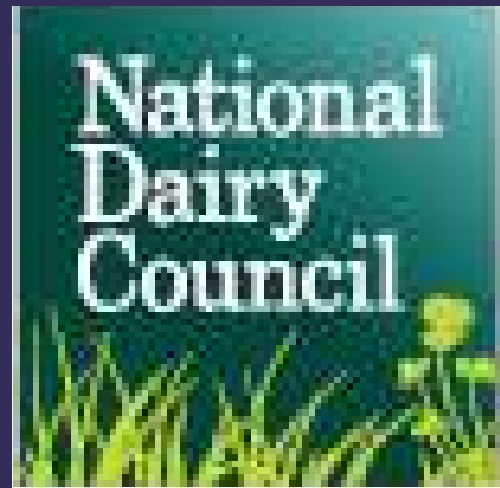




B-vitamins: mental health and the ageing brain

Evidence from the TUDA study

Catherine Hughes, PhD
INDI Symposium Dublin, 21st Sept 2023



Overview of Presentation



- Mental Health in Ageing
- Nutrition and the Ageing Brain
- Future Directions for Research in Mental Health and Ageing

Ageing population



Mental Health and neuropsychiatric disorders are leading cause of ill health and disability in older age

Data source: United Nations (2015). *World Population Prospects: The 2015 Revision*.

Project 2 billion aged 60 years and over by 2050

Mental Health Disorders in Ageing

Dementia¹⁻²

- >944,000 older people living with dementia in UK; 55,000 in Ireland
- Costed an estimated £25 billion in 2021
- Expected to triple by 2050

Anxiety³

- Affects 14-20% of 70 to 80 year olds

Depression⁴⁻⁵

- 2nd leading cause of disability
- £7.5 billion/ €3 billion
- 50% more common among women than men

¹Wittenburg *et al* (2019) Care Policy and Evaluation Centre. *London School of Economics*

²Alzheimer's Research UK (2021)

³Beaumont and Loft; *Office for National Statistics*

⁴The British Psychological Society; NICE National Clinical Practice Guideline 90. (2010)

⁵WHO (2023)

Mental Health Disorders in Ageing

Dem

944,000 older people living with dementia in UK
Estimated £25 billion in 2021

**Prevention and treatment
of mental health disorders
is a global health priority**

Depression⁴⁻⁵

- 2nd leading cause of disability
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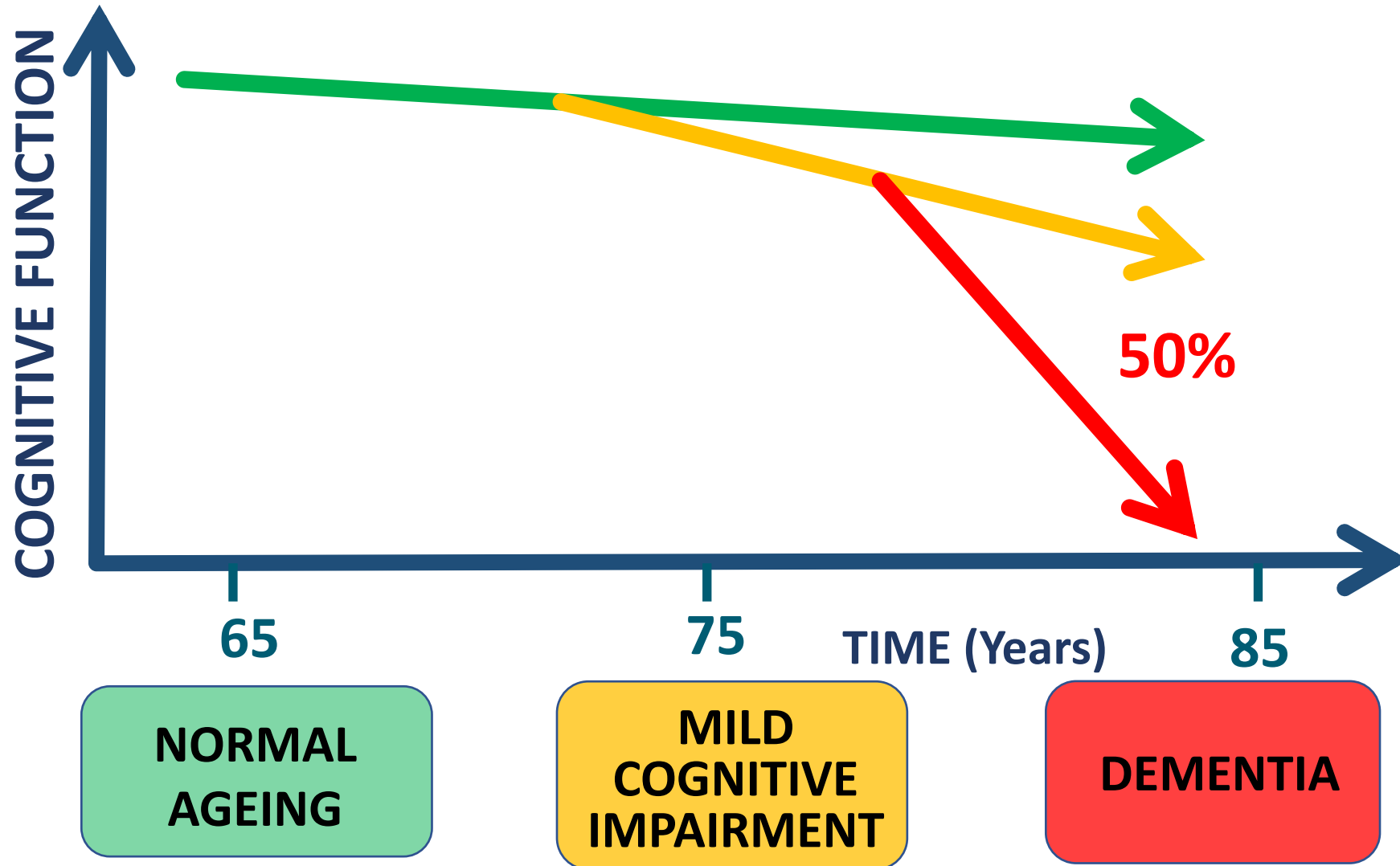
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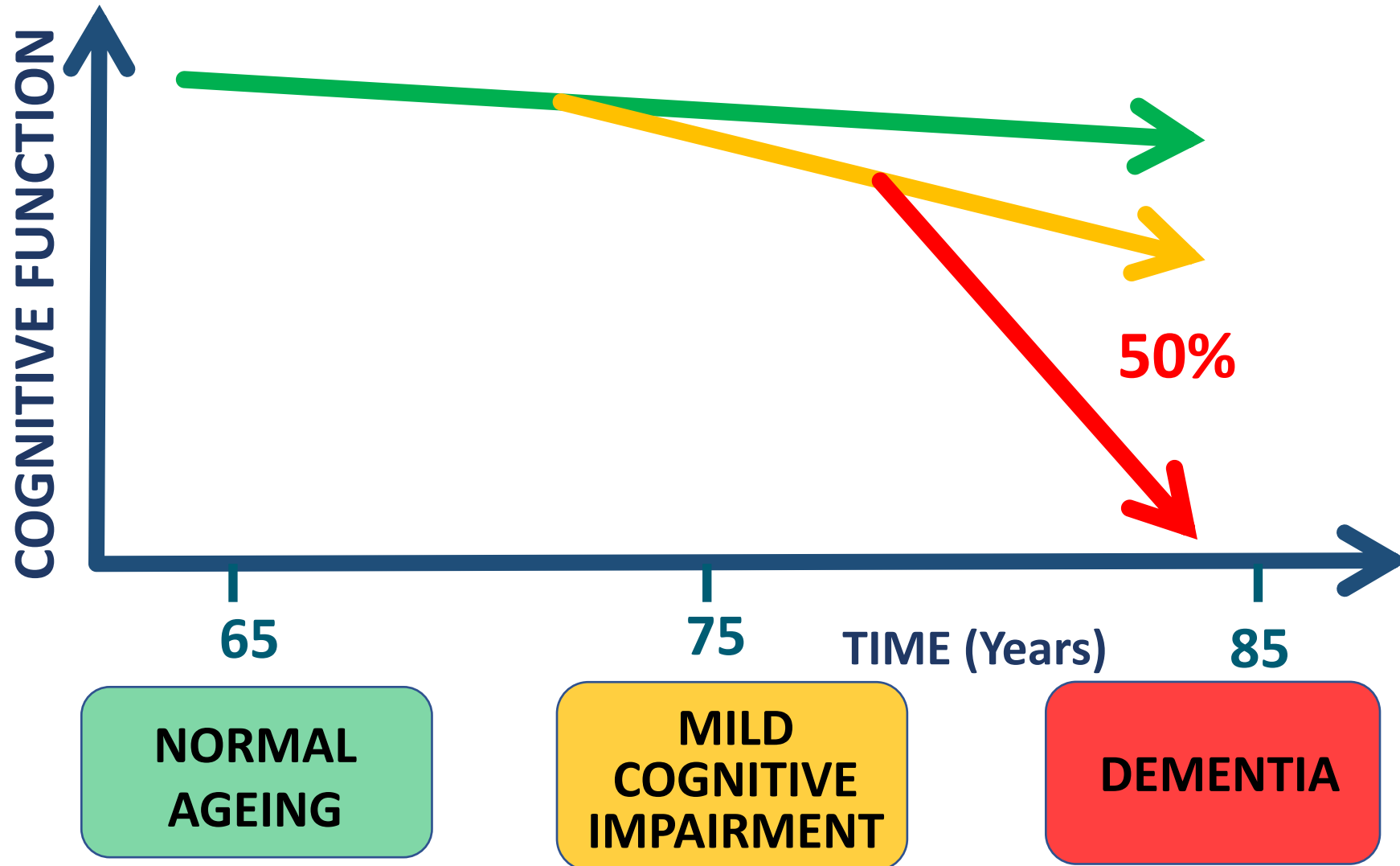
⁴The British Psychological Society; NICE National Clinical Practice Guideline 90. (2010)

⁵WHO (2023)

Cognitive Impairment Spectrum



Cognitive Impairment Spectrum



- Alzheimer's Disease
50-70%
- Vascular Dementia
Up to 20%
- Dementia with Lewy Bodies
10-15%
- Frontal Lobe Dementia
2%
- Other Dementia's

Age and Life Expectancy

Advancing age is the biggest risk factor for the development of Dementia

1 in 20 > Age 65

1 in 10 > Age 75

1 in 5 > Age 85

Differences in risk between men and women may be partially explained due to women's longer life expectancy

UK Males
79 y

UK Female
83 y

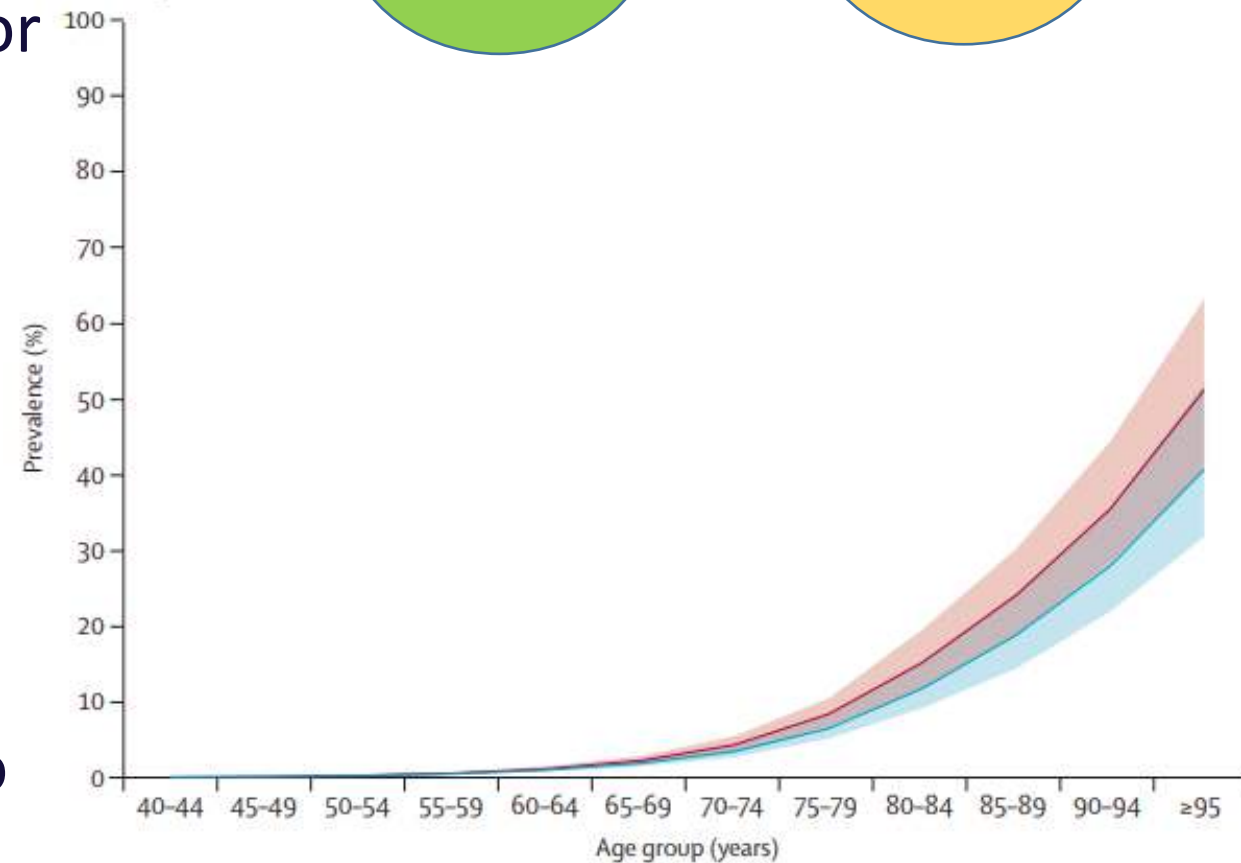


Figure: Global Prevalence of Dementia with age

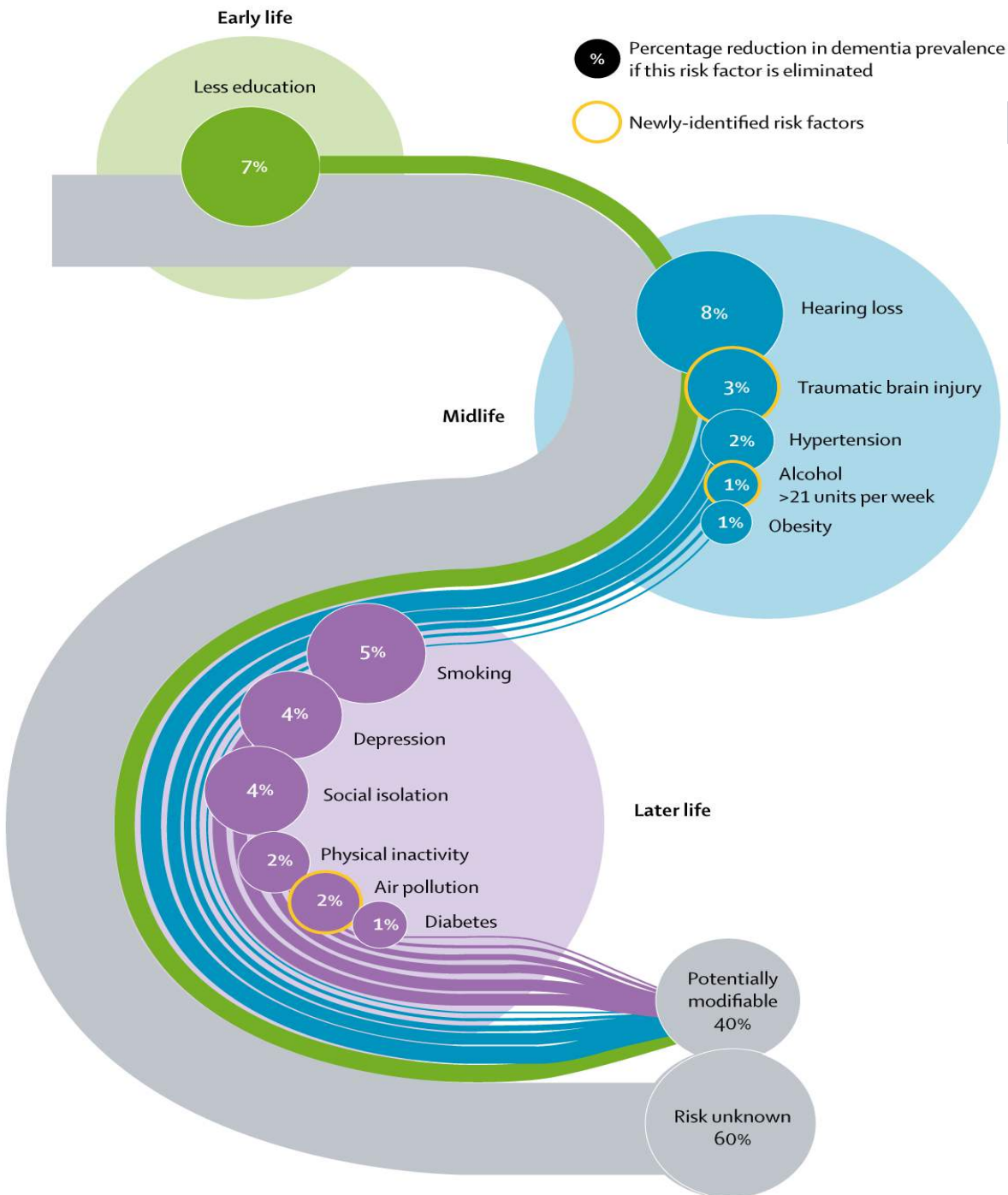
Genetics:

Apolipoprotein E (ApoE) – THE major genetic risk factor for Alzheimer's Disease

ApoE gene codes for a cholesterol-carrying protein that supports lipid transport and injury repair in the brain

ApoE comes in several different alleles^{12, 1}

- *ApoE* ϵ 2 is relatively rare
- *ApoE* ϵ 3 is the most common allele
- ***ApoE* ϵ 4 increases the risk of Alzheimer's disease**
 - heterozygotes X3 higher risk of Alzheimer's disease
 - homozygotes X15 higher risk of Alzheimer's disease



Modifiable Dementia Risk Factors

Novel life-course model of risk identifying 12 modifiable factors that could prevent 40% of all cases of dementia

Overview of Presentation

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- **Nutrition and the Ageing Brain**
- Future Directions for Research in Mental Health and Ageing





The Mediterranean Diet

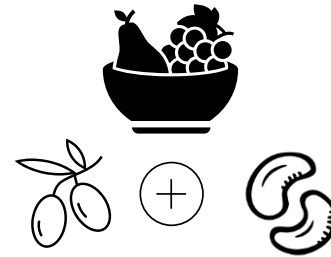


RCT Evidence: PREDIMED- NAVARRA

(Martínez-Lapiscina *et al.*, 2013).

Mediterranean diet

- (↑ fruit, vegetables, wholegrains, olive oil and fish)



Vs



MMSE and Clock Drawing Test (CDT)

Observational evidence

- Protects cognition function^{1, 2}
- Protective against depressive symptoms³

Findings:

Intervention with MedDiet +extra virgin olive oil and nuts had better cognitive scores

1. Shannon BMC Med. 2023 Mar 14;21(1):81; 2. Loughrey DG *et al.* Adv Nutr. 2017;8(4):571-586:

2. 3 Moore *et al.* Proceedings of Nutrition Society 2018

The MIND Diet Reduces the risk of developing dementia

MIND–Mediterranean-DASH Intervention for Neurogenerative delay

Eat These	Limit These
<p>Green leafy vegetables – 1 serving a day</p> <p>Other vegetables – 1+ servings a day</p> <p>Nuts – 5+ servings per week</p> <p>Berries – 2+ servings per week</p> <p>Beans – 4+ servings per week</p> <p>Whole grains – 3+ servings a day</p> <p>Fish – 1+ serving per week</p> <p>Olive Oil</p> <p>Poultry – 2+ servings per week</p> <p>Wine ?</p>	<p>Red Meat</p> <p>Butter and stick margarine – less than 1 tablespoon per day</p> <p>Cheese – less than one serving per week</p> <p>Pastries and sweets</p> <p>Fried or Fast food – less than once per week</p>

The MIND Diet Reduces the risk of developing dementia

MIND—Mediterranean-DASH Intervention for Neurodegenerative delay

Eat These

Green leafy

Other vegetables

Nuts – 5+

Berries –

Beans – 4

Whole grains

Fish – 1+

Olive Oil

Poultry – 2+

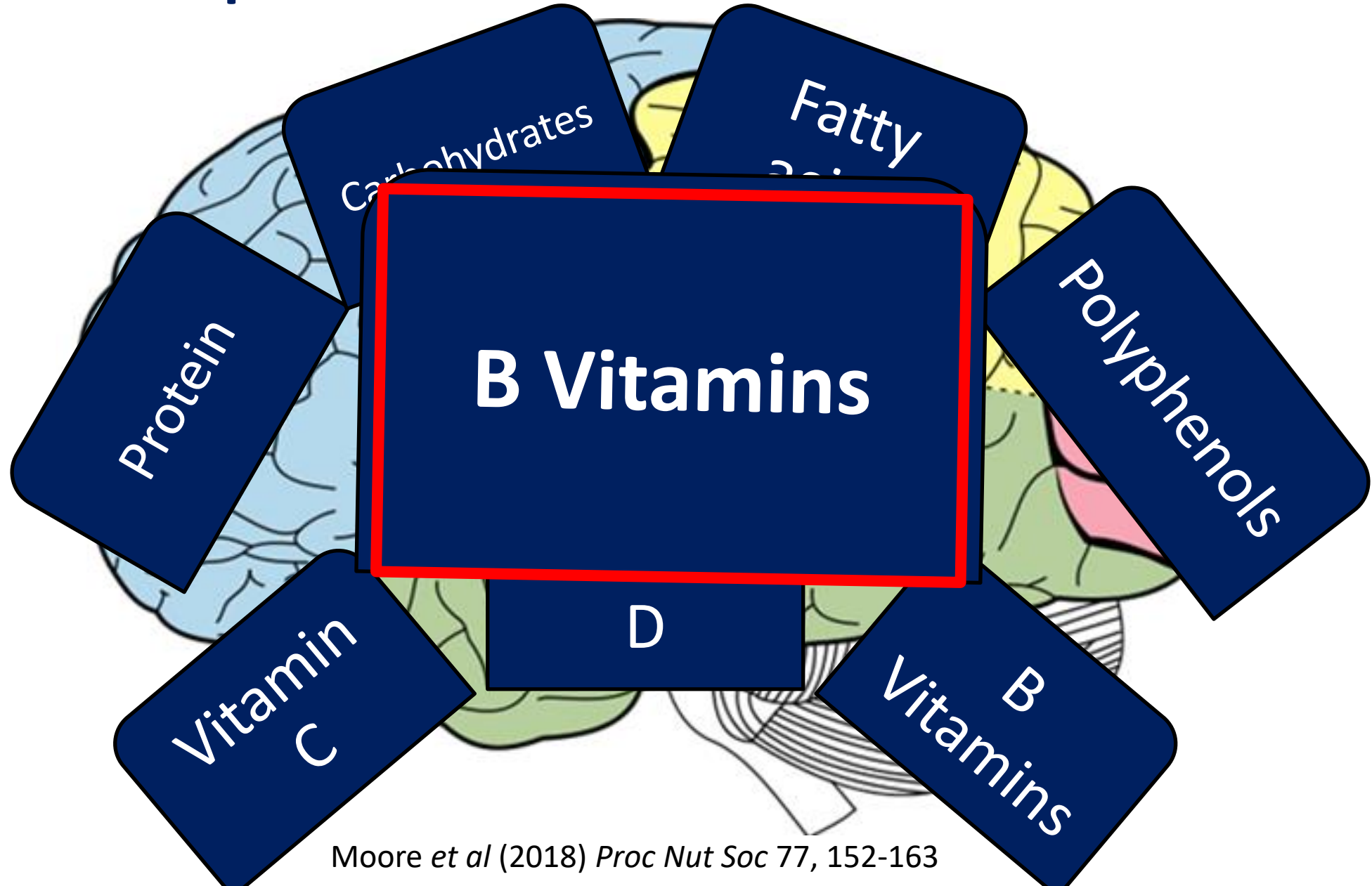
Wine ?

MIND Diet associated with

- 53% lower rate of Alzheimer's disease in those with highest MIND score
- 35% lower rate in those with moderate adherence to MIND diet

Morris et al. *Alzheimer's & Dementia*. 2015;11(9):1007-14.

Specific nutrients and brain health





TRINITY
COLLEGE
DUBLIN

The Trinity-Ulster-Department of Agriculture (TUDA) Study



5,186 adults
60 + years

Anthropometric details

**Demographic details and
measures of deprivation**

**Medications, supplements,
fortified foods**

**Lifestyle variables
Smoking, alcohol, dietary habits,
sun exposure**

**Medical history,
Heart disease, stroke, diabetes, hypertension,
falls, anxiety, depression**



The TUDA Study

Genetic: SNP & WGS

**Neuropsychiatric Test
MMSE, FAB, RBANS
HADS, Depression.**

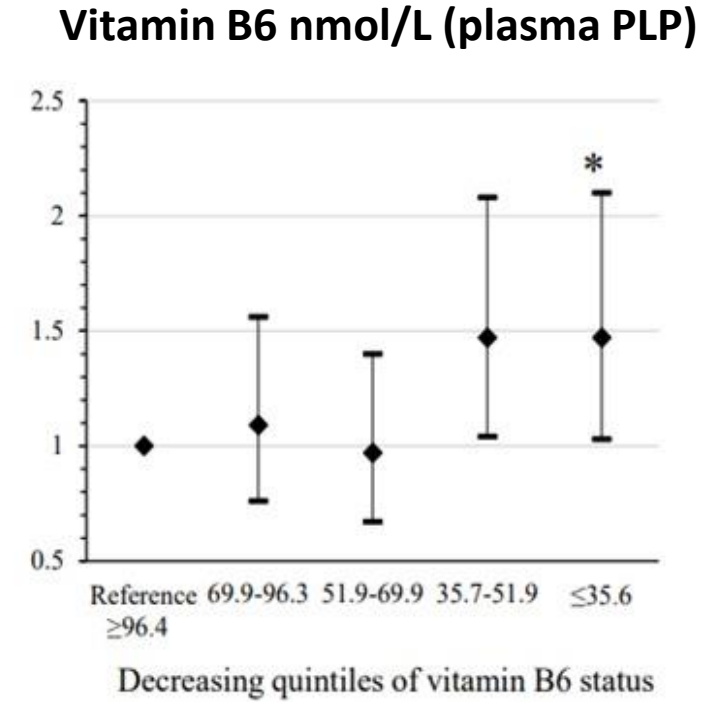
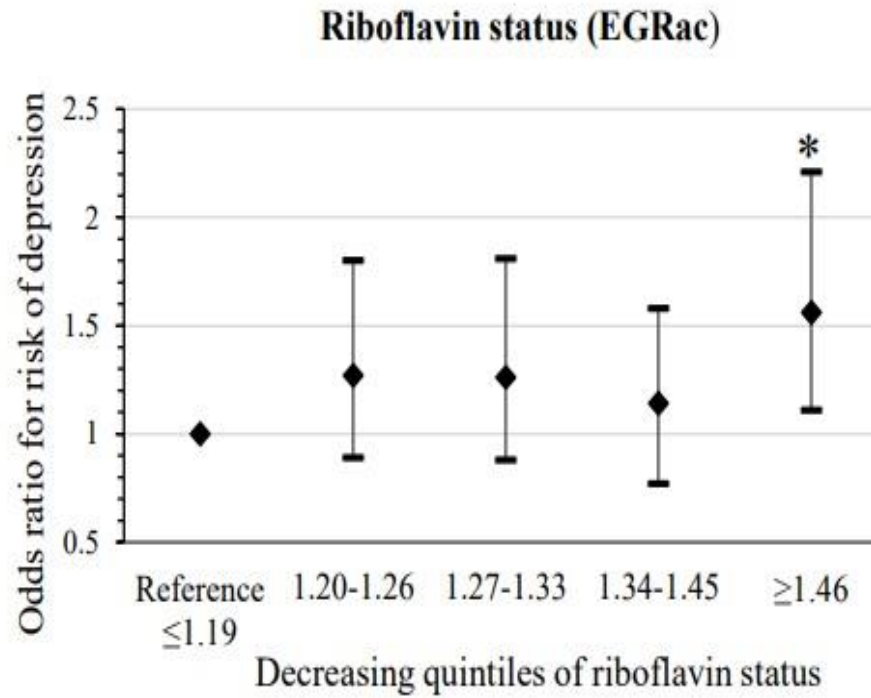
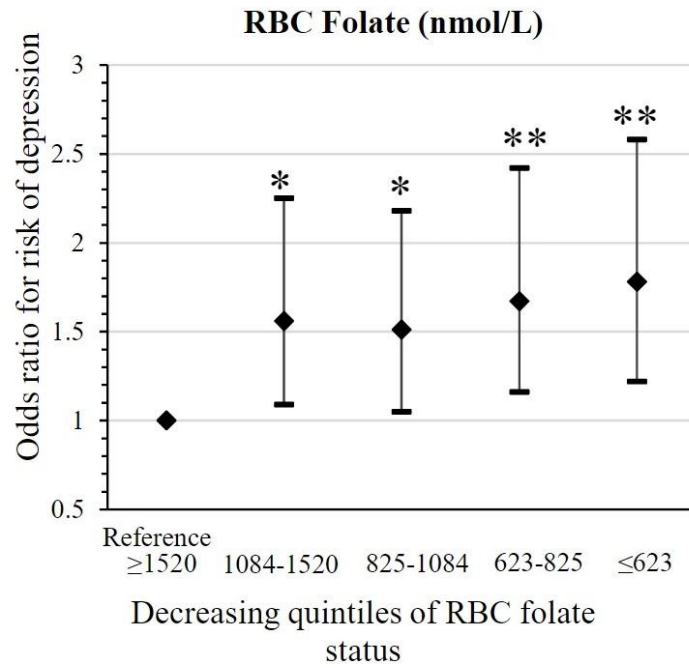
**DXA Bone scans, bone and
inflammatory biomarkers**

**Biomarkers of folate, vitamin
B12, B6, B2, vitamin D status**

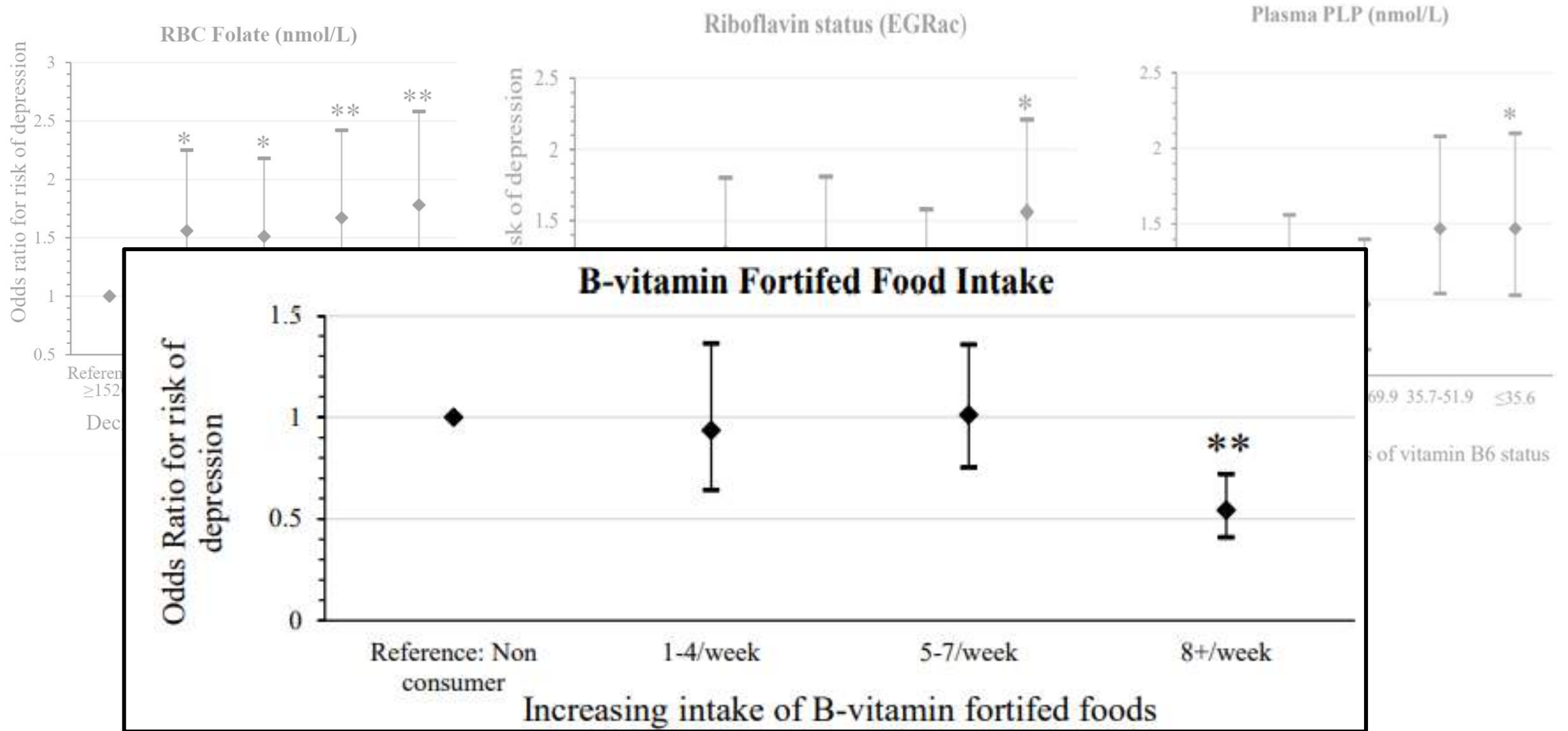
**Measures of frailty
Physical self maintenance, daily living
activities, mobility**

**Clinical parameters
BP, liver function, kidney function,
haematology, lipids, electrolytes**

Trinity-Ulster and Department of Agriculture (TUDA) study and depression



Trinity-Ulster and Department of Agriculture (TUDA) study and depression



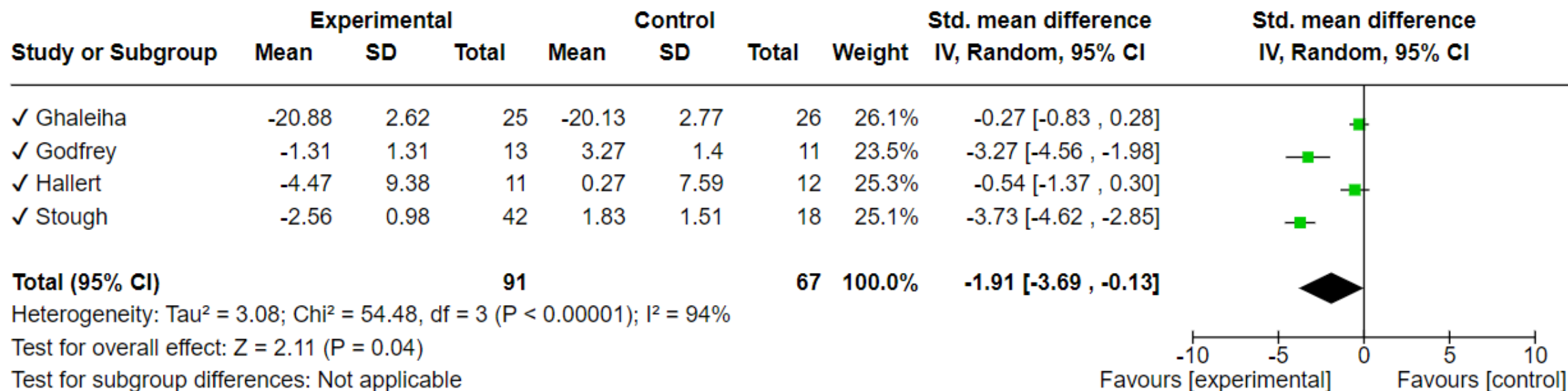
TUDA: Results in relation to depression

- Lower status of folate, B6 and riboflavin each increased risk of depression
- Consuming more than 1 portion/day fortified foods can contribute to a reduced risk of depression.

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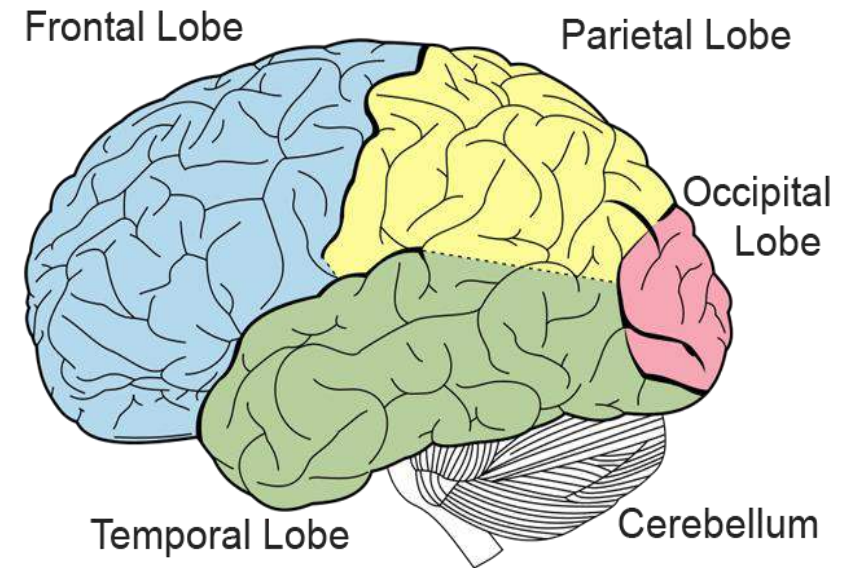
Meta-analysis of RCTs showing that B-vitamin supplementation has beneficial effect reducing the risk of depression



Neuropsychiatric Assessment

Cognition: Repeatable Battery for Neuropsychological Assessment (RBANS)

- Screening battery for global cognitive assessment
- Total RBANS score <80 generally indicative of cognitive impairment
- 5 component domains of cognition
 - Immediate Memory
 - Visuospatial /Constructional abilities
 - Language
 - Attention
 - Delayed memory



Depression: Centre for Epidemiologic Studies Depression Scale (CED-S)

Anxiety: Hospital Anxiety and Depression Scale (HADS)

TUDA follow-up cohort:

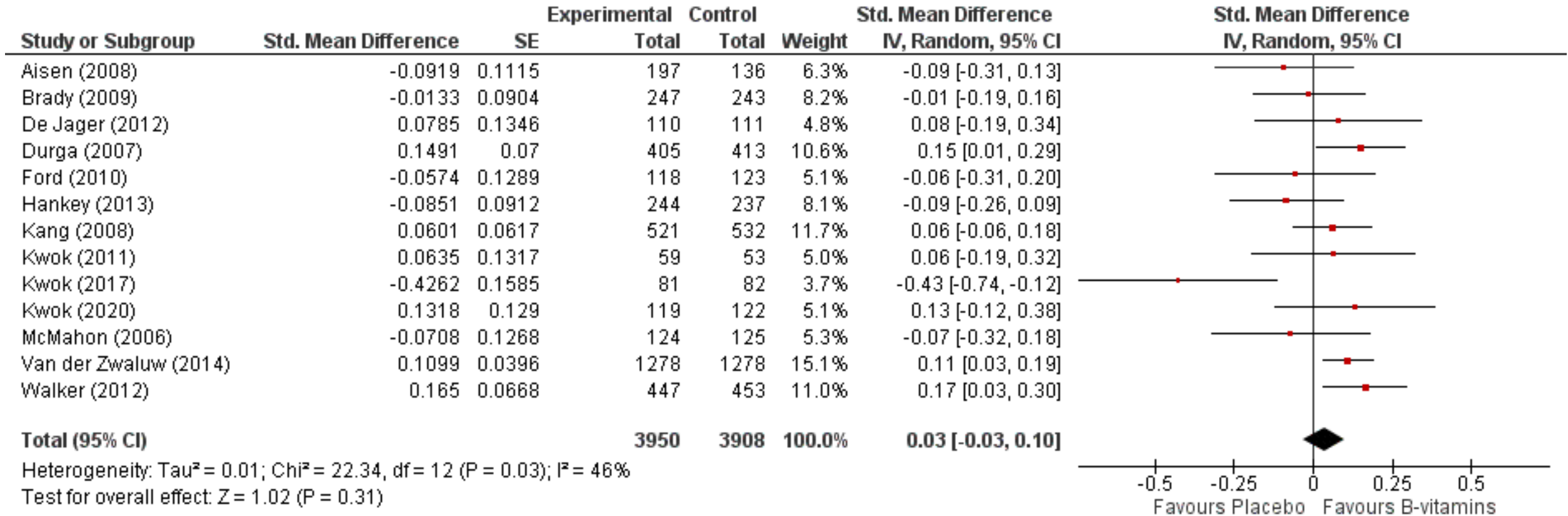
Risk of cognitive decline in relation to B-vitamin biomarkers at baseline

Age (years)	72.4 (5.0)		
Sex n (% Male)	274 (47)		
Age finished education	16.5 (3.0)		
B-vitamin Status	Odds Ratio	95% CI	P-value
Elevated homocysteine (≥ 13.0 $\mu\text{mol/L}$)	1.00	(0.67-1.51)	0.969
Low RBC folate (185-865 nmol/L)	1.21	(0.80-1.83)	0.367
Low serum vitamin B12 (58-251 pmol/L)	0.83	(0.56-1.25)	0.376
Low B6 (PLP 11.6-61.3 nmol/L)	1.75	(1.16-2.65)	0.008
Low riboflavin status (EGRAC)	1.63	(1.09-2.45)	0.018

Accelerated cognitive decline: rate of decline in the highest quartile for RBANS ≥ 7

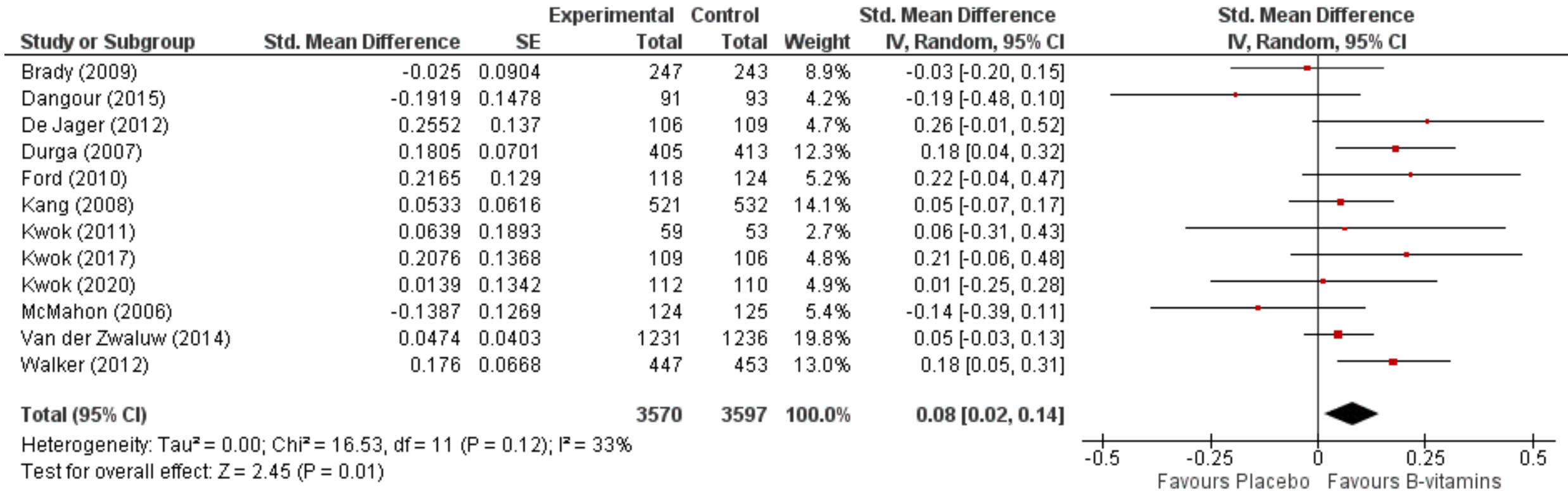
Binary logistic regression with adjustment for age, education, gender, depression and baseline cognitive score.

RCTs of B-Vitamins: Global Cognition



- There was no effect of B-vitamins on global cognition
 - No effect on executive function or processing speed (data not shown)
- Gordon et al. In preparation

RCTs of B-Vitamins: Memory



B-vitamin supplementation had a beneficial effect on memory

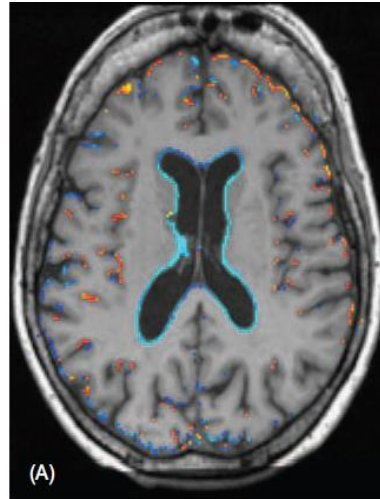
Gordon et al. In preparation

The VITACOG Trial: Intervention with B-vitamins for 2 years

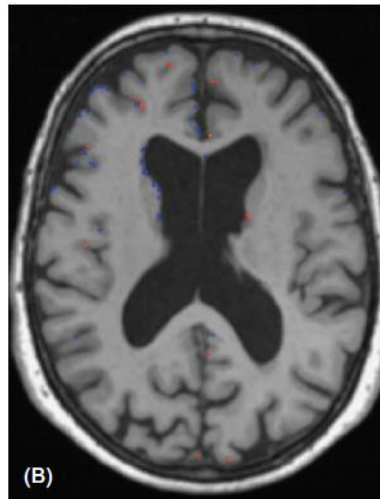
Cognitive Outcomes

- B-vitamin treatment stabilized executive function (CLOX)
- In participants with baseline homocysteine $\geq 11.3 \mu\text{mol/L}$, B vitamin treatment benefited
 - Global cognition
 - Episodic memory
 - Semantic memory

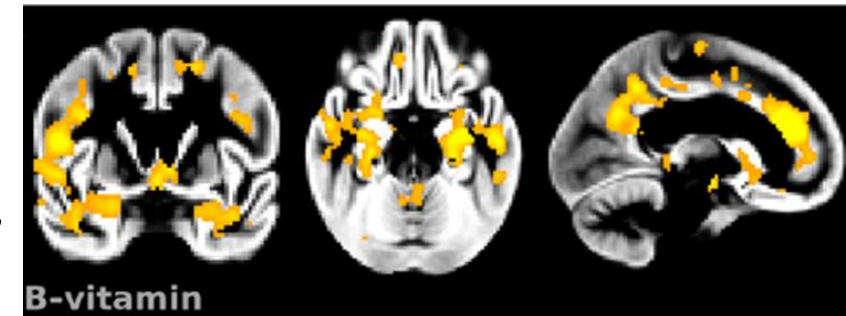
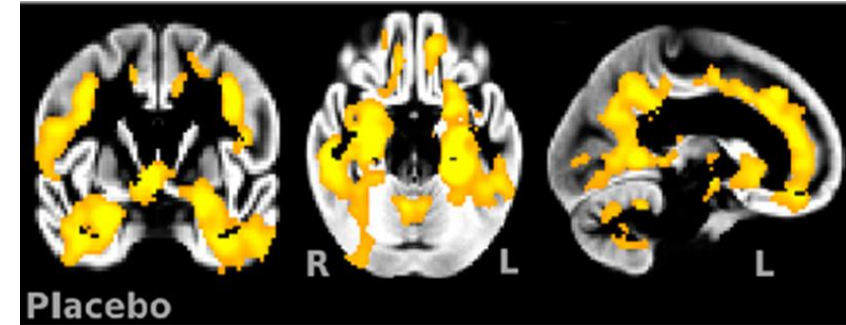
Neuroimaging Outcomes



A: Placebo
Rate of Atrophy:
2.5% per year



B: B Vitamins
Rate of Atrophy:
0.46% per year



Significantly greater loss in Grey Matter Volume in the placebo group
Douaud *et al.* (2013) *Proc of Natl Acad Sci USA* 110(23):9523-9528

The BrainHOP trial

Aim

To investigate the effect of a 2 year B-vitamin intervention (folic acid 400µg/d; vitamins B12 10µg/d;, B6 10mg/d and B2 10mg/d) on cognitive function in older adults.

Hypothesis

B-vitamins will help to maintain better cognitive function in older adults over a 2-year period.

Design: 2 year randomised controlled trial

BrainHOP- Intervention Results

Specific Cognitive Domains

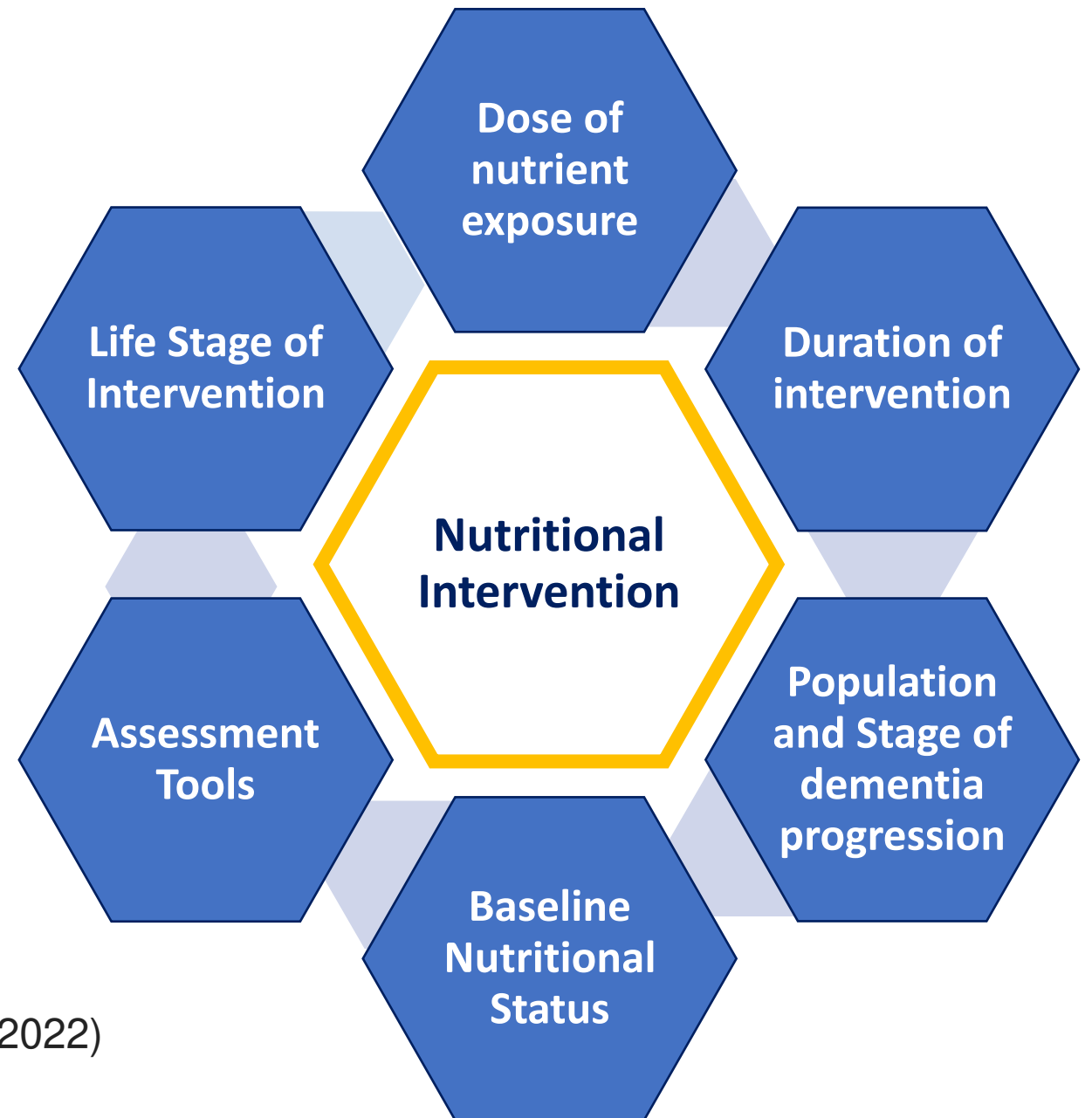
Cognitive Function	Placebo n 125	B-vitamin n 124	P-value
	Change	Change	
RBANS Global Score	2.5 (0.9)	4.2 (1.0)	0.194
<i>RBANS Specific Domains</i>			
Immediate Memory	2.3 (1.2)	1.7 (1.2)	0.739
Visuospatial	-2.7 (1.4)	3.7 (1.4)	0.002
Language	8.6 (0.9)	7.7(0.9)	0.515
Attention	-0.7 (1.2)	-0.1 (1.2)	0.710
Delayed Memory	1.7 (1.2)	2.2 (1.2)	0.818

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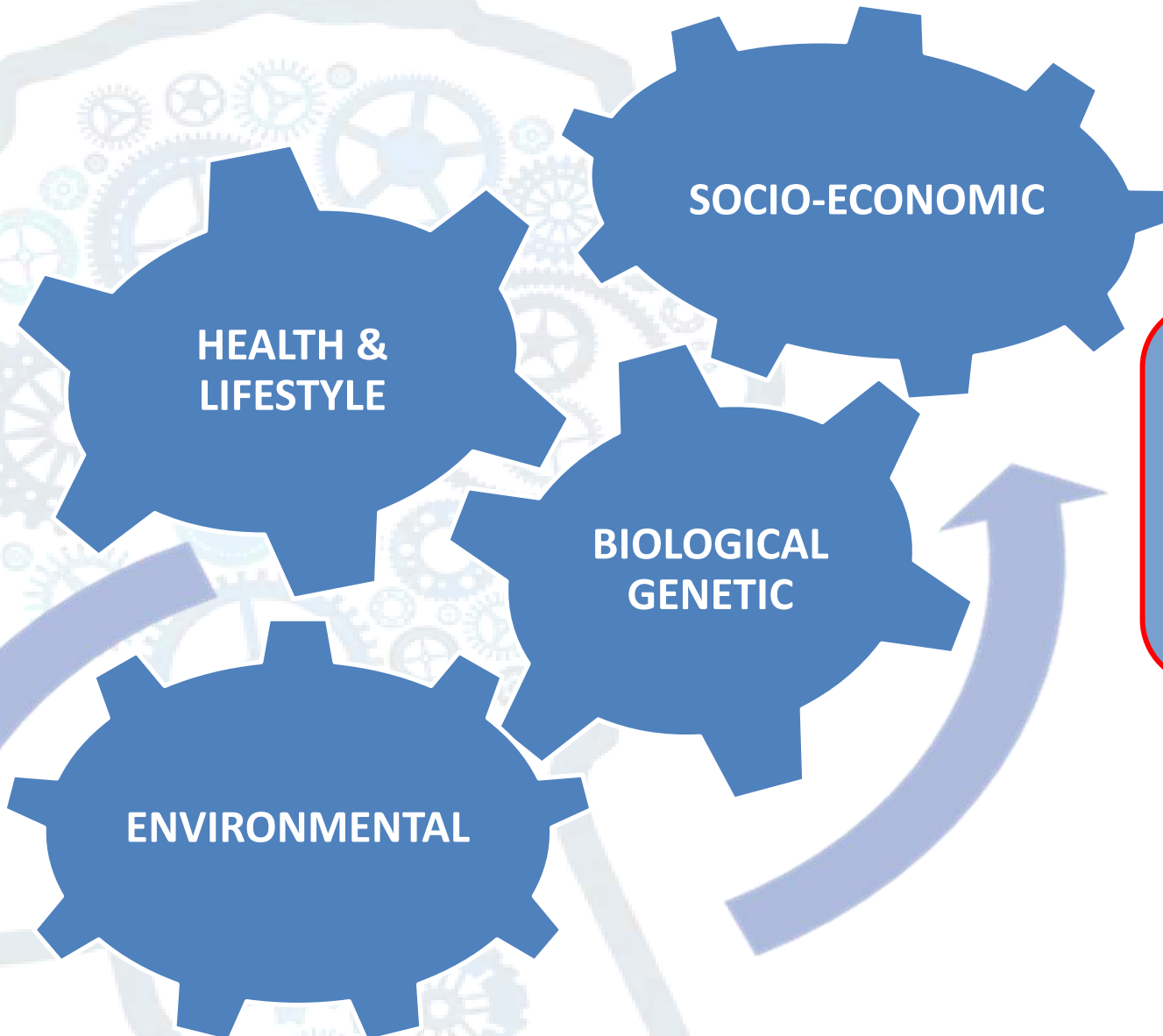


Key Challenges in Nutrition Intervention Trials



Nutrition for Dementia Prevention Working Group (2022)
Lancet Healthy Longev, 3(7), e501-e512.

Future Directions for Mental Health Research



Interdisciplinary research into these interactive effects utilising novel technologies is required

Effect of Area-Level Socioeconomic Deprivation on Risk of Cognitive Dysfunction in Older Adults

Adrian McCam, PhD,* Helene McNulty, PhD,*^{1b} Jan Rigby, PhD,[†] Catherine F. Hughes, PhD,*
Leane Hoey, PhD,* Anne M. Molloy, PhD,[‡] Conal J. Cunningham, MD,[§] Miriam C. Casey, MD,[§]
Fergal Tracey, MD,[‡] Maurice J. O’Kane, MD,*^{*} Kevin McCarroll, MD,[§] Mary Ward, PhD,*
Katie Moore, BSc,* J.J. Strain, PhD,* and Adrian Moore, PhD^{††}

Map showing the distribution of TUDA participants from (A) NI and (B) RoI



GREEN - Least-deprived 20%;
RED - Most-deprived 20%

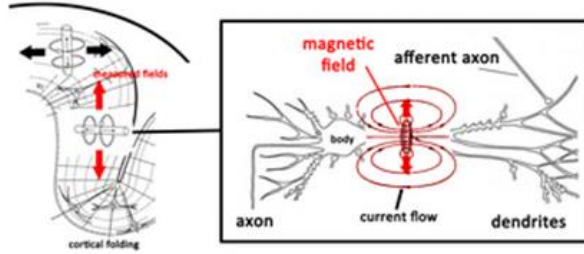
Lessons learnt to date from the TUDA study

We found that older adults (n=5186) living in the **most deprived (vs least)** areas of NI and ROI had

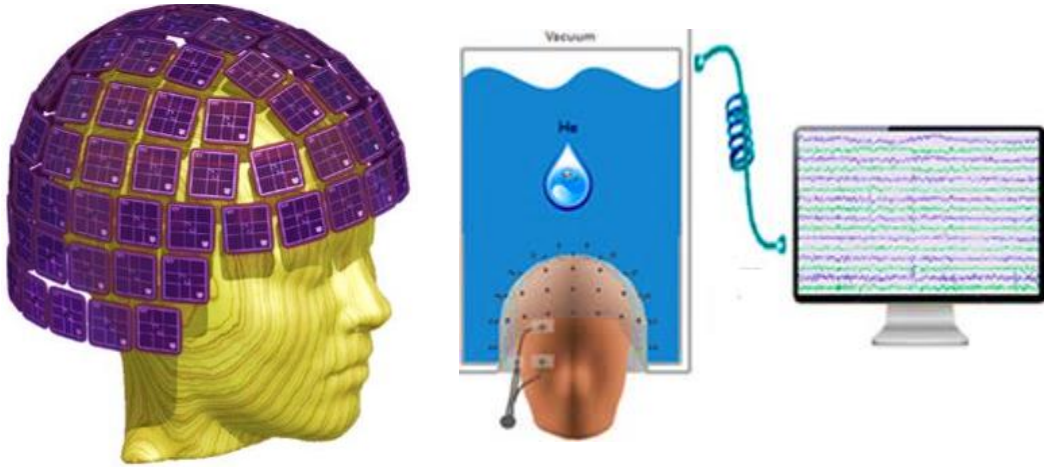
- less formal education;
- higher rates of smoking and alcohol consumption;
- higher rates of obesity;
- higher blood pressure;
- higher risk of diabetes;
- **40% higher risk of cognitive dysfunction**



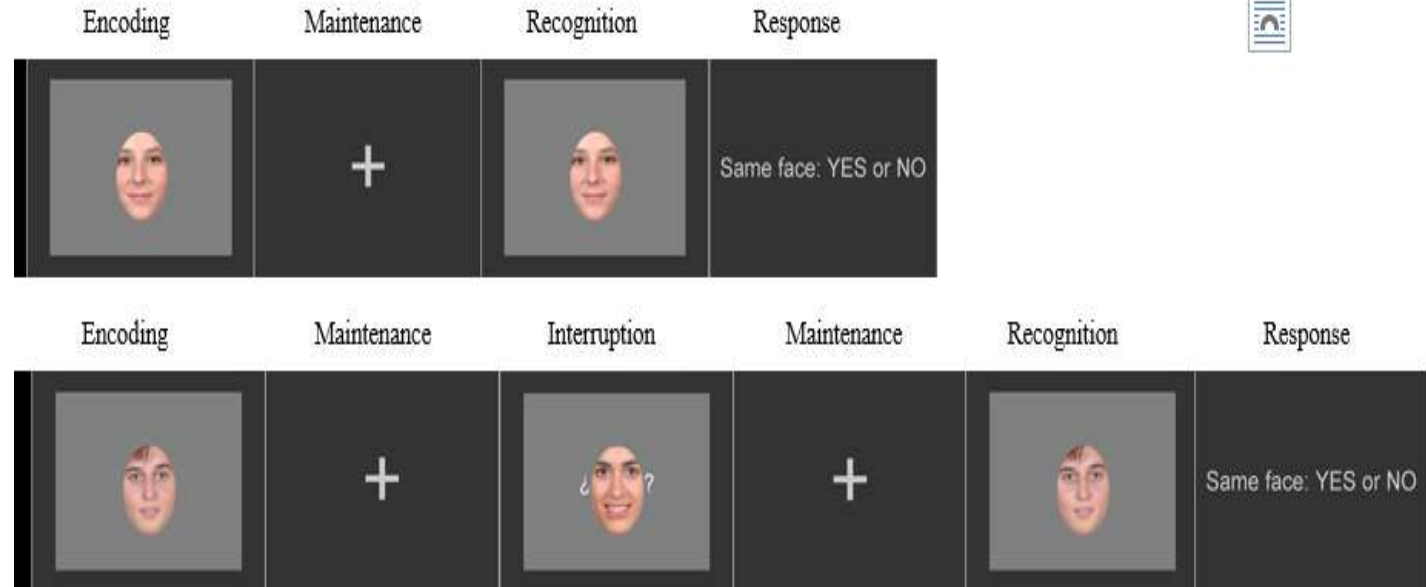
Magnetoencephalography (MEG)



Working Memory Paradigm¹



Maps brain activity by measuring the magnetic fields produced by neuronal activity with sub-millisecond precision.



¹Fernando Maestú and Noelia Serrano Martínez
Laboratory of Cognitive and Computational Neuroscience (LNCyC), University of Madrid, Spain.

BrainHOP Trial Results:

Accuracy in working memory task in response to B-vitamins

	% Accuracy		P*
	Placebo	Treatment	
No interference	87.7 (13.9)	91.2 (12.0)	0.346
Interference	76.7 (20.9)	92.4 (7.3)	0.041

Data presented as means (SD) *Data analysed using Mann-Whitney Test.

Delta band power, before and after interference in a working memory task

Delta (1-4 Hz)

Preliminary results suggest that better B-vitamin status is associated with improved neuronal functioning



Application of AI to the TUDA Study Dataset

Dementia Data Analytics Project:



Identifying Key Predictors of Cognitive Dysfunction in Older People Using Supervised Machine Learning Techniques: Observational Study

Debbie Rankin, BSc, PhD, Michaela Black, BSc, PhD, [...], and Helene McNulty, BSc, PhD

[Additional article information](#)

Associated Data

▶ [Supplementary Materials](#)

Aim: To identify key predictors of poorer cognitive performance in older people using machine learning techniques

Results: Frailty, age finished education, and memory concerns, plasma homocysteine, plasma PLP and HbA1c were identified as important determinants of cognitive dysfunction

Conclusions

These predictors could be used as a screening tool to identify patients that need further assessment and improve the efficiency of dementia screening



B-vitamins and Mental Health – Results Summary

- **Cognitive Health Outcomes - Results from the TUDA Study**
- Low status of vitamin B6 and riboflavin were each associated with and an accelerated rate of cognitive decline
- Combined B-vitamin supplementation *at low doses for 2 years* resulted in improved visuospatial cognitive function
- Objective evidence from MEG analysis suggests that better B-vitamin status results in improved neuronal functioning

- **Mental Health Outcomes – Results from the TUDA Study**
 - Lower status of folate, B6 and riboflavin each increased risk of depression
 - Consuming more than 1 portion/day fortified foods can contribute to a reduced risk of depression.

B-vitamins and Mental Health – Results Summary

- **Cognitive Health Outcomes - Results from the TUDA Study**

- Low status of vitamin B6 and riboflavin were each associated with and an
- acc

- Cor Optimising nutritional status in older populations may have
- imp important impacts on brain health. This in turn would help to

- Obj preserve better quality of life in ageing.
- res

- **Mental Health Outcomes – Results from the TUDA Study**

- Lower status of folate, B6 and riboflavin each increased risk of depression
- Consuming more than 1 portion/day fortified foods can contribute to a reduced risk of depression.

Take Home Messages

- Concerns about the rising rates of dementia are real, but not inevitable
- Focusing on **modifiable risk factors**, particularly in middle age, will play an important role in prevention of dementia in later life
- **Nutrition** can play a key role albeit one that is often overlooked
- Future research in this area **needs Interdisciplinary** research approaches and application of **state-of-art technologies**

My thanks to...co-investigators, collaborators, funders and research volunteers

NICHE

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Dr Geraldine Horigan
Dr Adrian McCann

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Local GP’s

Environmental Sciences at Ulster

Prof Adrian Moore

Computing and Engineering

Prof Michaela Black
Prof Jonathan Wallace
Dr Debbie Rankin
Dr Paul Carlin



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