Riboflavin lowers high blood pressure - a novel gene-nutrient interaction

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Outline

- **Hypertension burden**
- **Methylenetetrahydrofolate reductase (MTHFR) and blood pressure**
- **Manipulation of blood pressure through a novel gene-nutrient interaction**

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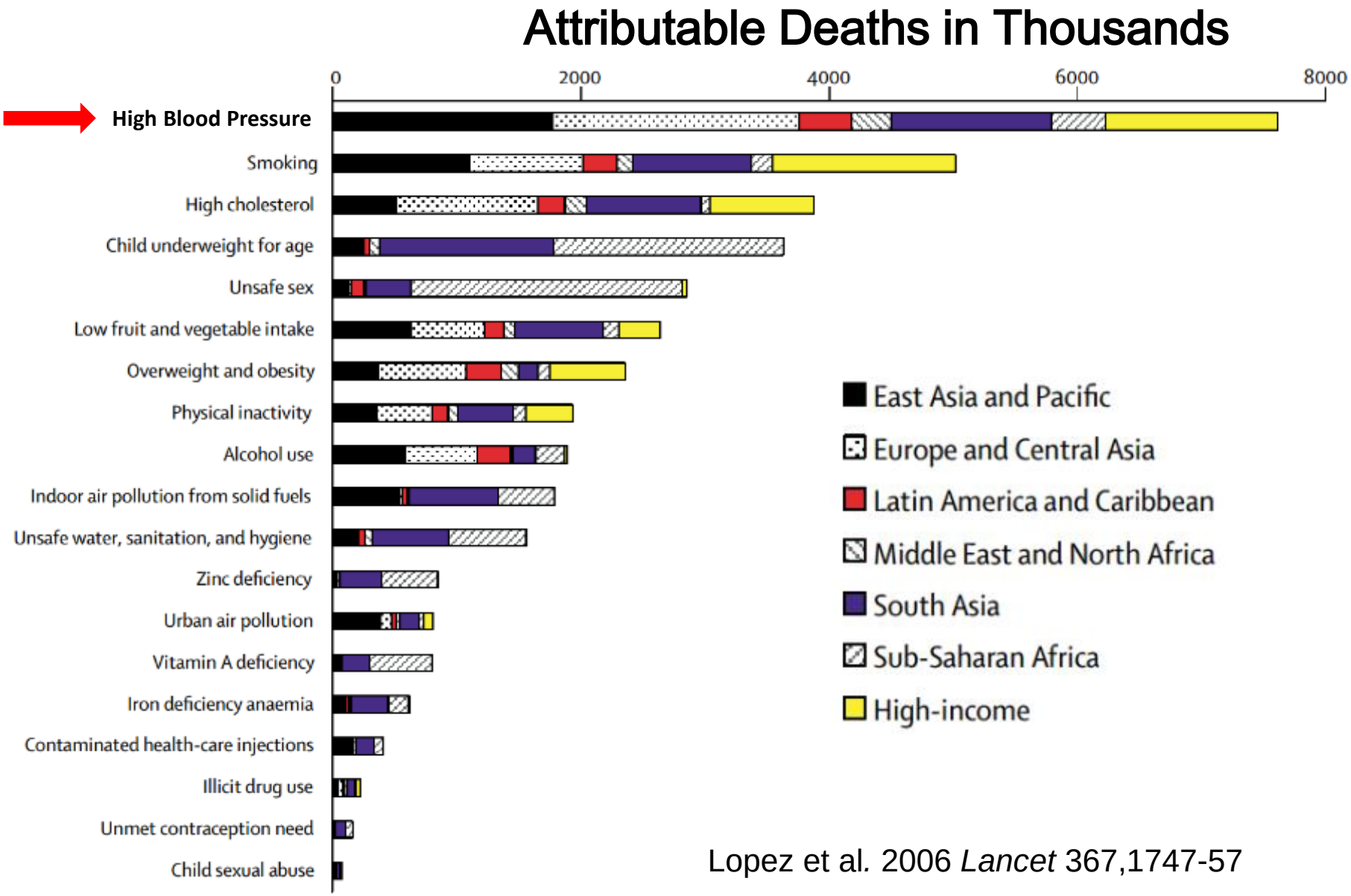
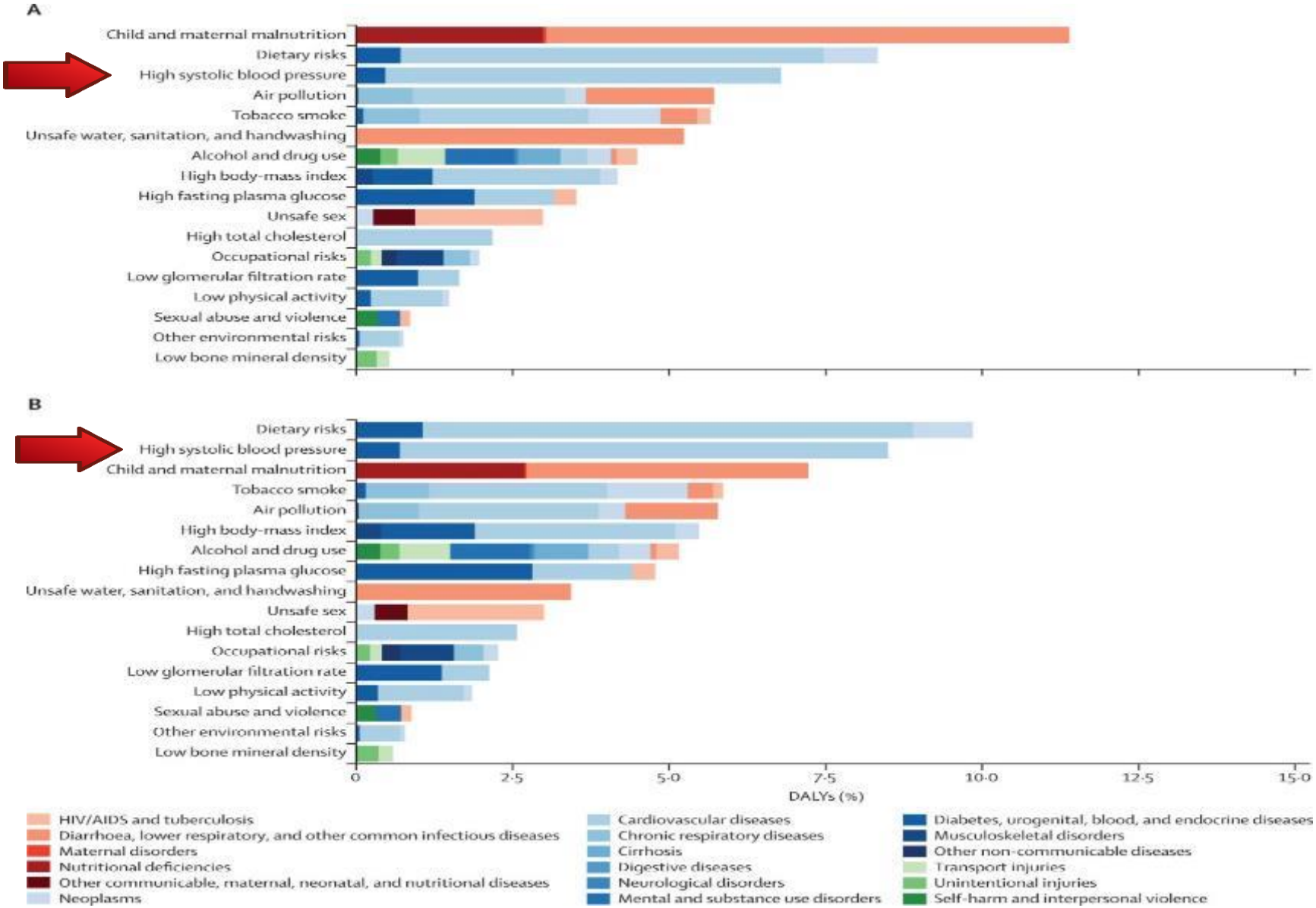
Mortality and global risk factors



Lopez et al. 2006 *Lancet* 367,1747-57



Global DALYs attributed to level 2 risk factors in 2000 for both sexes combined (A) and global DALYs attributed to level 2 risk factors in 2013 for both sexes combined (B)
DALYs=disability-adjusted life-years.

Risk Factors Collaborators *Lancet* 2015

Blood Pressure and CVD

- Hypertension is defined as a blood pressure (BP) of greater than 140/90 mmHg[1]
- Hypertension affects over 1 billion adults globally[2]
- Positive and continuous relationship between BP and CVD mortality[3]
- Hypertension estimated to cost **£1 billion** in drugs in UK[4]

[1]National Institute for Health and Clinical Excellence 2004
[2]Danaei *et al.* 2011 *Lancet* 377, 568-577
[3]Prospective Studies Collaboration 2002 *Lancet* 360,1903-1913
[4]NICE 2011

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Lifestyle factors targeted to reduce BP

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

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GWAS studies

- A large number of genetic variants appear to contribute modestly to BP variability[1]

- Genome-Wide Association Studies (G-WAS) have linked a number of genetic loci including the MTHFR loci to the variation in blood pressure[2,3]

- Regions identified may contain other unknown or unconsidered genetic variants associated with BP

[1]Kurtz *et al.* 2010 *Hypertension* 56,1021-25
[2]Global BPgen Consortium. 2009 *Nat Genet* 41, 666-76
[3]Ehret *et al.* 2011 *Nature* 478, 103-109

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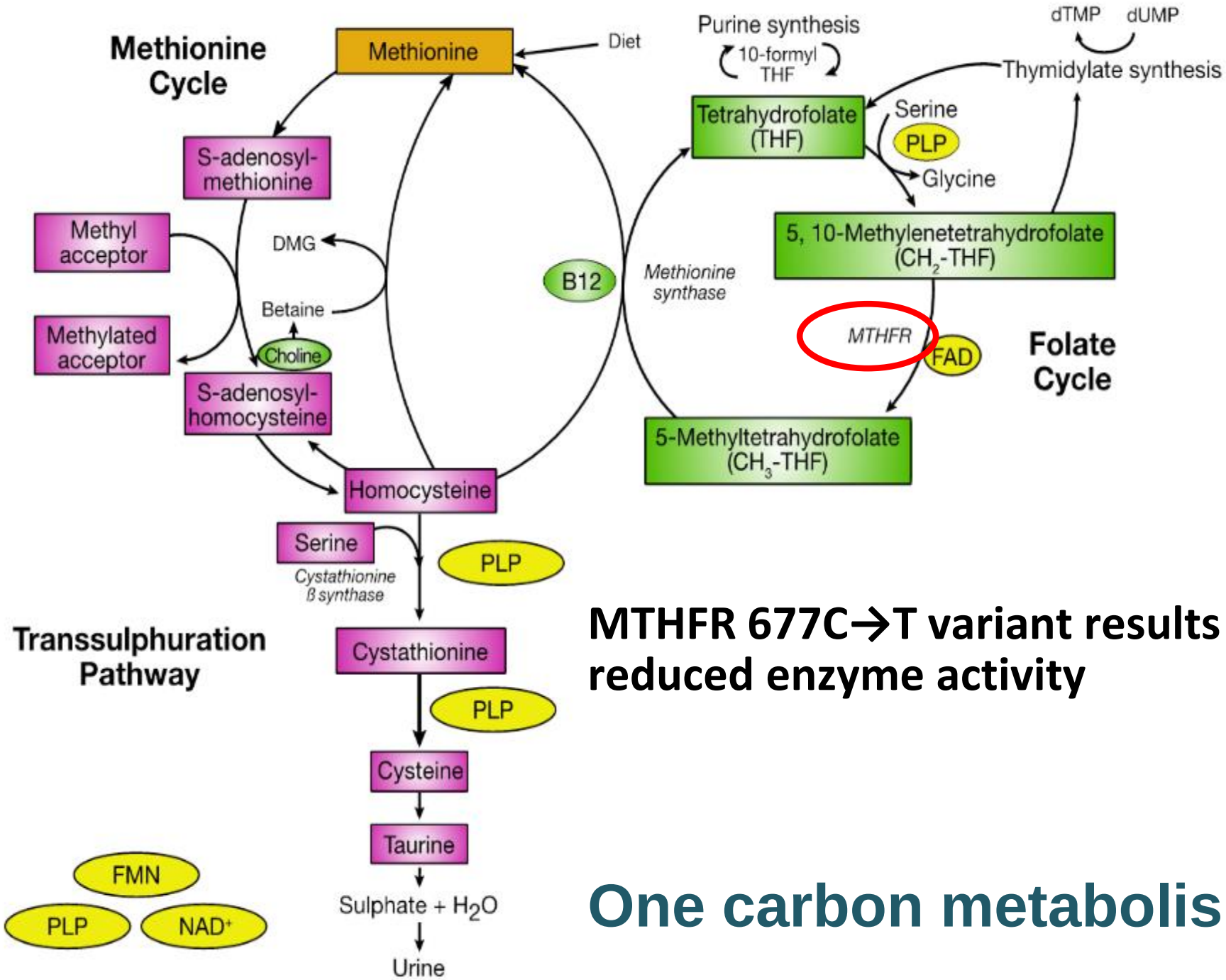

MTHFR 677C→T variant results in reduced enzyme activity

One carbon metabolism

MTHFR 677C→T Polymorphism

- 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

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

[1]Wald DS et al. *BMJ* 2002;.[2]Klerk et al. *JAMA* 2002;
[3]Lewis et al. *BMJ* 2005; [4]Holmes et al. *Lancet* 2011

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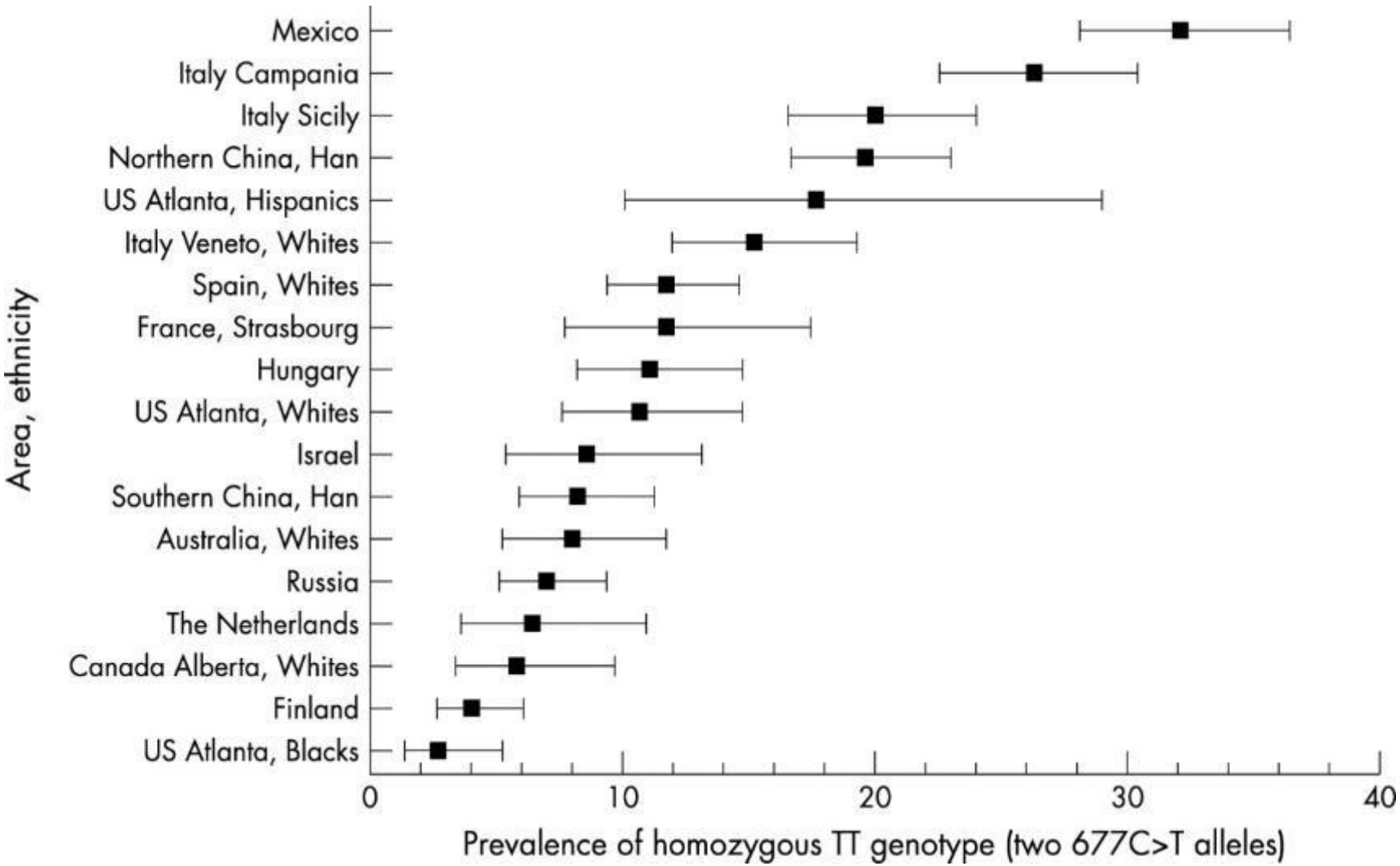
MTHFR 677TT genotype frequency



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

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*

* P<0.05 denotes significance determined by independent t-tests split by treatment

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

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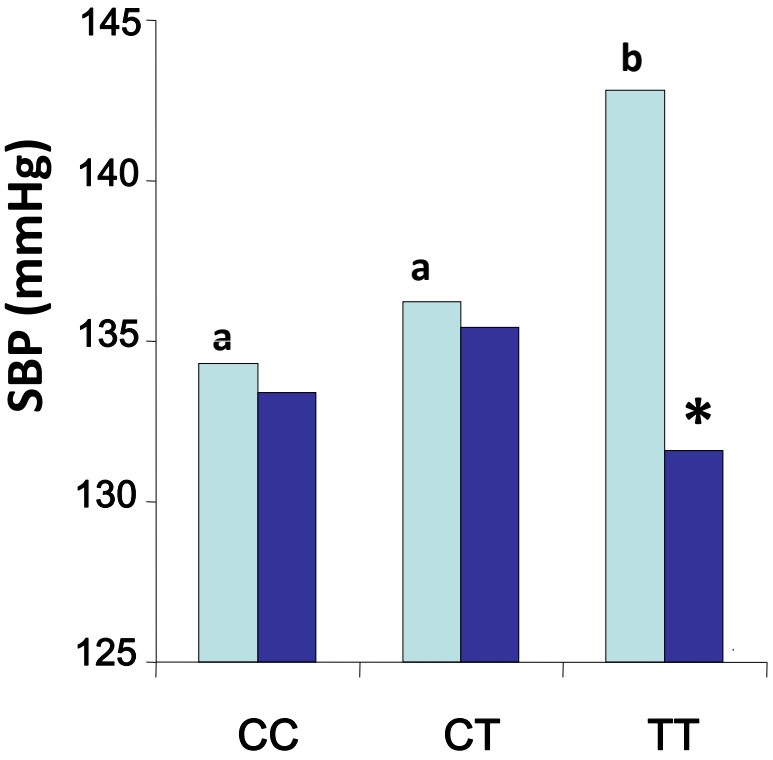
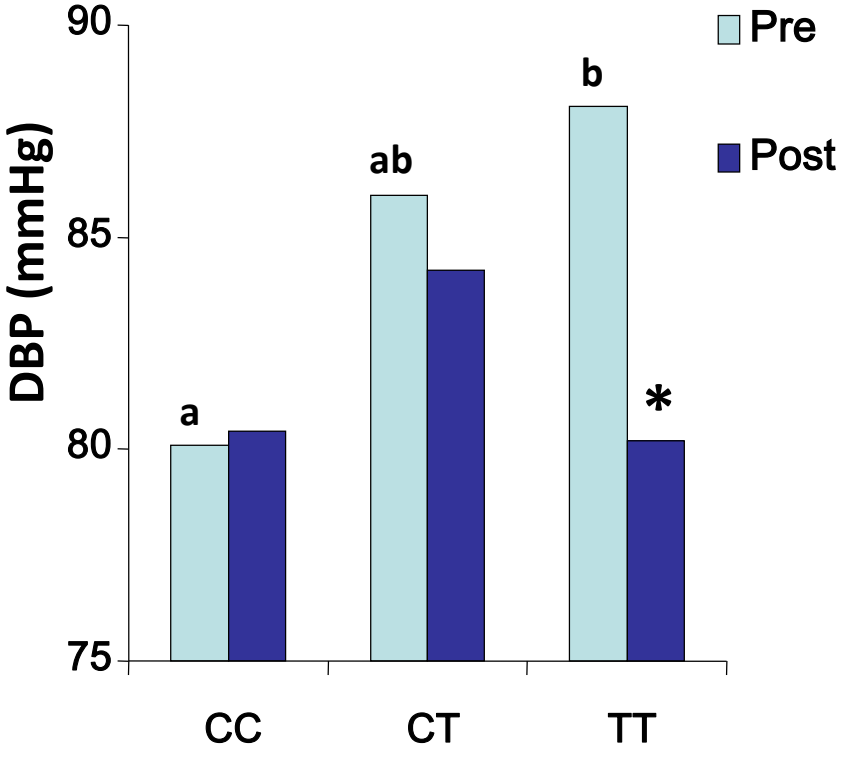
Role of this gene-nutrient interaction in BP





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

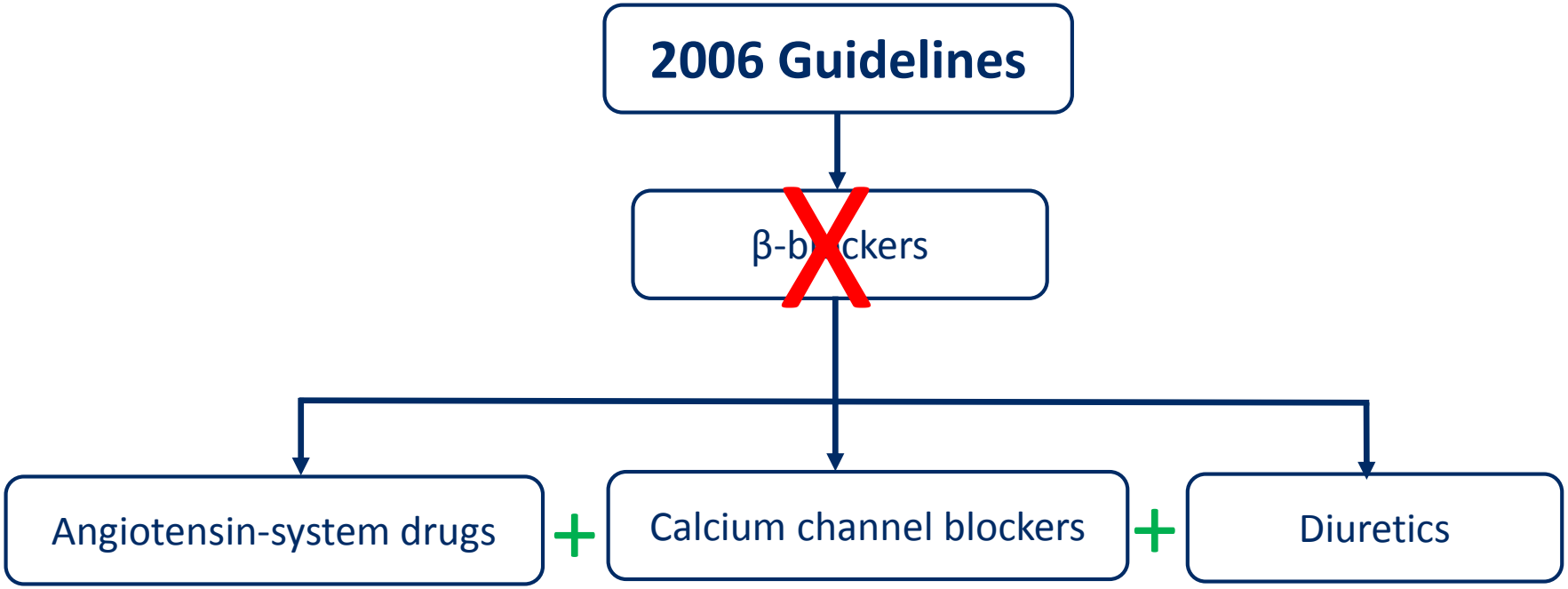
Our 4-year follow-up study

- In light of significant changes in the therapeutic management of hypertension, we wished to:

  - Confirm the role of this polymorphism as a determinant of BP

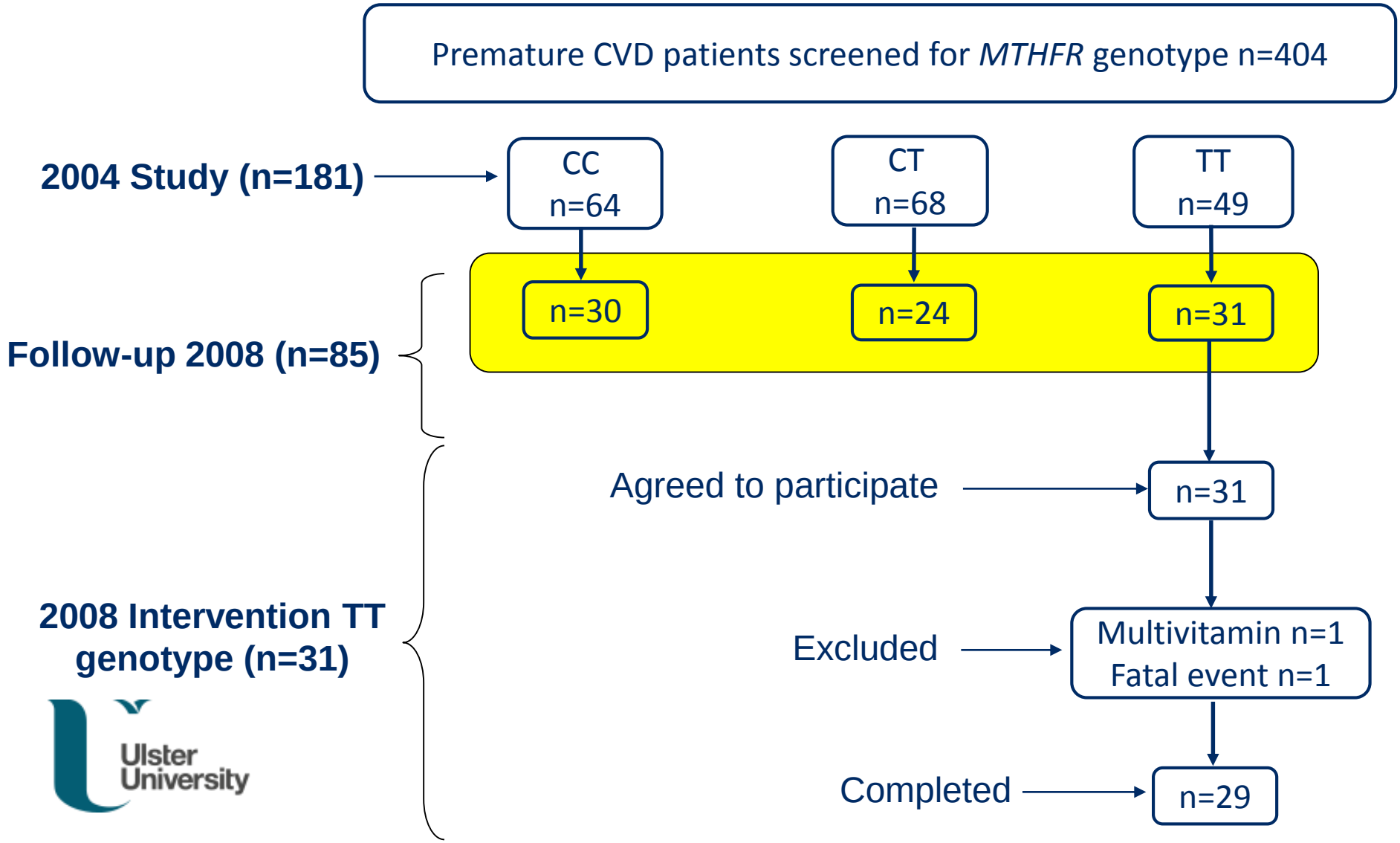
  - Re-investigate the ability of riboflavin to manipulate BP in patients with the TT genotype

BP medication changes

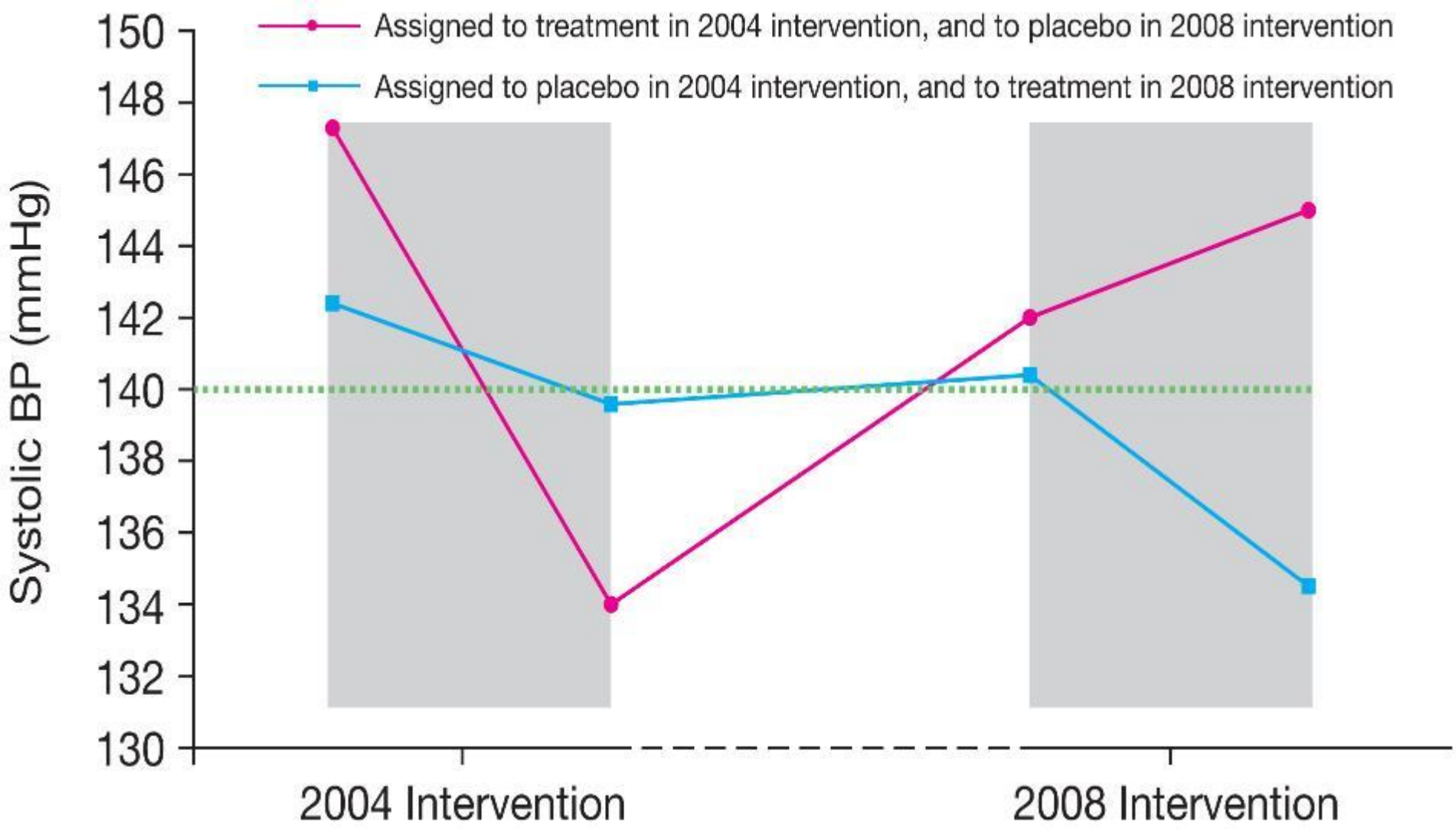


- Three major changes occurred:
  - β-blockers omitted
  - Shift from monotherapy to polytherapy
  - Drug choice depended on age and race

Study design and completion rates



Systolic BP response in patients with the TT genotype



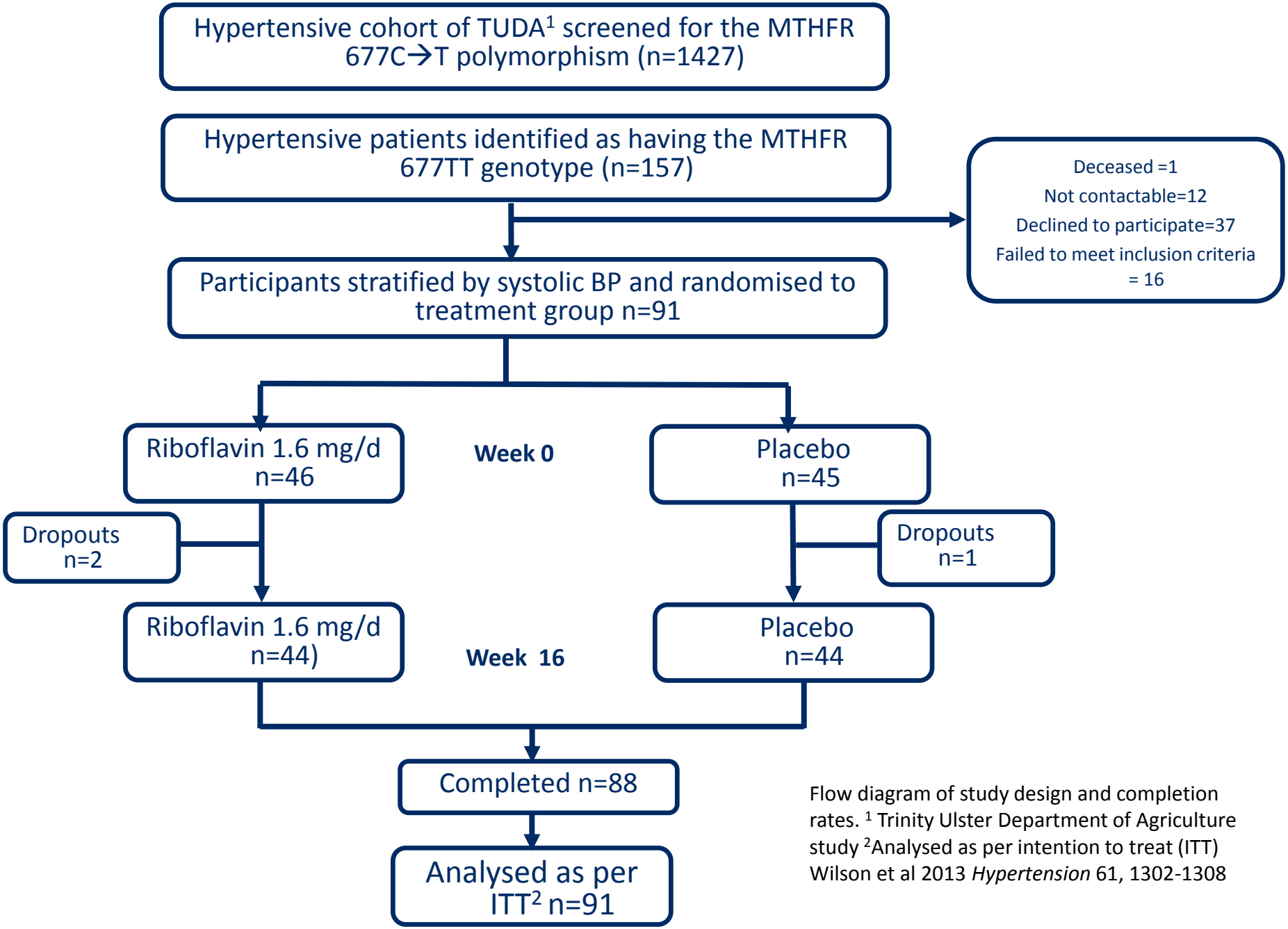
Study results

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

- Riboflavin supplementation resulted in an overall decrease of 9mmHg SBP and 6mmHg DBP (2004 and 2008 interventions combined)

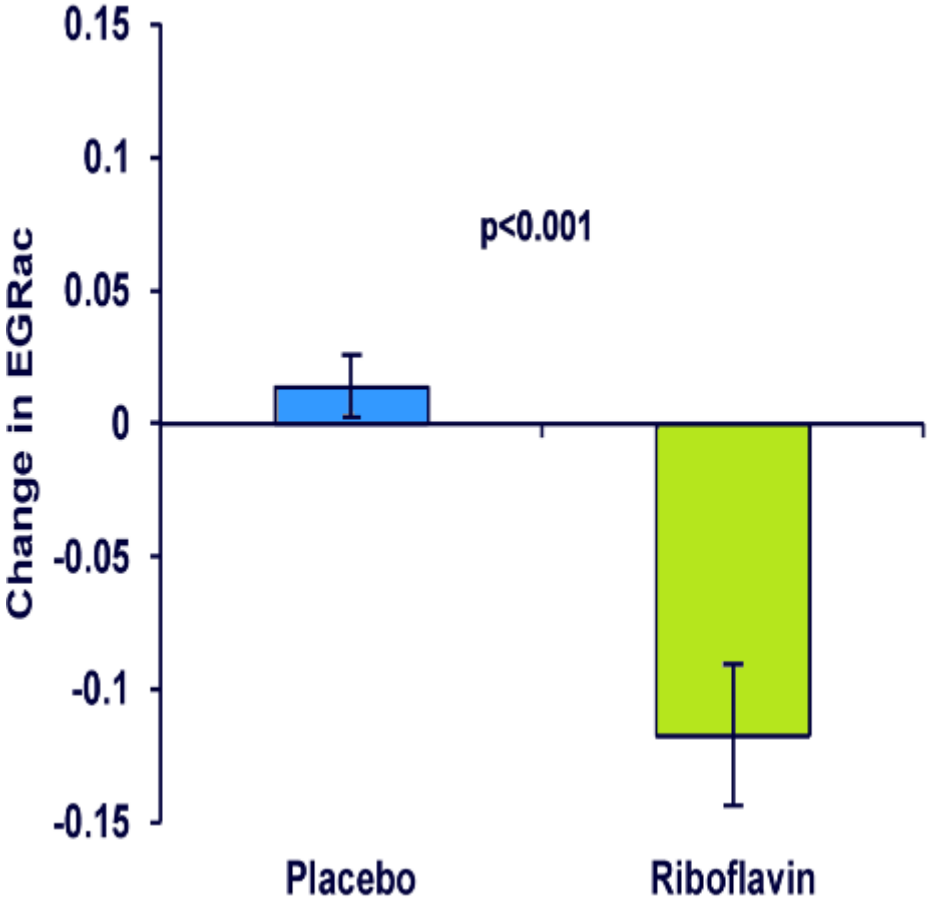
- This genotype-specific BP-lowering effect of riboflavin was evident irrespective of current antihypertensive therapy

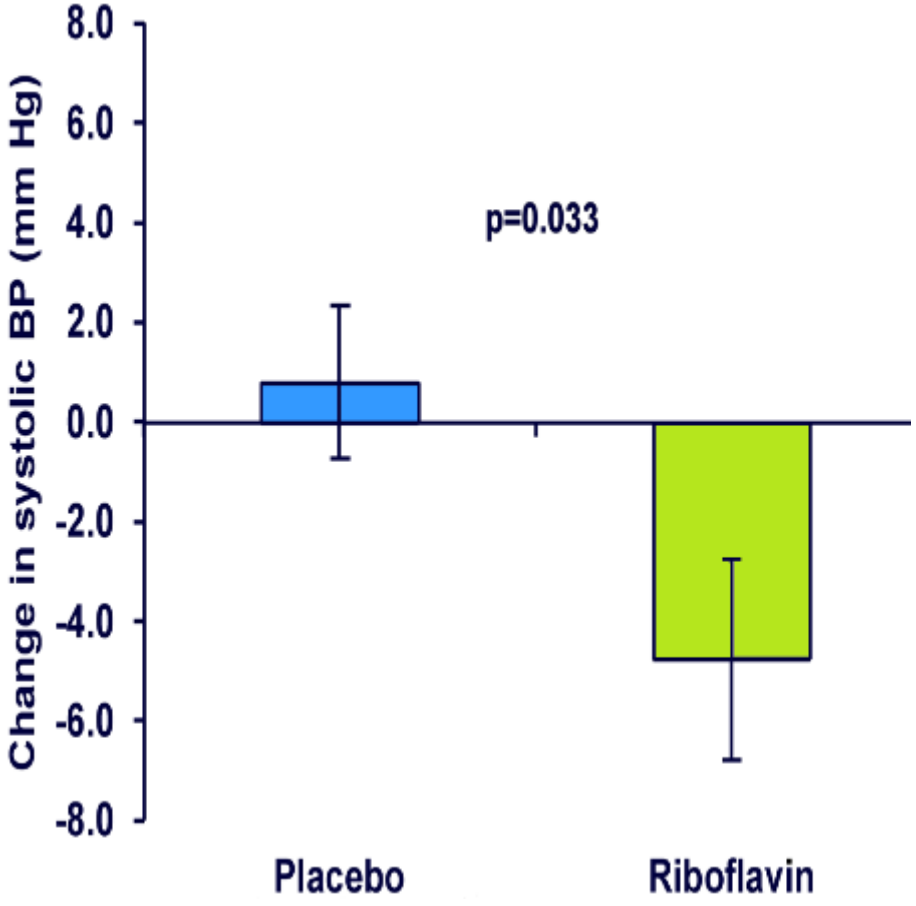
Wilson *et al.* 2012 *AJCN* 95, 766-772



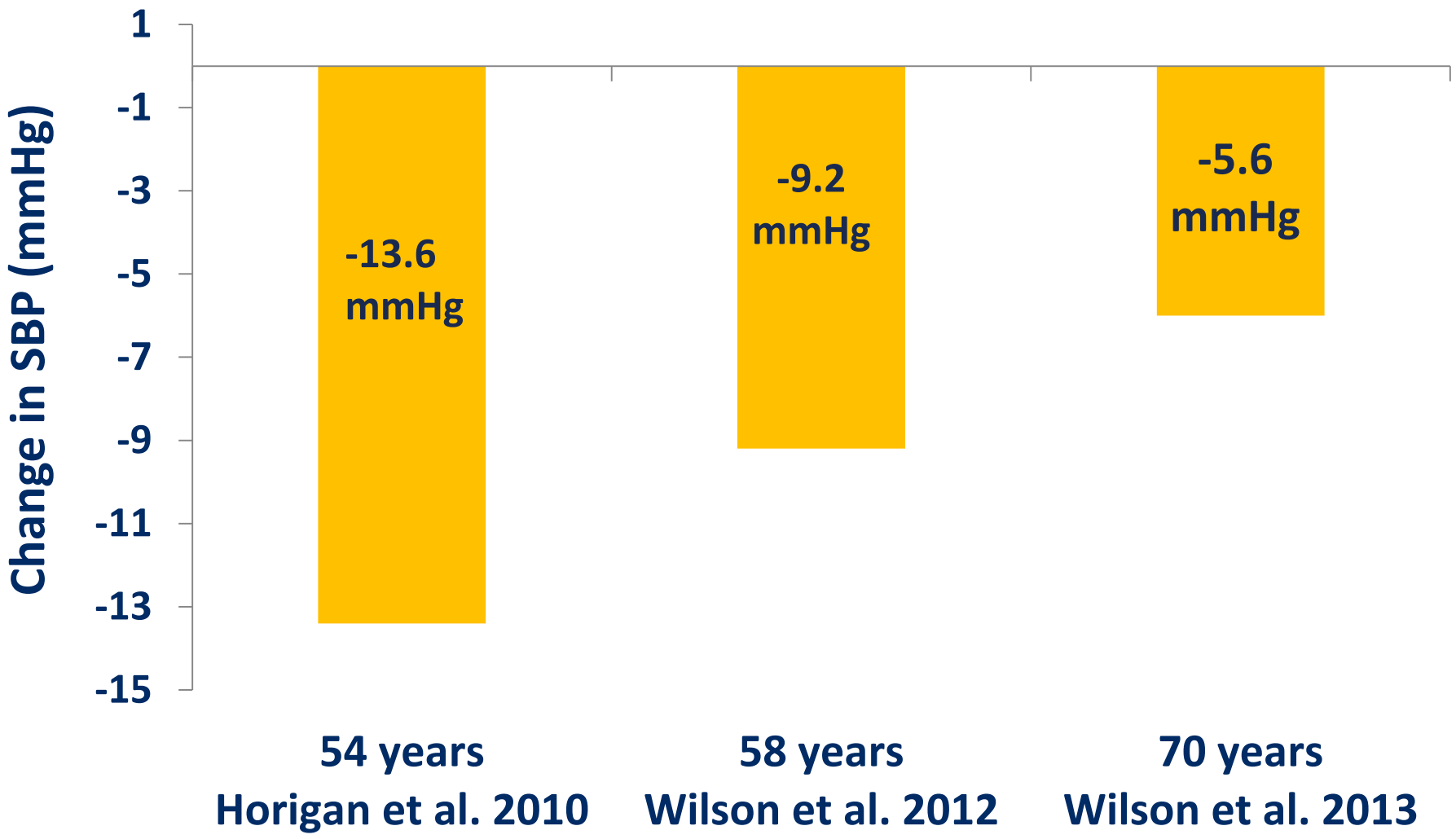
Flow diagram of study design and completion rates. [1] Trinity Ulster Department of Agriculture study [2]Analysed as per intention to treat (ITT) Wilson et al 2013 *Hypertension* 61, 1302-1308

Responses of riboflavin and systolic BP to intervention with riboflavin (1.6 mg/d for 16 weeks) or placebo in those with the *MTHFR* 677TT genotype

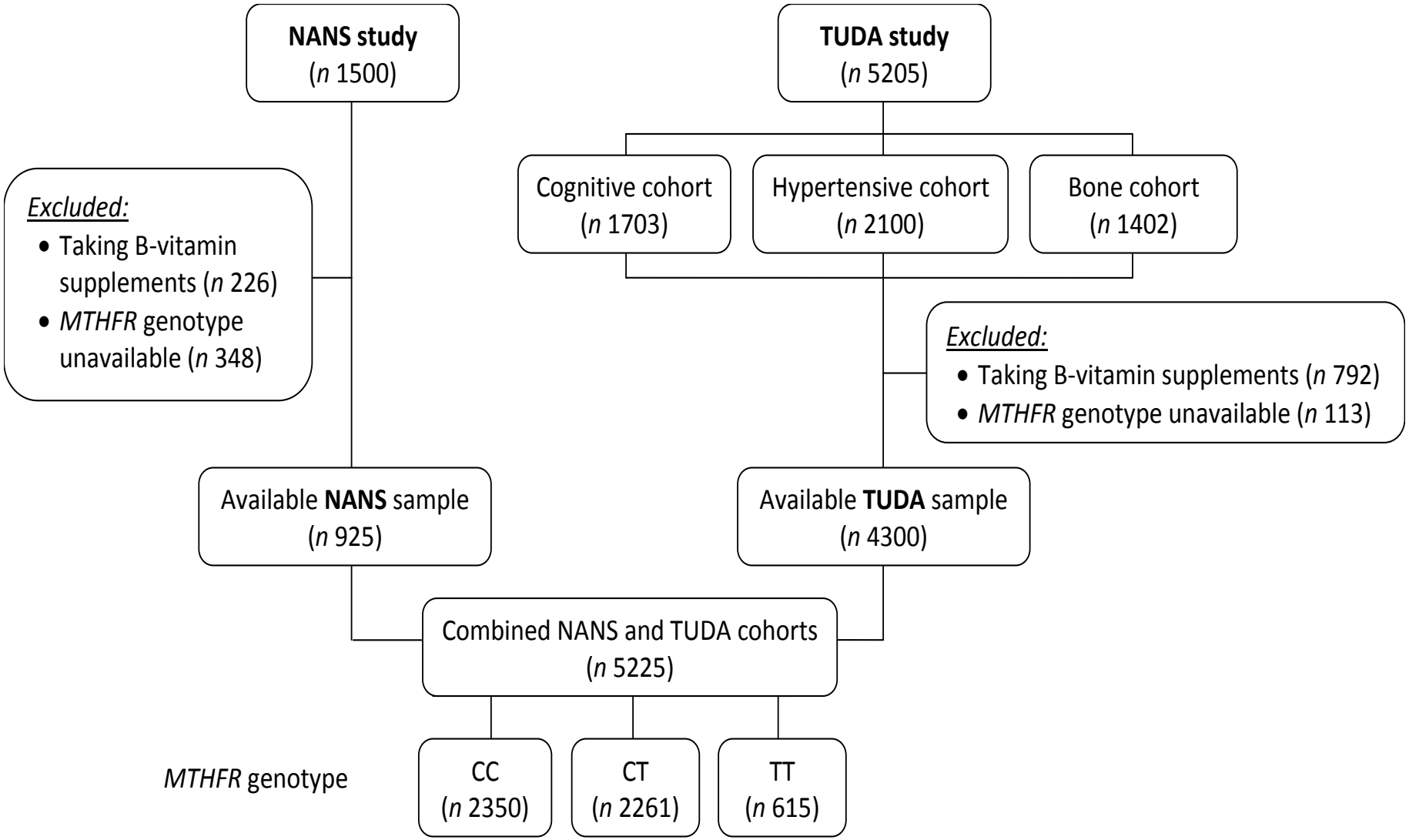




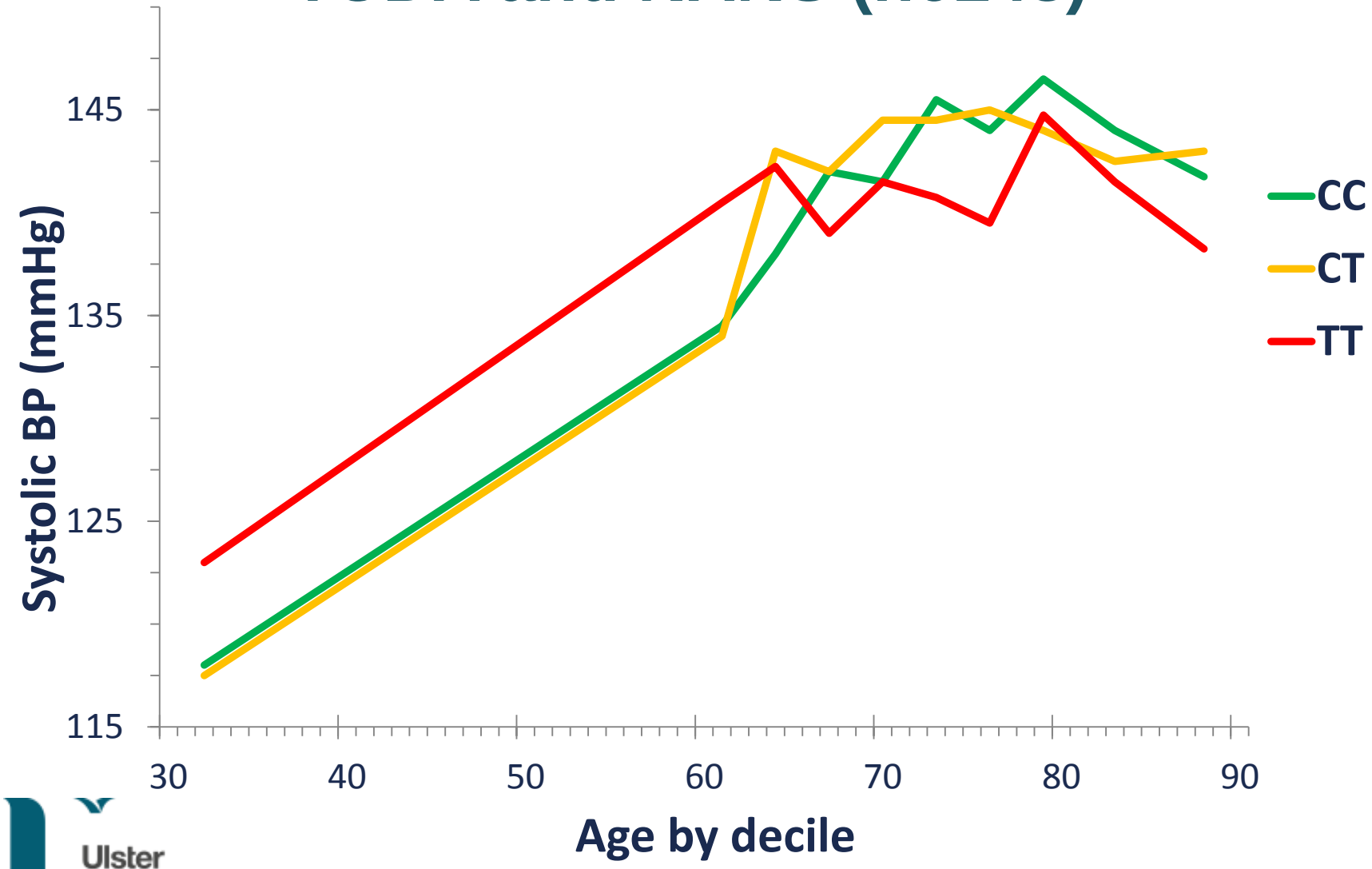
BP lowering by riboflavin (1.6mg/d)



Study design: combined TUDA and NANS studies



Effect of MTHFR genotype on BP by age TUDA and NANS (n6148)



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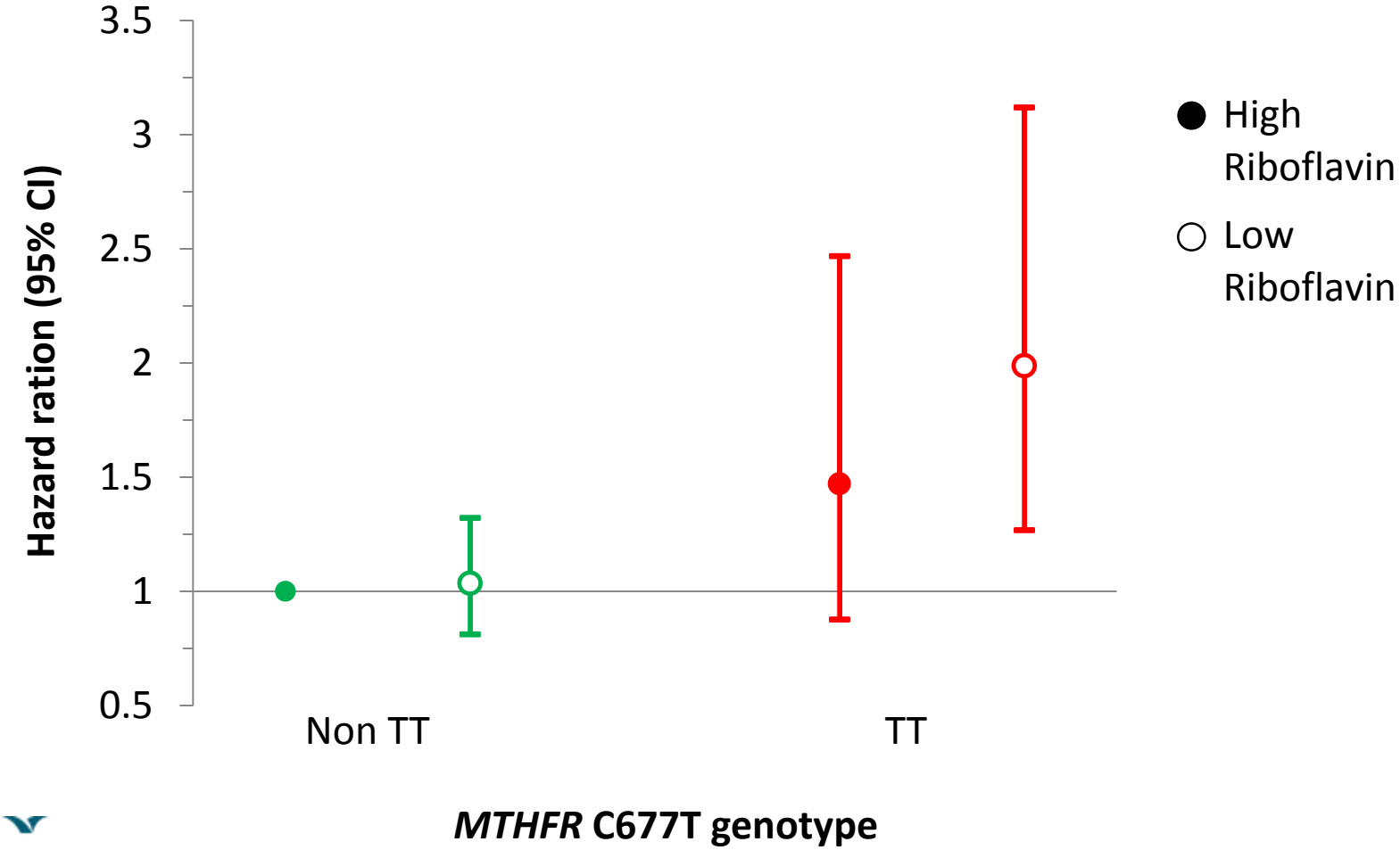
Reilly *et al* unpublished

Gene-Nutrient interaction and risk of hypertension



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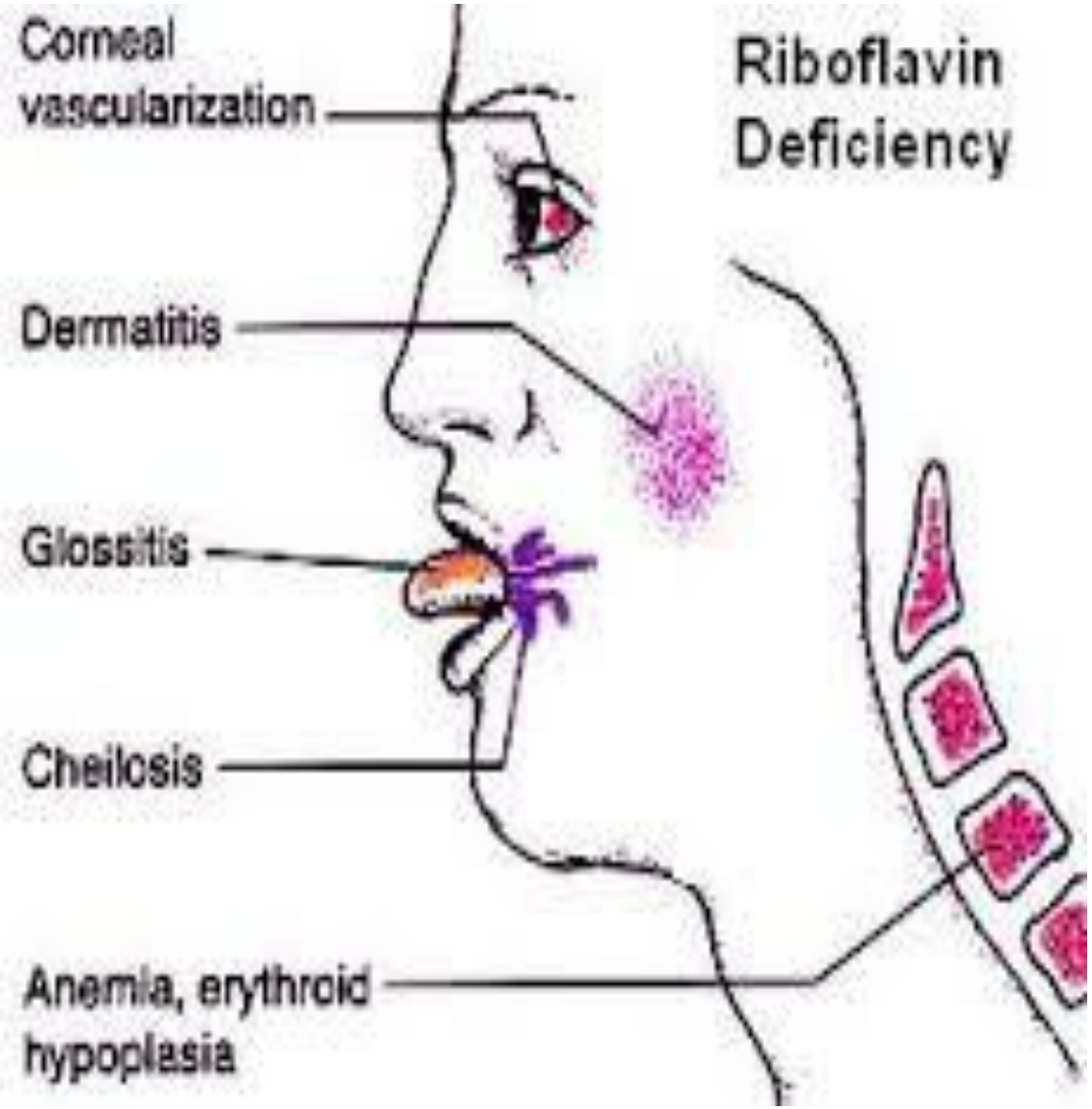
Riboflavin deficiency



Cheilosis

Glossitis

Riboflavin deficiency

- Clinical signs of B_2 deficiency in humans appear at intakes of less than 0.5-0.6 mg/day[2]

- Riboflavin deficiency commonly seen in developing countries where rice is the stable diet[3]

- Sub-optimal status reported in developed countries: vegans, adolescents (girls) and chronic alcoholics

[2]Food and Nutrition Board, Institute of Medicine (1998) Riboflavin. *Dietary Reference Intakes* 87-122
[3]Boisvert *et al*. (2003) *AJCN* 58, 85-90

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Riboflavin sources

	Source	mg/average serving
	Milk	0.45
	Yoghurt	0.35
	Egg	0.26
	Fortified Breakfast Cereal	0.22
	Spinach	0.21
	Beef (cooked roast)	0.15
	Cheddar Cheese	0.11
	Bread (Whole-wheat/White)	0.06-009

Lifestyle factors targeted to reduce BP

Lifestyle factor	SBP decrease (mmHg)
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Riboflavin (genotype-specific)	6 -13
Physical activity	4 - 9
Sodium reduction	2 - 8
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Modified from Chobanian *et al.* 2003 JNC 7 report

Conclusions and future work

What we now know:

- Riboflavin supplementation can significantly lower BP in premature CVD patients and in hypertensive patients with the TT genotype

What is yet to be determined:

- Can riboflavin at a dose >1.6mg/d achieve optimal BP lowering in individuals with the TT genotype?
- What is the mechanism which might explain how this gene-nutrient interaction affects BP irrespective of current antihypertensive therapy?

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