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Longevity and Biological Ageing: Enhancing Health into Advanced Age



SESSION 2

Professor Helene McNulty

B Vitamins, Nutritional Epigenomics and Age-related Disease

11:15-12:00pm

An event by:  Nutritional Medicine Institute

Platinum sponsors:   regenerus labs

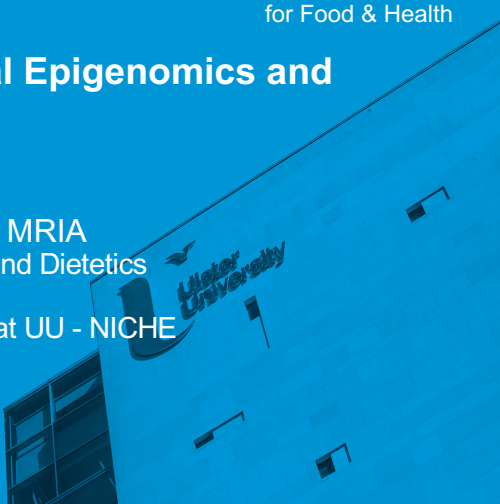


NICHE
Nutrition Innovation Centre
for Food & Health

B vitamins, Nutritional Epigenomics and Age-related Disease

Helene McNulty PhD RD MRIA
Professor of Human Nutrition and Dietetics
Director of Nutrition Research at UU - NICHE

'Global Excellence in Nutrition Research & Education'



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Presentation Outline

- Folate and related B vitamins in one-carbon metabolism
- Roles of B vitamins in human health and prevention of age-related disease
- Precision nutrition and novel role of riboflavin in blood pressure
- Impacts

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Metabolic role of folate

One-Carbon Metabolism

Transfer and utilisation of one-carbon units for key biological reactions, including

- biosynthesis of DNA and RNA
- amino acid metabolism (serine, glycine, methionine)
- methylation processes (DNA, RNA, proteins, phospholipids)
- when methylation is impaired (owing to low folate), plasma homocysteine will be elevated

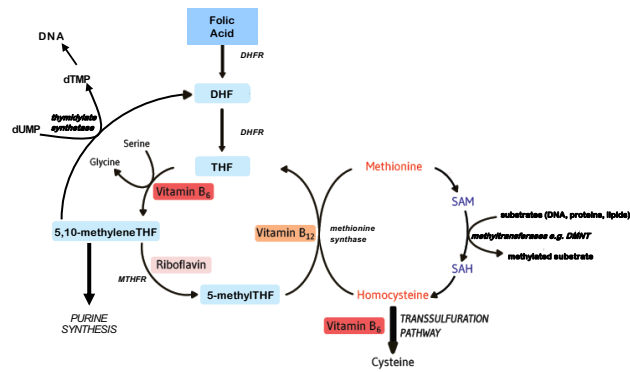
Other B vitamins - B12, B6, riboflavin

- essential for folate recycling and functioning
- folate metabolism will become impaired with deficiency of any of the 3 other B vitamins - even if folate adequate

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Folate functioning within one-carbon metabolism

Other B vitamins are involved



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Terminology Folate vs Folic acid

- **Folates:**
 - Natural forms of the vitamin
 - as found in plant and animal tissues
- **Folic acid:**
 - Synthetic form
 - as found in supplements, fortified foods
- Chemical differences between folate and folic acid
 - important implications for **folate bioavailability** from the diet

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The Challenge

Natural food folates compared with folic acid

- **Folic acid** is
 - fully oxidised
 - a monoglutamate
- **Food folates** are
 - reduced molecules
 - predominantly polyglutamates but converted to monoglutamates for absorption
- **The potential to optimise folate** status by means of natural food folate sources only is very limited
 - unstable during cooking (McKillop et al 2002)
 - incomplete bioavailability once ingested (McNulty & Pentieva 2004)

McKillop et al *BJN* 2001;285:2981-6
McNulty & Pentieva *Proc Nutr Soc.* 2004; 63(4):529-36.

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Options to achieve optimal folate status

Intervention	Strategy shown to be effective in	
	individuals	populations
Natural food folates	no	no
Folic acid supplementation	yes	no
Folic acid-fortification	yes	yes

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Folate and related B vitamins throughout the Lifecycle	
Known and emerging roles in human health	
	Strength of Evidence
Early life	
• Maternal health in pregnancy	Conclusive
• Fetal development	Conclusive
• Folate in pregnancy and Offspring health	New
Later life	
• Prevention of heart disease/stroke	Convincing
• Cancer prevention	Promising
• Bone health	Possible role
• Cognitive function in ageing	Possible role

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Beyond NTD
Are there beneficial effects of folic acid intervention at other lifecycle stages ?
What about the metabolically-related B vitamins?
Heart health?
Brain health?

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Folate, related B vitamins and CVD risk

Summary of the evidence

- Elevated plasma homocysteine
 - ✓ implicated in CVD and stroke in particular
 - ✓ very responsive to lowering with folic acid
- Folate-related B vitamins
 - ✓ required for normal folate functioning
 - ✓ additional roles in preventing homocysteine accumulation (*B-12 and B-6*)
 - ✓ particularly important in the face of genetic predisposition to impaired folate metabolism (*riboflavin*)
- Potential benefits of folic acid and related B vitamins in CVD prevention may
 - ✓ relate to their homocysteine-lowering effects *or*
 - ✓ be independent of homocysteine

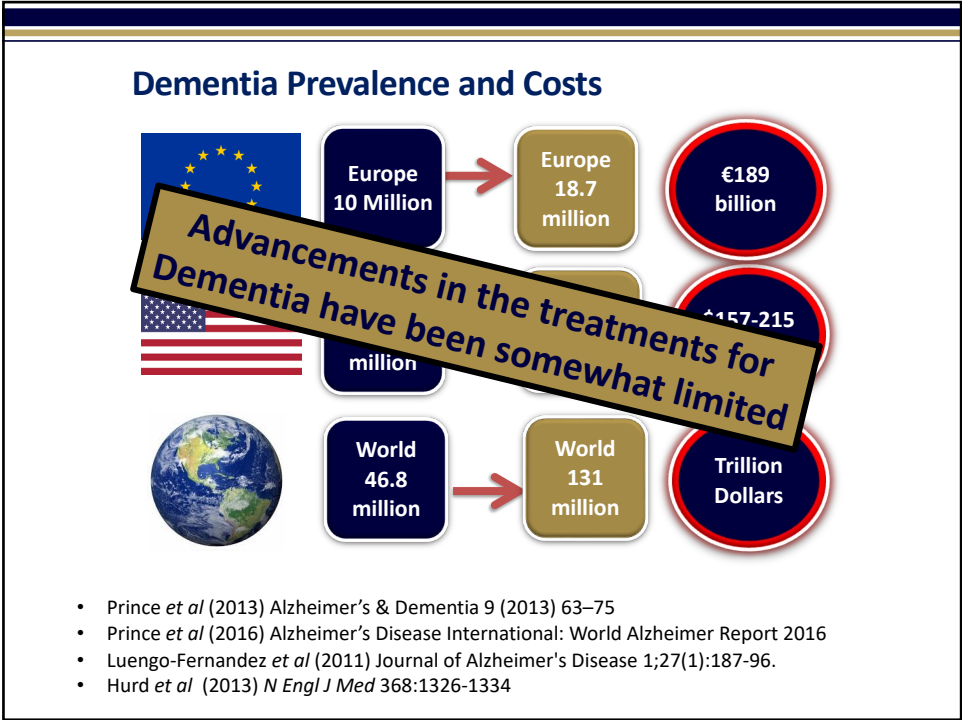
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Randomized Trials of folic acid and risk of stroke: a meta-analysis

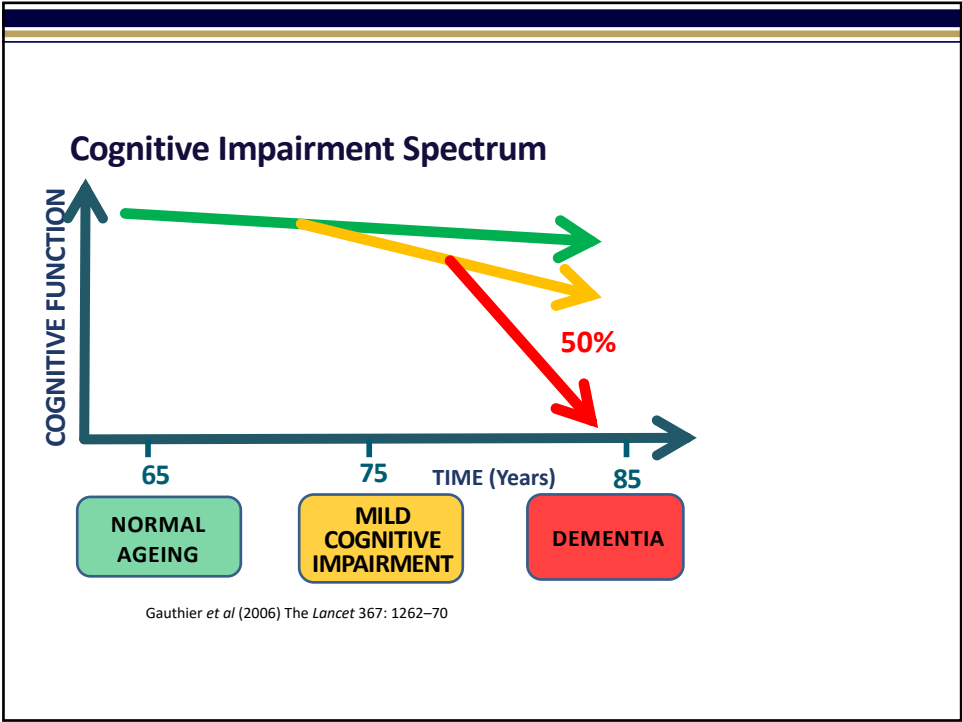
Wang et al 2007 *Lancet*;369:1876-82

	Relative risk (95% CI)	P value
Overall	0.82 (0.68-1.00)	0.045
Duration of intervention		
≤36 months	1.00 (0.83-1.21)	0.95
>36 months	0.71 (0.57-0.87)	0.001
Homocysteine lowering		
<20%	0.89 (0.55-1.42)	0.62
≥20%	0.77 (0.63-0.94)	0.012
History of stroke		
Yes	1.04 (0.84-1.29)	0.71
No	0.75 (0.62-0.90)	0.002

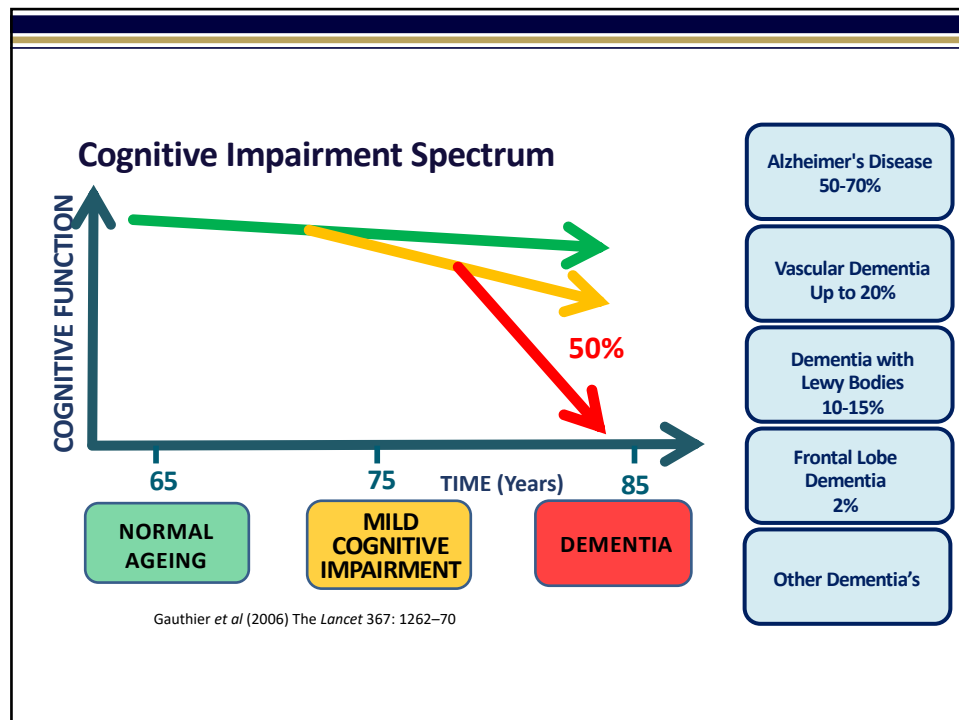
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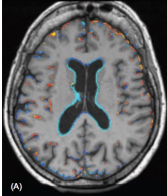
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B-vitamins and Cognitive Function: RCTs		
Author	Dose (mg/d)	Findings
McMahon 2006	B12 (0.5), FA (1) and B6 (10) for 2 years <i>n</i> 253	No effect
Durga 2007	FA (0.8) for 3 years <i>n</i> 836	Improved cognition
Kwok 2010	B12 (1) and FA (5) for 2 years <i>n</i> 140	No effect
Walker 2012	B12 (0.1) and FA (0.4) for 2 years <i>n</i> 900	Improved cognition
VITACOG Smith 2010 De Jager 2012 Douaud 2013 Jernerén 2015	B12 (0.5), FA (0.8) and B6 (20) for 2 year <i>n</i> 266	Improved cognition MRI: ↓grey matter ↓ brain atrophy by 30%
Van der Zwaluw 2014	B12 (0.5), FA (0.4) and D3 (0.15) for 2 years <i>n</i> 856	No effect

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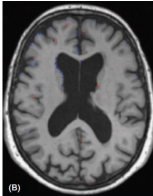
The VITACOG Study

Neuroimaging Outcomes



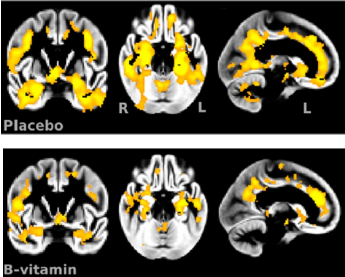
A: Placebo

*Rate of Atrophy:
2.5% per year*



B: B Vitamins

*Rate of Atrophy:
0.46% per year*



Placebo

B-vitamin

Significantly greater loss in Grey Matter Volume in the placebo group

Smith *et al.* (2010) *Plos One* 5(9):e1224

Douaud *et al.* (2013) *Proc of Natl Acad Sci USA* 110(23):9523-9528

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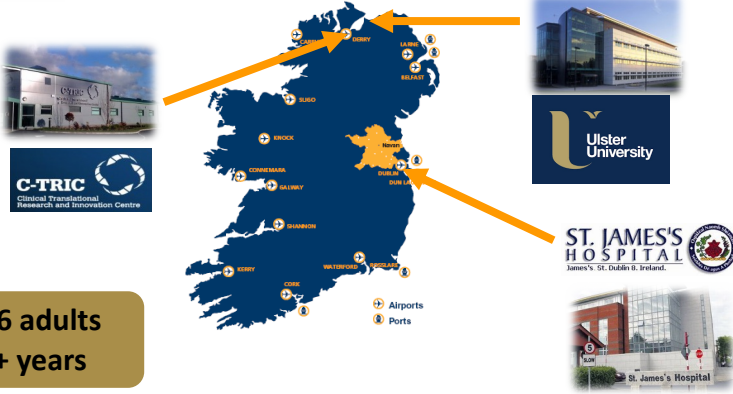


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The Trinity-Ulster-Department of Agriculture (TUDA) Study



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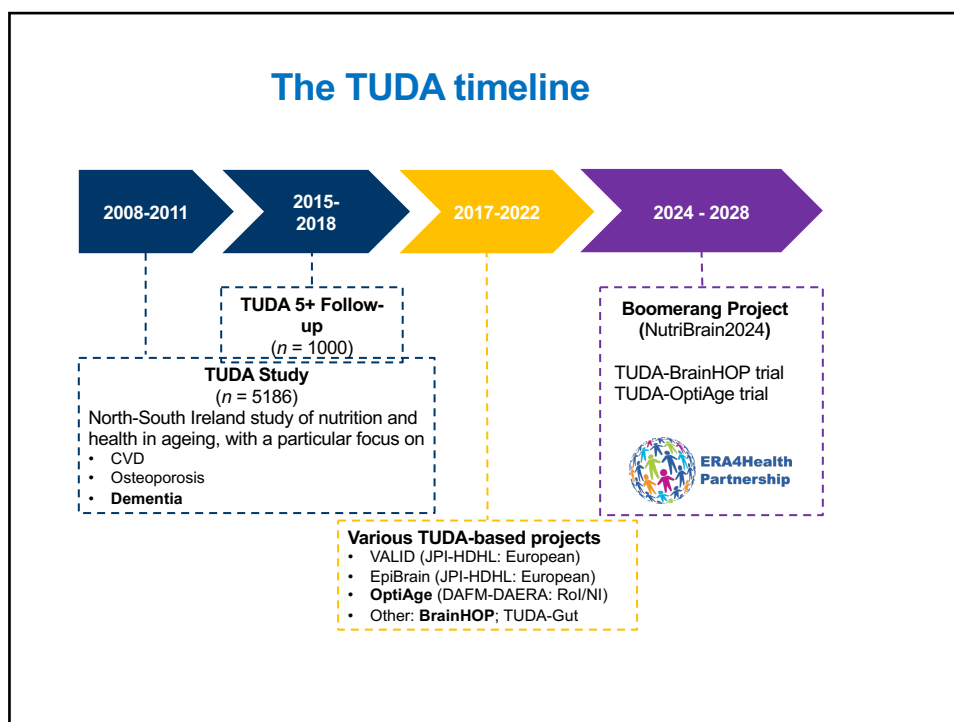


**ST. JAMES'S
HOSPITAL**
James's, St. Dublin 8, Ireland.

**5,186 adults
60 + years**

✈ Airports
🚢 Ports

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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)

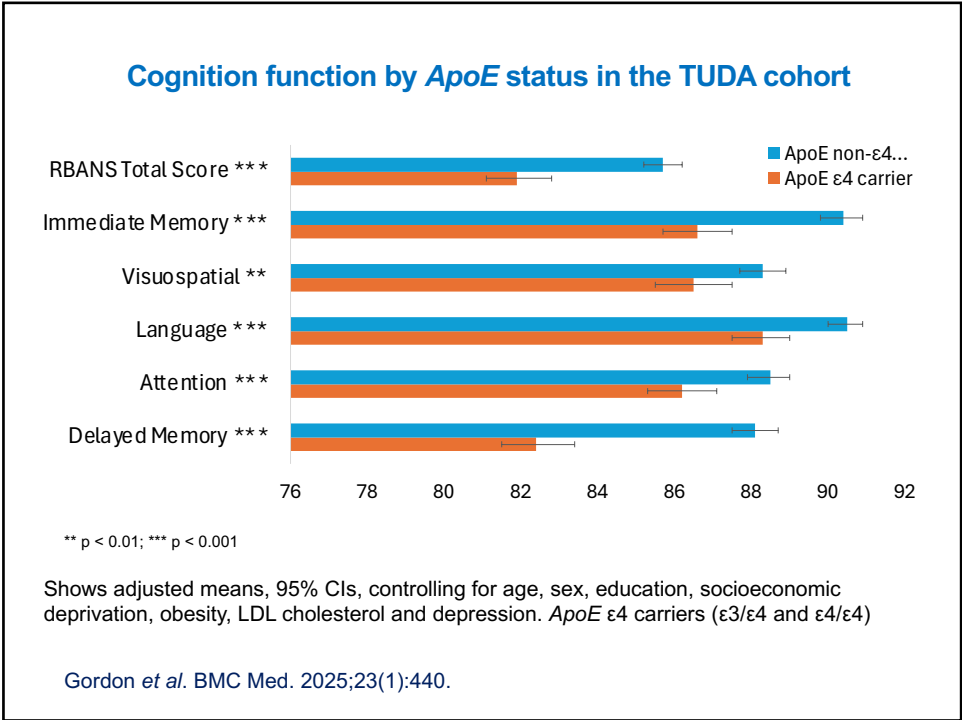
Anxiety: Hospital Anxiety and Depression Scale (HADS)

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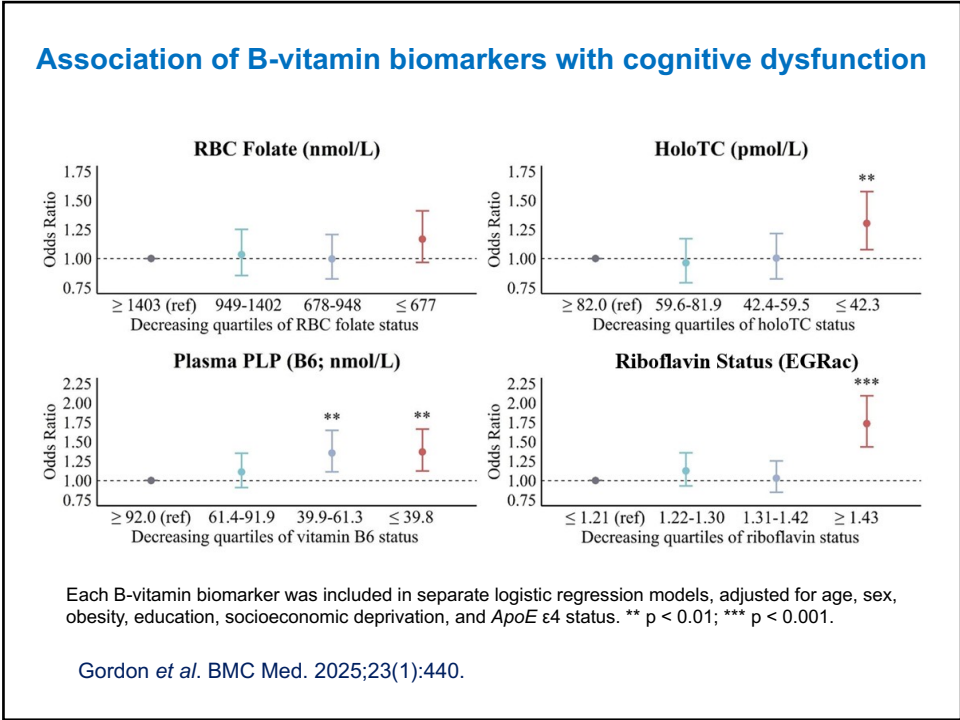
Apolipoprotein E (ApoE) – Major risk factor for AD

- ▶ ApoE is a cholesterol carrying protein that supports lipid transport and injury repair in the brain
- ▶ ApoE alleles
 - ε2 is relatively rare (Frequency ~ 8%)
 - ε3 is the most common allele (78%)
 - ε4 increases the risk of AD (14%)
- ▶ Some studies have investigated potential gene-nutrient interactions
 - Individuals with ApoE ε4 combined with low B12 had the lowest cognitive function scores

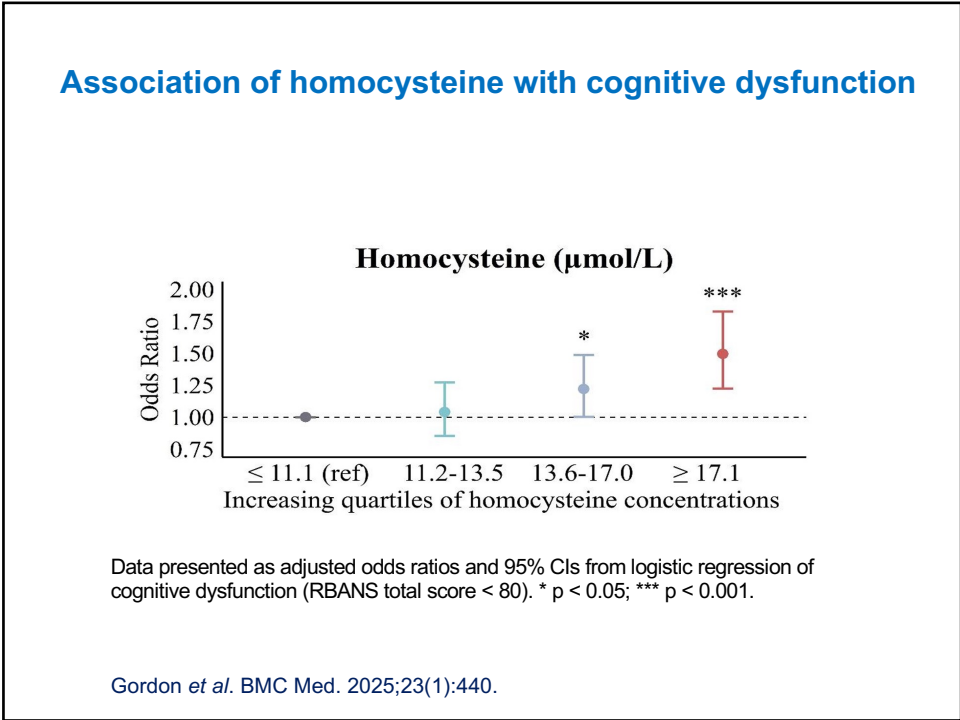
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Interactions between B-vitamins and ApoE ε4 on cognitive dysfunction

	β	OR _{adj}	95% CI	P
ApoE ε4 x lowest B-vitamin status				
RBC folate	0.188	1.21	0.89 – 1.63	0.222
Serum folate	-0.068	0.93	0.69 – 1.27	0.662
Total vitamin B12	0.184	1.20	0.89 – 1.63	0.231
HoloTC	0.336	1.40	1.03 – 1.90	0.030
Plasma PLP	0.107	1.11	0.82 – 1.51	0.488
EGRac (Riboflavin)	0.041	1.04	0.77 – 1.41	0.789
Plasma total Hcy	0.413	1.51	1.11 – 2.05	0.008

P-values were obtained from logistic regression analysis of cognitive dysfunction (RBANS total score < 80).
ApoE ε4 status (ε3/ε4 and ε4/ε4) and each B-vitamin biomarker were analysed in separate regression models, comparing the lower quartiles to the higher quartiles of B-vitamin status.

Gordon *et al.* BMC Med. 2025;23(1):440.

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B-vitamins and ApoE ε4 on cognitive dysfunction in TUDA

Gordon *et al.* BMC Med. 2025;23(1):440.

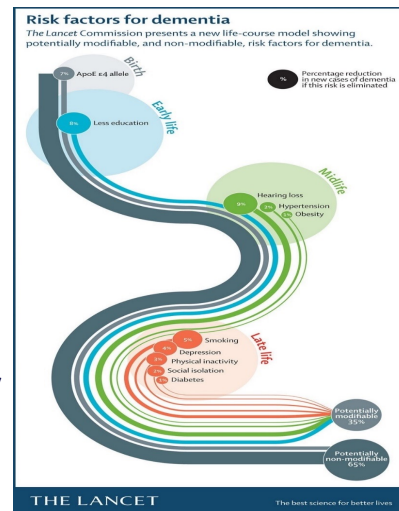
- **B-vitamins and cognitive function**
 - Lower status of vitamin B12, B6, riboflavin, and/or elevated homocysteine concentrations, are each associated with a greater risk of cognitive dysfunction
- **ApoE ε4 & B-vitamin interaction**
 - A novel interaction between ApoE ε4 and low vitamin B12 (and/or homocysteine) was identified
- **Public Health**
 - These findings may provide key targets that could be included in public health strategies aimed at the prevention of cognitive dysfunction and dementia

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Preventing Dementia

A Life-course model

- More than a third of dementia cases are theoretically preventable.
- Great potential to prevent or delay onset of dementia through focusing on modifiable risk factors at different life stages.
- Optimising folate and related one-carbon metabolism may play an important preventative role.
- **The TUDA study** provides an excellent resource by which the role of folate and related B vitamins in preventing cognitive dysfunction and dementia can be investigated

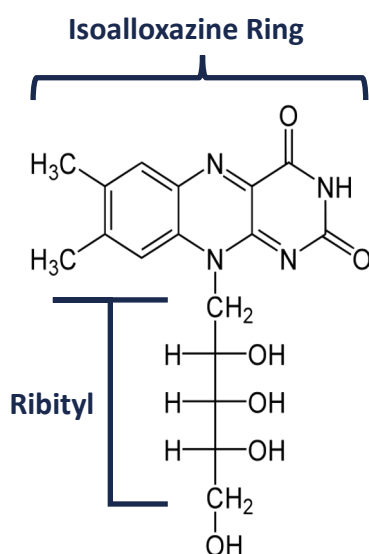


Livingston G, Huntley J, Liu KY. et al. 2024 report of the Lancet standing Commission. The Lancet. 2024;404, 572–628.

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Riboflavin (vitamin B2)

7,8-dimethyl-10-ribityl-Isoalloxazine



- Water soluble vitamin first identified in 1879 from milk whey
- Precursor for coenzymes:
 - Flavin adenine dinucleotide (**FAD**)
 - Flavin mononucleotide (**FMN**)
- Fundamental role in:
 - Oxidation-reduction reactions
 - Energy production
 - Cellular antioxidant function
 - Synthesis of niacin from tryptophan
 - **iron metabolism**
 - **One-carbon metabolism**
 - **Vitamin B6 metabolism**
- **Food sources:** Widely distributed in small amounts; Important dietary sources are milk and dairy products
- **Biomarker status** is rarely measured, but deficient/low status may be widespread

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Riboflavin Deficiency

Corneal vascularization

Dermatitis

Glossitis

Cheilosis

Anemia, erythroid hypoplasia

Riboflavin Deficiency

Cheilosis



Glossitis



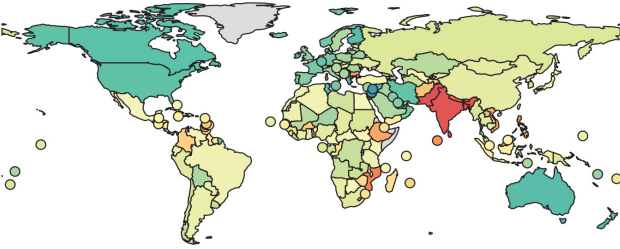
Clinical signs of deficiency in humans appear at intakes of less than 0.5-0.6 mg/day¹

McNulty et al (2023) Causes and Clinical Sequelae of Riboflavin Deficiency. *Ann Rev Nutr* **43**, 101-22

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Inadequate riboflavin intake – a global problem

Riboflavin, 4.1 billion (55%)



No biomarker data!

Proportion of population with inadequate intake (%)

0 25 50 75 100

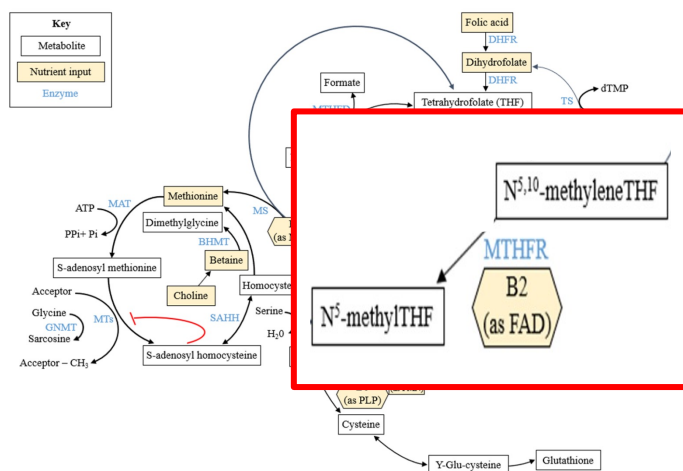
Passarelli et al (2024) Global estimation of dietary micronutrient inadequacies: a modelling analysis. *The Lancet Global Health*, 12(10), e1590–e1599.

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OPEN ACCESS

Lancet Glob Health 2024;
12: e1590–99
Published Online
August 29, 2024

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Riboflavin in one carbon metabolism



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Genes and blood pressure

- Genome-Wide Association Studies (GWAS) have identified genetic variants that appear to contribute modestly to blood pressure variability
- The **MTHFR** gene is among 8 genetic loci linked to the variation in blood pressure in GWAS^{1,2}

1. Global BPgen Consortium. 2009 *Nat Genet* **41**, 666-76

2. Ehret *et al.* 2011 *Nature* **478**, 103-109

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MTHFR 677TT genotype, CVD and BP

Author	n	Cohort	OR (95% CI)	Outcome
Klerk et al. 2002	23,920	CHD patients	1.16 (1.05, 1.28)	↑ HD
			1.42 (1.11, 1.84)	
Wald et al. 2002	16,849	CVD patients	1.65 (0.66 to 4.13)	↑ HD ↑ Stroke
Holmes et al. 2011	59,995	Stroke patients	1.37 (1.25, 1.50)	↑ Stroke
Qian et al. 2007	2814 cases 3099 controls	Hypertensive patients	1.24 (1.02, 1.50)	↑BP
Niu et al. 2012	1520 cases 1334 controls	Hypertensive patients	1.87 (1.31, 2.68)	↑BP
Yang et al. 2014	5418 cases 4997 controls	Hypertensive patients	1.59 (1.32, 1.92)	↑BP
Wu et al. 2014	5207 cases 5383 controls	Hypertensive patients	1.62 (1.32, 1.99)	↑BP

McNulty et al. *Molecular Aspects of Medicine* 2017;53:2-9

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Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C→T polymorphism in MTHFR

Geraldine Horigan^a, Helene McNulty^a, Mary Ward^a, J.J. Strain^a, John Purvis^b and John M. Scott^c

J. Hypertens. 2010 Mar;28(3):478-86. doi: 10.1097/HJH.0b013e328334c126.

Am J Clin Nutr. 2012 Mar;95(3):766-72. doi: 10.3945/ajcn.111.026245.

Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow-up¹⁻³

Carol P Wilson, Mary Ward, Helene McNulty, J J Strain, Tom G Trouton, Geraldine Horigan, John Purvis, and John M Scott

Hypertension
Volume 61, Issue 6, June 2013, Pages 1302-1308
<https://doi.org/10.1161/HYPERTENSIONAHA.111.01047>



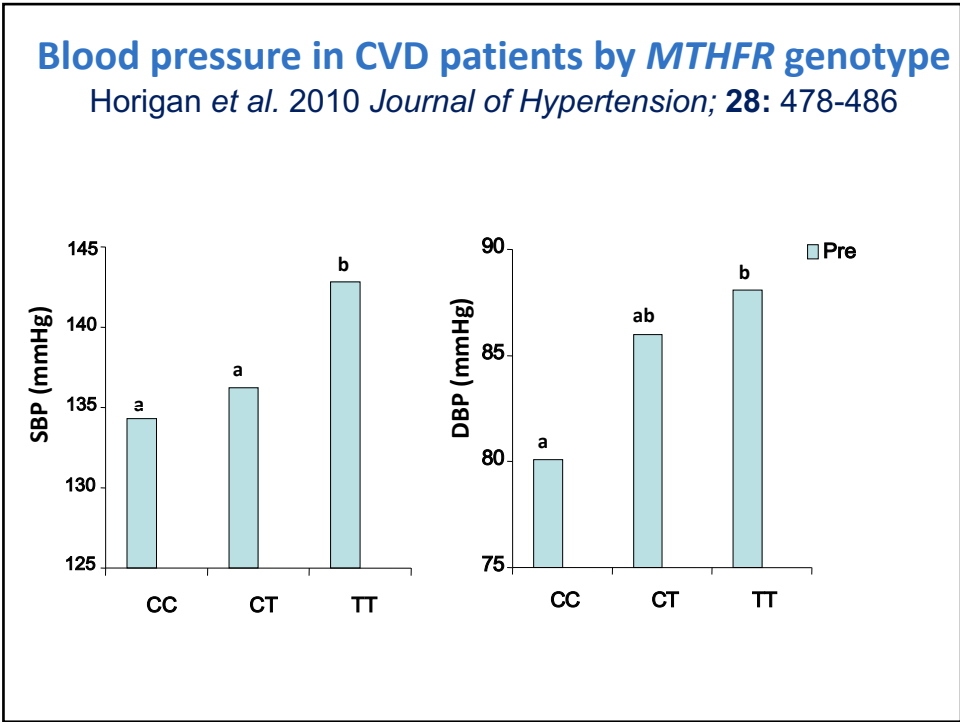
ORIGINAL ARTICLE - STRATIFIED TREATMENT OF HYPERTENSION
STRATIFIED TREATMENT OF HYPERTENSION

Blood Pressure in Treated Hypertensive Individuals With the MTHFR 677TT Genotype Is Responsive to Intervention With Riboflavin

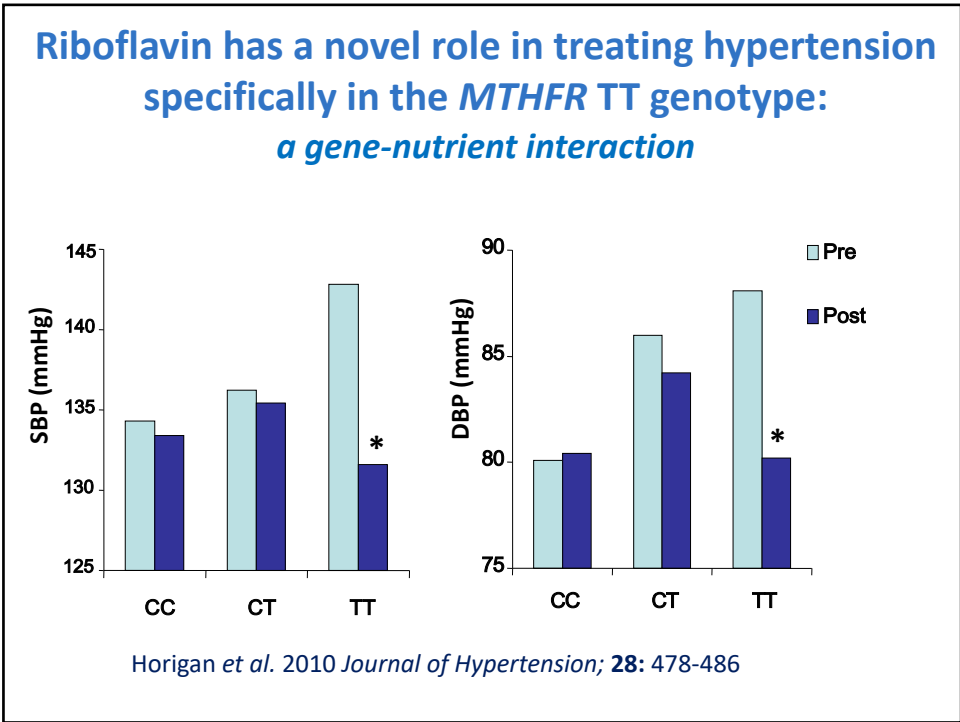
Findings of a Targeted Randomized Trial

Carol P. Wilson, Helene McNulty, Mary Ward, J.J. Strain, Tom G. Trouton, Birgit A. Hoeft, Peter Weber, Franz F. Roos, Geraldine Horigan, Liadhan McAnena, and John M. Scott

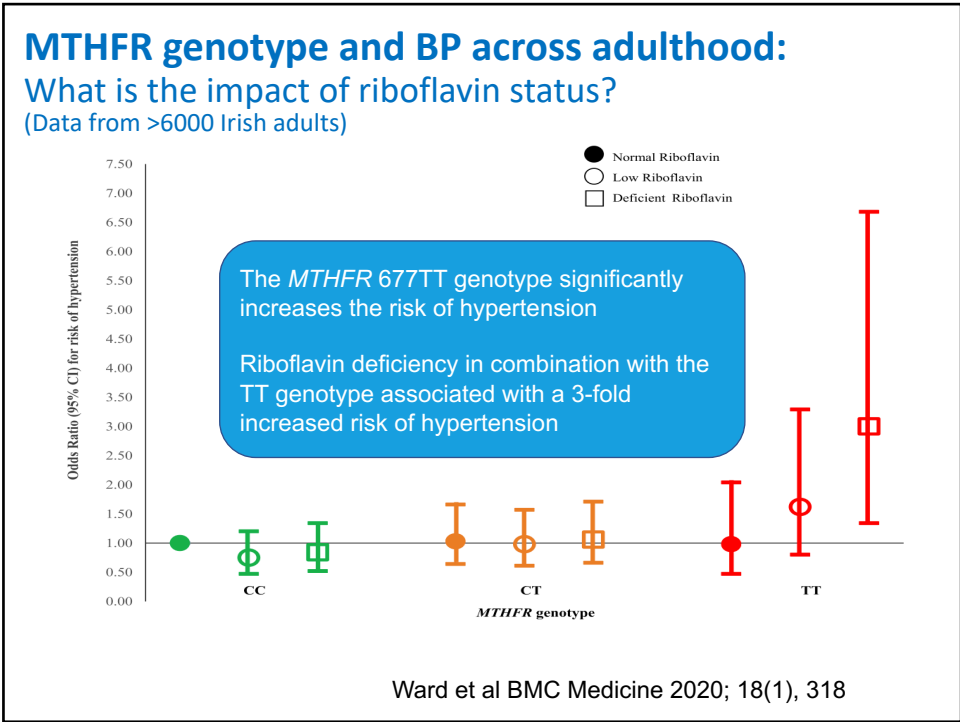
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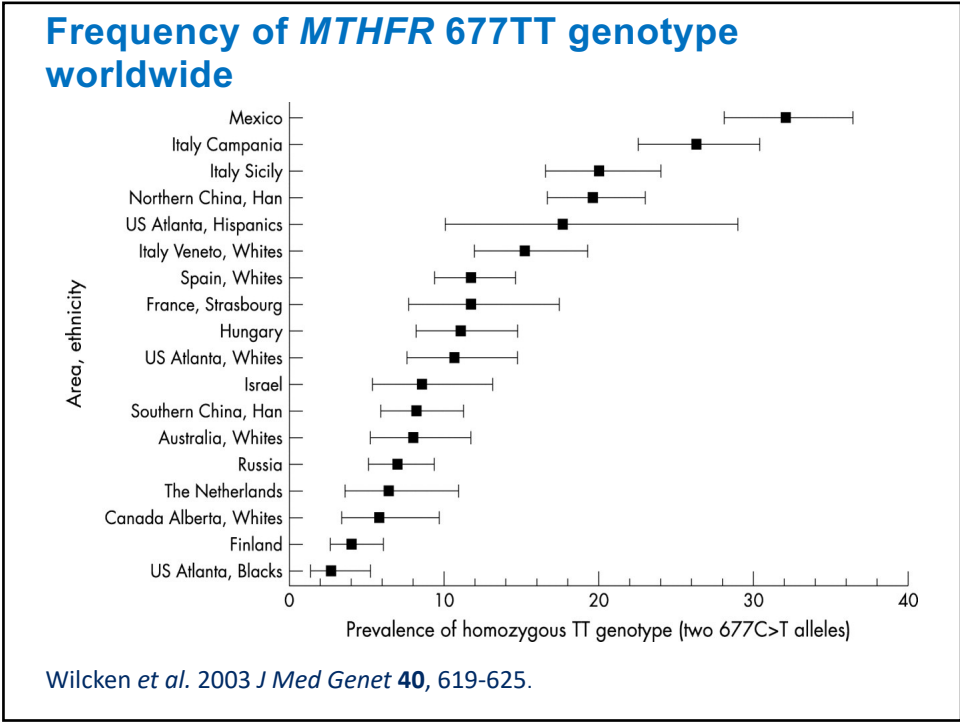
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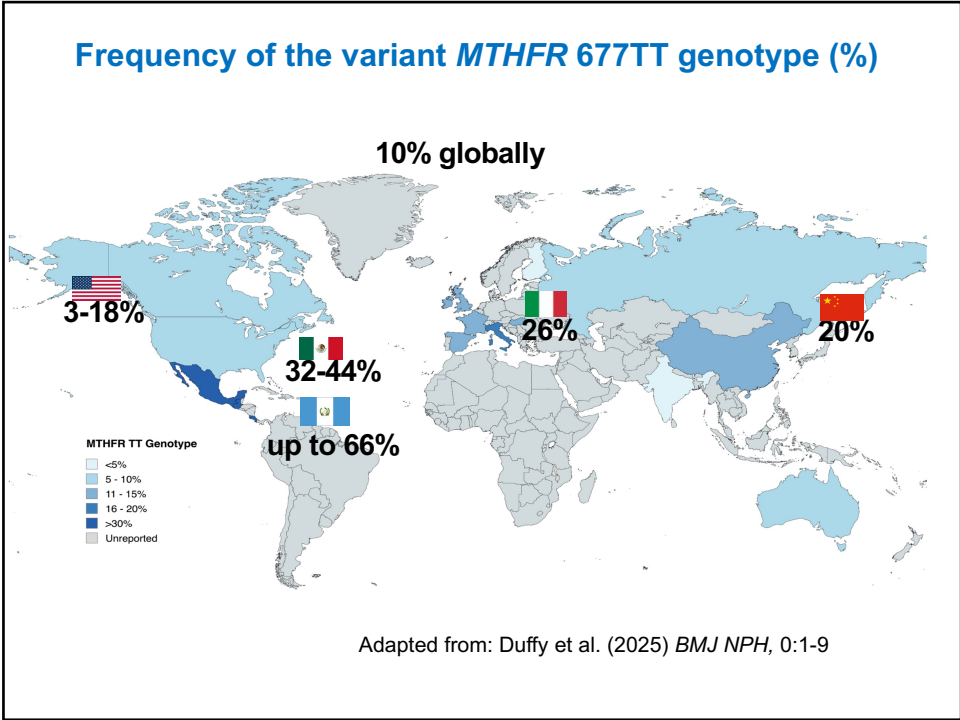
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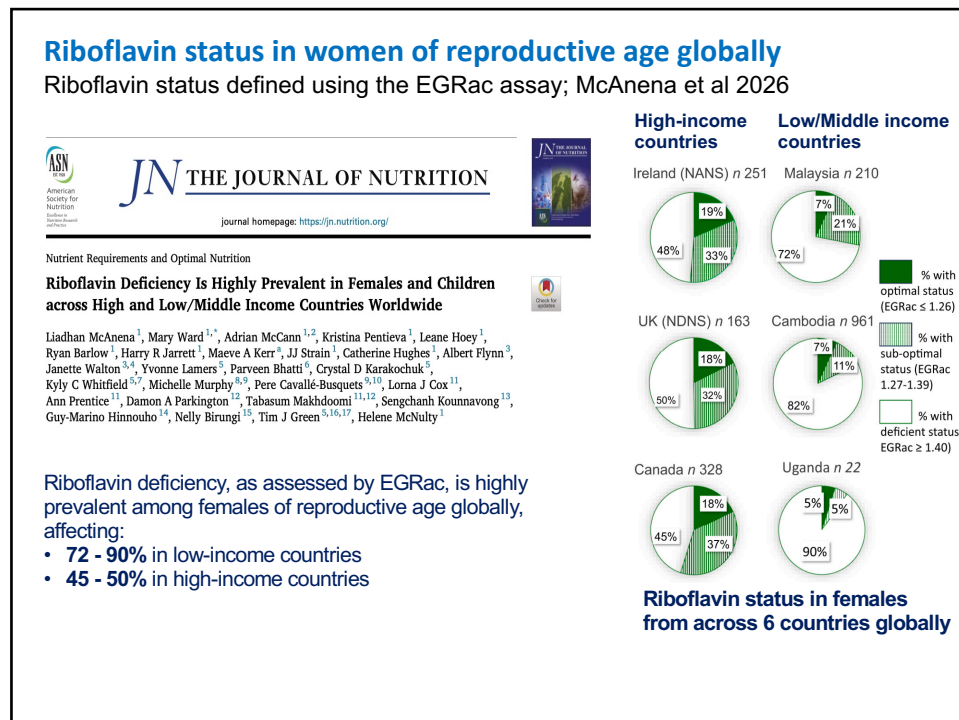
Riboflavin intake and new-onset hypertension in Chinese adults

- $n=12,245$ adults enrolled on the China Health and Nutrition Survey;
- An inverse association between riboflavin intakes and new onset Hypertension

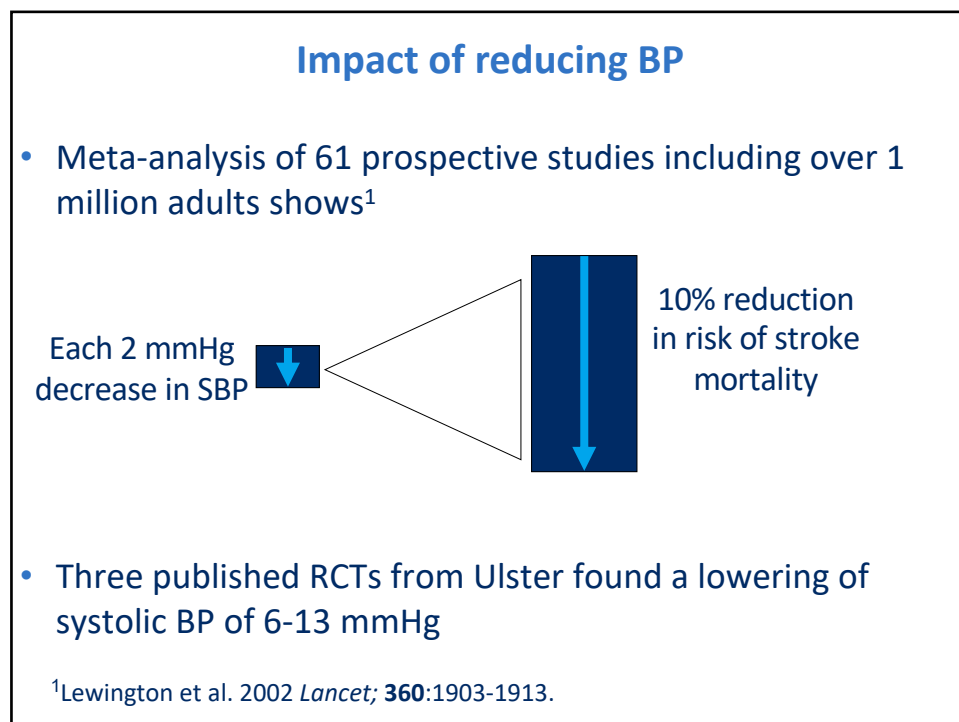
Riboflavin intake, mg/d	n	Cases (incidence rate*)	Crude model		Adjusted model†	
			HR (95% CI)	P value	HR (95% CI)	P value
Quartiles						
Q1 (<0.59)	3061	1167 (55.5)	Ref		Ref	
Q2 (0.59 to <0.72)	3061	1056 (40.2)	0.72 (0.66–0.78)	<0.001	0.75 (0.68–0.82)	<0.001
Q3 (0.72 to <0.88)	3061	1074 (40.9)	0.73 (0.67–0.79)	<0.001	0.72 (0.65–0.80)	<0.001
Q4 (≥0.88)	3062	1007 (45.8)	0.83 (0.76–0.90)	<0.001	0.79 (0.70–0.89)	<0.001
Category						
Q1 (<0.59)	3061	1167 (55.5)	Ref		Ref	
Q2–Q4 (≥0.59)	9184	3137 (42.1)	0.75 (0.70–0.80)	<0.001	0.74 (0.68–0.80)	<0.001

Liu et al. (2020) *Hypertension* **76**, 1709-1716

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Folate and related B-vitamins in health and Disease

Take-home messages - 1

- Folate has a number of important roles in health and prevention of disease through the lifecycle
- Optimal folate status: an urgent public health priority
 - But cannot be achieved through natural food folates alone; solution requires intervention with folic acid
- The metabolically-related B vitamins (i.e. vitamins B12, B6, riboflavin)
 - are important in maintaining normal folate status
 - may be particularly important in the face of genetic predisposition to low folate status (e.g. riboflavin)

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Nutrition, B vitamins and the Ageing brain

Take-home messages - 2

- 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
 - Optimizing B vitamin status could be key.
- Future research in this area needs **Interdisciplinary** research approaches and application of **state-of-art technologies**

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Riboflavin, *MTHFR* genotype and hypertension

Take-home messages - 3

- **The common C677T polymorphism in *MTHFR* predisposes to**
 - Increased BP throughout adulthood
 - Higher risk of developing hypertension and hypertension in pregnancy
 - **Riboflavin has a novel role** in people with the variant TT genotype in *MTHFR* in maintaining healthier blood pressure and treating hypertension *independently* of antihypertensive therapy
- **Riboflavin is a much-neglected vitamin, yet one with important health impacts for populations globally**
 - Maintenance of optimal riboflavin status (through improved diet, fortification or supplementation) may reduce hypertension

McNulty H, Pentieva K, Ward M. Annual Review of Nutrition 2023; 44:101–122

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Acknowledgements

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Prof Sean Strain

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Prof Adrian Moore

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Prof Girijesh Prasad

Computing and Data Analytics

Prof Michaela black

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Prof John Scott - RIP
Prof Anne Molloy
Prof Conal Cunningham (TUDA)
Dr Kevin McCarroll (TUDA)

Clinical Collaborators in NI

Prof James Dornan (FASSTT) - RIP
Dr Barry Marshall (FASSTT)
Dr Mark Rollins (FASSTT)
Dr Maurice O'Kane (TUDA)
Dr Fergal Tracey (TUDA)



All the participants!



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SESSION 2

Professor Helene McNulty

B Vitamins, Nutritional Epigenomics and Age-related Disease

11:15-12:00pm

An event by:



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NMI SUMMIT 2026

Longevity and Biological Ageing: Enhancing Health into Advanced Age

Friday 9th October

Featuring Dr. Jeffrey Bland, Professor Helene McNulty, Natalie Burrows, Professor Anna Nicolaou, Dr. Sally Moorcroft, Dr. Nina Fuller-Shavel and Dr. Laurens Maas



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