Interaction of Riboflavin with MTHFR Genotype in relation to Hypertension

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Riboflavin, MTHFR Genotype and Hypertension

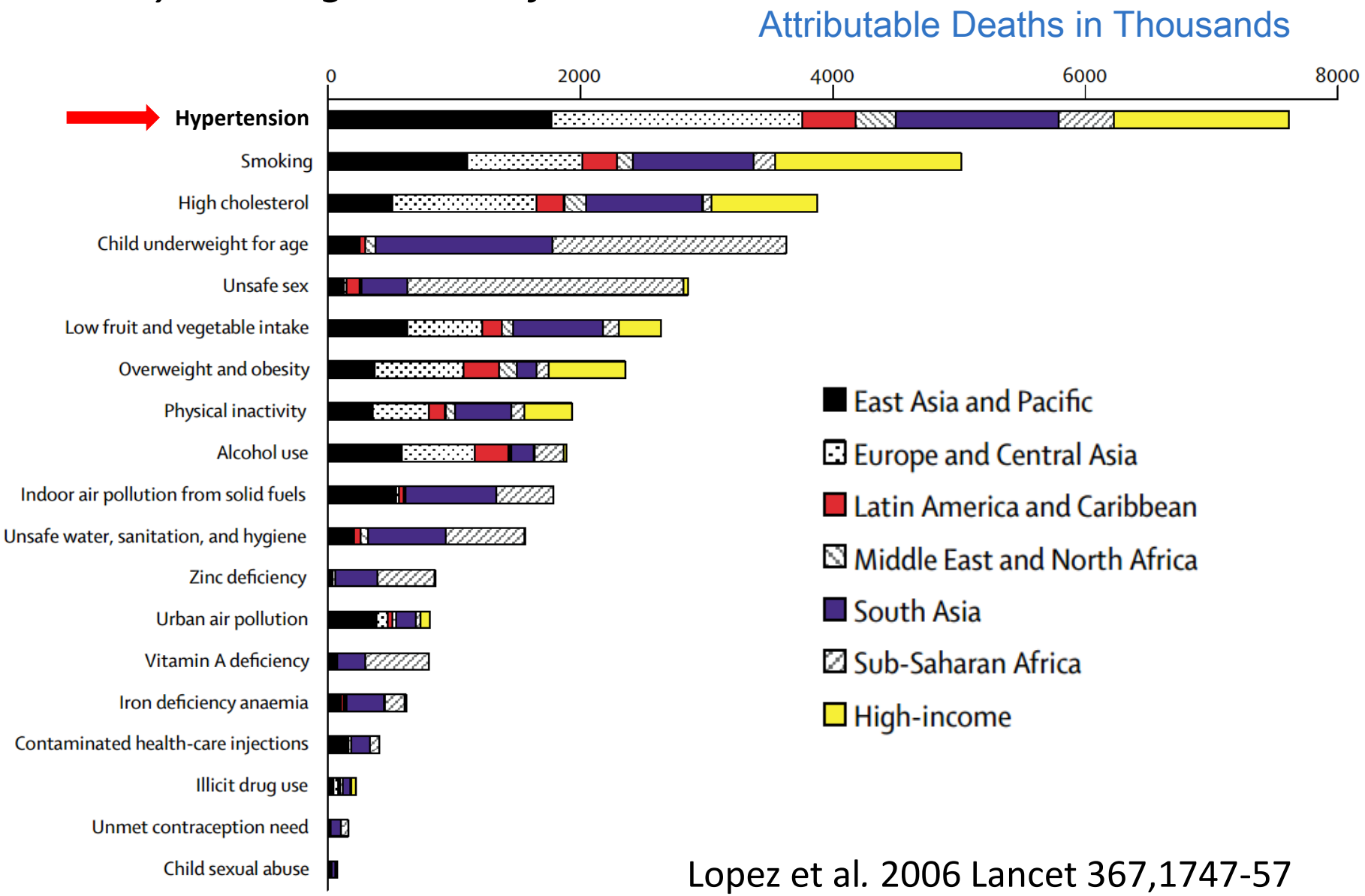
This talk will address

- Hypertension
- MTHFR genotype and hypertension
- Riboflavin as a personalised nutrition strategy for
  - Treating hypertension
  - Preventing hypertension
- Impact

Ulster University

High BP (Hypertension) – a global health concern

Mortality due to global risk factors



Lopez et al. 2006 Lancet 367,1747-57

Hypertension

- The major risk factor for cardiovascular disease, and stroke in particular
- Defined as a blood pressure (BP) of greater than 140/90 mmHg
- Multiple lifestyle, nutritional and genetic factors known to affect BP
- Antihypertensive drugs are highly effective yet hypertension remains a global problem
- Dietary approaches to lower BP
  - Weight loss; salt reduction; DASH diet; alcohol

Nutrition and Lifestyle factors targeted to reduce blood pressure

Lifestyle factor	SBP decrease (mmHg)
Weight loss (per 10 kg)	5 - 20
Physical activity	4 - 9
Sodium reduction	2 - 8
Limit alcohol	2 - 4

Modified from Chobanian *et al.* 2003 JNC 7 report

Genes and blood pressure

- A number of genetic variants appear to contribute modestly to blood pressure variability
- The **MTHFR gene** is among 8 genetic loci linked to the variation in blood pressure in Genome-Wide Association Studies (GWAS studies)[1,2]

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

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

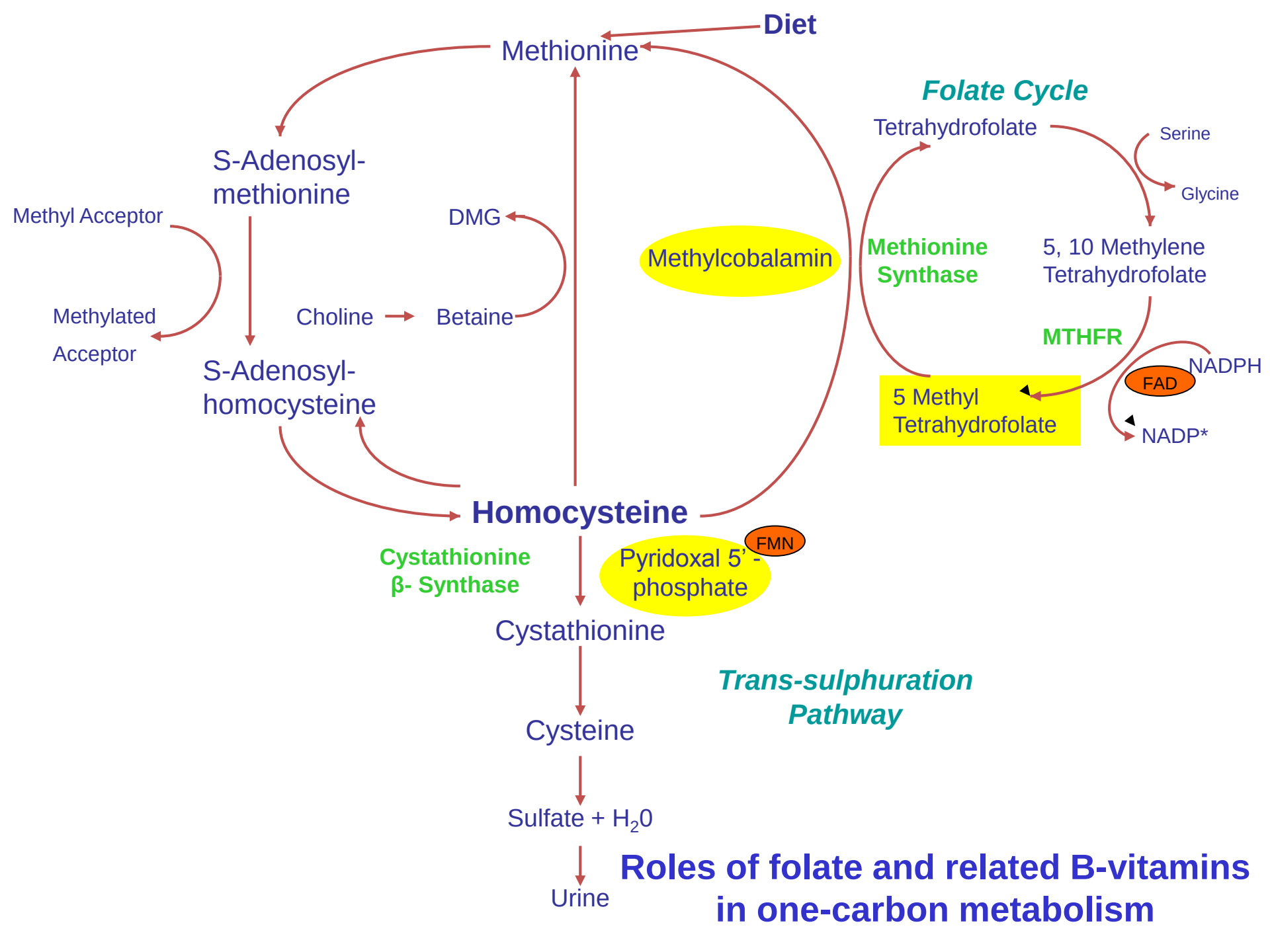
ARTICLES

nature genetics

Genome-wide association study identifies eight loci associated with blood pressure

Christopher Newton-Cheh[1–3,94*], Toby Johnson[4–6,94], Vesela Gateva[7,94], Martin D Tobin[8,94], Murielle Bochud[5], Lachlan Coin[9], Samer S Najjar[10], Jing Hua Zhao[11,12], Simon C Heath[13], Susana Eyheramendy[14,15], Konstantinos Papadakis[16], Benjamin F Voight[1,3], Laura J Scott[7], Feng Zhang[17], Martin Farrall[18,19], Toshiko Tanaka[20,21], Chris Wallace[22–24], John C Chambers[9], Kay-Tee Khaw[12,25], Peter Nilsson[26], Pim van der Harst[27], Silvia Polidoro[28], Diederick E Grobbee[29], N Charlotte Onland-Moret[29,30], Michiel L Bots[29], Louise V Wain[8], Katherine S Elliott[19], Alexander Teumer[31], Jian'an Luan[11], Gavin Lucas[32], Johanna Kuusisto[33], Paul R Burton[8], David Hadley[16], Wendy L McArdle[34], Wellcome Trust Case Control Consortium[93], Morris Brown[35], Anna Dominiczak[36], Stephen J Newhouse[22,23], Nilesh J Samani[37], John Webster[38], Eleftheria Zeggini[19,39], Jacques S Beckmann[4,40],

Newton-Cheh C, Johnson T, Gateva V *et al.* (2009) *Nat Genet* **41,** 666-676.

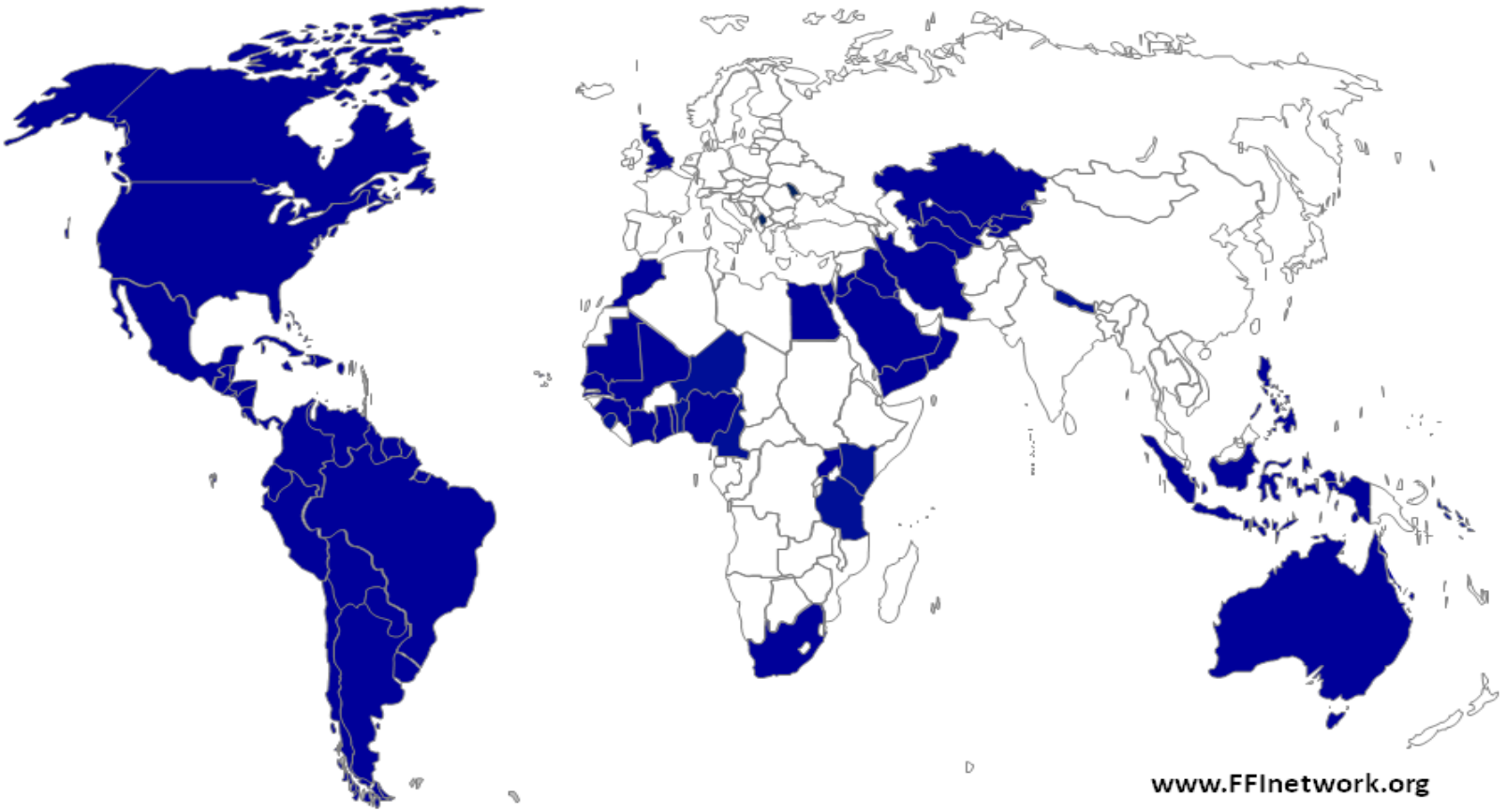

Diet
Methionine
S-Adenosyl-
methionine
Methyl Acceptor
Methylated
Acceptor
DMG
Choline
Betaine
S-Adenosyl-
homocysteine
Homocysteine
Methylcobalamin
Folate Cycle
Tetrahydrofolate
Serine
Glycine
Methionine
Synthase
5, 10 Methylene
Tetrahydrofolate
MTHFR
NADPH
FAD
NADP*
5 Methyl
Tetrahydrofolate
Cystathionine
β- Synthase
Pyridoxal 5' -
phosphate
FMN
Cystathionine
Trans-sulphuration
Pathway
Cysteine
Sulfate + H_20
Urine
Roles of folate and related B-vitamins
in one-carbon metabolism

Folate and related B vitamins

- Required for one-carbon metabolism
- Have a major metabolic role in methylation processes
- Prevent homocysteine accumulation
- Health benefits may
  - relate to their homocysteine-lowering effects *or*
  - be independent of homocysteine

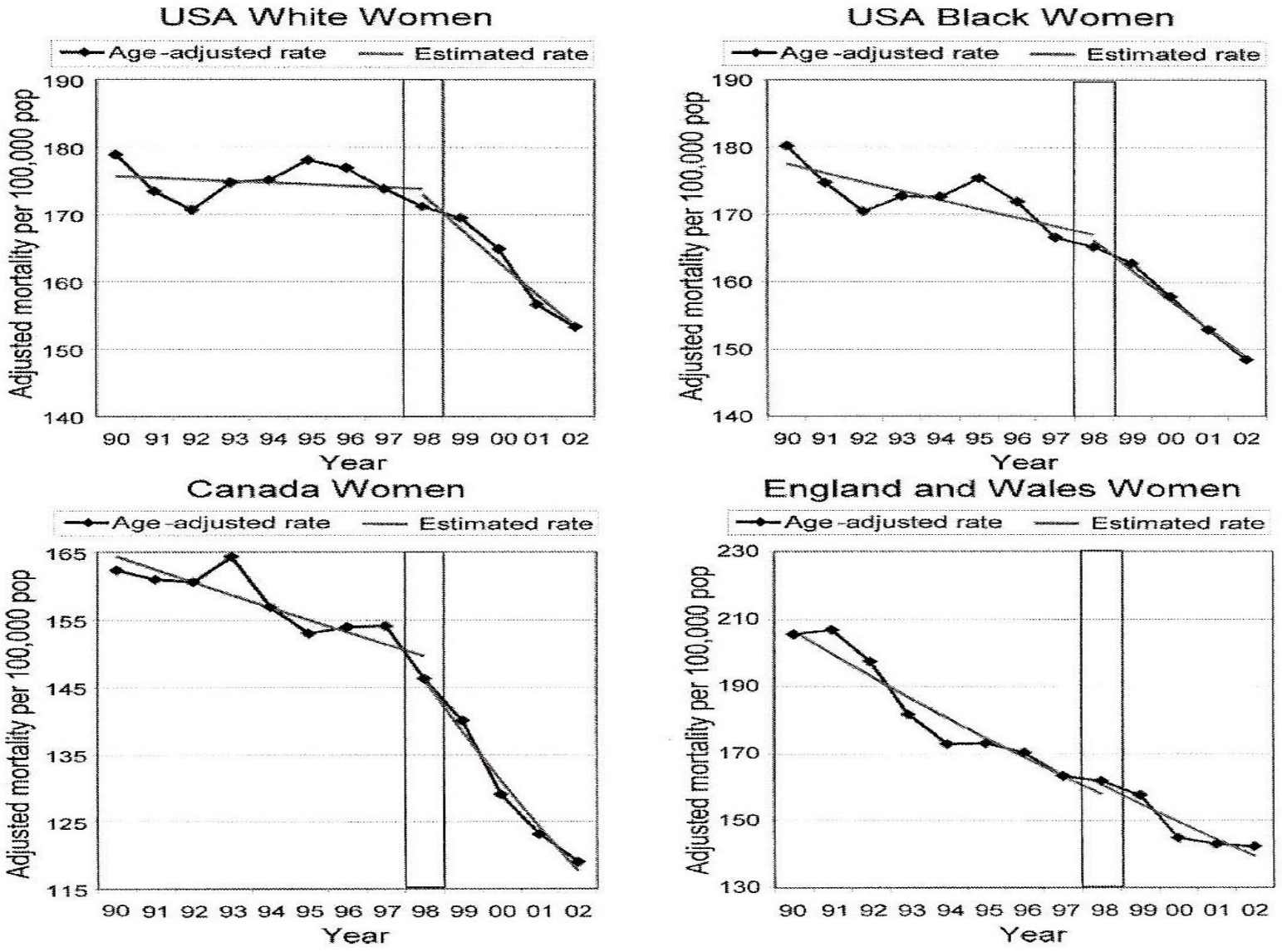
Wheat Flour Fortification Legislation

October 2012: 75 countries require iron and/or folic acid in wheat flour

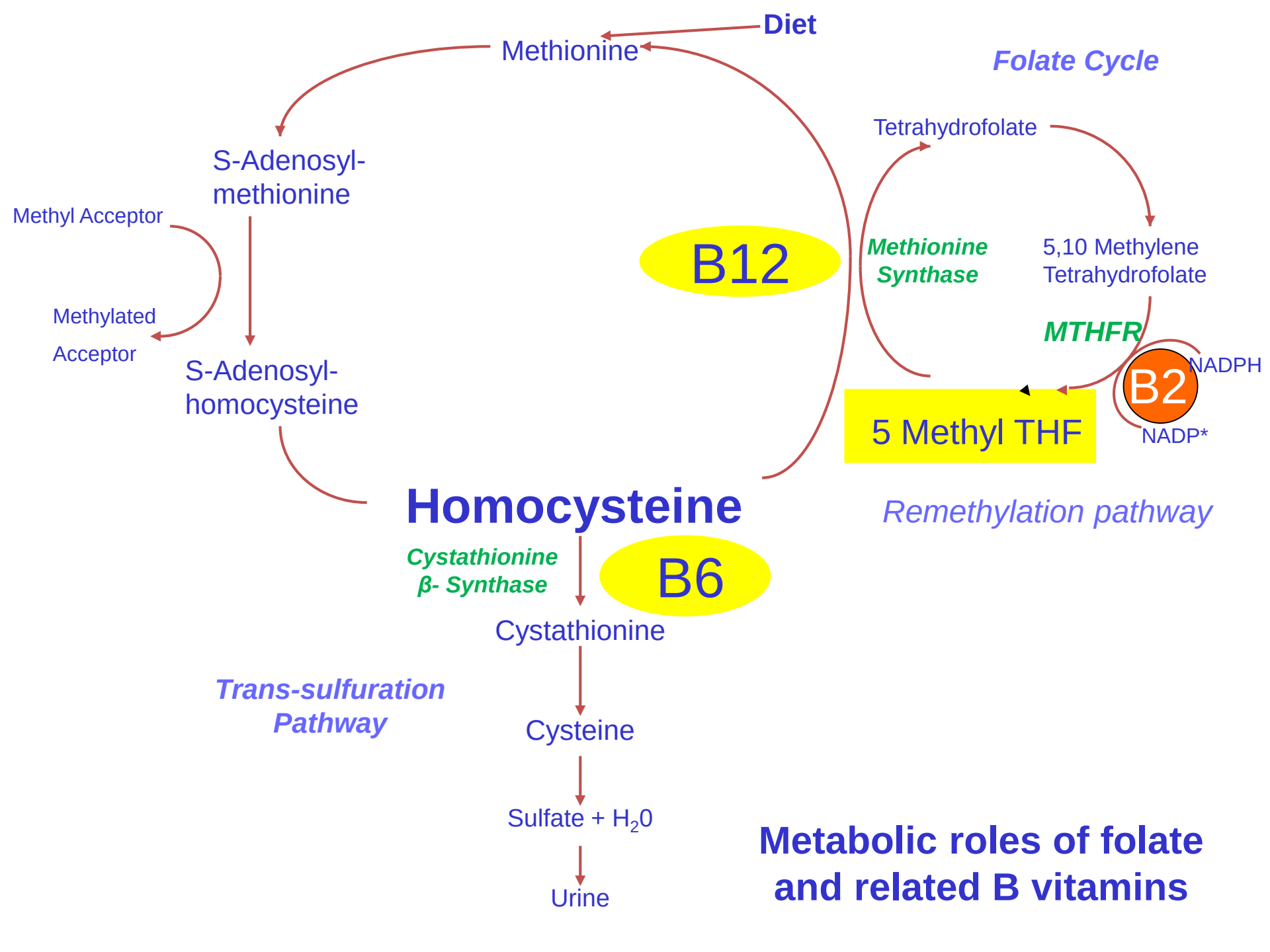


All countries in blue fortify flour with iron and folic acid except
Australia which does not include iron, and
Venezuela, the **United Kingdom**, the **Philippines**, and **Trinidad and Tobago** which fortifiy with iron only and do not include folic acid.

Decline in stroke related mortality in the US and Canada



Yang et al 2006 *Circulation*;113:1335-43


Diet
Methionine
Folate Cycle
S-Adenosyl-
methionine
Tetrahydrofolate
Methyl Acceptor
B12
Methionine
Synthase
5,10 Methylene
Tetrahydrofolate
Methylated
Acceptor
MTHFR
NADPH
B2
S-Adenosyl-
homocysteine
5 Methyl THF
NADP*
Homocysteine
Remethylation pathway
Cystathionine
β- Synthase
B6
Cystathionine
Trans-sulfuration
Pathway
Cysteine
Sulfate + H_20
Urine
Metabolic roles of folate
and related B vitamins

Methylenetetrahydrofolate reductase (MTHFR)

SUBSTRATE: 5,10 methylenetetrahydrofolate

PRODUCT: 5 methyltetrahydrofolate

COFACTOR: Flavin Adenine Dinucleotide (FAD)

PRECURSOR: Riboflavin (vitamin B2)

- Polymorphic mutations in MTHFR
  - *MTHFR* 677C→T Polymorphism
    - C to T substitution at base pair 677
    - Alanine/valine change in the amino acid sequence
    - Functionally defective enzyme

Is this common folate polymorphism a risk factor for cardiovascular disease?

- Homozygosity (TT genotype) results in lower MTHFR enzyme activity and increased homocysteine concentrations *in vivo*

- Excess risk of CVD (by 14-21%)[1-4] in individuals with the TT genotype, but large geographical variation between countries

[1]Wald DS et al. *BMJ* 2002; **325**: 1202–1206.
[2]Klerk et al. *JAMA* 2002; **288**: 2023–2031.
[3]Lewis et al. *BMJ* 2005; **331**: 1053–1056.
[4]Holmes et al. *Lancet* 2011; **378**: 584-594

MTHFR 677TT genotype and hypertension

Journal of Human Hypertension (2011), 1–9

www.nature.com/jhh

ORIGINAL ARTICLE

Strong association of methylenetetrahydrofolate reductase gene C677T polymorphism with hypertension and hypertension-in-pregnancy in Chinese: a meta-analysis

W-Q Niu[1,2,3,6], Y-G You[4,6] and Y Qi[5]
[1]*State Key Laboratory of Medical Genomics, Shanghai Key Laboratory of Vascular Biology and Department of Hypertension, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;* [2]*Laboratory of Vascular Biology, Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Shanghai, China;* [3]*Shanghai Institute of Hypertension, Shanghai, China;* [4]*Beijing Tropical Medicine Research Institute, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing, China and* [5]*Department of Epidemiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Beijing, China*

Meta-analysis of 20 studies ; 4461 participants

- **OR 1.87 (95% CI 1.31-2.68); *P*=0.001**

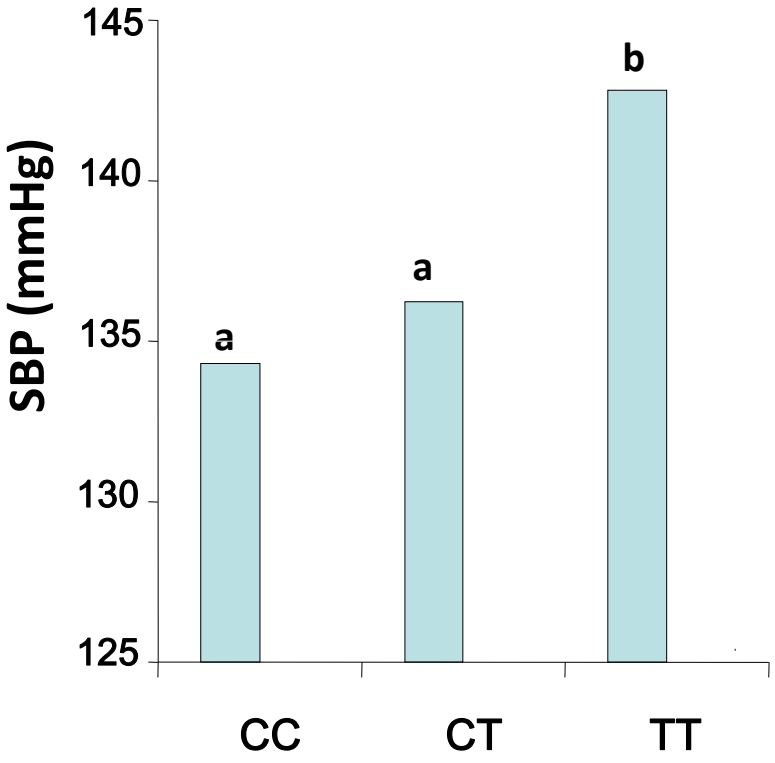
Niu WQ, You YG, Qi Y. (2012) *J Hum Hypertens.* **26**, 259-67.

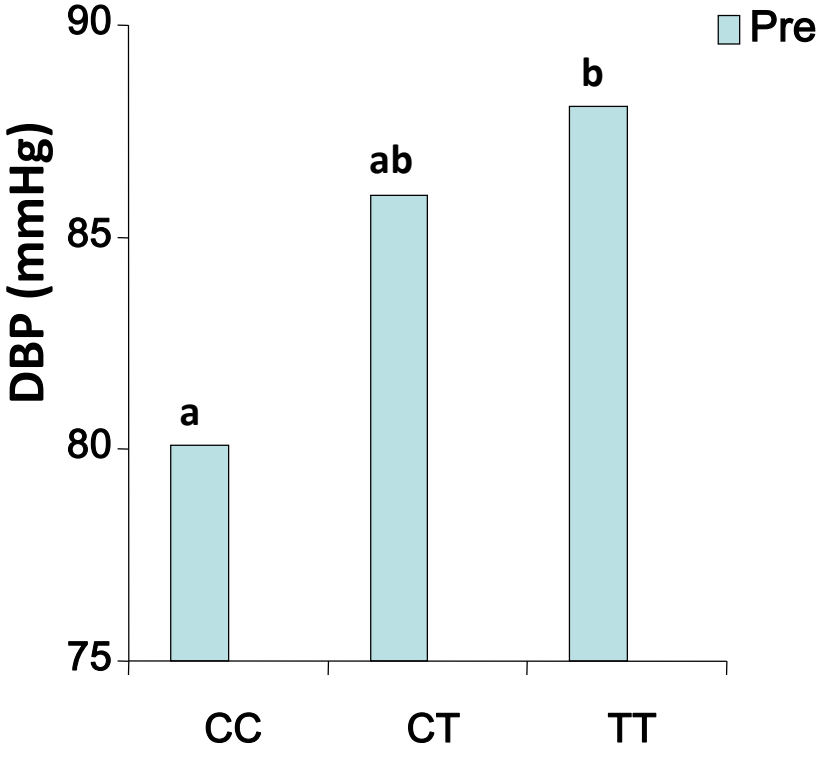
Genotype-specific response to riboflavin

	Mean homocysteine (µmol/L)		
	CC (n = 27)	CT (n = 26)	TT (n = 34)
Baseline	10.7	12.2	17.6
Riboflavin 1.6mg/d 12 weeks	↓	↓	↓
After intervention	10.9	11.8	13.0*

McNulty *et al.* 2006 *Circulation* **113**(1), 74-80

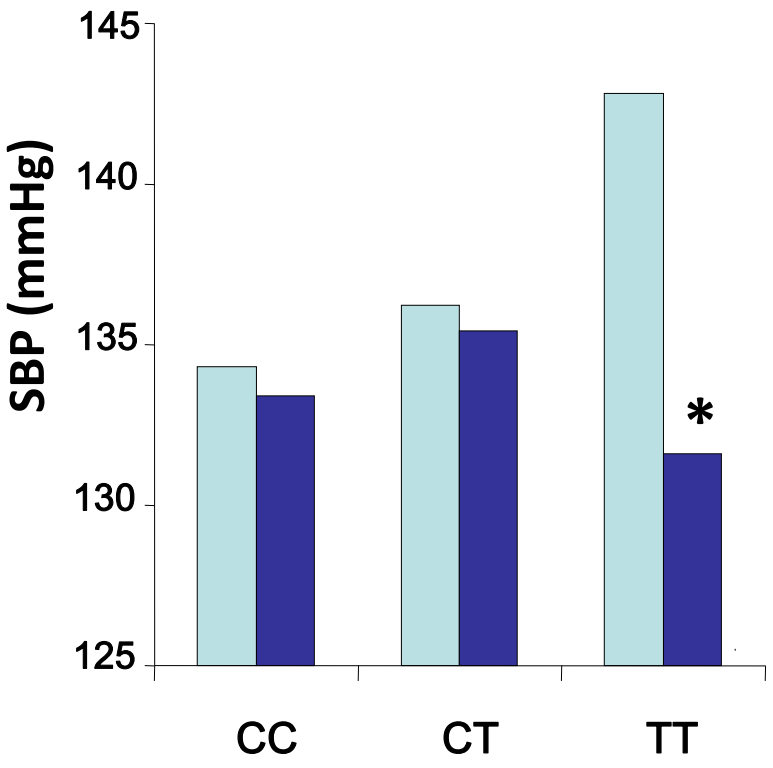
This gene has an important role in determining blood pressure in CVD patients

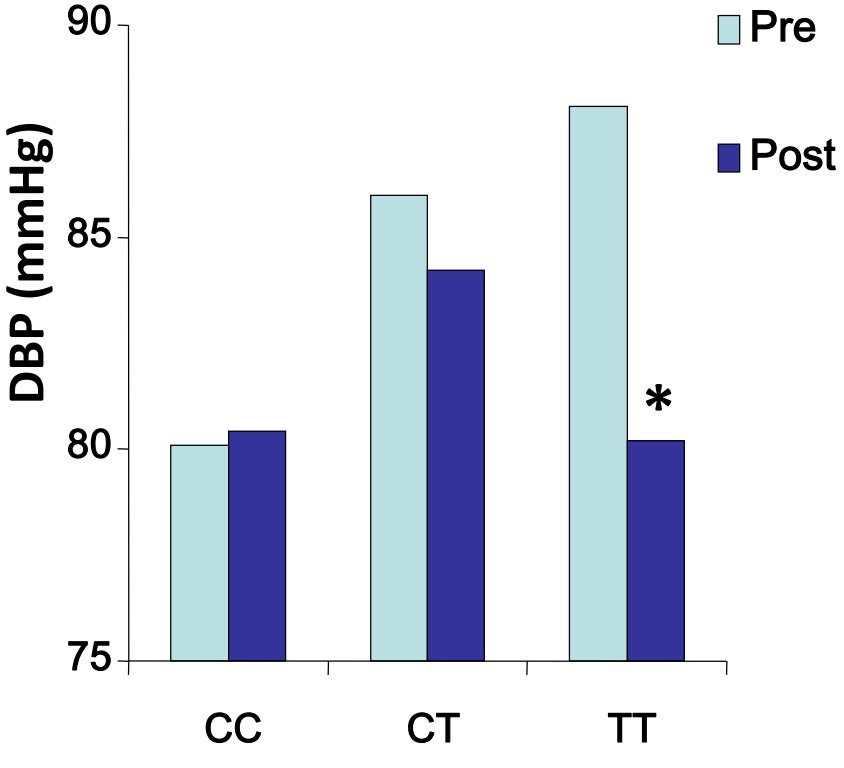




Horigan *et al.* 2010 *Journal of Hypertension;* **28:** 478-486.

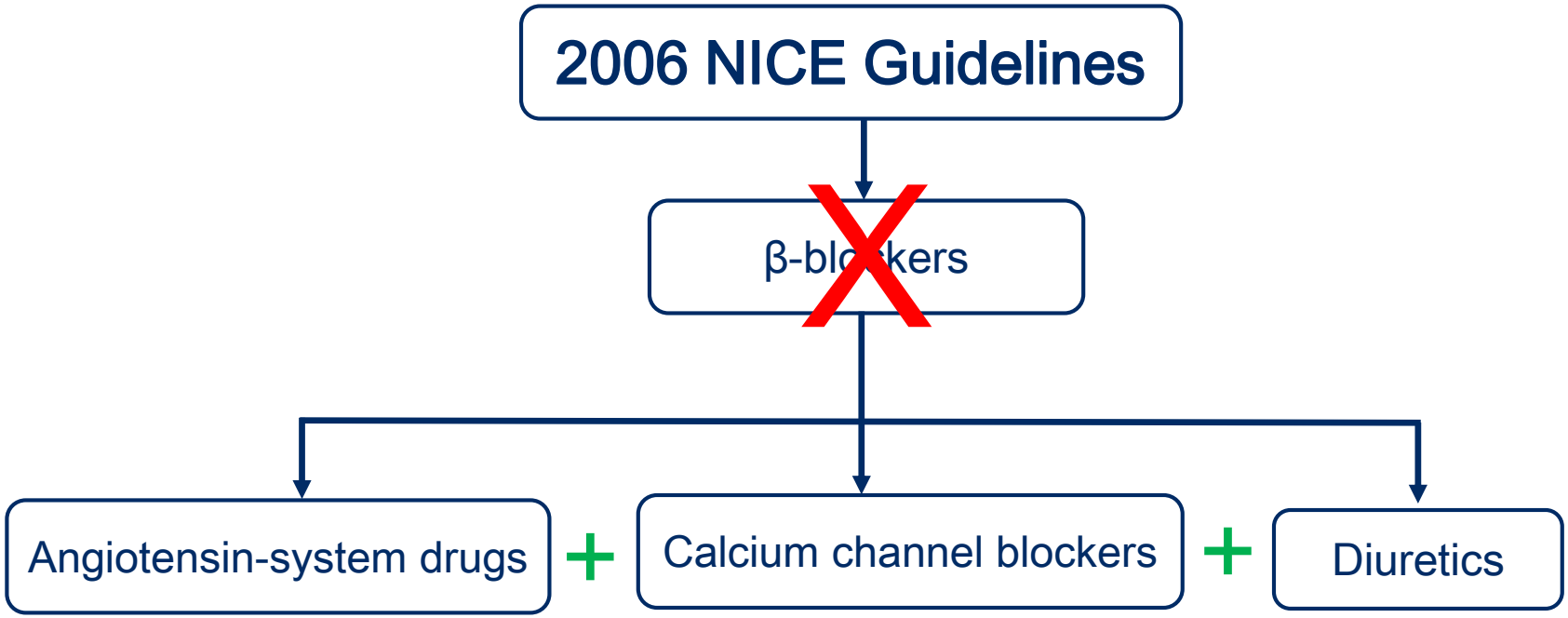
This gene-nutrient interaction has a novel role in treating hypertension in CVD patients





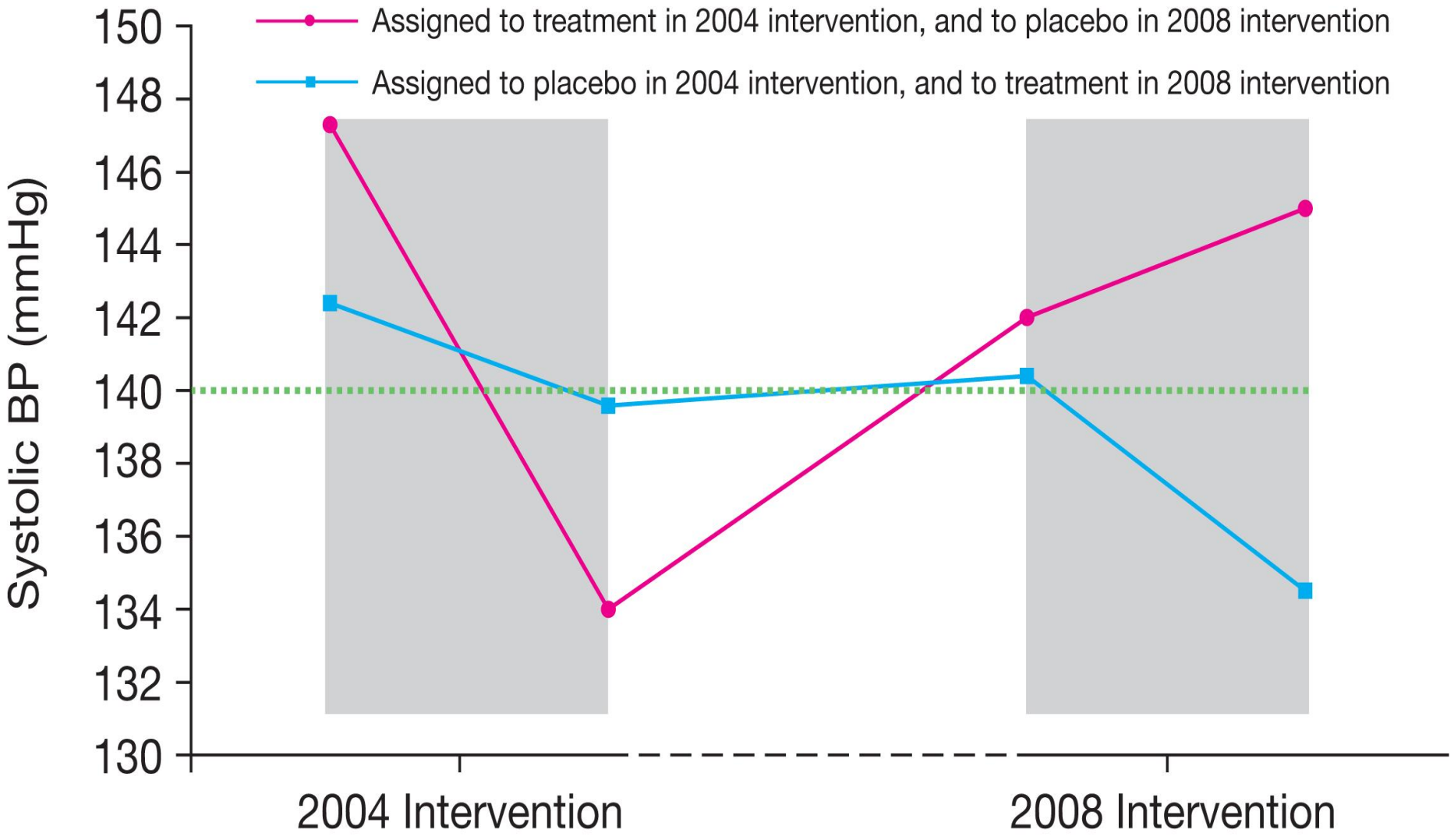
Horigan *et al.* 2010 *Journal of Hypertension;* **28:** 478-486.

BP medication changes



- Three major changes occurred:
  - β-blockers omitted
  - Shift from monotherapy to polytherapy
  - Drug choice depended on age and race

Systolic BP response in CVD patients with the TT genotype



Wilson *et al.* 2012 Am J Clin Nutr; **95**:766–72.

Results of 4-year follow-up

Wilson *et al.* 2012 Am J Clin Nutr; 95:766–72

- The MTHFR 677TT genotype *remained* a risk factor for hypertension in this high-risk cohort over the 4-year period

- Riboflavin intervention resulted in an overall decrease of 9mmHg SBP and 6mmHg DBP
  - *This BP-lowering effect of riboflavin occurred irrespective of current antihypertensive therapy*

Role of this novel gene nutrient interaction in treating hypertension (no overt CVD)

Hypertension
Journal of the American Heart Association

American Heart Association®

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

Hypertension. 2013;61:1302-1308; originally published online April 22, 2013;
doi: 10.1161/HYPERTENSIONAHA.111.01047
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

- **Blood pressure in <u>treated</u> hypertensive individuals with the MTHFR 677TT genotype responded significantly to riboflavin**

Primary Prevention of CVD

Wilson *et al*. 2013 Hypertension; **61**:1302-1308.

Role of this novel gene-nutrient interaction in the prevention of hypertension?

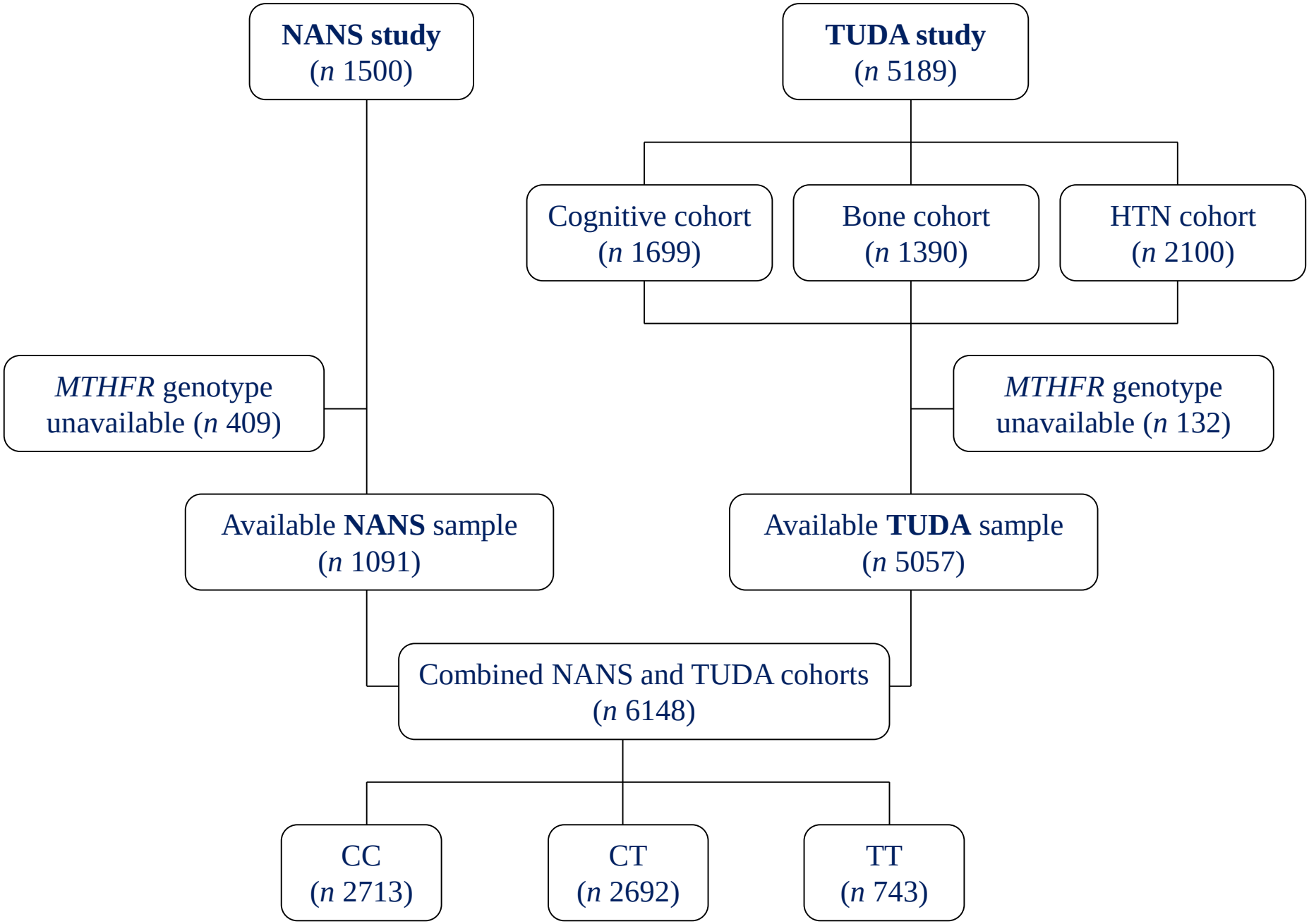
Some unanswered questions

- What are the determinants of blood pressure in adults at all ages?
  - How important is MTHFR genotype relative to other factors?
  - And what about drugs?

- Can *MTHFR* genotype increase the risk of <u>developing</u> hypertension?
  - Does riboflavin status matter?

- The **JINGO** project provided the means to address these questions

Some slides showing unpublished data from the JINGO project have been removed from this presentation

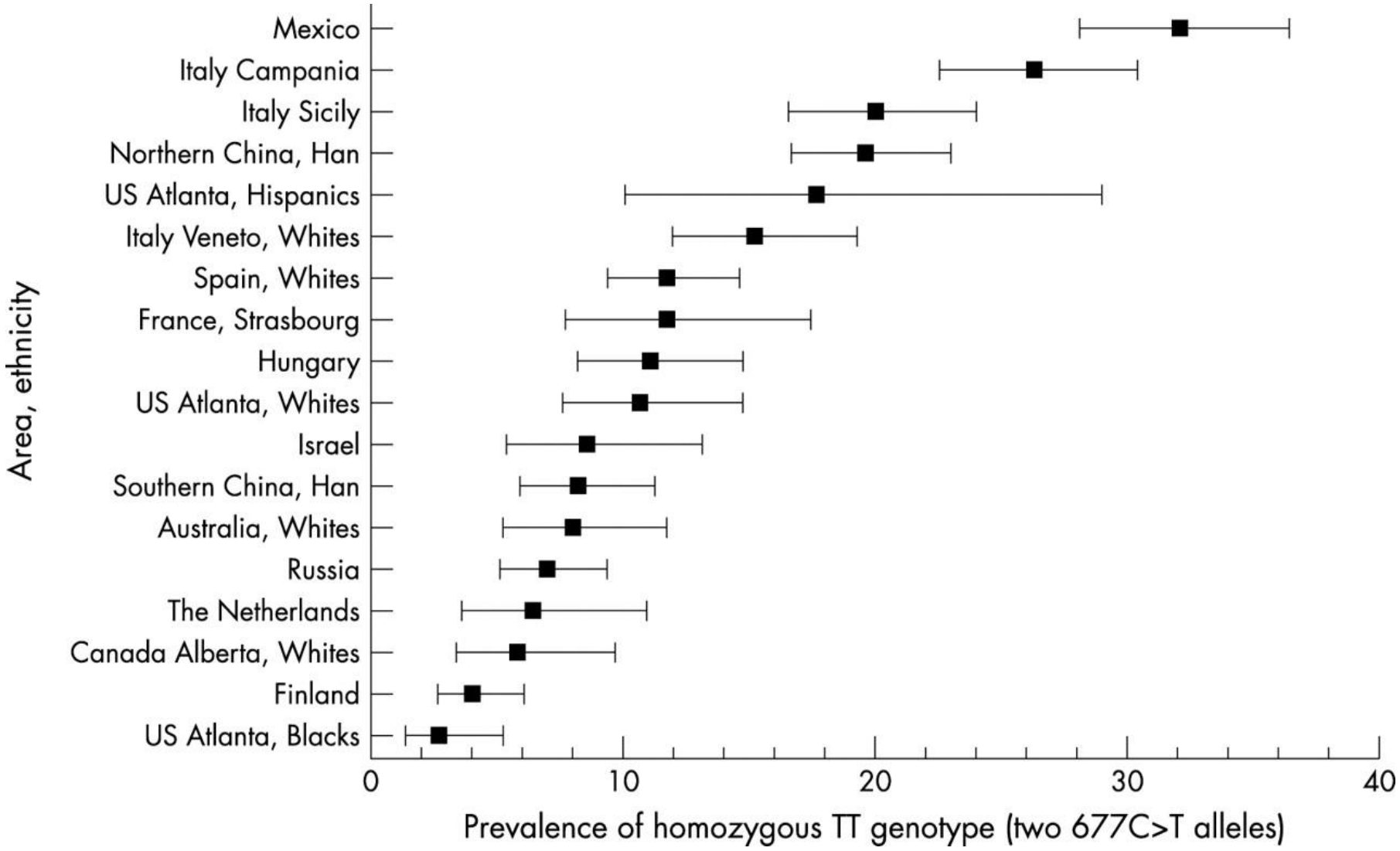

NANS study (*n* 1500)
TUDA study (*n* 5189)
Cognitive cohort (*n* 1699)
Bone cohort (*n* 1390)
HTN cohort (*n* 2100)
MTHFR genotype unavailable (*n* 409)
MTHFR genotype unavailable (*n* 132)
Available **NANS** sample (*n* 1091)
Available **TUDA** sample (*n* 5057)
Combined NANS and TUDA cohorts (*n* 6148)
CC (*n* 2713)
CT (*n* 2692)
TT (*n* 743)

Impact

Potentially affected population who can benefit?

- Gene x nutrient = phenotype
- MTHFR gene x riboflavin = blood pressure
- ‘Normalising’ the activity of the variant MTHFR enzyme by increasing riboflavin status will lower blood pressure and prevent the development of hypertension
- The ***affected population*** who can benefit in will be influenced by both the genetic factor (i.e. frequency of TT genotype) *and* riboflavin status (i.e. prevalence of deficient or low status).

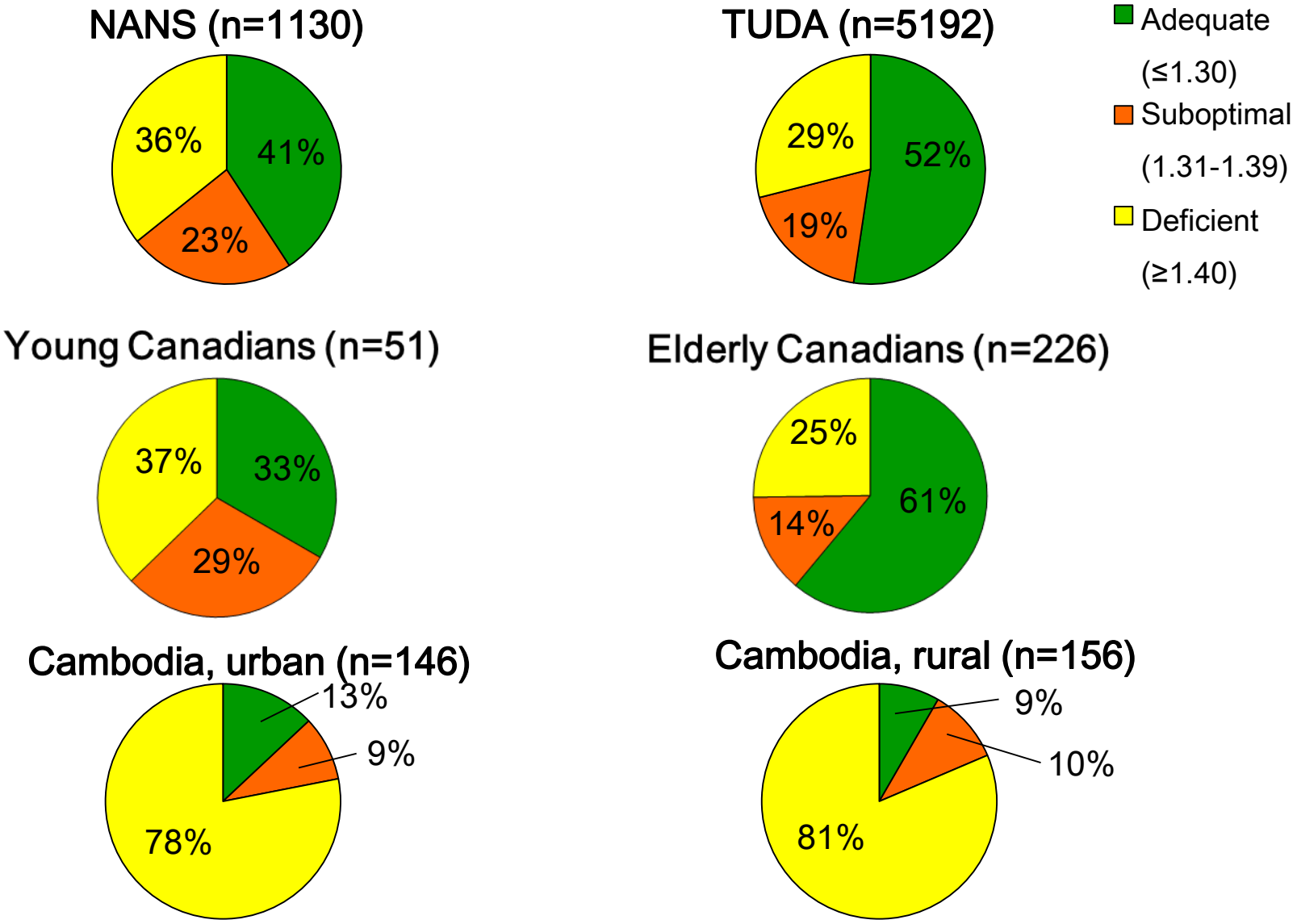
Frequency of *MTHFR* 677TT genotype worldwide



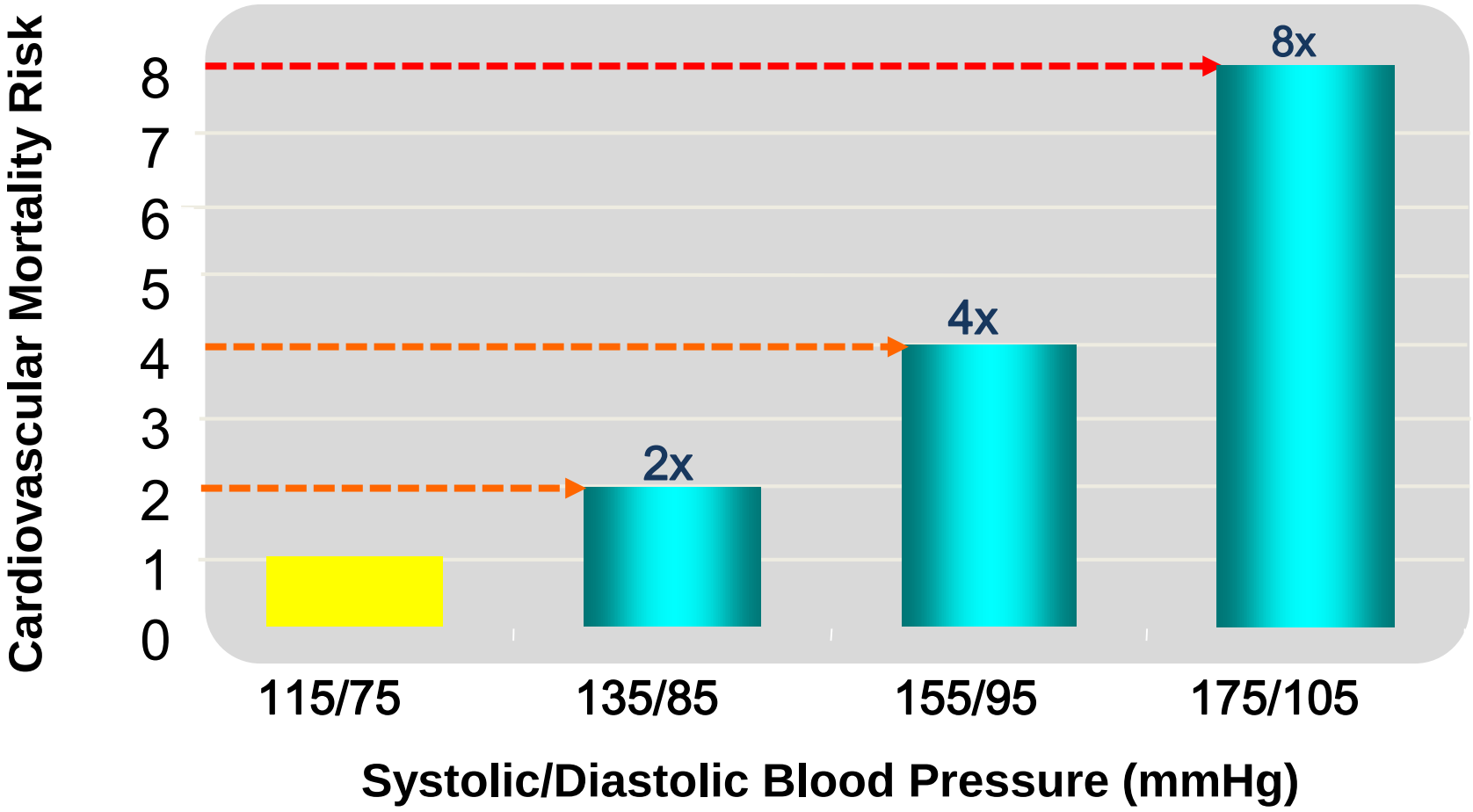
Data published in Wilcken *et al.* 2003 *J Med Genet* **40**, 619-625.

Low riboflavin status is a global health issue

[Unpublished data from Ulster in collaboration with UBC, Vancouver Canada]



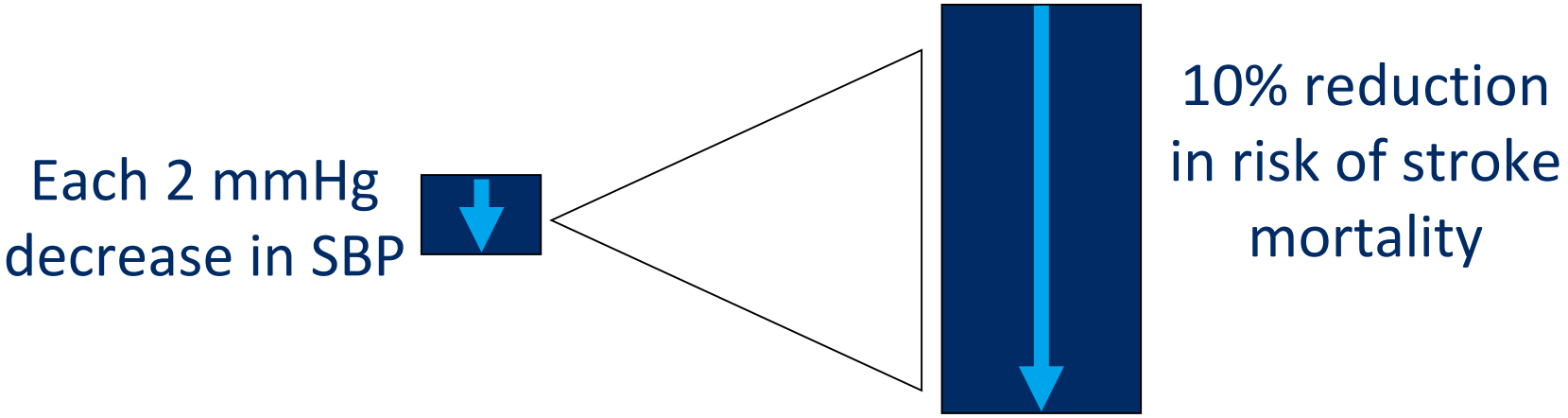
CVD mortality risk increases as BP rises



Lewington S et al. *Lancet* 2002;**360**:1903-1913
Chobanian AV et al. *JAMA* 2003;**289**:2560-2572

Impact of reducing BP

- Meta-analysis of 61 prospective studies including over 1 million adults[1]



Potential public health significance of this gene-nutrient interaction on BP could be very significant

[1]Lewington et al. 2002 *Lancet;* **360**:1903-1913.

Impact of riboflavin intervention (personalised)

Relative to other Nutrition/Lifestyle factors to reduce BP

Lifestyle factor	SBP decrease (mmHg)
Weight loss (per 10 kg)	5 - 20
Riboflavin (genotype-specific)	6 -13*
Physical activity	4 - 9
Sodium reduction	2 - 8
Limit alcohol	2 - 4

Data (modified) from Chobanian *et al.* 2003 JNC 7 report.

*Data from 3 published trials from Ulster: Horigan et al 2010; Wilson et al 2012 & 2013

Interaction of Riboflavin with MTHFR Genotype in relation to Hypertension

Take-home messages

- **Individual** as well as **Population-based** approaches are needed to prevent hypertension and thus cardiovascular disease
- **A novel genetic risk factor***, present in 10% of people worldwide, increases the risk of *developing* hypertension
- **Riboflavin** (vitamin B2) can play an important role in treating and preventing hypertension *specifically* in people with the relevant genetic variant
    - Independent of current antihypertensive therapy

- **Ongoing and Future work**
    - Potential for maintaining better cardiovascular health through a *personalised approach* to preventing/treating hypertension
    - Confirmation of these results in other populations in the world
    - Hypertension in pregnancy

***TT genotype for the C677T polymorphism in the MTHFR gene*

My thanks to…….All my colleagues in NICHE especially

Our Collaborators in TCD and SJH

Mary Ward
Sean Strain
Kristina Pentieva
Leane Hoey
Catherine Hughes

John Scott
Anne Molloy
Conal Cunningham
Miriam Casey

The JINGO (inc TUDA and NANS) project teams at Ulster, TCD UCD, UCC

PhD students past and present

Geraldine Horigan (2006)
Carol Wilson (2010)
Rosie Reilly (2014)
Emma Hughes (current)
Amy McMahon (current)

Clinical Collaborators

Maurice O'Kane
John Purvis
Tom Trouton

DSM
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