CLUB VITA and Nationwide

THE RISK OF **LIVING LONGER**

Thank you for joining us – the webinar will start shortly

Douglas and Uli ask the ultimate question of human longevity for financial institutions:

How long can we go?

Season 2 program

Session 1 Sept 10th, 2024	*Longevity Science* *– Advancing from Cure to Prevention*	• Dominik Thor, Geneva College of Longevity Science	Recording available here
Session 2 Oct 22, 2024	*Quantifying the effects of gero-science*	• Chris Martin & Nicky Draper Crystallise	Recording available here
Session 3 Nov 14th, 2024	*Behavio(u)ral change*	• Francois Millard (Vitality) • Tina Woods (Business for Health)	Recording available here
Session 4 Dec 3rd, 2024	*Preventing dementia*	• Baroness Professor Susan Greenfield Neuro-Bio Ltd	Today!

For full details and registration for the series,
visit: www.clubvita.net/us/events or follow http://linkedin.com/company/club-vita

Watch the replays of season 1 here: www.clubvita.net/us/events/event-recording

THE RISK OF **LIVING LONGER**

Preventing dementia

Douglas Anderson

Ulrich Stengele

Baroness Professor
Susan Greenfield

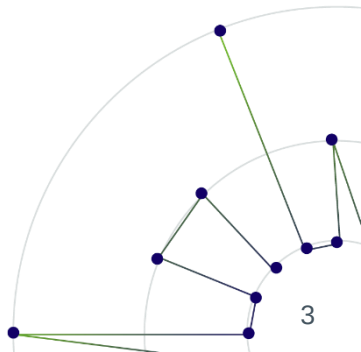
CLUB VITA
Ahead of the *longevity* curve

Nationwide

NeuroBio

Today's agenda

1. Materiality of dementia (for actuarial calculations)
2. The development of dementia
3. Your dementia detective work
4. Your vision for preventing dementia
5. Q&A

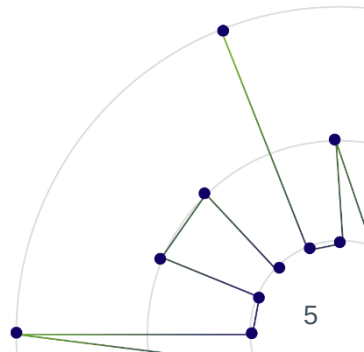


1. Materiality of dementia

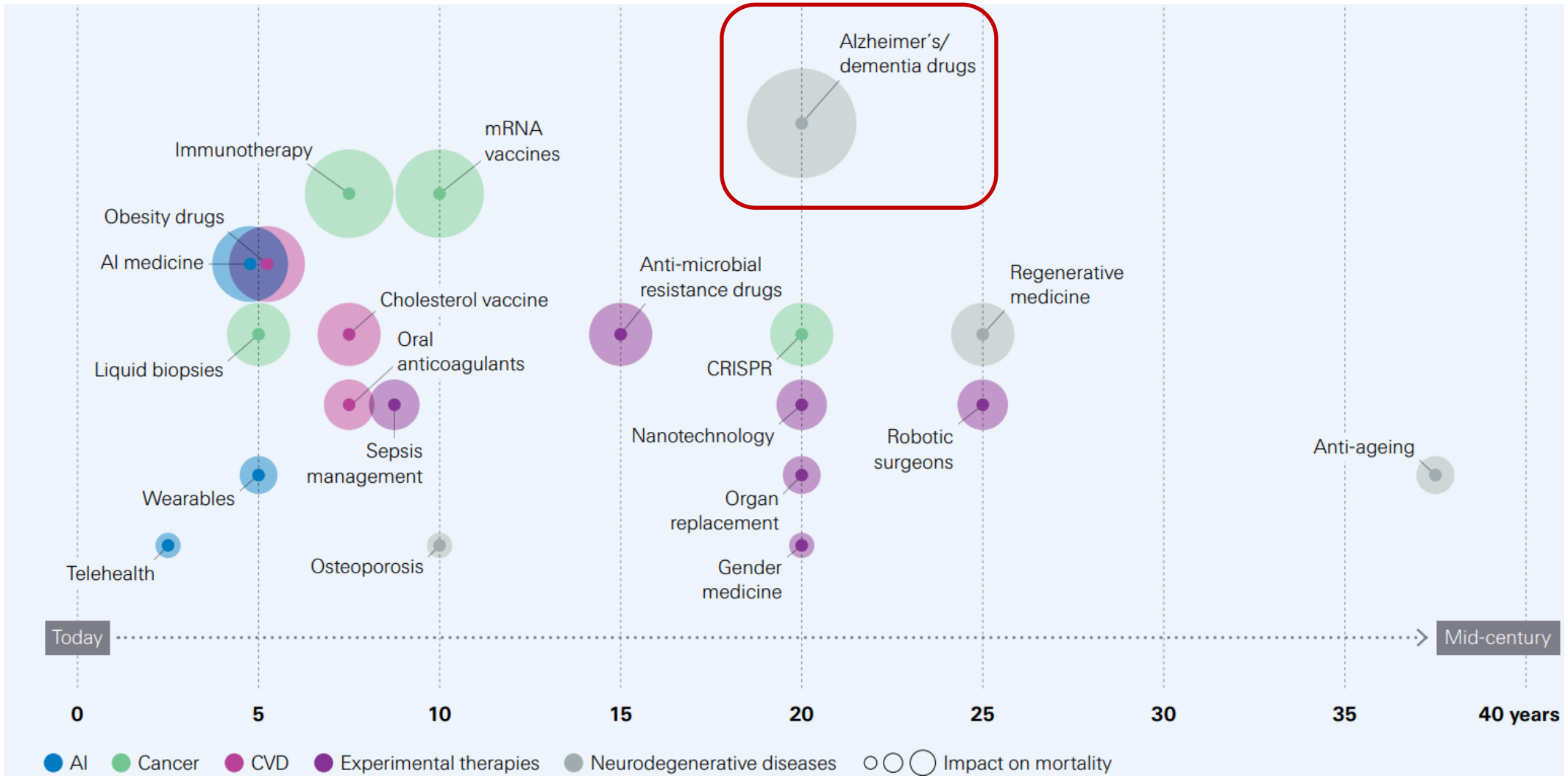
Poll question

"How do you think dementia will affect life expectancy at 60 over the next 20 years?

- *Reduce by over 2 years*
- *Reduce by 0-2 years*
- *No significant change*
- *Increase by 0-2 years*
- *Increase by over 2 years*

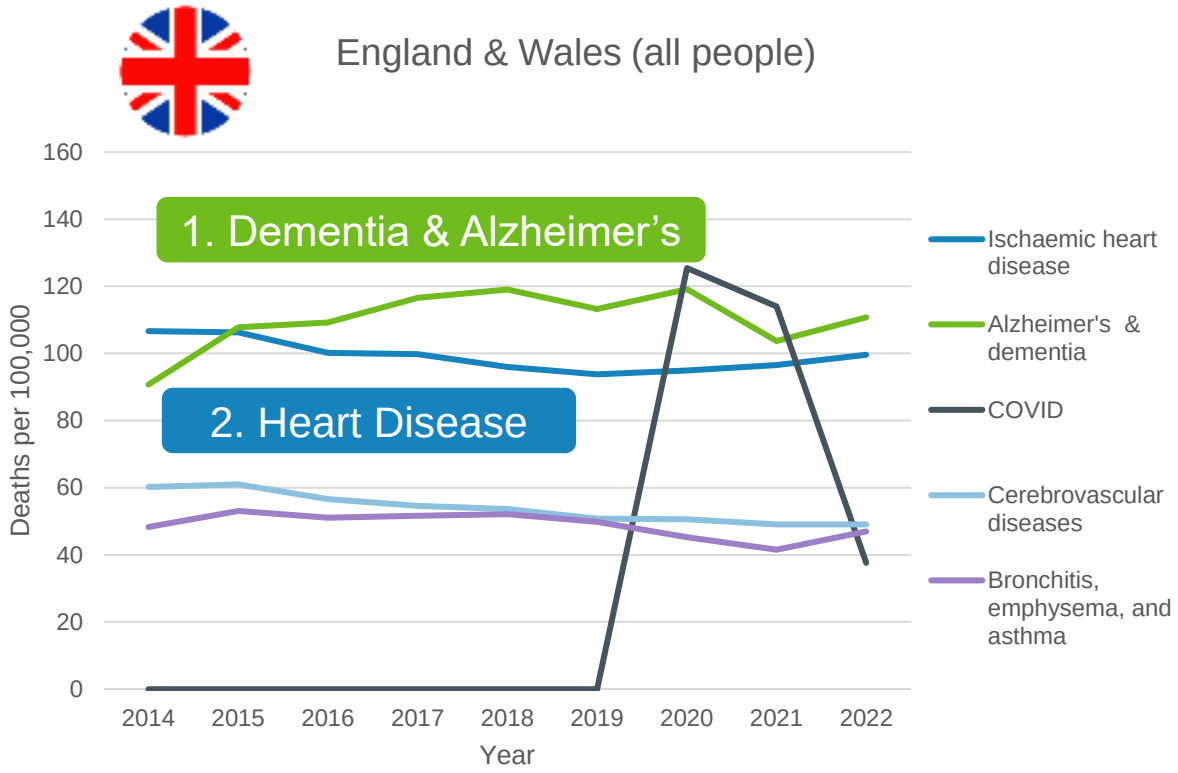


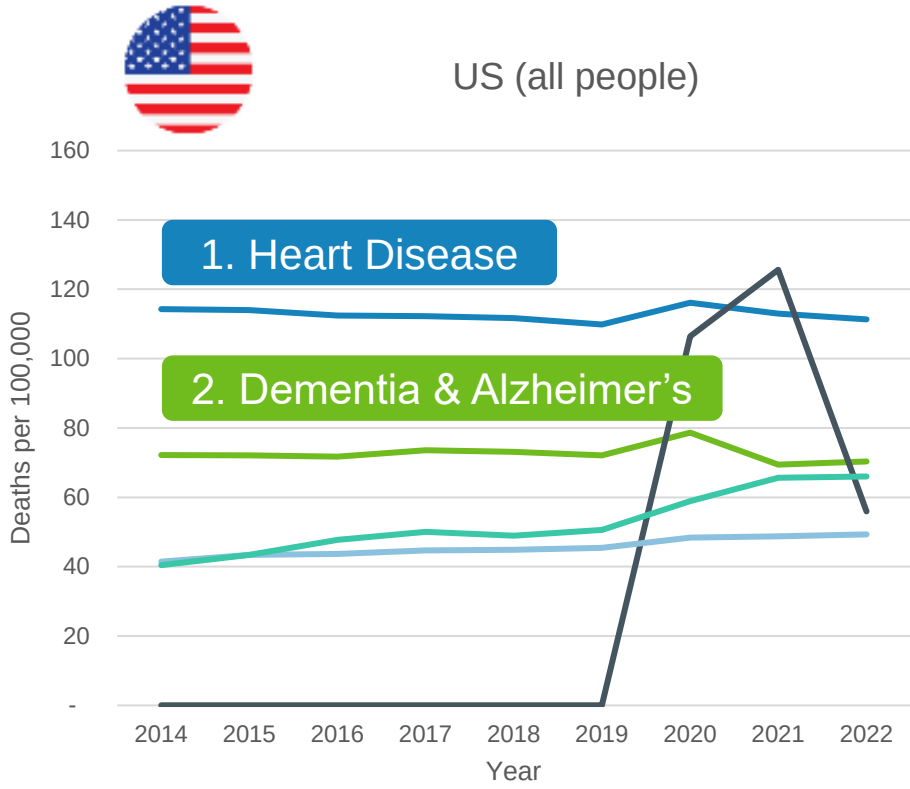
Drivers of lifespan extension



Source: Mortality trends driving life expectancy in insurance, Swiss Re Institute

Top five causes of death

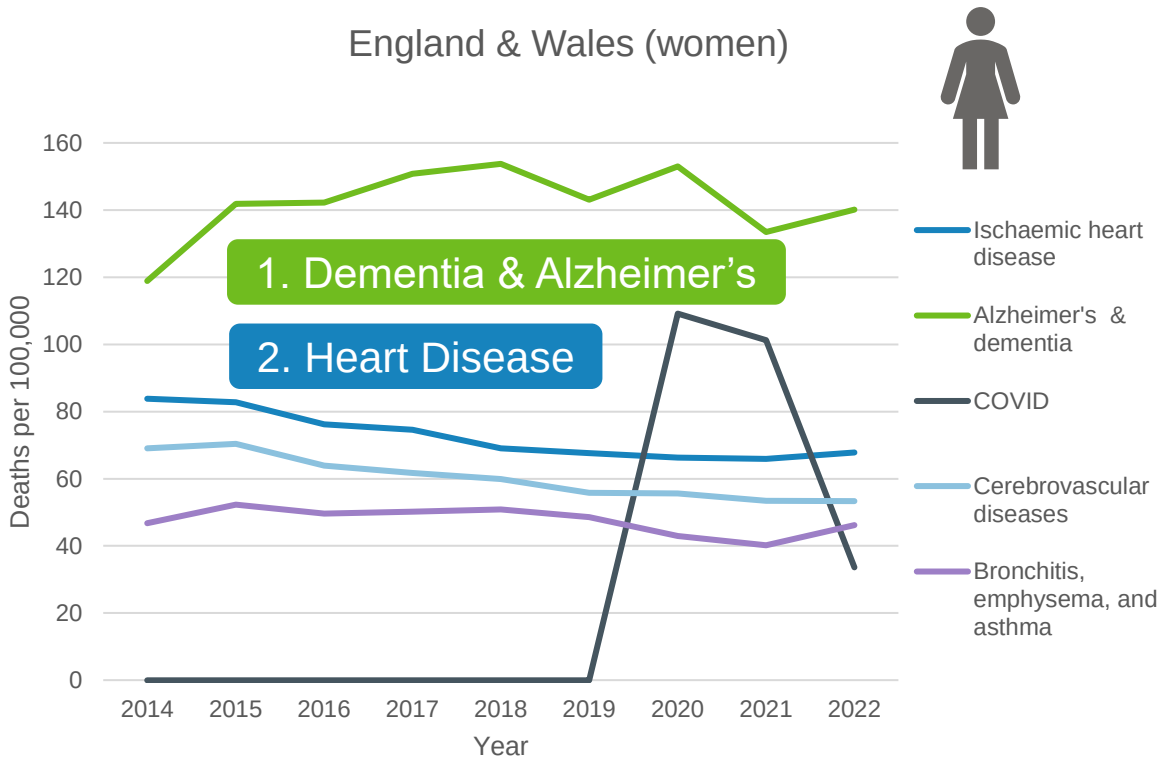


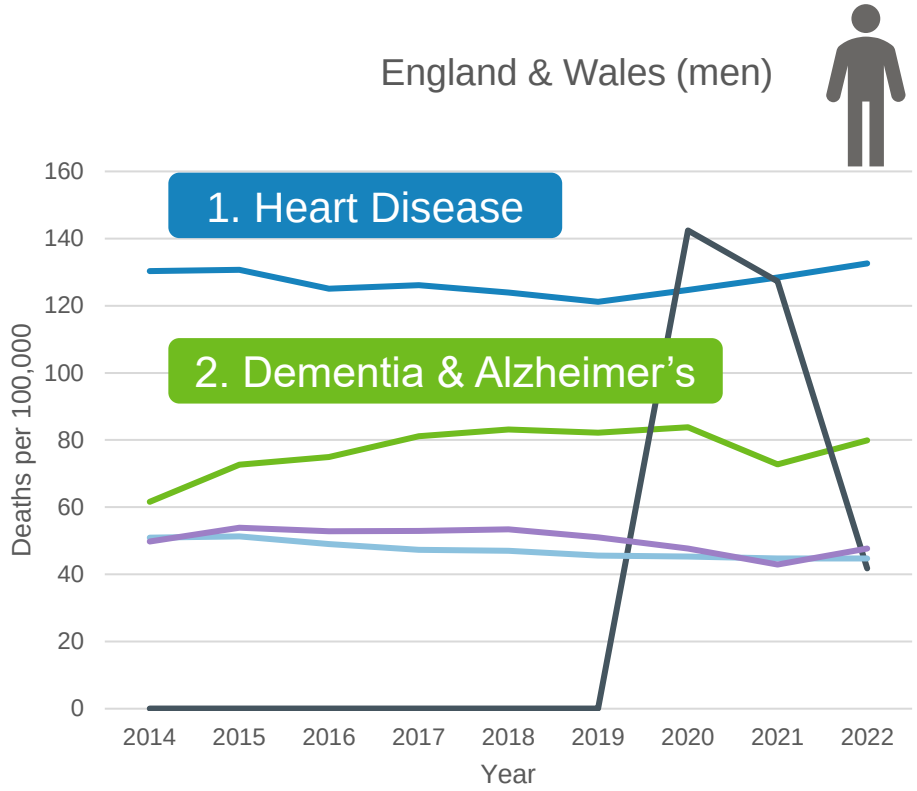


- **Dementia & Alzheimer's** number 1 cause of death in England and Wales, number 2 cause in US
- US currently has a younger population – US proportion of over 75-year-olds is c30% lower than UK

More details here: https://www.clubvita.net/uk/news-and-insights/top-charts-24-11-the-rise-of-alzheimers-and-dementia

Differences between sexes in UK

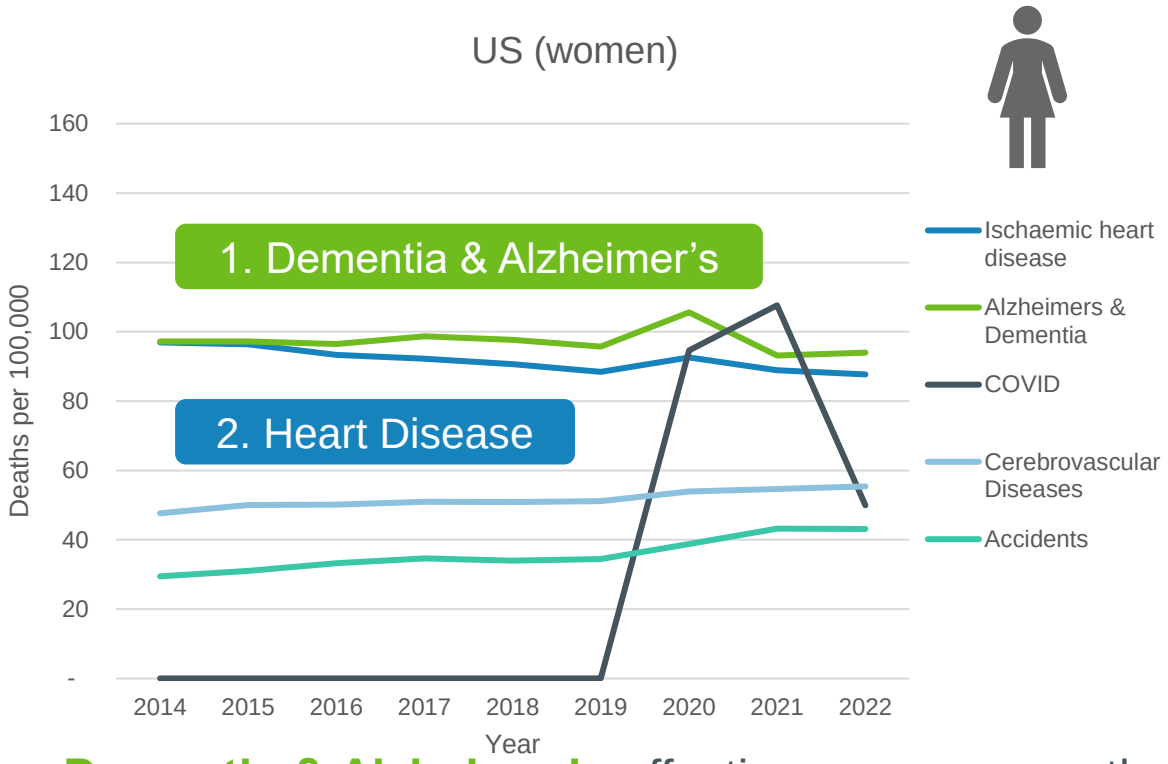


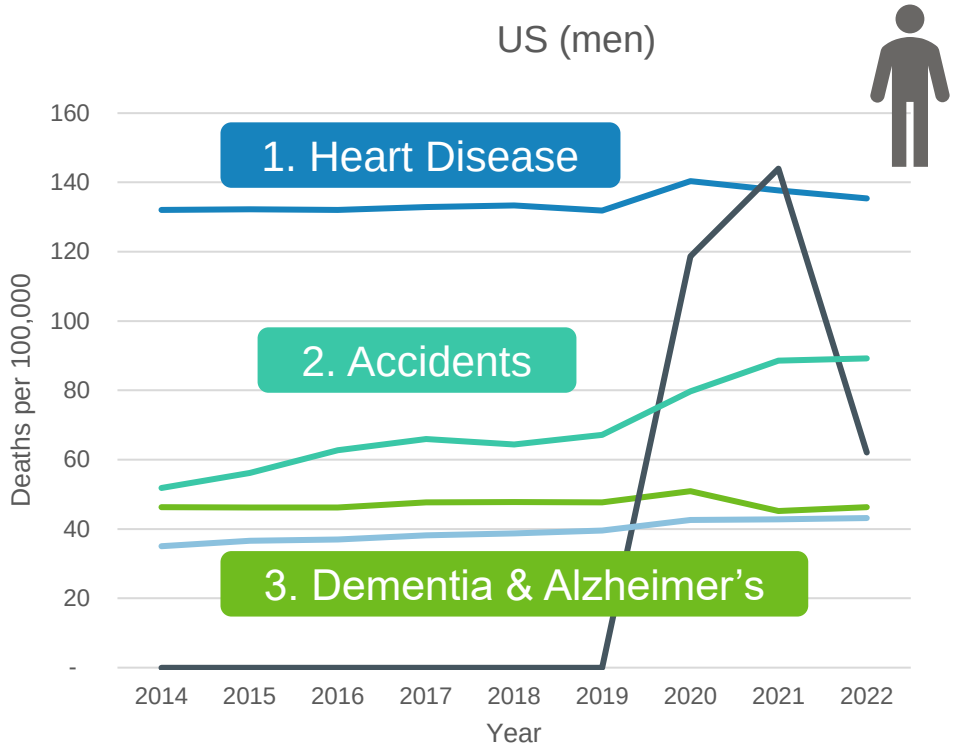


- **Dementia & Alzheimer's** affecting women more than men in England and Wales
- E&W has a younger male population – c27% lower proportion of over 75-year-olds compared to females

More details here: https://www.clubvita.net/uk/news-and-insights/top-charts-24-11-the-rise-of-alzheimers-and-dementia

Differences between sexes in US

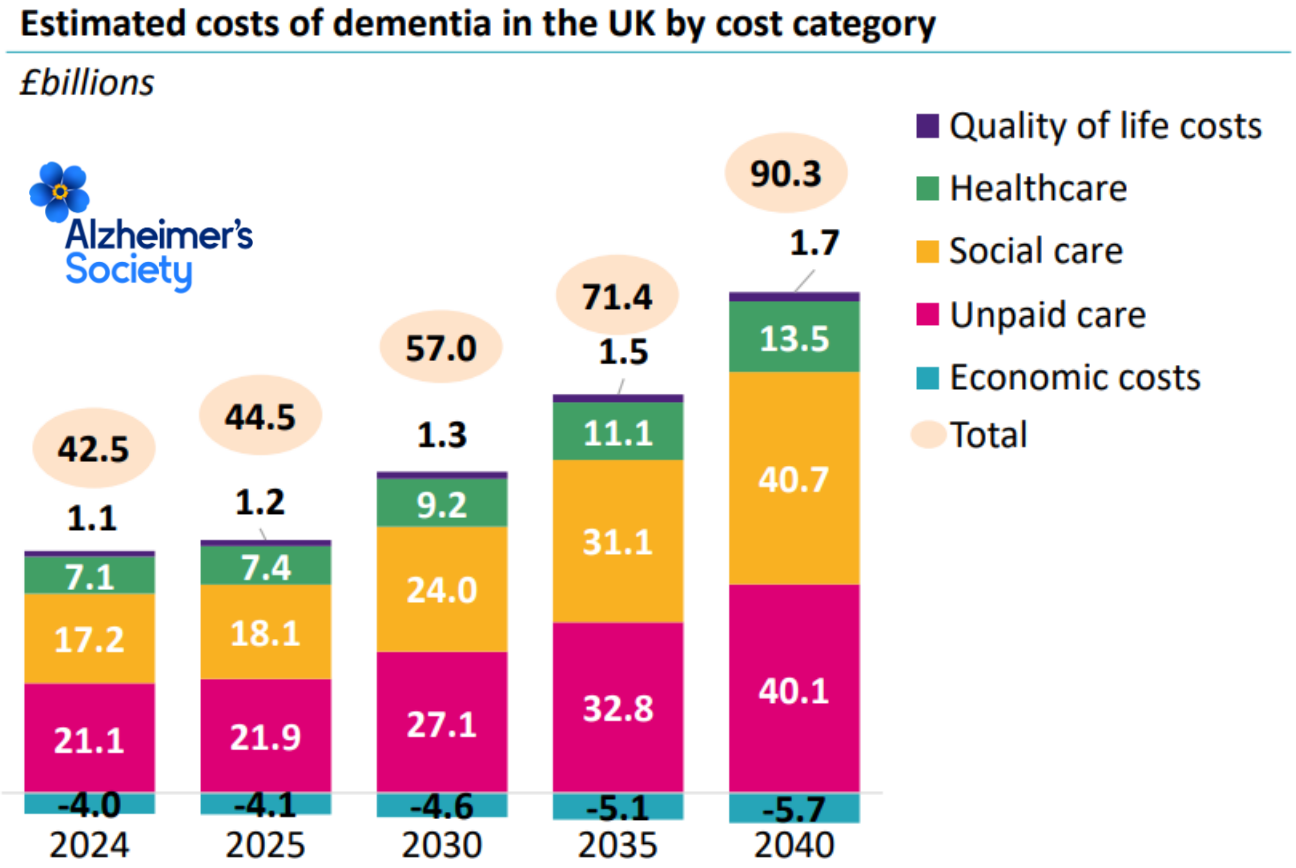




- **Dementia & Alzheimer's** affecting women more than men in US – difference even bigger than E&W
- US male population is younger – c36% lower proportion of over 75-year-olds compared to females

More details here: https://www.clubvita.net/uk/news-and-insights/top-charts-24-11-the-rise-of-alzheimers-and-dementia

The economic strain of dementia



- Economic strain from dementia expected to more than double over next 15 years
- For comparison, the total annual current taxpayer spending on health and social care is around £190bn
- Rise of £50bn over next 15 years is equivalent to annualised rate of 1.5% a year above inflation
- Much of the strain comes from opportunity cost of unpaid carers

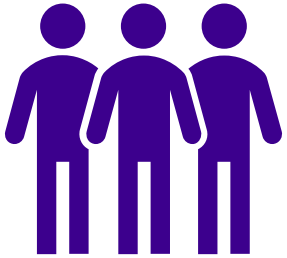
https://www.alzheimers.org.uk/sites/default/files/2024-05/the-annual-costs-of-dementia.pdf

2. The development of dementia

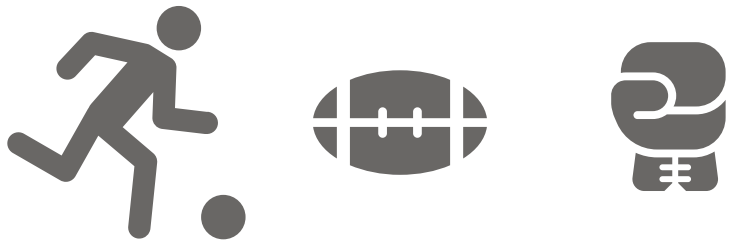
Preventing dementia today

Healthy lifestyle

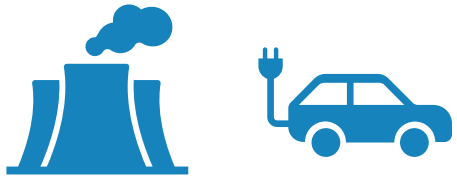
Social networks



Avoid head injuries

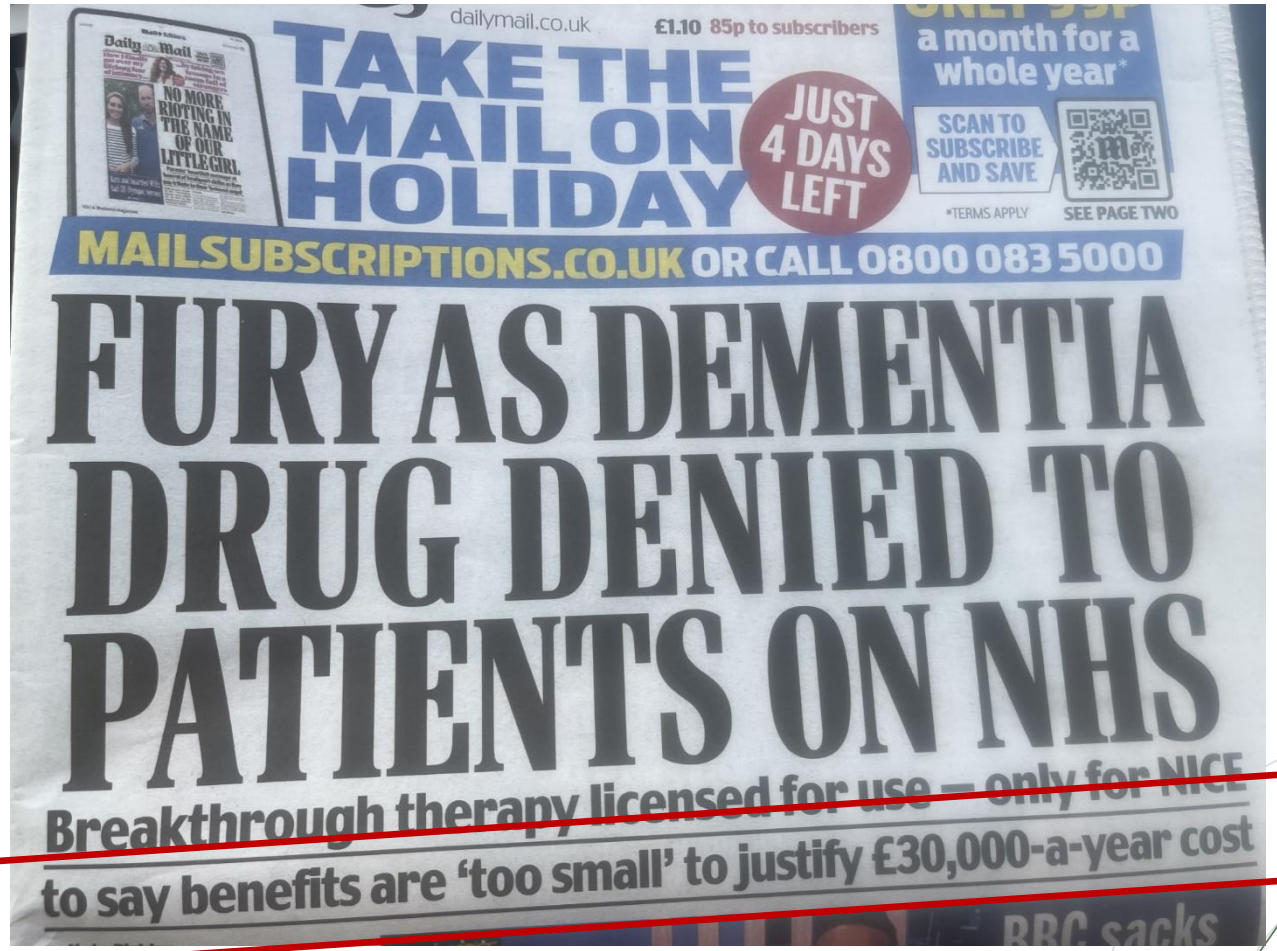


Avoid atmospheric pollution



The case against treating Amyloid

1. Amyloid not present in early stages
2. No narrative to explain why Amyloid is the culprit
3. When Amyloid is targeted with an antibody, the treatment is not effective



NORMAL

(Braak 0) T14 ⟷

- Primarily vulnerable cells selectively retain a growth mechanism not shared with rest of brain.
- This mechanism for cell growth: T14.
- T14 mechanism only operational in immature brain during development.
- No Amyloid, T14 levels LOW

20 YRS TO MEMORY LOSS

(Braak I-II) T14 ↑

- IC cells damaged (stroke/injury/free radicals)
- The T14 mechanism mobilised to 'compensate'
- Now, T14 actions are TOXIC!
- No Amyloid

10 YRS TO MEMORY LOSS

(Braak III-IV) T14 ↑↑

- T14 mechanism now causes more cell loss.
- Still more cells die

MEMORY LOSS

(Braak V-VI) T14 ↑↑↑

- More cells attempt compensation.
- Cell death continues: damage spreads to 'higher' areas linked to memory.

THE PROCESS OF NEURODEGENERATION

T14 is a brain molecule in the primarily vulnerable cells, driving growth
BUT it can be a Jekyll-and-Hyde...

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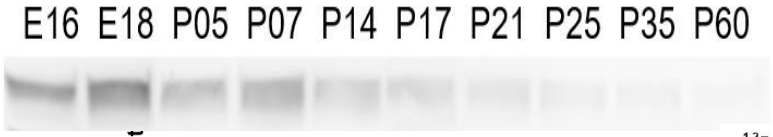
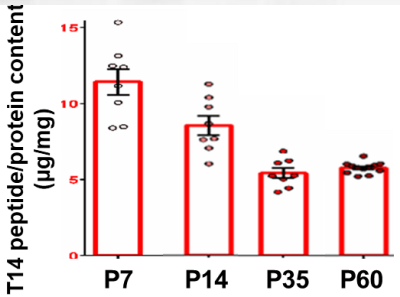
3. Your dementia detective work

T14: AN AGENT FOR CELL GROWTH via mTOR, DECLINING WITH AGE

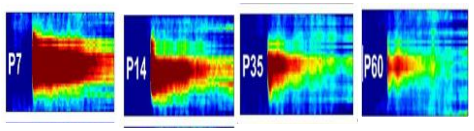
Developing rat brain

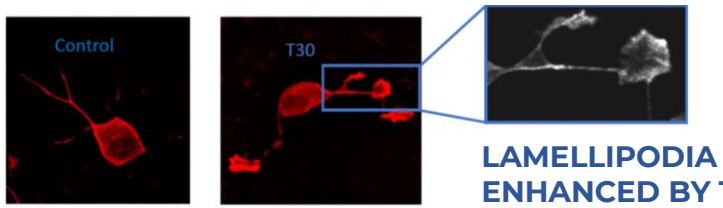


Badin et al 2016

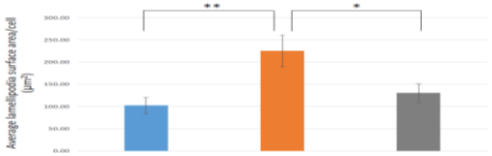


T14 REFLECTS NEURONAL ACTIVITY (Optical imaging) Ferrati et al 2018





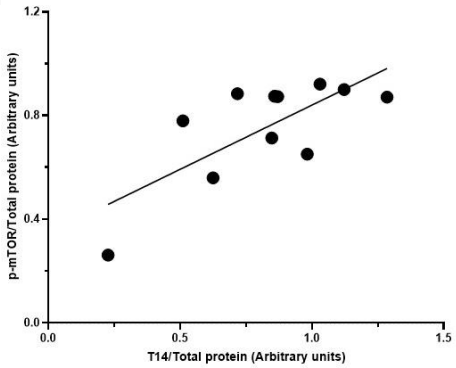
LAMELLIPODIA ENHANCED BY T30 (T14)
Graur et al., 2023



Control **T30 (T14)** **T30 + Rapamycin**

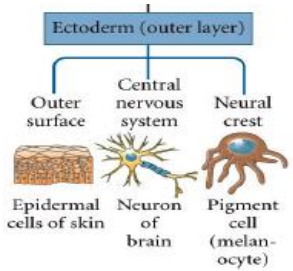
Human adult

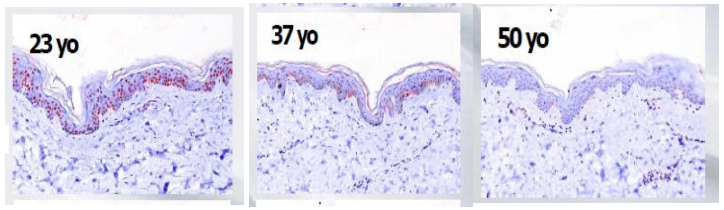
Correlation mTOR vs T14: P=0.0104
Ranglani et al 2023



Human epidermis

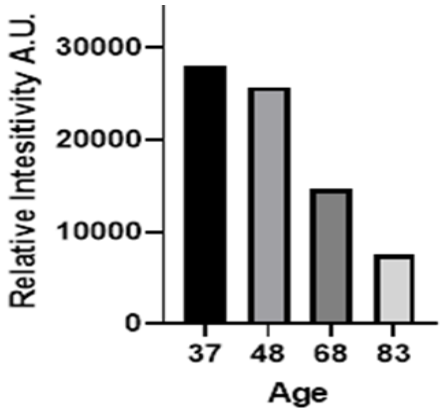
T14 REFLECTS KERATYNOCITES AGEING.
Rocha et al 2023



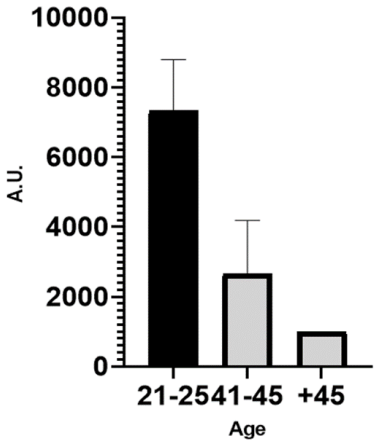


Adult brain (pilot)

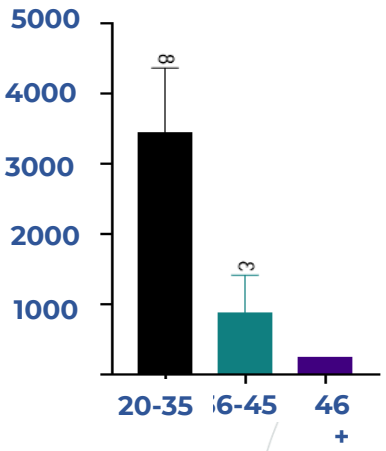
T14 REFLECTS AGEING



Sebum (pilot)



Saliva (pilot)



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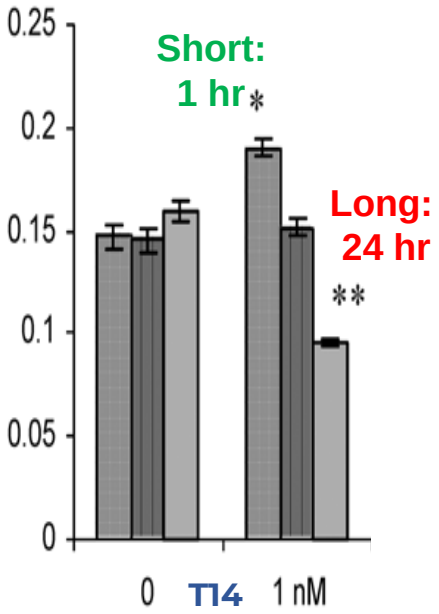
T14: A JEYKLL & HYDE MOLECULE

A trophic agent can turn toxic depending on…

(i) DURATION OF APPLICATION

Day et al, 2004

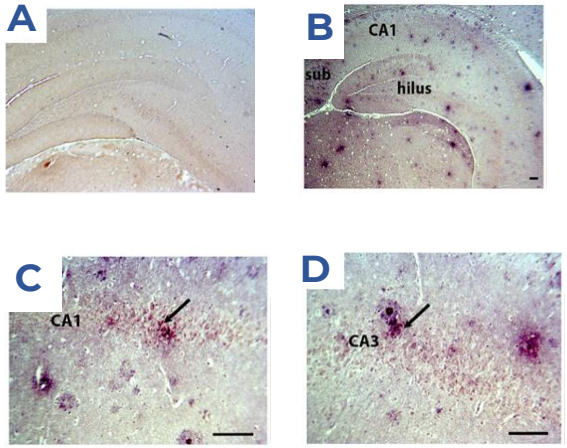


(ii) AGE!

'The Ca-dependent LETHAL PROCESS is MORE DEVELOPED in OLDER NEURONS' *Eimerl and Schramm*, 1994

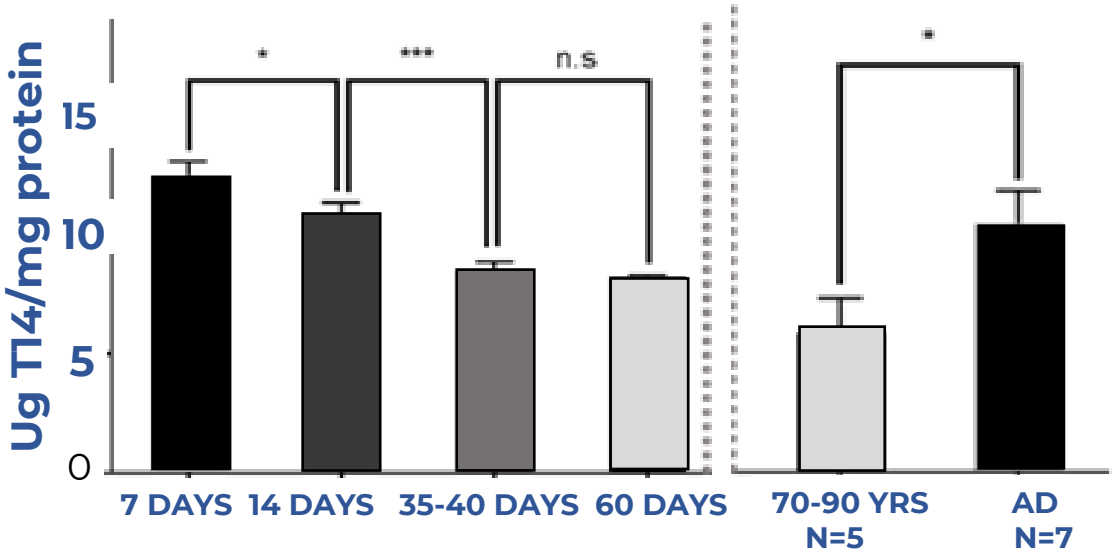
T14 VERY LOW HIPPOCAMPUS IN TRANSGENE –VE MOUSE,

BUT IN 5XFAD ADULT, T14ir PLAQUES



(Greenfield et al., 2022)

NEURODEGENERATION AS AN ABERRANT FORM OF DEVELOPMENT



RAT BRAIN

HUMAN MIDBRAIN

(Garcia-Rates et al., 2016)

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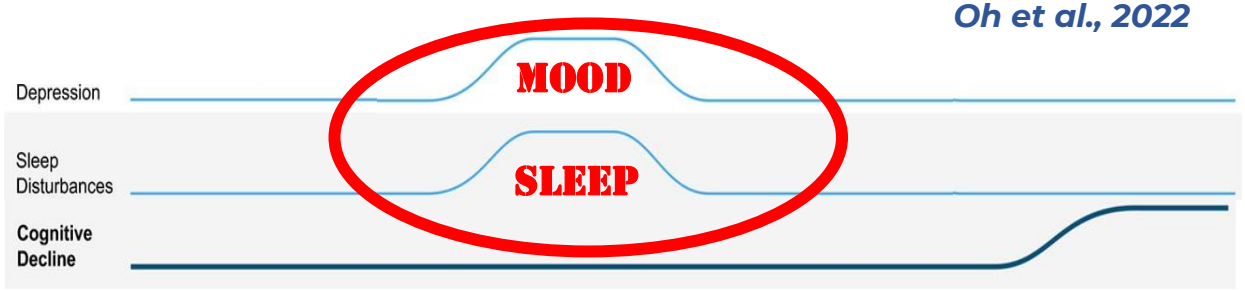
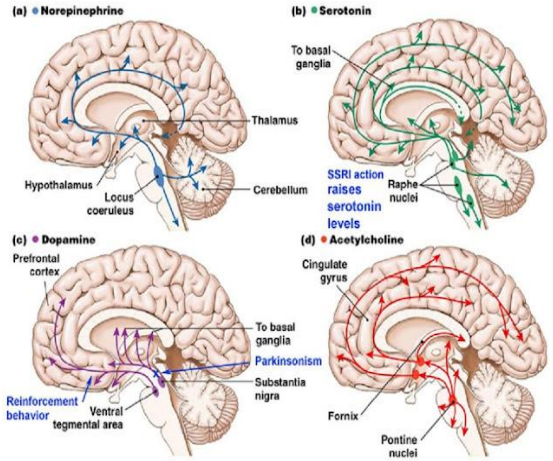
+/- MOOD DISORDER AS A (NON-EXCLUSIVE) PRELUDE TO AD

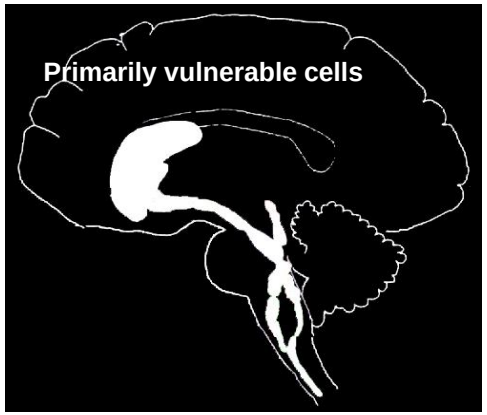
SLEEP & MOOD DISORDERS PRESENT BEFORE COGNITIVE DECLINE

Oh et al., 2022



Neurotransmitters underlying arousal levels and mood originate from the primarily vulnerable cells





COULD THIS BE AN EARLY DIFFERENTIATOR IN CONTROLS?

Clínic Barcelona

LIVING CSF

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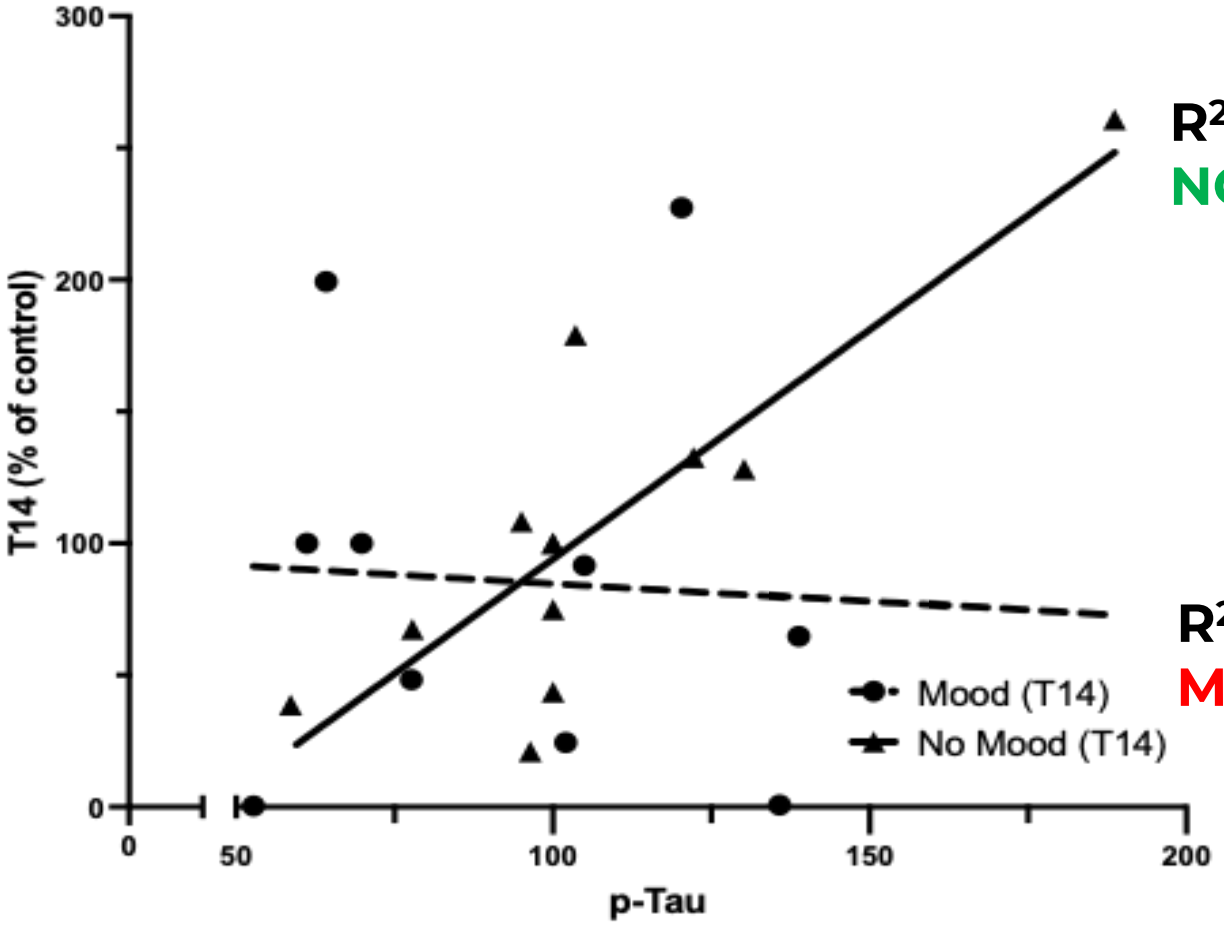
TOWARDS A TRULY *PRE-SYMPTOMATIC* TEST

Testing possible early-stage neurodegeneration within a cognitively homogenous group

Mood Disorder N=10 No Mood Disorder N=12: Living CSF



$R^2 = 0.7$

NO MOOD DISORDER

$R^2 = 0.0033$

MOOD DISORDER

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A TWO-STEP DIAGNOSTIC STRATEGY…

STEP A: A RAPID SCREEN – LFT/ANTIGEN TEST

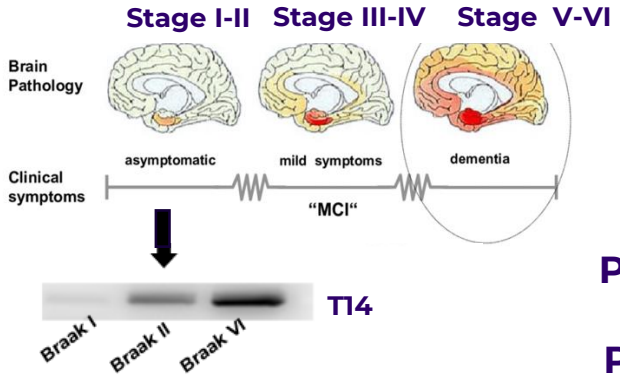
- Available from pharmacies
- Home use
- Low cost
- A binary ‘Brain Health’ test

STEP B: A CLINICAL DIAGNOSTIC TEST

- Under medical supervision
- Saliva sample sent for off-site quantification
- Determines if neurodegeneration ongoing and when symptoms likely to present
- Results off-line later and, if positive, detailed care-plan with personalised timeline

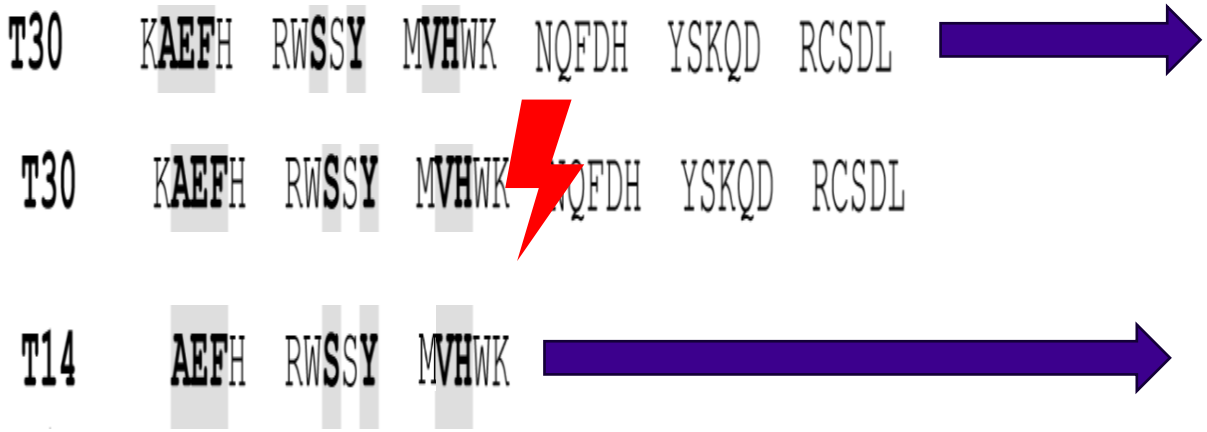
(B) DETECTION OF AD IN SALIVA

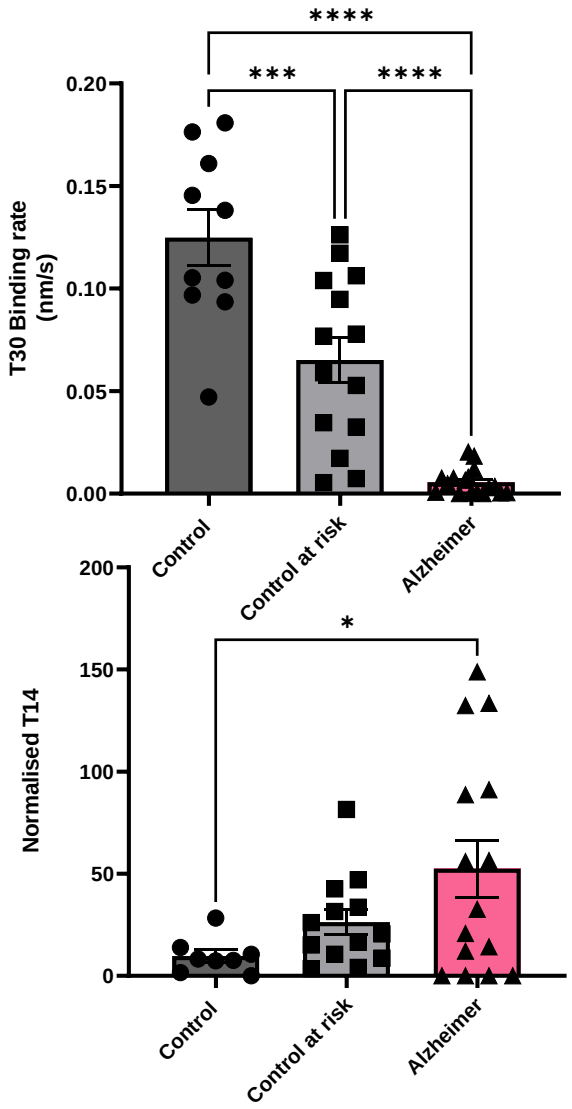
T14 will increase at the expense of its parent molecule T30



PRECISION for medicine

Preliminary data conducted using saliva samples from Precision for Medicine, USA





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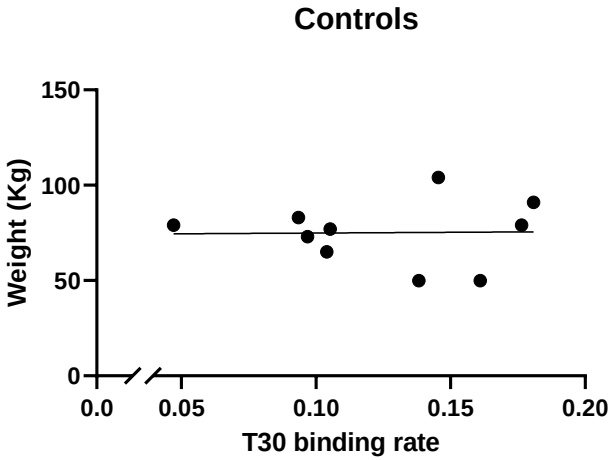
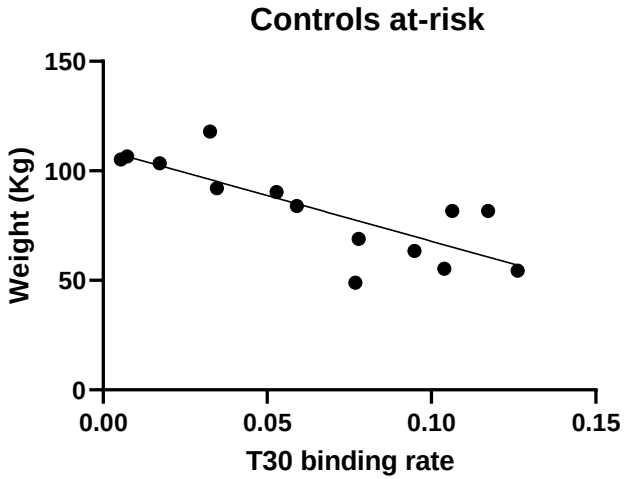
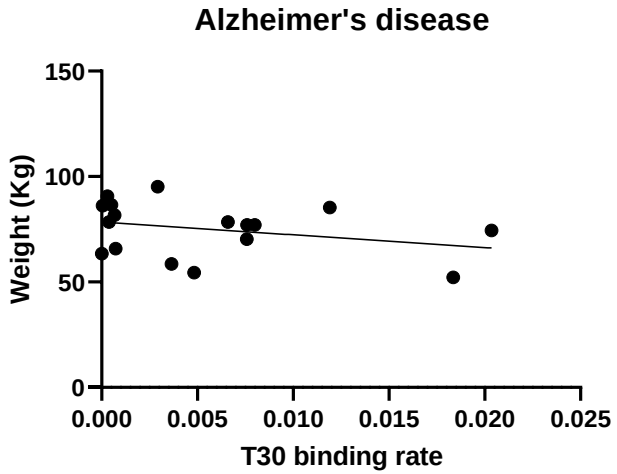
‘AT RISK’ GROUP ONLY
Significant correlation of T30 and body weight



Pearson r	
r	0.01956
95% confidence interval	-0.6177 to 0.6413
R squared	0.0003827
P value	
P (two-tailed)	0.9572
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	10



Pearson r	
r	-0.7946
95% confidence interval	-0.9322 to -0.4565
R squared	0.6314
P value	
P (two-tailed)	0.0007
P value summary	***
Significant? (alpha = 0.05)	Yes
Number of XY Pairs	14



Pearson r	
r	-0.3008
95% confidence interval	-0.6827 to 0.2102
R squared	0.09049
P value	
P (two-tailed)	0.2407
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	17

-T30 levels correlate with body weight only in the control ‘at-risk’ group.

- Hence correlates with a known risk factor (obesity) for AD.

https://www.sciencedirect.com/science/article/pii/S1550413115004076

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4. The future of dementia

NBP14 COMPARED TO ANTI-AMYLOID DRUGS

	NBP14	ANTI-AMYLOID
EFFICACY	Prevents any further neurodegeneration.	Impact on cognition only, reducing rate of decline over an initial, short period.
PRICE	Annual price competitive with current drug regimes BUT much more cost-effective: Intranasal home treatment.	Lecanemab $26,500/year Donanemab $50,000/year Further indirect costs: Intravenous (day in hospital).
MECHANISM OF ACTION	Intercepts the primary driver of neurodegeneration. Significantly higher binding.	Blocks downstream marker amyloid.
BRAIN ACCESS	Effective brain penetrance.	A very small % into the brain.
SIDE EFFECTS	Acts exclusively at one receptor (Raglani et al., 2024). No known side effects as of yet.	Adverse side effects.

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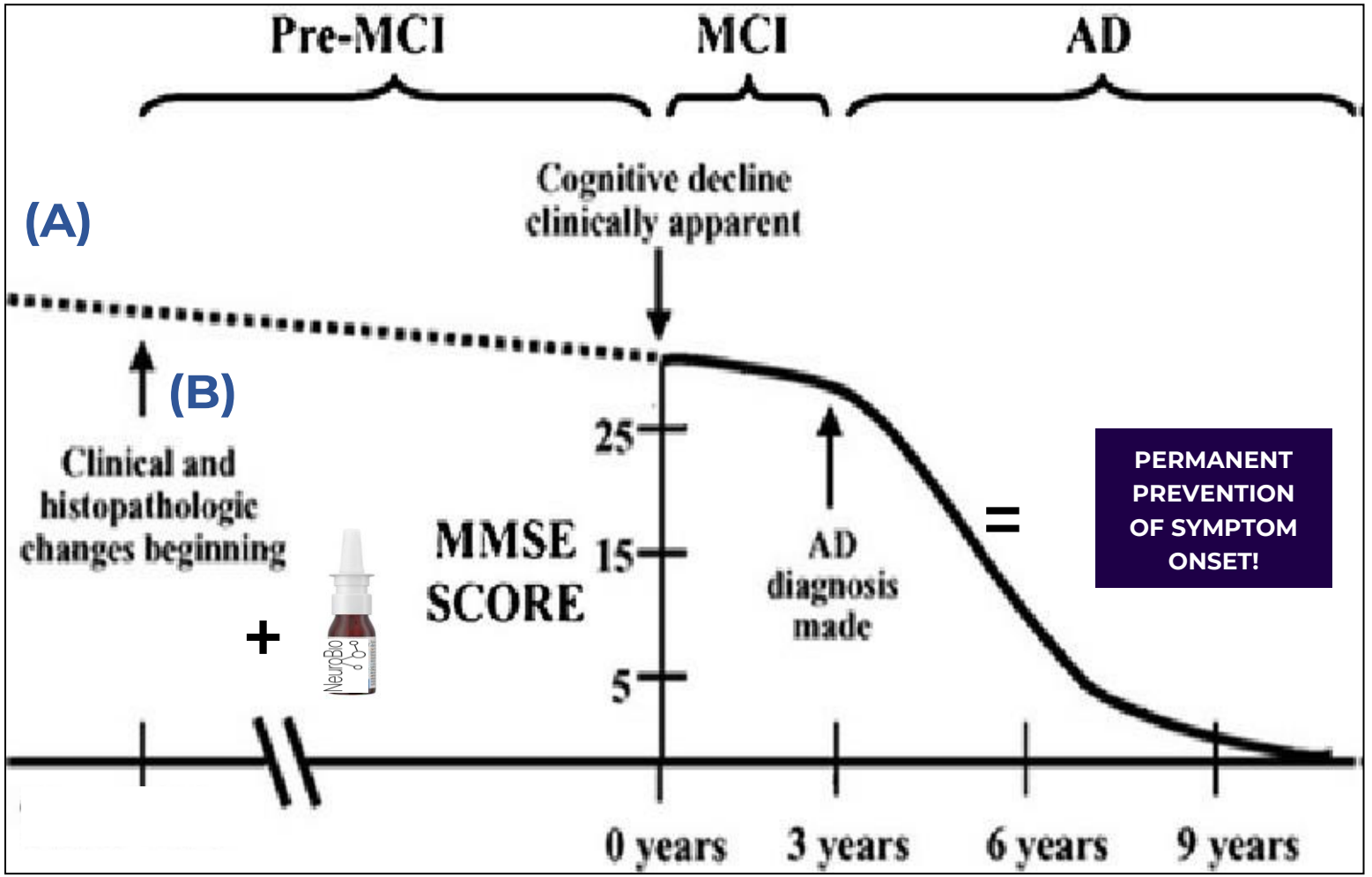
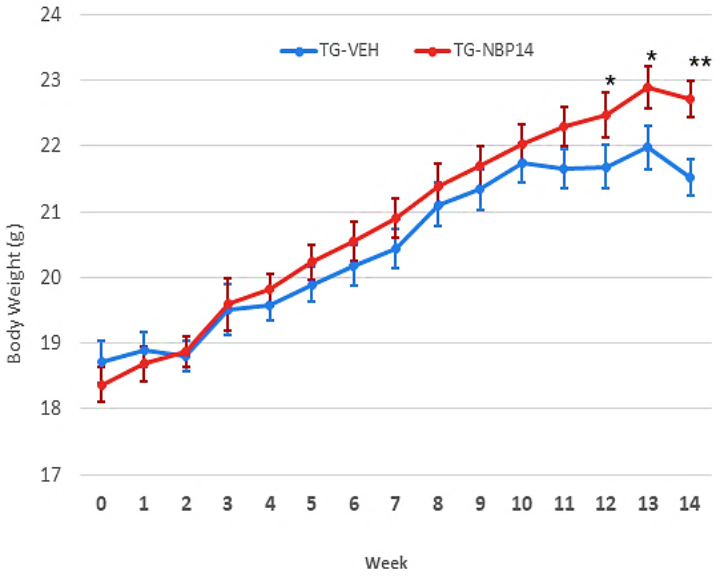
Vision for future dementia treatment



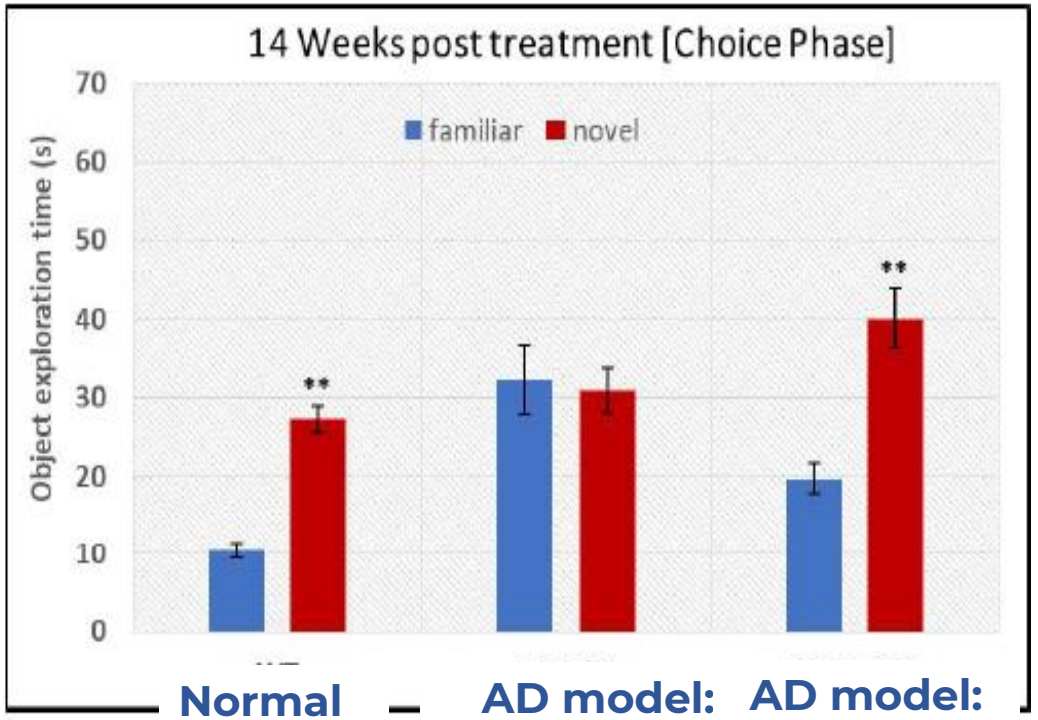
NBP14: Effects

5XFAD MODEL MICE: TREATMENT INTRANASAL NBP14 TWICE WEEKLY FOR 14 WEEKS

Better weight gain



Novel object recognition



Normal

Wild-type mice explore novel (red) object more than familiar (blue)

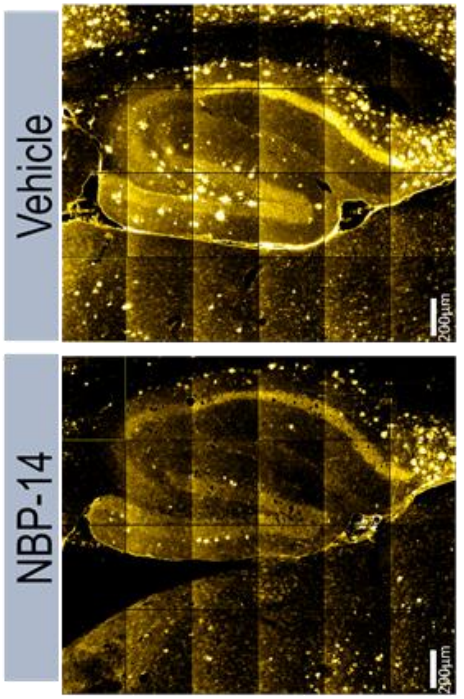
AD model: Saline

Mice cannot distinguish familiar from novel objects

AD model: NBP14

Mice remember if object familiar (blue) vs novel (red).

Lower amyloid



Brain amyloid (gold blobs) significantly lower in hippocampus

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5. Q&A

And finally …

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

EVIDENCE FOR A NOVEL NEURONAL MECHANISM DRIVING ALZHEIMER'S DISEASE, UPSTREAM OF AMYLOID

Garcia-Ratés, S; Garcia-Ayllon, MS*; Falgàs, N*; Brangman, SA; Esiri, MM, Coen, CW; Greenfield, SA.

- **Co-authors include 3 Alzheimer clinicians: a neurologist, a geriatrician and a neuropathologist**
- **Five authors are external to Neuro-Bio**

https://pmc.ncbi.nlm.nih.gov/articles/PMC8983808/pdf/TRC2-8-e12274.pdf

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Poll question

“On a scale of
1 (not for me) to 5 (fantastic)
how would you rate today’s webinar?”

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How long can we go?

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Session 2 Oct 22, 2024	*Quantifying the effects of gero-science*	• Chris Martin & Nicky Draper Crystallise	Recording available here
Session 3 Nov 14th, 2024	*Behavio(u)ral change*	• Francois Millard (Vitality) • Tina Woods (Business for Health)	Recording available here
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