How has the COVID pandemic affected dementia research?

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Conflicts of interest

- Paid advisory board membership and speaker’s fees from
  - Biogen
  - Roche
  - Nutricia

Many angles to this:

- How has COVID 19 affected our patients and their detection/diagnosis?
  - Does Alzheimer's disease (AD) increase susceptibility to COVID 19 and morbidity from COVID 19?
  - Are risk factors for (more severe) COVID 19 also AD risk factors?
  - Does COVID 19 cause or accelerate cognitive decline in those with cognitive impairment, or in those who were cognitively normal?
  - Has the pandemic delayed diagnosis of those with dementia?
  - Has the pandemic worsened non-cognitive features of AD/other dementias?
  - Has the pandemic affected caregivers of those with dementia?
- How has the pandemic affected dementia research?
  - How has our research been impacted and how has it adjusted
  - And has there been any useful research during the pandemic?

AD and COVID 19- susceptibility and morbidity

- Post-mortem studies showed that ACE-2 expression is increased in the brain of AD patients in comparison to controls
- Additionally, genome-wide association studies (GWAS) showed that the expression of ACE-2 gene is elevated in the brain tissue of AD patients with increased levels in severe forms
- Thus, enhanced ACE-2 expression could represent a risk factor for COVID-19 transmission in AD patients.
- It has been postulated there is a direct link between AD and ACE-2 expression, mediated by oxidative stress

AD and COVID 19- susceptibility and morbidity

- Patients with cognitive impairment less likely to understand/adhere to social distancing
- And less likely to adhere to mask wearing/handwashing

AD and COVID 19- susceptibility and morbidity

- So any evidence that AD and other causes of cognitive impairment was indeed a risk factor for COVID 19?
  - ie independent of age?
- New York study[1], N=3,703 (202 with dementia-5.5%)
  - Dementia associated with increased risk of
    - Hospitalization (OR 8.77, 95% CI 5.45-14.14)
    - Death (OR 3.00, 95% CI 2020-4.08)
  - But decreased use of mechanical ventilation
    - OR 0.55, 95% CI 0.37-0.82.

1. J Med Virol 2021. https://doi.org/10.1002/jmv.26337

Conclusions/Discussion

“Dementia was associated with increased odds of hospitalization but, because patients with dementia are less likely to receive mechanical ventilation, dementia was associated with increased odds of death.

People with dementia are at increased risk of contracting COVID-19 for several reasons, including the inability to follow recommendations from public health authorities to reduce disease transmission, monitoring/reporting symptoms, and self-isolating at home.[22, 23]

Additionally, people with dementia often need supportive living environments (nursing homes) in which social distancing is difficult to maintain, therefore further increasing the risk of infection.[22]

Age is an established risk factor for both dementia and more severe COVID-19 and death.[22]

Dementia is also associated with multiple physical comorbidities, a risk factor for more severe disease. An additional risk factor associated with potentially more severe COVID-19 in patients with dementia is that hospitalization, a new environment, can lead to increased stress, behavioral problems, and delirium.[22, 23]

Another important factor affecting outcome is that many patients with dementia have “do not resuscitate” status. These patients therefore did not receive mechanical ventilation, which was shown by our data, resulting in poorer survival”.

Further evidence linking AD/dementia to COVID 19 risk

- A study examining COVID-19 deaths in the electronic health records of 17 million adults in the UK's National Health Service (NHS) suggests that people with dementia and/or stroke were at a higher risk of COVID-19 hospital deaths[1]
  - HR 2.34 (95% CI 2.18-2.51)

1. https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1.full.pdf

Dementia as a risk factor for mortality from COVID 19

- Meta-analysis: 7 studies
- N= 27,952
- Mean age range 67-86
- The pooled mortality rates of dementia and non-dementia older adults infected with COVID-19 were 39% (95% CI: 0.23–0.54%, I^2 = 83.48%) and 20% (95% CI: 0.16–0.25%, I^2 = 83.48%), respectively.

Saragih et al. Geriatric Nursing, accepted 14 March 2021

Are risk factors for (more severe) COVID 19 also AD risk factors?-APO E

- UK Biobank Community Cohort[1] (N=398,073 alive at time of analysis)
- 622 COVID positive (mean age 68)
  - Positivity rate 410/100,000 if E4/E4, compared to 179/100,000 if E3/E3
  - OR 2.31 (95% CI 1.65-3.24) for E4/E4 compared to E3/E3
  - EXCLUDING those with known dementia, OR 2.39 (95% CI 1.71- 3.35) for E4/E4 compared to E3/E3

1. J Gerontol A Biol Sci Med Sci, 2020, Vol. 75, No. 11, 2231–2232

ApoE e4e4 allele increases risks of severe COVID-19 infection, independent of preexisting dementia, cardiovascular disease, and type-2 diabetes.

ApoE e4 not only affects lipoprotein function (and subsequent cardio-metabolic diseases) but also moderates macrophage pro-/anti-inflammatory phenotypes.

APOE ε4 is associated with increased cytokine production in response to inflammatory stimuli, which could intensify the already aggressive inflammatory response associated with COVID-19, resulting in a so-called cytokine storm. The cytokine storm has been directly associated with lung injury, multi-organ failure and severe COVID-19 outcomes, including death

Another link with ApoE:

The novel coronavirus SARS-CoV-2 causing COVID-19 uses the ACE2 receptor for cell entry.

ACE2 is highly expressed in type II alveolar cells in the lungs, where ApoE is one of the highly co-expressed genes.

Are risk factors for (more severe) COVID 19 also AD risk factors?

- Other risk factors for COVID 19 and death from COVID 19 are also AD risk factors:
    - Age
    - Cardiovascular disease
    - Hypertension
    - Diabetes
    - Obesity

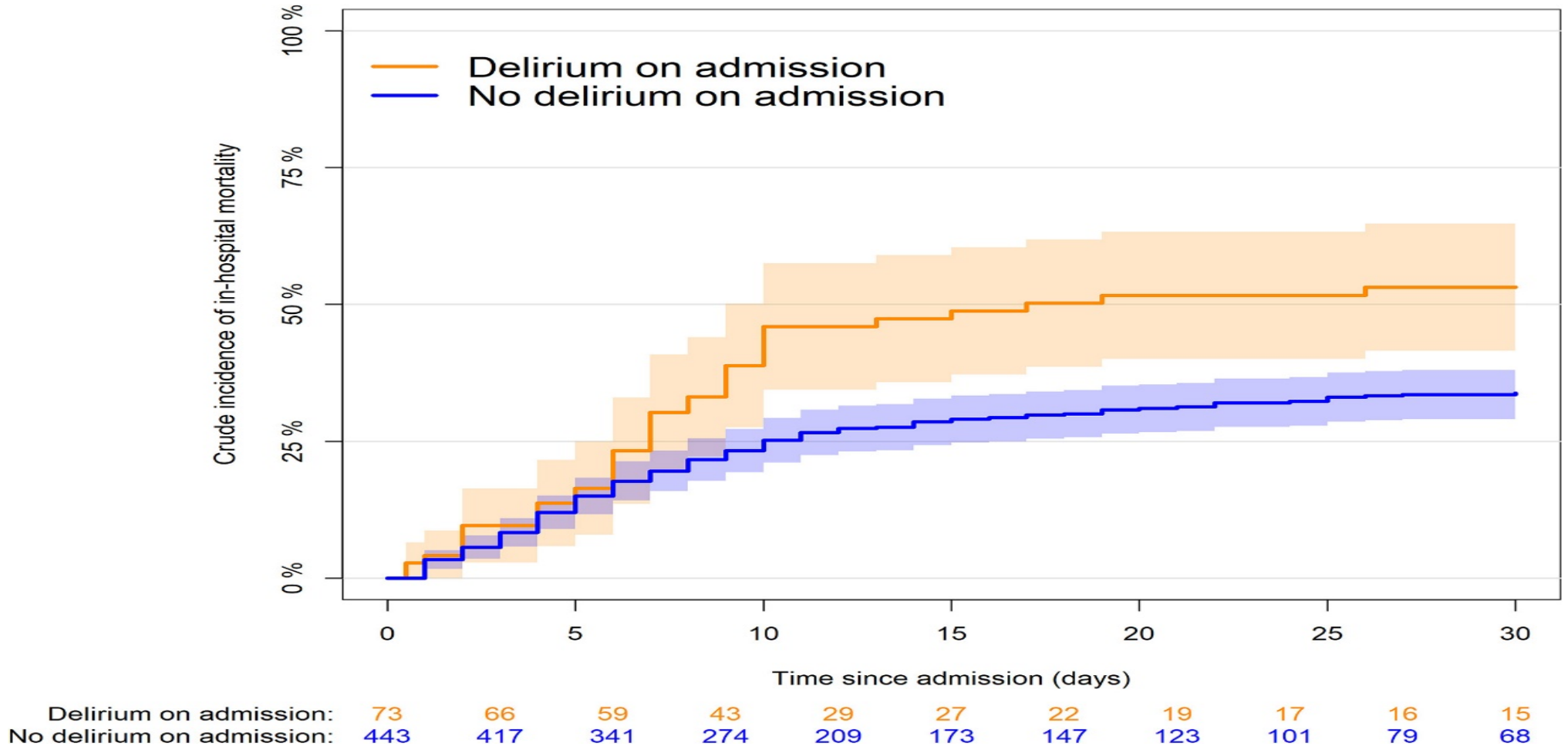
Does COVID 19 cause or accelerate cognitive decline in those with cognitive impairment, or in those who were cognitively normal?

- High levels of these cytokines, related to COVID 19, increase vascular permeability, edema, and widespread inflammation with consequent damage in cellular mechanism for energy production (mitochondria) and protein folding.
- Thus it is possible that by a direct biological effect, SARS-Cov2 could worsen brain function in all, but particularly those with already impaired brain function
- Also, SARS-Cov2, as well as other coronaviruses, can remain inside some neurons without being acutely toxic.
- This persistence can be linked to abnormal misfolding and aggregation of proteins in patients who survive and recover from their acute SARS-Cov2, and can thus theoretically lead to brain degeneration decades late.

In addition, delirium associated with SARS-Cov2 infection increases in-hospital mortality

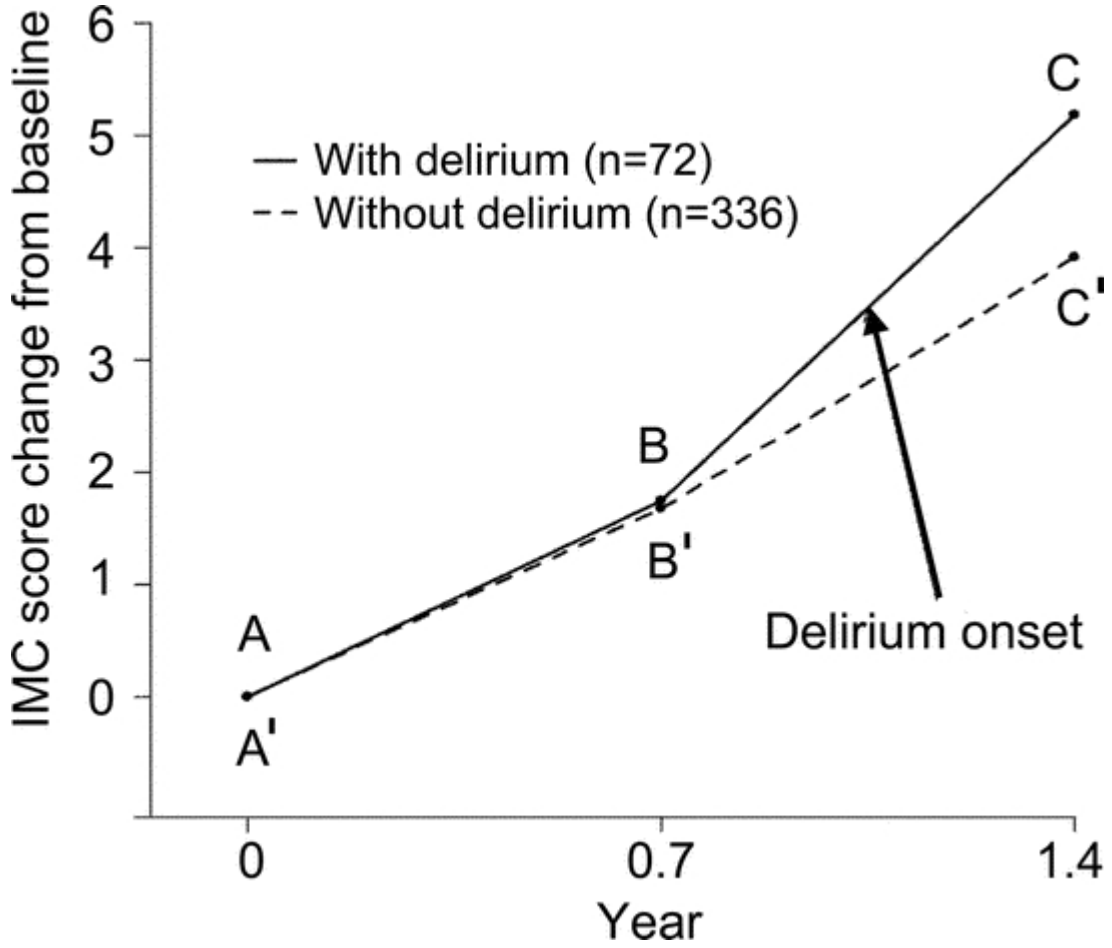
- As does all delirium
- And delirium is known to increase the risk of dementia and the rate of cognitive decline in those with dementia
  - Delirium damages the brain

Delirium in Patients with SARS-CoV-2 Infection: A Multicenter Study



Journal of the American Geriatrics Society, Volume: 69, Issue: 2, Pages: 293-299, First published: 27 November 2020, DOI: (10.1111/jgs.16969)

Cognitive trajectories of patients with Alzheimer disease with and without delirium



IMC= Information-Memory-Concentration subscale of Blessed Dementia Scale

Fong et al. Neurology 2009; 72:1570-5

Has the pandemic delayed diagnosis of those with dementia (and thus potential trial participants)?

- Undoubtably!
  - Already considerable delays (months to years from symptom onset)
    - 4.0 ±7.4 months (1.2 ±3.6 months if not referred to a secondary physician, and 5.3 ±8.3 months if referred)[1].
  - Numerous factors delayed diagnosis under the pandemic:
    - Less access the clinics/clinicians
      - Most memory clinics in Melbourne closed for many months
      - So too the St James memory clinic in London
      - Likely elsewhere too
    - Patient/carer reluctance
    - Clinician reluctance/furlow/redeployment
    - Not seen as a health priority
- Consequences
  - Less access to targeted health care
  - Less access to supports
  - Increased caregiver burden

1. Black, Woodward et al. International Psychogeriatrics 2019

Has the pandemic worsened non-cognitive features of AD/other dementias?

- Many factors at play:
  - Loss of routine
  - Loss of visits by family/friends in lockdown
  - Reduced visits by support services
  - Less access to external supports/respite
  - Limited ability to exercise
    - eg 5km rule and curfew in Melbourne
  - Caregiver burden

Has the pandemic worsened non-cognitive features of AD/other dementias?

- In a Spanish study[1], 40 subjects diagnosed with MCI (20) or mild AD (20) who had performed neuropsychological and clinical assessment during the month prior to the lockdown were re-evaluated after 5 weeks of social isolation via the neuropsychiatric scale (NPI) and EuroQol- 5D.
- The total basal NPI score worsened by about 6 points, from 33.75 to 39.05 after confinement, with the appearance of various neuropsychiatric symptoms including apathy and anxiety in subjects with MCI and apathy, agitation, and aberrant motor behavior in AD patient.

1. Lara BB, Carnes A, Dakterzada F et al (2020).
Neuropsychiatric symptoms and quality of life in Spanish Alzheimer's disease patients during COVID-19 lockdown.
Eur J Neurol. https://doi.org/ 10.1111/ene.14339

Depression and Anxiety during the lockdown

- Isolation and loss of usual routine contributed
- Fifty-eight participants with AD in French Retirement Homes consented to participate in the study[1].
- The participants rated their depression and anxiety during and before the Covid-19 crisis.
- Participants reported higher depression ($p = .005$) and anxiety ($p = .004$) during than before the Covid-19 crisis.

1. Psychiatry Research 291, 2020. https://doi.org/10.1016/j.psychres.2020.113294

Has the pandemic affected caregivers of those with dementia?

- This works both ways
  - Harder if the person with dementia was at home
    - Loss of usual activities outside the home
    - Isolation
    - Increased “responsive behaviours”
  - If the person with dementia was in RCF
    - Less ability to visit had some positive effects
    - Generally however very difficult
      - esp when there was an outbreak in RCF
        - Limited information
        - Fear (well founded!) their loved one was not being cared for

Has the pandemic affected caregivers of those with dementia?

- In a (Greek) community caregiving study[1] (N=67):
- Caregiver distress severity during the confinement (lockdown) period was influenced by memory deficits ($p = 0.009$) and neuropsychiatric symptoms ($p < 0.001$) of patients
- Also by caregiver hyperarousal ($p = 0.003$) and avoidance symptoms ($p = 0.033$) and worries directly linked to the COVID-19 crisis ($p = 0.022$).
- So both patient AND caregiver attributes affected caregiver burden

1. Alexopoulos et al. COVID-19 Crisis Effects on Caregiver Distress in Neurocognitive Disorder. J Alz Disease 2021.

Has the pandemic affected caregivers of those with dementia?

- Several recent studies have demonstrated increased caregiver burden during COVID lockdown/restrictions
  - Study of 58 dyads living at home in Brazil [1]
    - Increased caregiver burden/psychological distress and worsening of cognition in the people with dementia
      - And there was a correlation between these
  - Study of 389 caregivers living at home with people with dementia in France [2]
    - Poorer mental health (depression, anxiety, perceived burden) in the caregivers and worsened behavioural and psychological symptoms (BPSD) in those with dementia
      - And, again, a correlation between these

1. Borelli et al. JAD. Epublished Feb 2021
2. Pongan et al. JAD. Epublished Feb 2021

How has the pandemic affected dementia research?

- Yes, but compared to rest of world we have been somewhat spared
- Issues
  - Patients and study partners not willing to volunteer for trials that require them to leave home
    - Or to continue in trials that require such visits
  - Staff redeployed and unavailable for research assessments
    - Doctors and others
  - Facilities prohibiting non- essential visits
    - Our HREC put a halt on all new trials and new randomizations for existing trials
    - Affected monitors too
  - Subjects, study partners and staff becoming infected or furlowed
  - Missing data, data not reviewed so not corrected
  - Trial integrity compromised by less recruitment, loss of subjects, loss of data

Has there been useful dementia trials research during the pandemic?

- Most DTAus sites have continued existing trials and commenced new trials at the same rate
- Recruitment may have been impacted
- Site monitoring has been impacted

Ways to adjust research in a pandemic

- Remote cognitive assessments
  - MoCA can be validly administered remotely
    - Hantke NC, Gould C. Examining older adult cognitive status in the time of COVID-19. J Am Geriatr Soc. 2020;68(7):1387-8. http://doi.org/10.1111/ jgs.16514
  - Others: CDR vital as usually the primary outcome
    - Reliability of remote neuropsychological assessment has been established
      - Marre DE, Hamlet KM, Bauer RM, Bowerd D. Validity of teleneuropsychological assessment for older adults in response to COVID 19. Clin Neuropsychol.2020;9:1042.
- Develop new assessment tools/instruments
  - But be careful: Booth T, Murray A, MunizTerrera G. Are we measuring the same thing? Psychometric and research considerations when adopting new testing modes in the time of COVID-19. Alzheimer's Dement 2021; 17: 251-254.
- Remote administration of IP and in-home assessments
  - Home nursing used extensively in Roche and other trials
  - But some participants love coming to site (and for some their only outing!)
- Streamline assessments and skip non-essential ones
- Extend trial duration to reduce the loss of power

But patient (and staff) safety remains the priority

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, Megan E. O'Connell, John D. Fisk, Serge Gauthier, Richard Camicioli, Zahinoor Ismail, for the Alzheimer Society of Canada Task Force on Dementia Care Best Practices for COVID-19
Alzheimer Dement 2020, DOI: 10.1002/dad2.12111

- Reviewed a range of cognitive assessment scales
  - Across numerous domains
    - Attention
    - Executive
    - Memory
    - Language
    - Visuospatial
    - Social cognition
  - Administration time
  - Whether in public domain
  - Whether suitable for telephone or telemedicine
  - Final recommendation (use or don't use)
- Reviewed remote computerized assessments
- Also reviewed remote assessment of affect, behavior and function

Remote assessment- Canadian Taskforce

- A number of issues limit telemedicine implementation.
- In all cases, an assessment of the videoconferencing readiness of the patient should be completed before deciding to engage in remote dementia care.
- There are numerous questions that must be addressed:
  - Where will the videoconferencing occur?
  - Is the environment sufficiently free of distractions and orientation cues that render tests invalid?
  - Does the patient's condition make them more susceptible to distractions in a non-controlled environment?
  - Do they have sensory impairments that contraindicate telephone or videoconferencing?
- Even if videoconferencing appears clinically indicated, remote training for patients and families in how to use the videoconferencing platform for remote healthcare visits may be required, and alternative methods for contacting patients in the event of technological failure are necessary.
- Home environments for remote assessments are by nature variable, making consistency of assessments across patients, and across visits with the same patient longitudinally, challenging.
- Identification of clinical meaningful change in the telemedicine environment is, therefore, difficult.
- So too, is the assessment of key aspects of mental status or patient behavior such as body language conveying affect and informant or patient discomfort

What useful dementia research findings have surfaced in 2021/22?

- Blood based biomarkers shown accurate
  - p-tau181
    - blood-based p-tau181 can predict tau and amyloid β neuropathology, differentiate Alzheimer's disease from other neurodegenerative disorders, and identify Alzheimer's disease across the clinical continuum
      - Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol 2020; 19: 422–33.
  - p-tau287
    - good ability to differentiate clinically diagnosed Alzheimer's disease from other neurodegenerative conditions, and it differentiated individuals with Alzheimer's disease neuropathology from those without diagnostic levels of Alzheimer's disease neuropathology, either by post-mortem analysis or by neuroimaging and CSF analysis. In the same study, the diagnostic accuracy of p-tau217 was superior to that of other Alzheimer's disease biomarkers, including plasma p-tau181, plasma neurofilament light chain, and structural neuroimaging
      - Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 2020; 324: 772–81
  - Amyloid still controversial

2020/2021 dementia research

- Lipidomics
  - Another promising study of blood-based biomarkers aimed to map the complexity of Alzheimer's disease pathophysiology by describing changes in "omics" profiles.
  - A lipidomic analysis was done that included individuals from two longitudinal cohorts with normal cognition, mild cognitive impairment, or dementia due to Alzheimer's disease. Lipid signatures were associated with prevalent and incident Alzheimer's disease.
  - Replicability of these findings will be crucial to validate such an approach. Nonetheless, advances in identifying and validating blood-based biomarkers for early detection of pathology are important to identify people at risk of dementia, who can be enrolled in trials aimed at preventing or delaying dementia onset
    - Huynh K, Lim WLF, Giles C, et al. Concordant peripheral lipidome signatures in two large clinical studies of Alzheimer's disease. Nat Commun 2020; 11: 5698

2020/21 dementia research

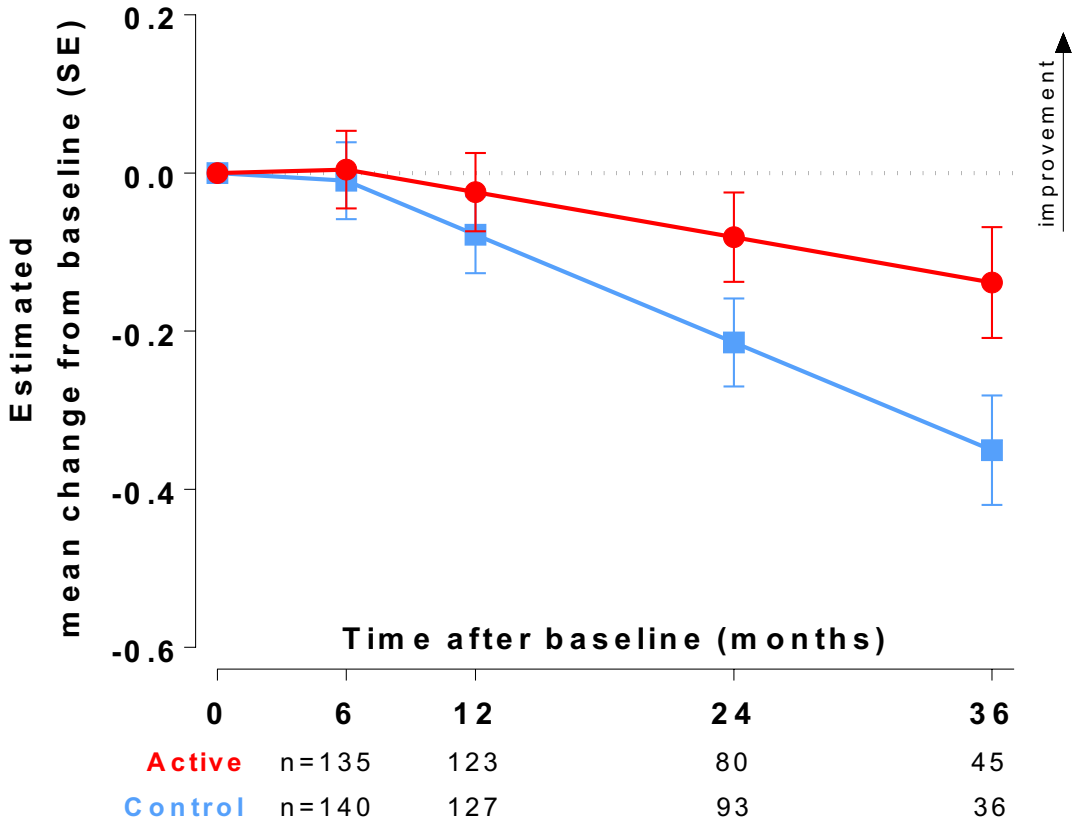
- With respect to **dementia prevention through nonpharmacological interventions**, encouraging news has come from the LipiDiDiet trial, in which a nutritional intervention was tested in 311 individuals with prodromal Alzheimer's disease.
- Results of 36-months' follow-up showed amelioration of global cognition and function and a slower rate of both whole-brain and hippocampal atrophy. LipiDiDiet is a trial model suggesting that early and long-term interventions could be effective in improving cognitive trajectories in individuals with Alzheimer's disease pathology.
- The trial findings also show the role of adequate nutrition in individuals at risk of dementia, a population in whom it can be difficult to achieve sufficient intake of nutrients.
  - Soininen H, Solomon A, Jelle Visser P, et al. 36-month LipiDiDiet multinutrient clinical trial in prodromal Alzheimer's disease. Alzheimers Dement 2020; published online Sept 13. https://doi.org/10.1002/alz.12172

LippiDiDiet-NTB 5-item composite & NTB memory

Benefit over 36 months

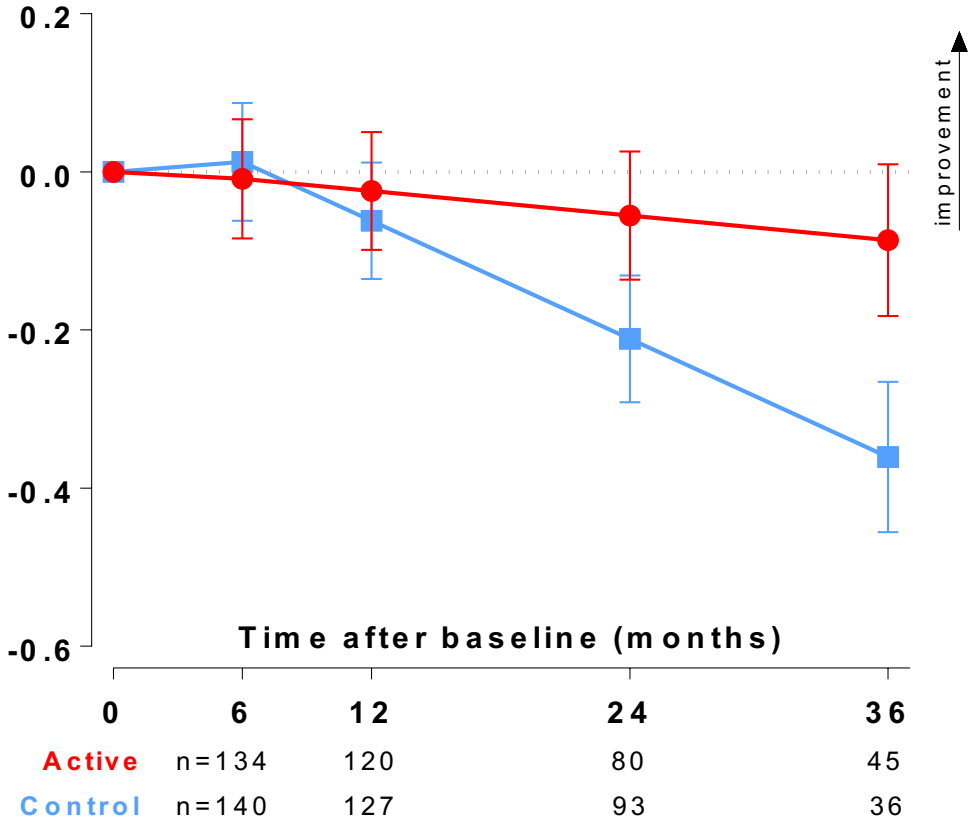
NTB 5-item composite (z-score)

p value: 0.014
slope reduction: 60%
Cohen's *d*: 0.26



NTB memory (z-score)

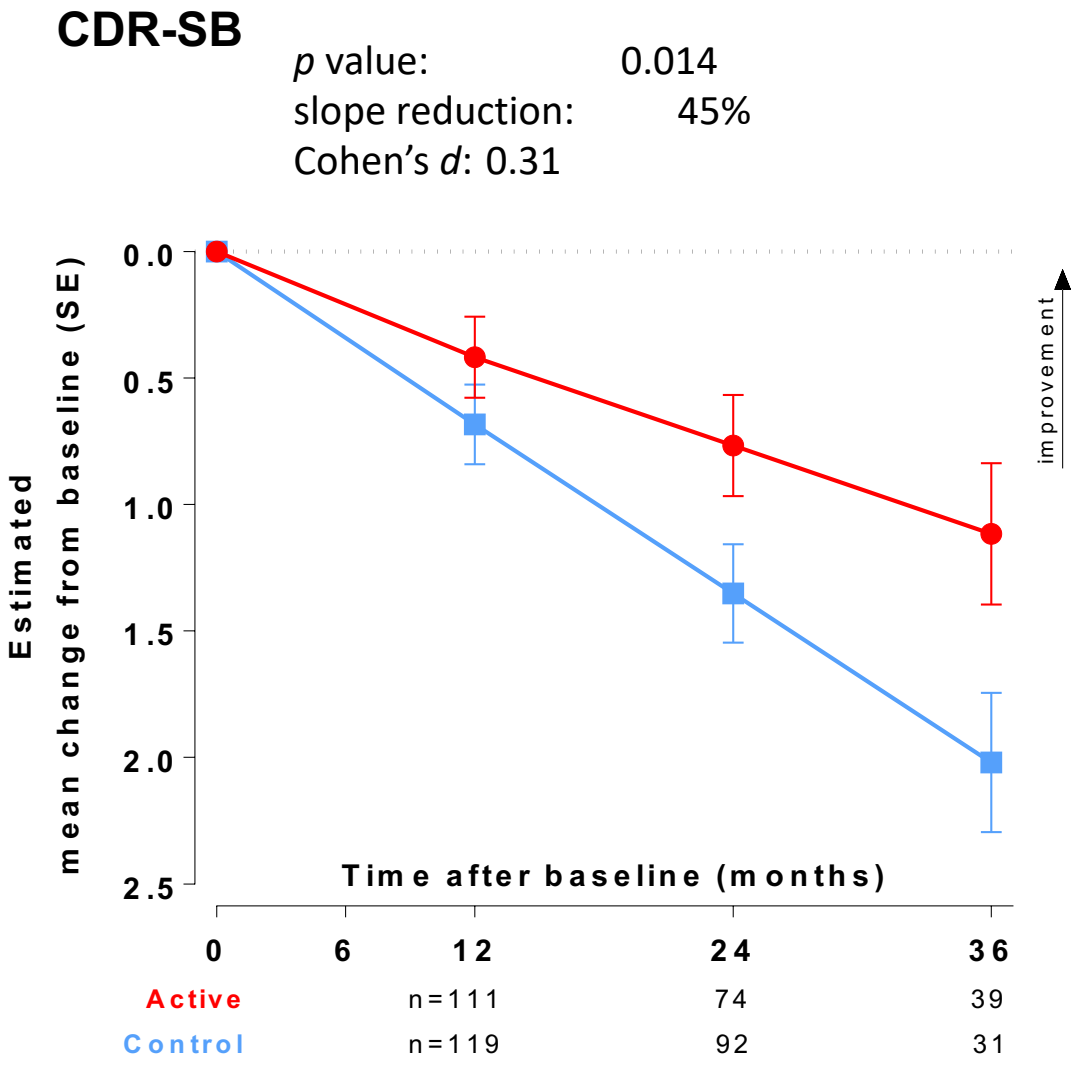
p value: 0.008
slope reduction: 76%
Cohen's *d*: 0.25

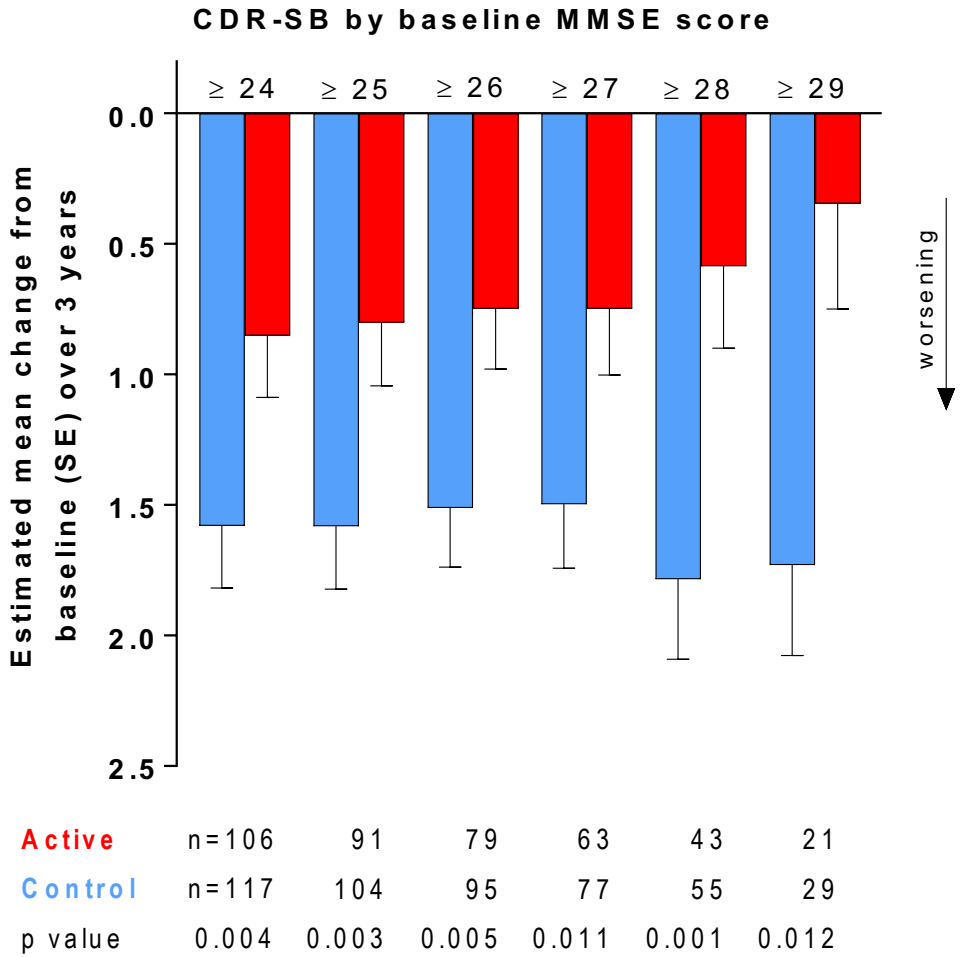


Soininen *et al.* 2020 Alzheimer's & Dementia

P value for linear mixed model for longitudinal data as before (Soininen et al, 2017. Lancet Neurol.) Slope reduction based on estimated mean change from baseline in each group. NTB: neuropsychologica

LippiDiDiet: Clinical Dementia Rating scale - Sum of Boxes





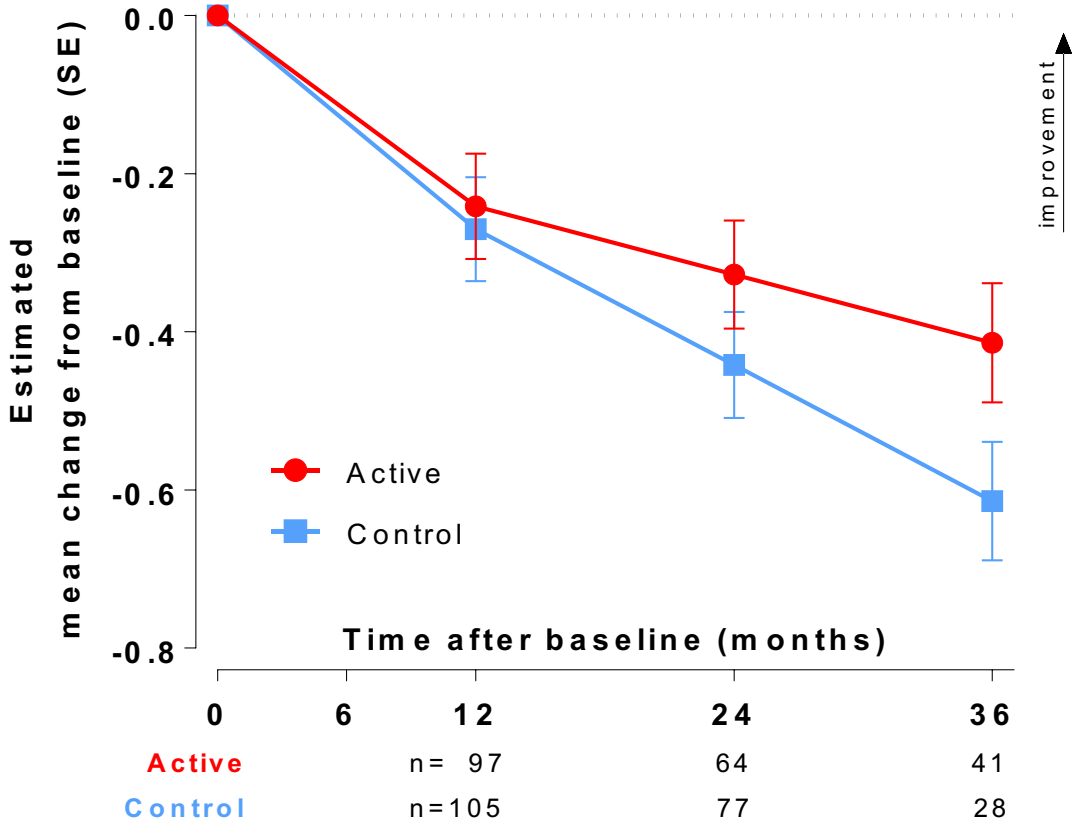
Soininen *et al.* 2020 Alzheimer's & Dementia

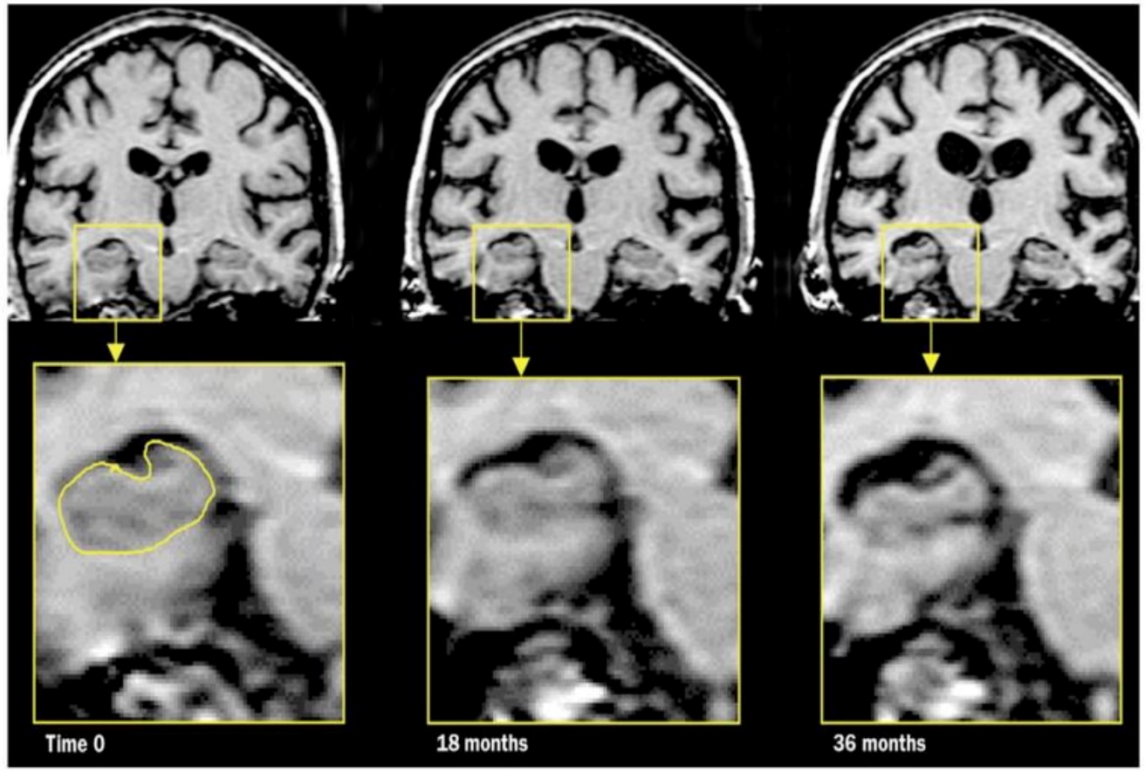
P value for linear mixed model for longitudinal data as before (Soininen et al, 2017. Lancet Neurol.); Slope reduction based on estimated mean change from baseline in each group. CDR-SB: Clinical Dementia Rating - Sum of Boxes | SE: standard error.

LippiDiDiet: MRI hippocampal volume

Reduced progression of hippocampal atrophy over 36 months

p value: 0.002
slope reduction: 33%
Cohen's *d*: 0.27





Scheltens et al.

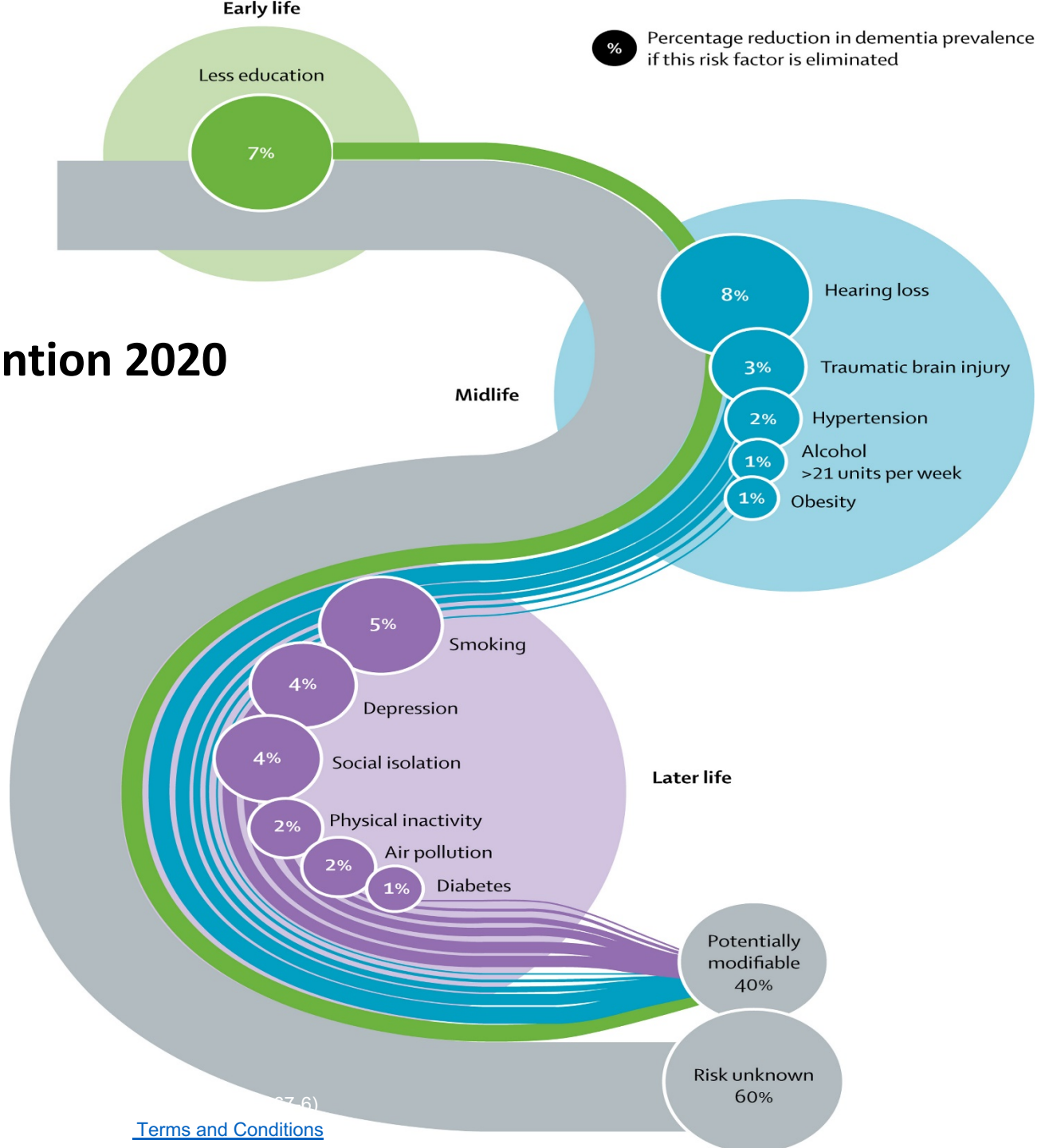
Soininen *et al.* 2020 Alzheimer's & Dementia

P value for linear mixed model for longitudinal data as before (Soininen et al, 2017. Lancet Neurol.); Slope reduction based on estimated mean change from baseline in each group. MRI: magnetic resonance imaging | Units cm^3 | SE: standard error.

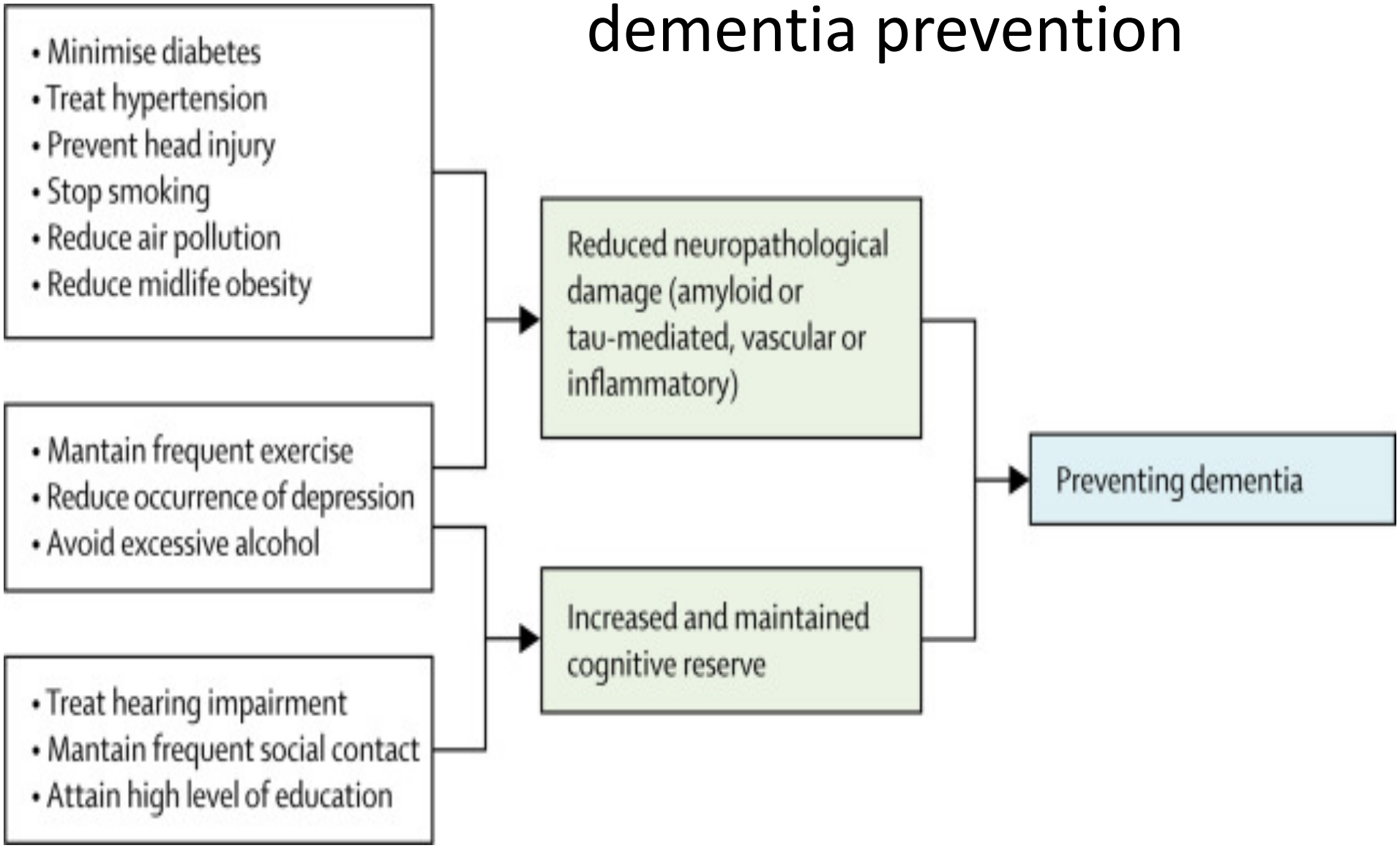
2020/21 dementia research

- In the context of **dementia prevention**, the 2020 Lancet Commission on Dementia prevention, intervention, and care identified 12 modifiable factors that can be targeted to reduce risk.
- These factors include diabetes, mid-life hypertension and obesity, physical inactivity, smoking, low education, hearing loss, traumatic brain injury, excessive alcohol consumption, social isolation, depression, and air pollution.
- Compared with the findings reported in the 2017 Lancet Commission, three additional factors have been added, and the estimated proportion of preventable cases has increased from 35% to 40%, indicating that we can be more optimistic on prevention opportunities
  - Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017; 390: 2673–734.

Lancet Prevention 2020



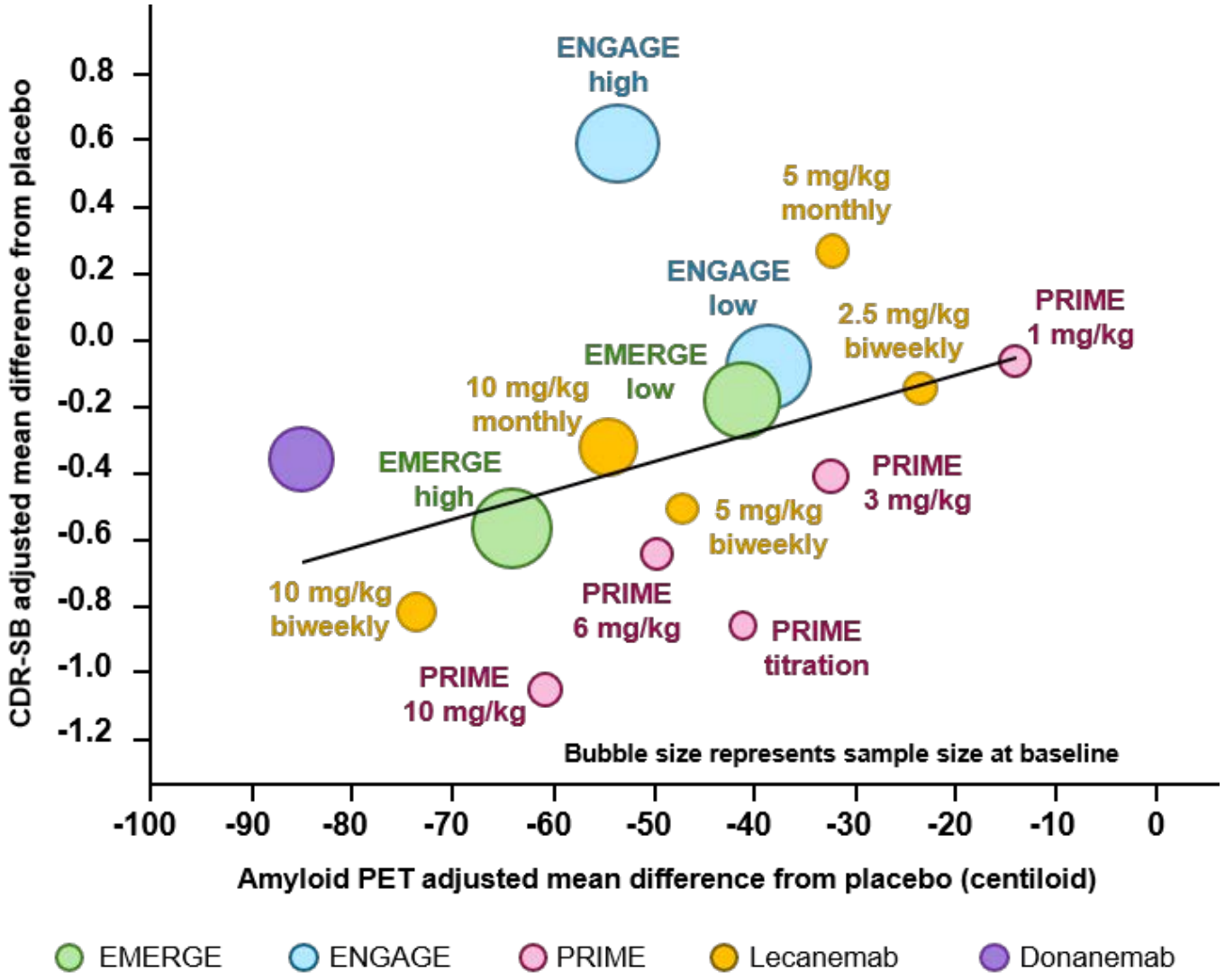
A theoretical approach to dementia prevention



Maybe the biggest research breakthrough EVER in our field- the first disease modifying drug for AD

Biogen 2021

Reduced brain amyloid correlates with less decline on CDR-SB with monoclonal antibodies targeting aggregated Aβ



Trials of different therapeutic agents were not designed to be compared head to head.

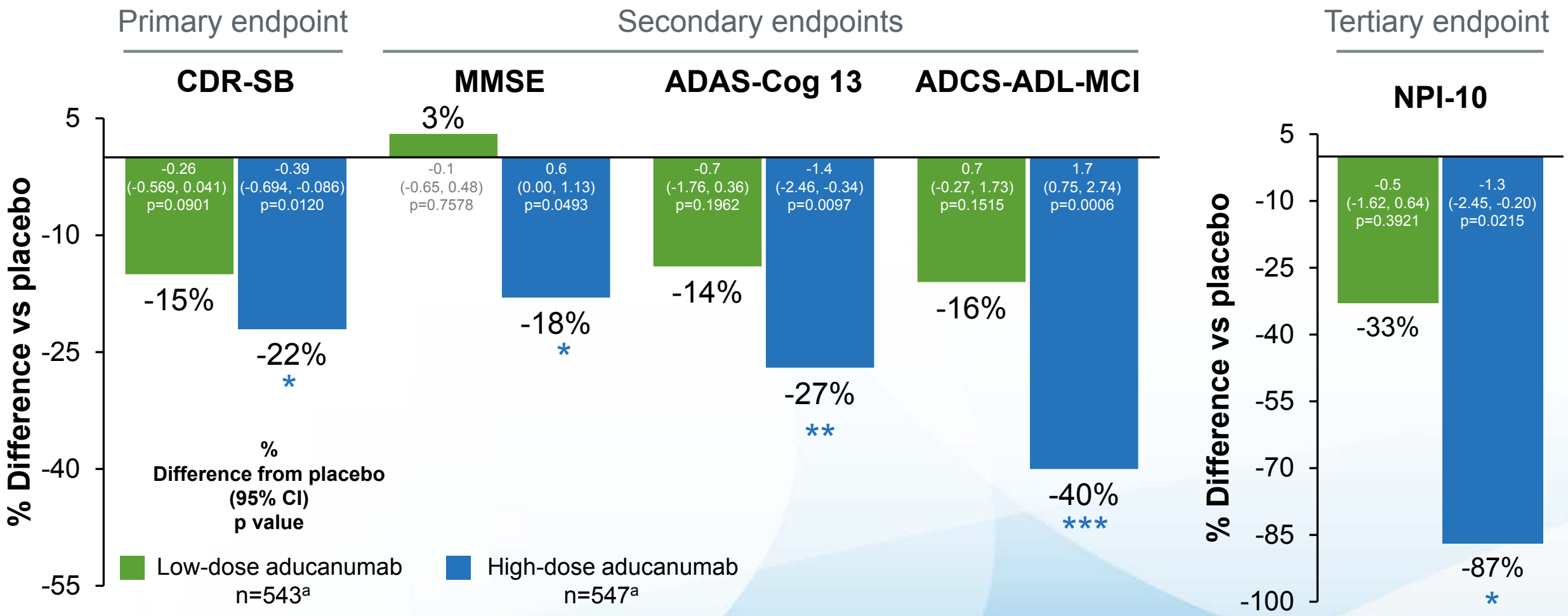
Results for the aducanumab studies were from the Aβ PET substudy population, in which longitudinal Aβ PET data was available.

Aβ, amyloid beta; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; PET, positron emission tomography; SUVR, standardized uptake value ratio.

1. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704; 2. Swanson CJ, et
Data presented at CTAD 2018; 3. Swanson CJ, et al. Data presented at AAIC 2(

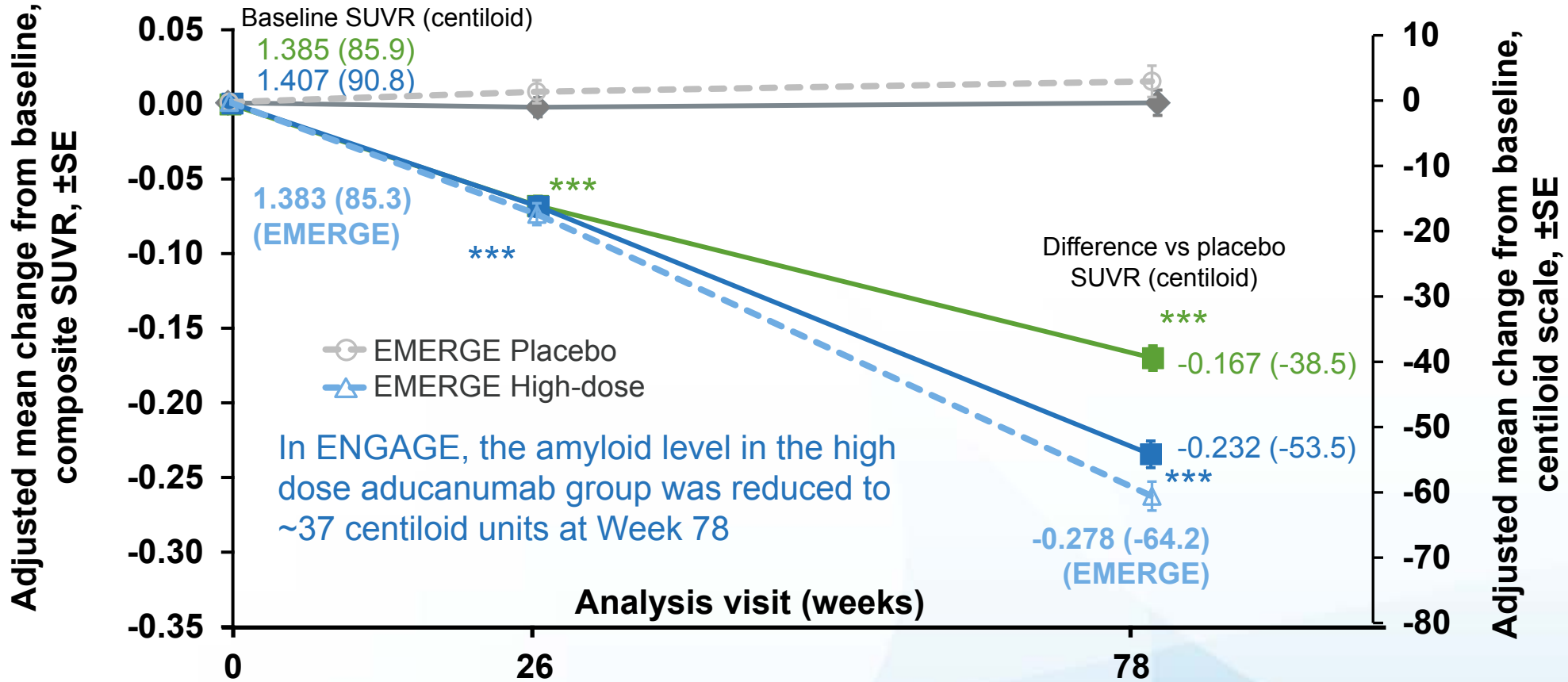
EMERGE: Clinical endpoints at Week 78

High dose aducanumab met all clinical endpoints assessing cognition, function and behavior at Week 78



[a] n=numbers of randomized and dosed patients included in the analysis. *p <0.05, **p <0.01, and ***p <0.001 compared with placebo (nominal for NPI-10).
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating; CI, confidence interval; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item).

ENGAGE: Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab



Placebo	n=204	168	124
Low-dose adu	n=198	169	138
High-dose adu	n=183	156	112

Mean cumulative dose at Week 78:

ENGAGE
109.1 mg/kg

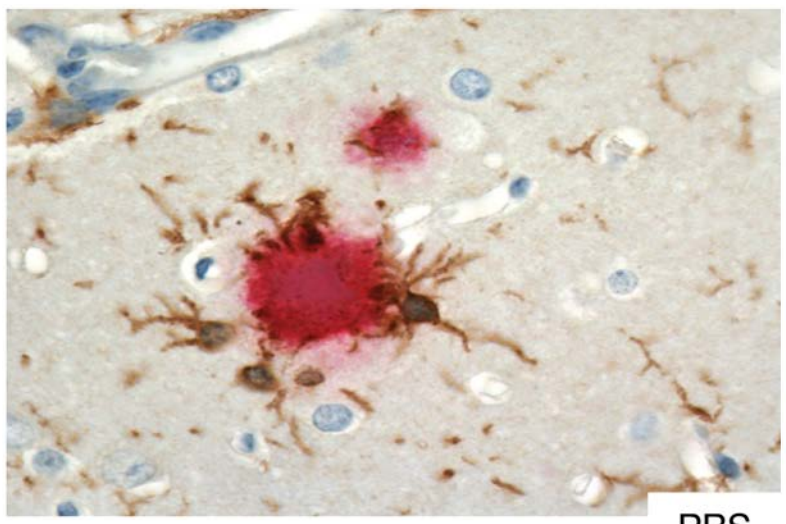
EMERGE
118.3 mg/kg

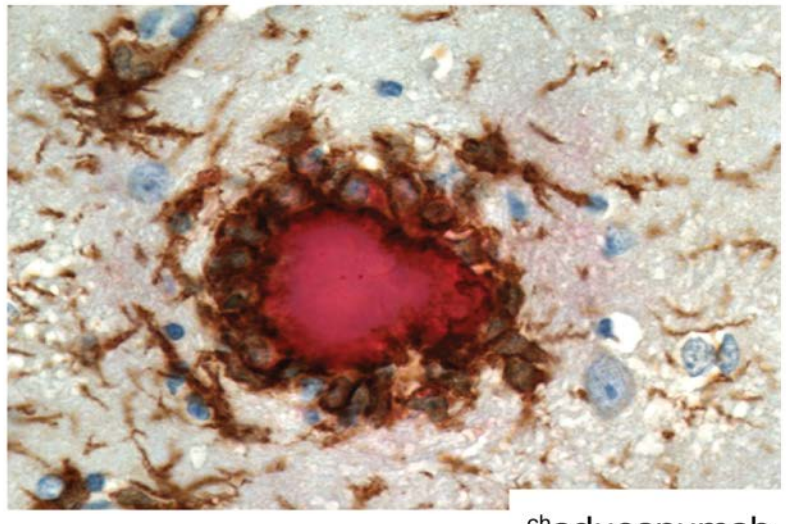
The magnitude of treatment effect observed in ENGAGE high dose (-0.232) is 16.5% less than that observed in EMERGE high dose (-0.278)

^{18}F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

adu, aducanumab; ApoE, apolipoprotein E; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Increased recruitment of microglia around parenchymal Aβ plaques upon ^{ch}aducanumab treatment in mice





Amyloid plaque

Microglia

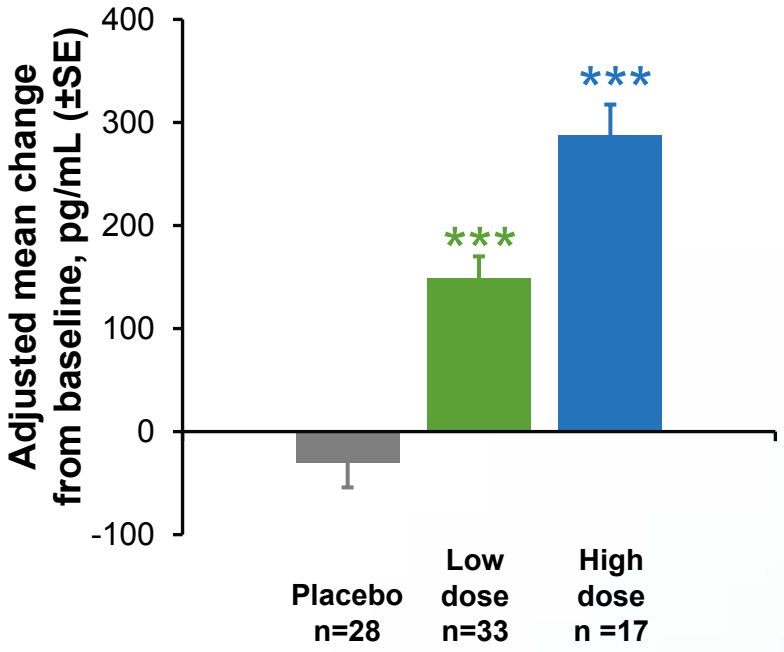
Immunostaining of Tg2576 mouse brain sections shows recruitment of microglia around parenchymal Aβ plaques upon ^{ch}aducanumab treatment

- Sevigny J et al. Nature. 2016;537:50-56.
- PBS, phosphate buffered saline.

EMERGE: CSF biomarkers of Alzheimer's disease and downstream pathology were impacted by aducanumab treatment

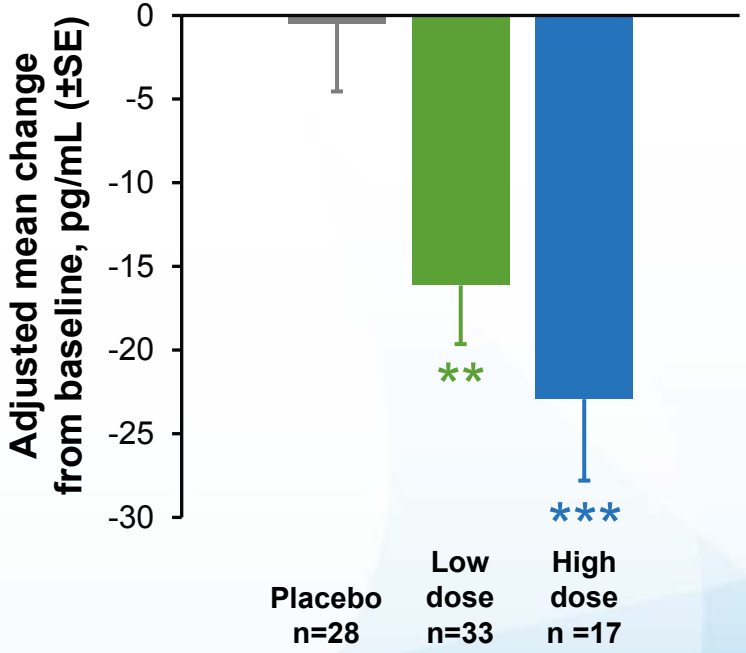
$A\beta_{1-42}$

Anti-amyloid target engagement, pathophysiology of Alzheimer's disease



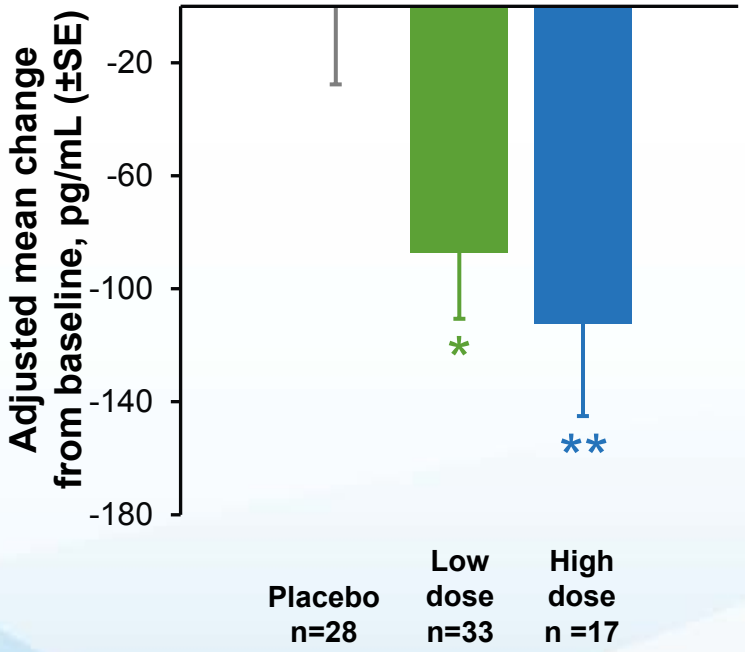
p-tau

Pathophysiology of Alzheimer's disease



t-tau

Neurodegeneration



CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). *p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and laboratory ApoE ε4 status (carrier and non-carrier) as the independent variables. Aβ, amyloid beta; ANCOVA, analysis of covariance; ApoE, apolipoprotein; CSF, cerebrospinal fluid; p-tau, phosphorylated tau 181; SE, standard error; t-tau, total tau.

Conclusions

- The pandemic has been especially tough on those with cognitive impairment
  - And likely has caused/accelerated cognitive decline in some
    - We may not fully see this for years
- The pandemic has increased the burden of those caring for people with dementia (study partners in trials)
- Research HAS proceeded, and (arguably) produced the biggest breakthrough yet in AD therapies
  - And better understanding of biomarkers, prevention and nutritional interventions
- COVID 19 has a silver lining (somewhat!)
  - A call to arms for aged care reform
  - Changes the way we do things even in non pandemic times
    - eg research
  - People we'd least expect have become Facebook, Zoom, Skype and Teams experts
  - Has created heroes!
    - We have many of our own Captain Sir Tom Moores.
      - One patient of mine, in RCF (ex AFL footballer) has been an absolute hero