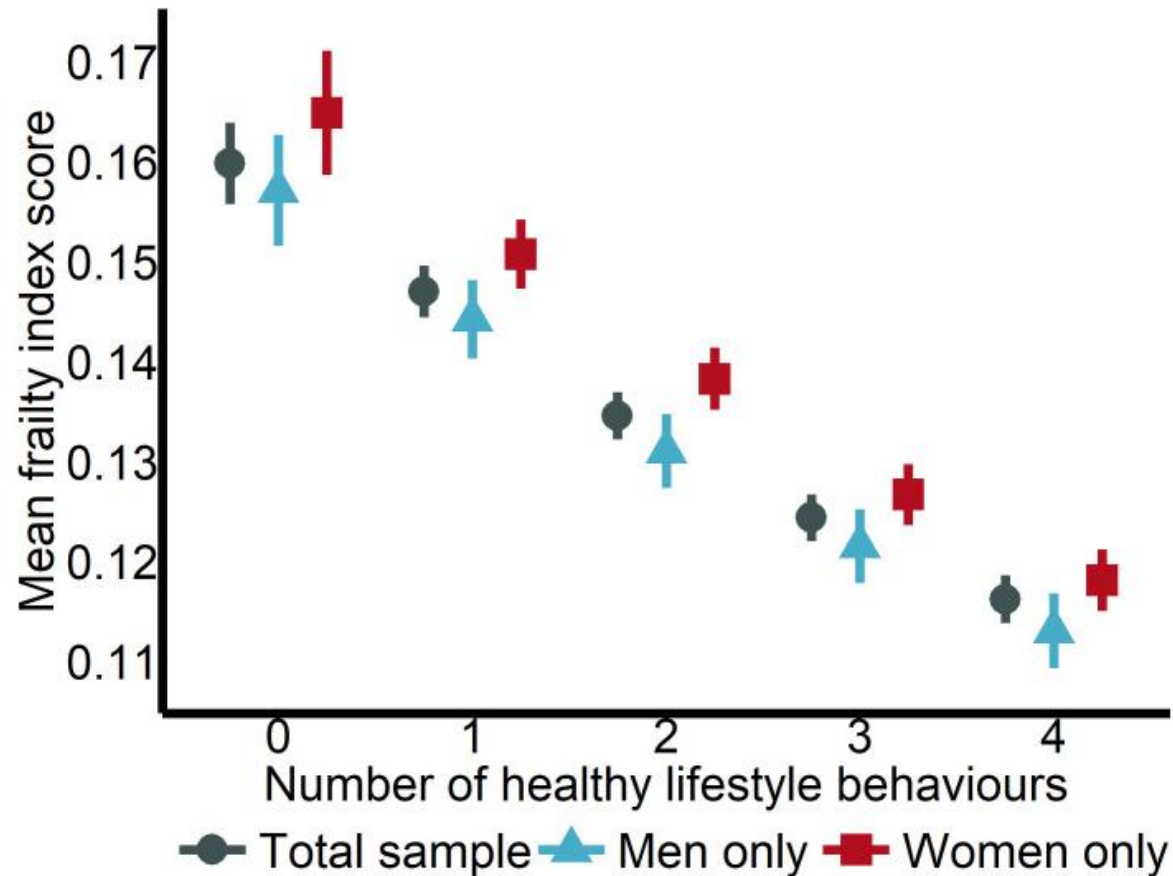
Poursalehi *et al.*, *Ageing Res Rev*; E-pub Mar5
Moderate certainty

Zhou *et al.*, *PLoS ONE* 2022;17:e0278226
moderate certainty

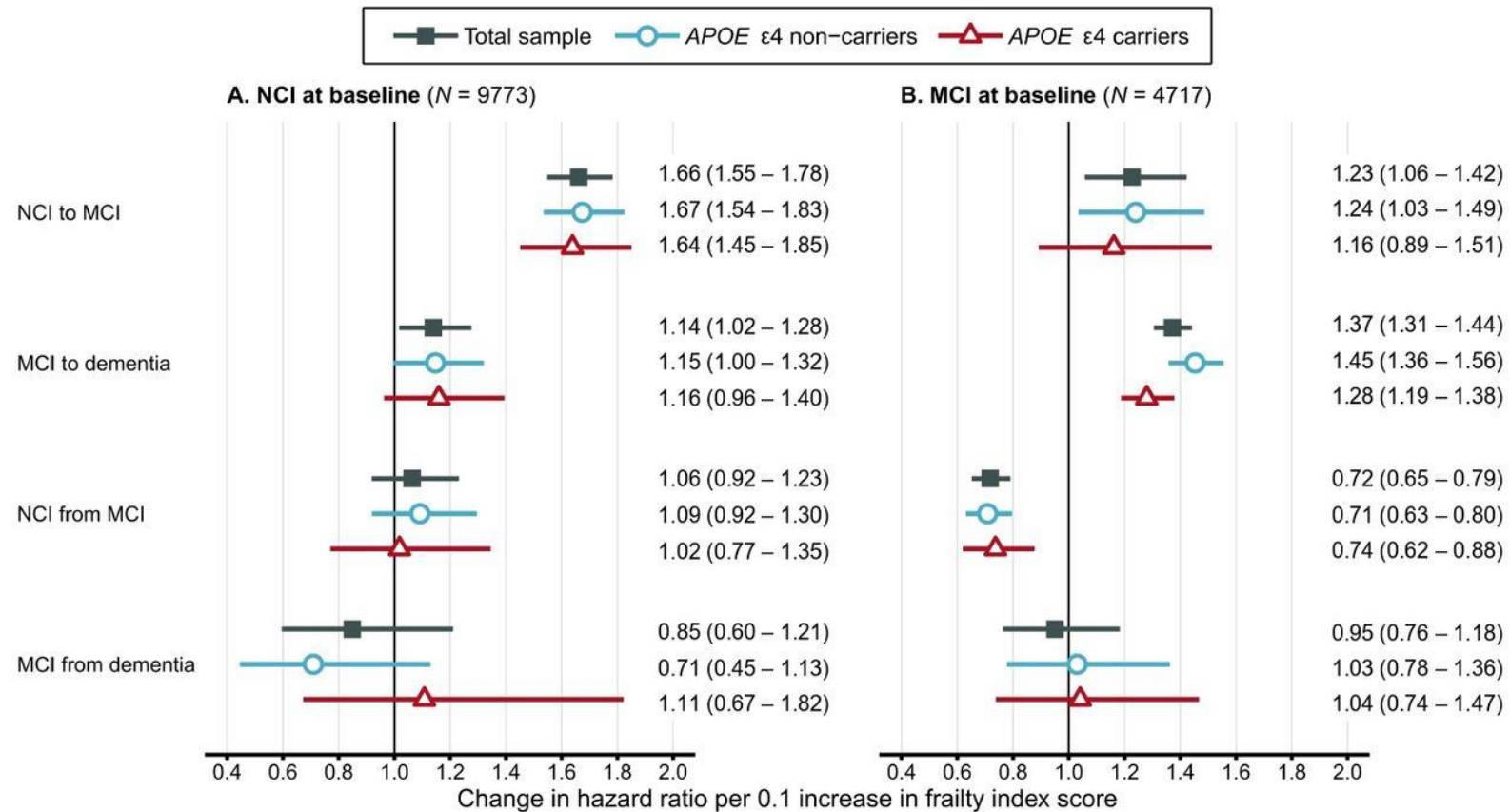
Huguet, et al., *Gerontology* **Single RCT**,
multicomponent

Tchalla et al., *Arch Gerontol Geriatr*
2023;114:10510 **Cohort study**

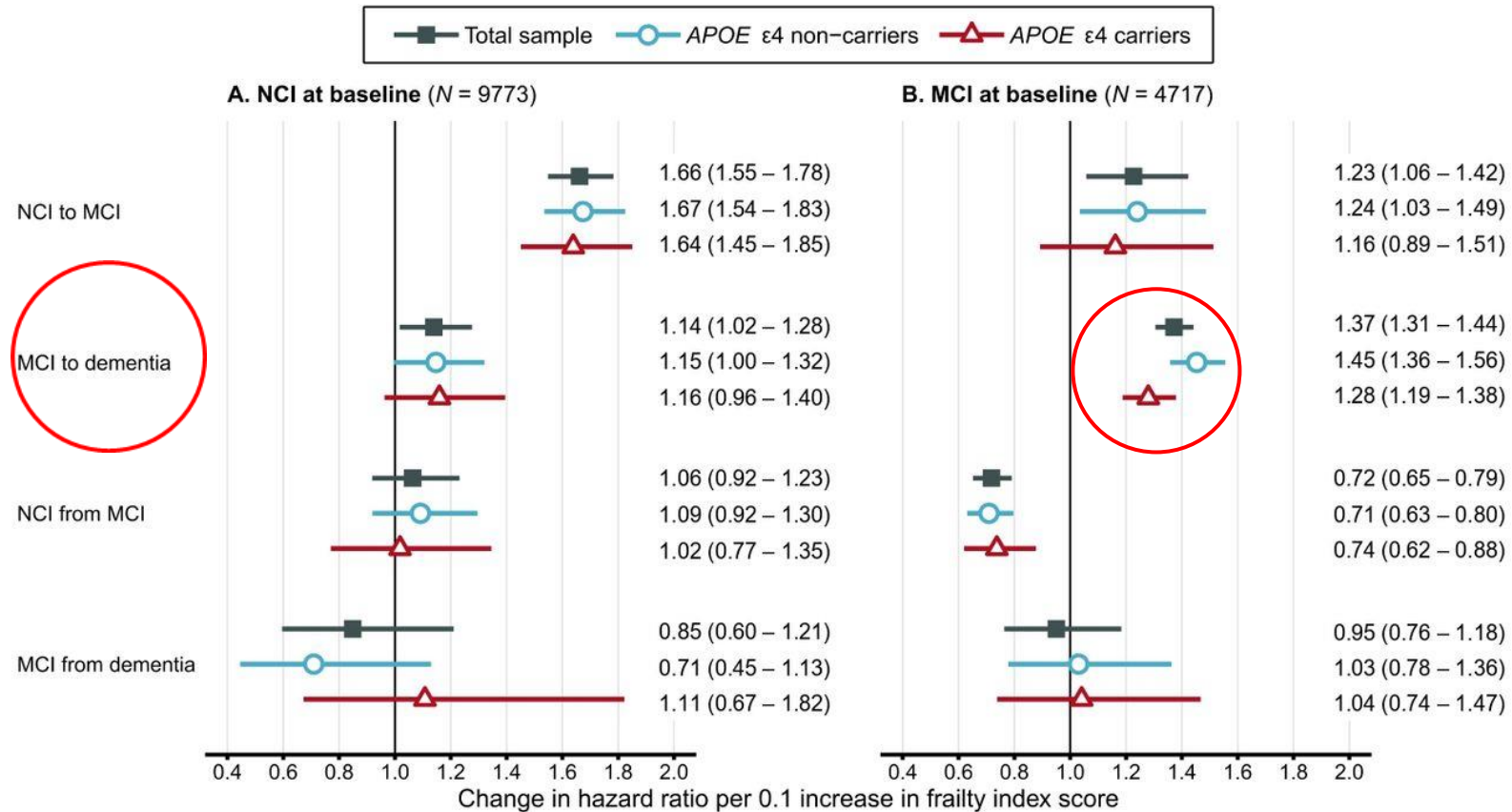
Frailty mediates the risk conferred by unhealthy lifestyle behaviours.



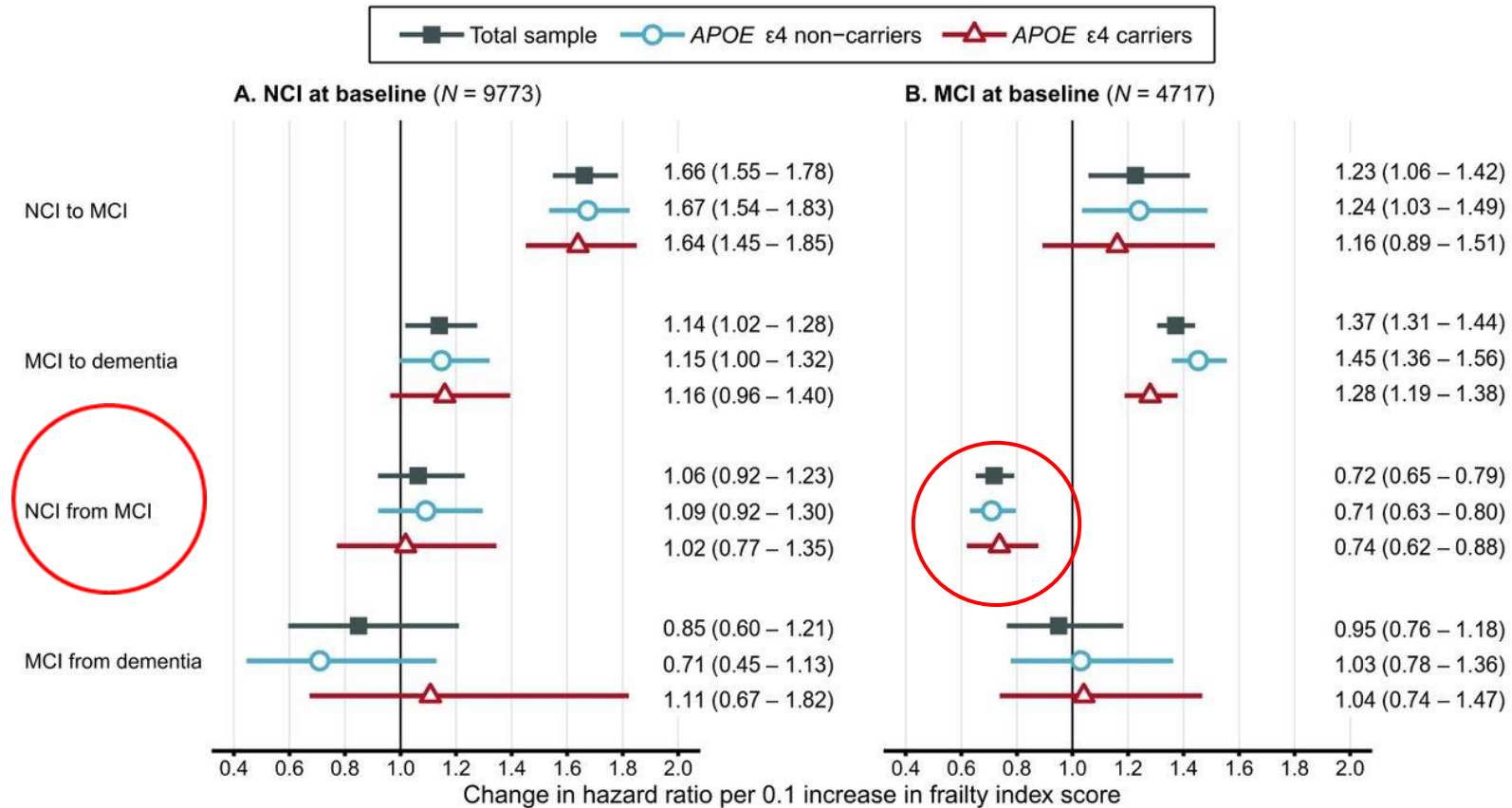
In clinical settings (esp. US) progression to MCI is more common than recovery to NCI, but in both directions, frailty / fitness are influential.



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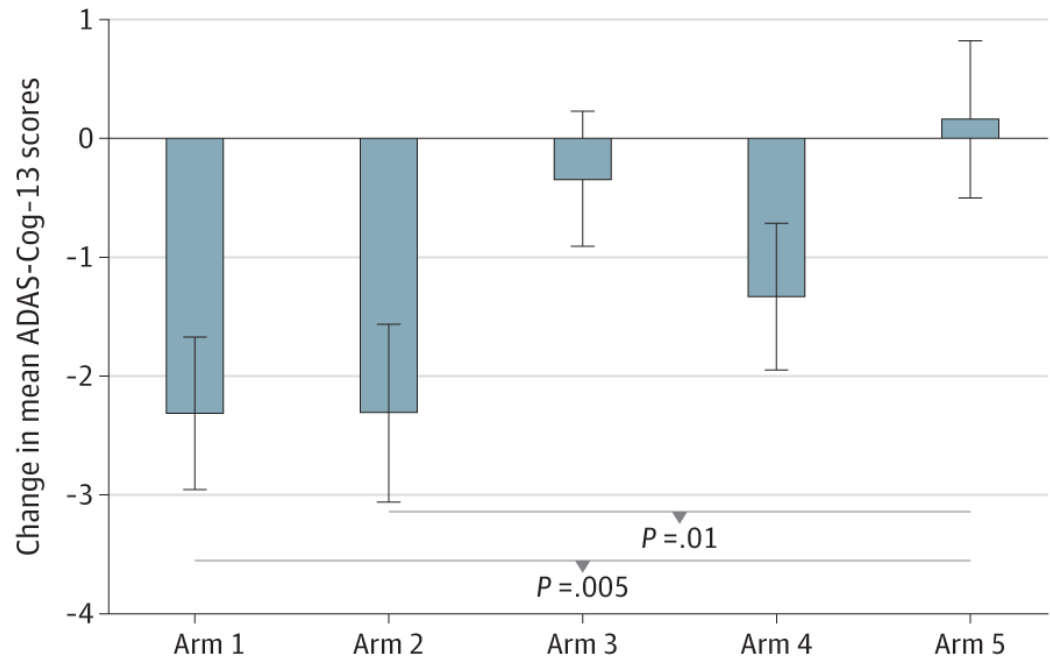




JAMA Netw Open. 2023;6(7):e2324465. doi:10.1001/jamanetworkopen.2023.24465

Synergic Trial

A Estimated mean change in ADAS-Cog-13 from baseline to 6 mo per group



Group changes in the ADAS-Cog Lower = better.

Exercise*
+ Cog training
+ Vitamin D

Exercise*
+ Cog Training
+ VitD
Placebo

Exercise*
+ sham
Cog training
+ VitD

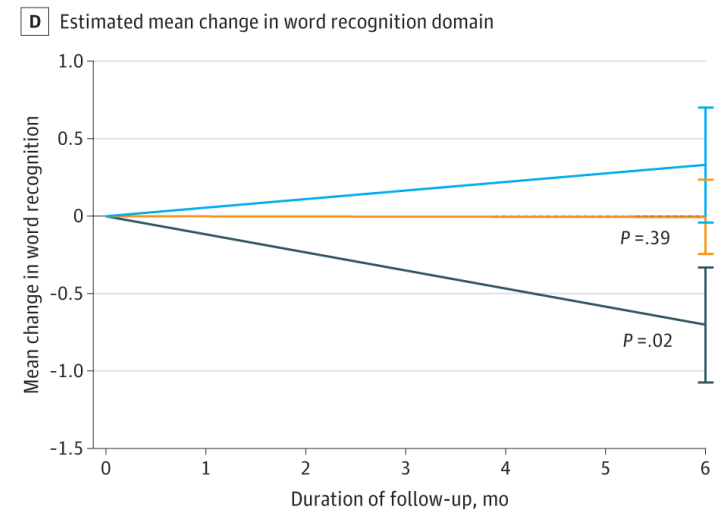
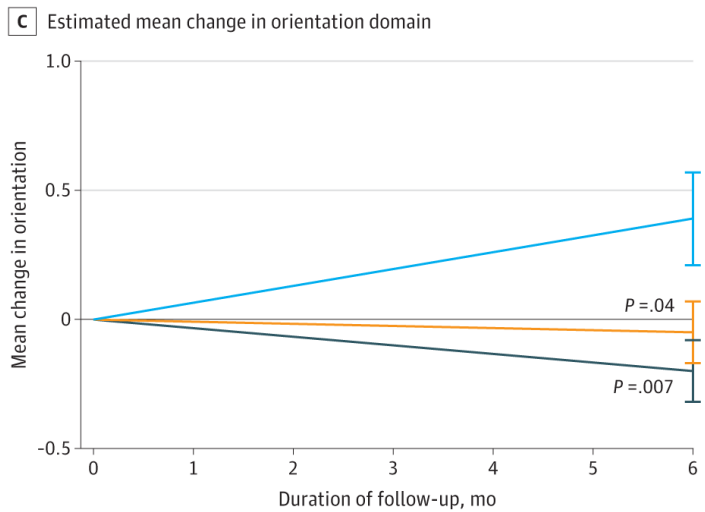
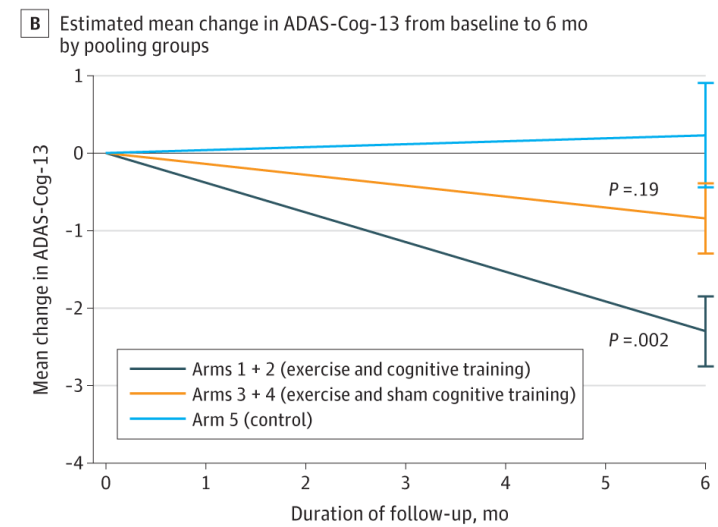
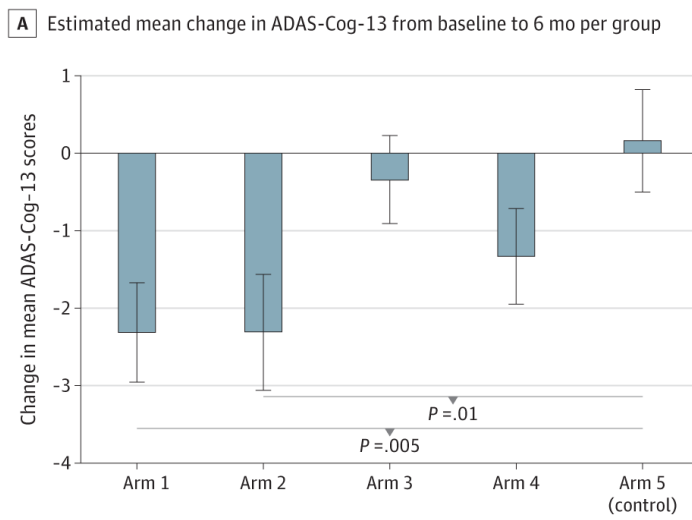
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Synergistic Trial



Dietary interventions

Often subject to co-intervention.

Confounded by factors that also increase risk (access, education, co-morbidities).

Tend to have unrepresentative populations.

Dietary benefits

Reduce calories from highly processed foods.

(all fast foods and candies, baked goods, chocolates, deli meats, ice cream, etc. etc.)

Everything else is controversial, including time-restricted eating. (Still, it works for many people.)

Exercise Benefit

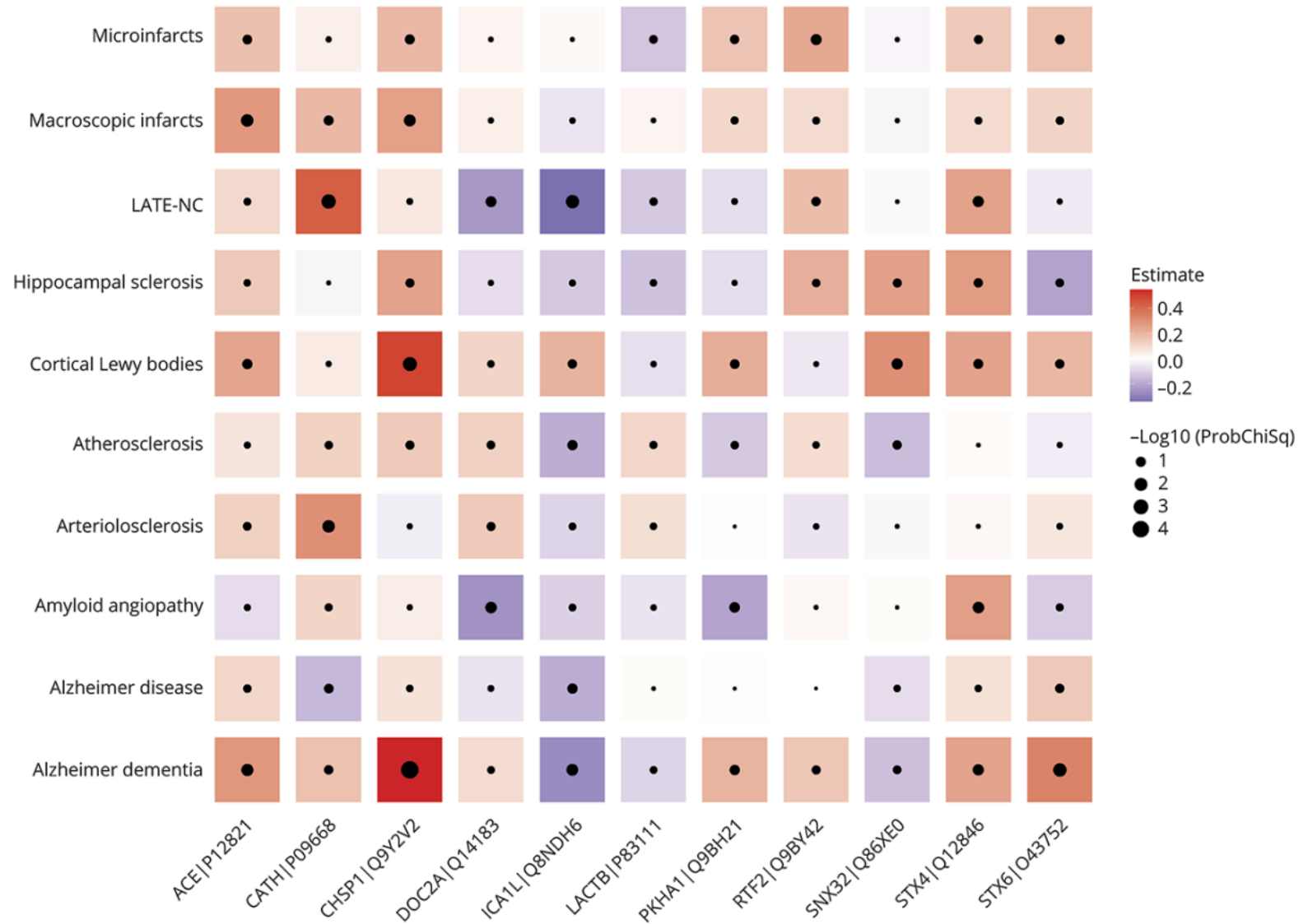
Most exercise benefit, including hippocampal growth (not just slowing of atrophy) comes from walking 50 minutes a day, five days a week.

Erickson et al., *Proc Natl Acad Sci USA*. 2011; 108: 3017-22.

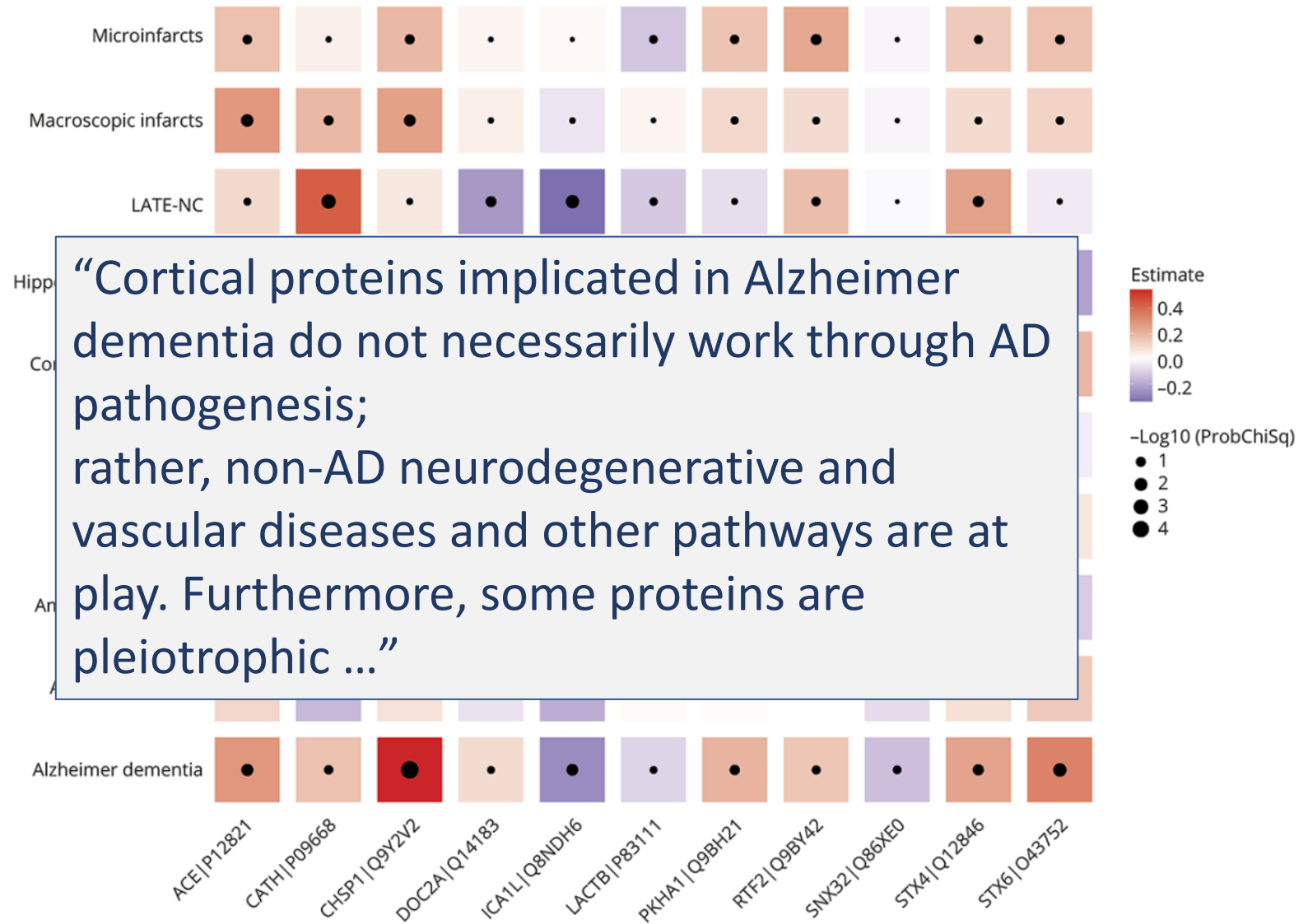
Most of that can be achieved at 30 minutes a day, three days a week, of moderately brisk walking.

Laurin et al., *Arch Neurol*. 2001; 58: 498-504.

**Yu L ... Bennett DA.
Neuropathologic
correlates of human
cortical proteins in
Alzheimer disease and
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Neurology. 2022;98(10):
e1031-e1039**



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Summary (1)

In MCI management, let's leverage the crucial role that frailty plays in genetic risk, biomarkers, and neuropathologic changes being expressed as multiply-determined, multifactorial, late-life dementia by lessening the frailty-related risk.

We can take our cue from Synergic, the most successful such study to date.

Summary (2)

MCI is non-controversially a risk for dementia.

Still, it is not destiny.

Community risk is different from clinic risk,
but we are seeing people in clinic.

Summary (2)

MCI is non-controversially a risk for dementia.
Still, it is not destiny.

Community risk is different from clinic risk,
but we are seeing people in clinic.

“Be ambitious about prevention”.

Still, aim for the 80/20: the maximum benefit
for the least effort.

Meet people where they are.

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