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High Blood Pressure in Irish Adults

Preliminary findings and lessons learned from two JINGO cohorts

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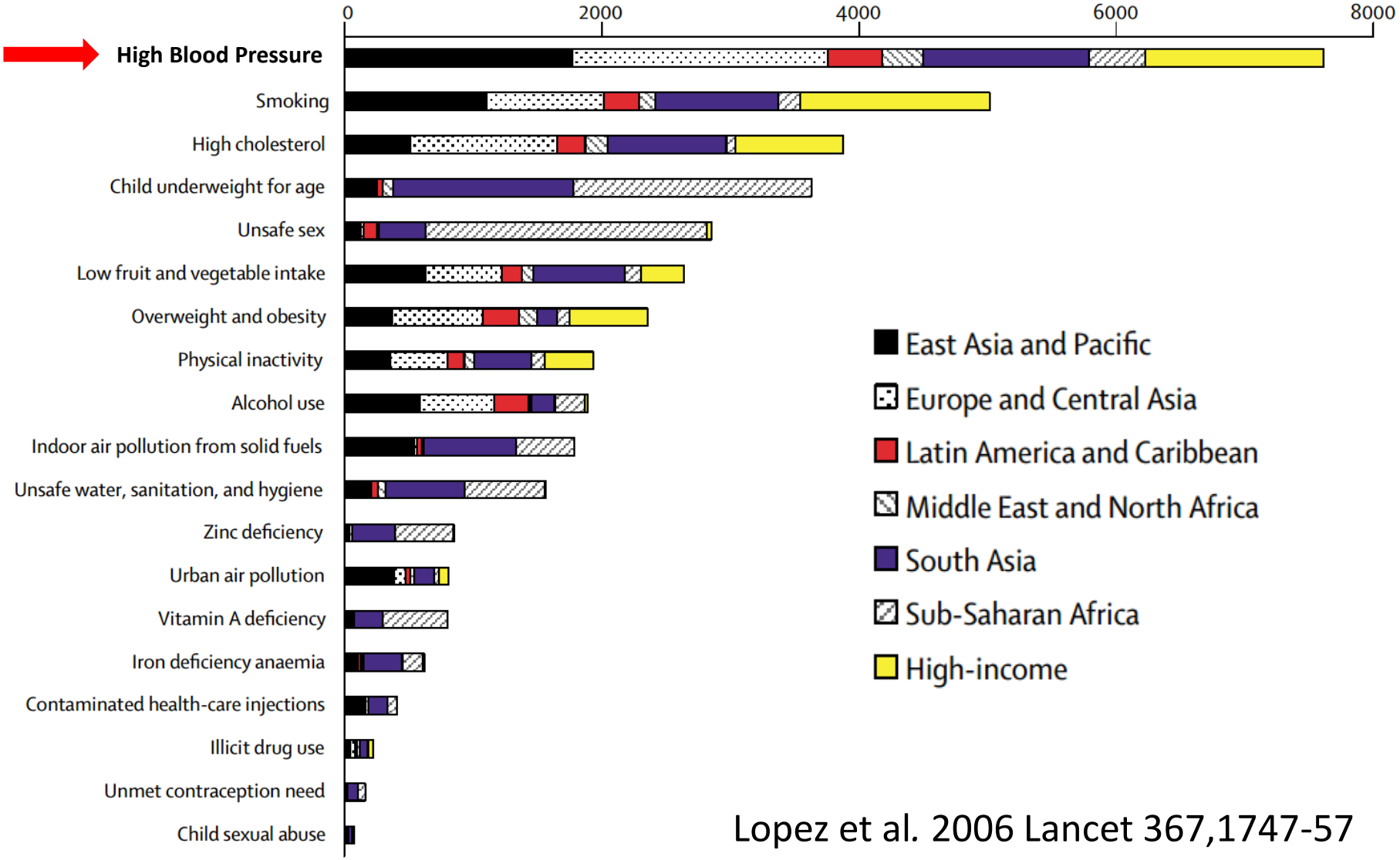
Mortality due to global risk factors

Attributable Deaths in Thousands

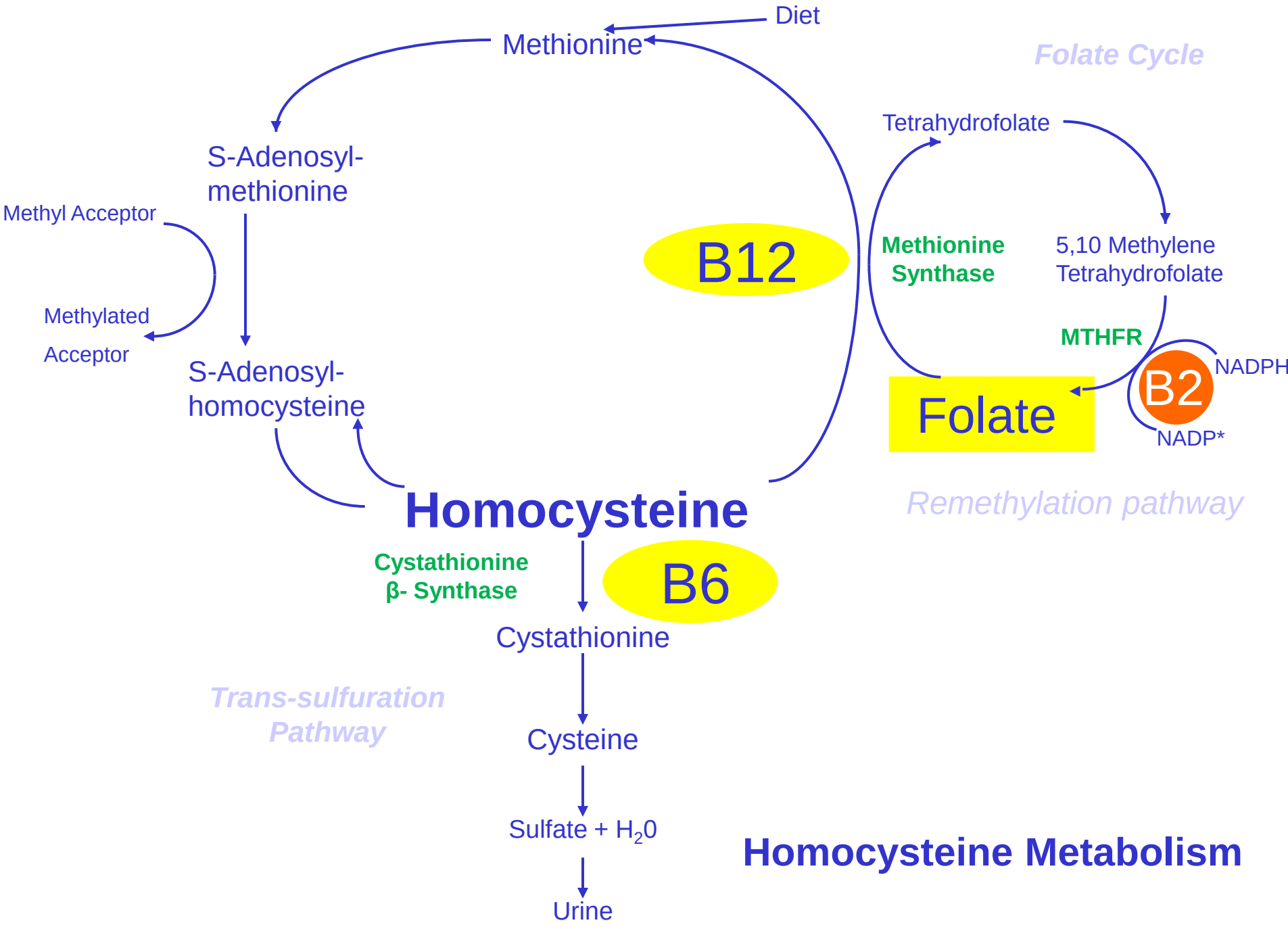


Lopez et al. 2006 Lancet 367,1747-57

High Blood Pressure in Irish Adults

This talk will address

- High blood pressure and genetic risk
- High blood pressure in Irish adults: what the latest analysis shows
- Impact


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
Folate
NADP*
Homocysteine
Remethylation pathway
Cystathionine
β- Synthase
B6
Cystathionine
Trans-sulfuration
Pathway
Cysteine
Sulfate + H20
Urine
Homocysteine Metabolism

Is the *MTHFR* 677C→T Polymorphism a risk factor for CVD?

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

- Meta-analyses[1-4] estimate that the TT genotype carries an excess risk of CVD by 14-21% , but large geographical variation in the reported excess risk among 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

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

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

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.

ARTICLES

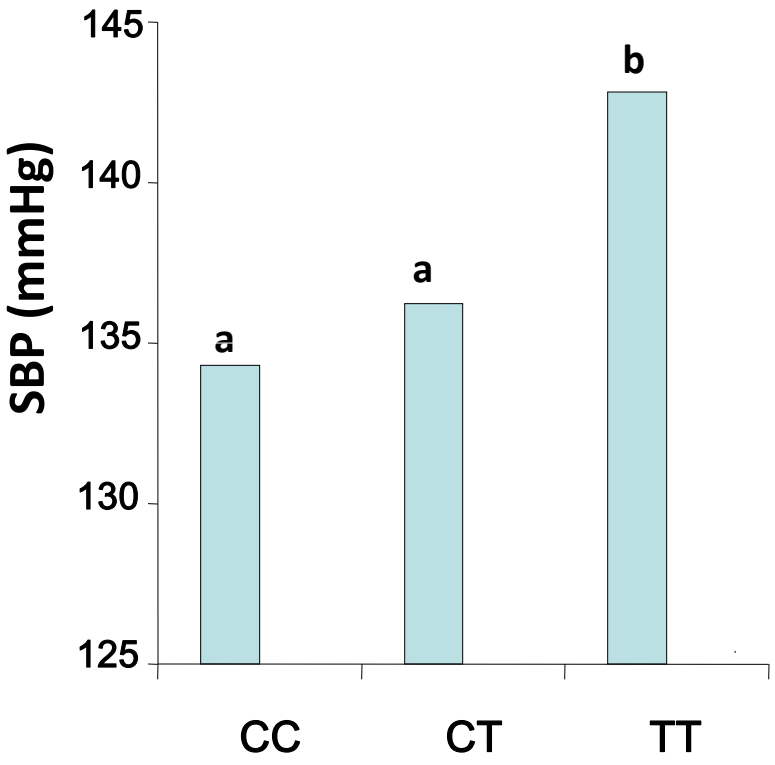
nature genetics

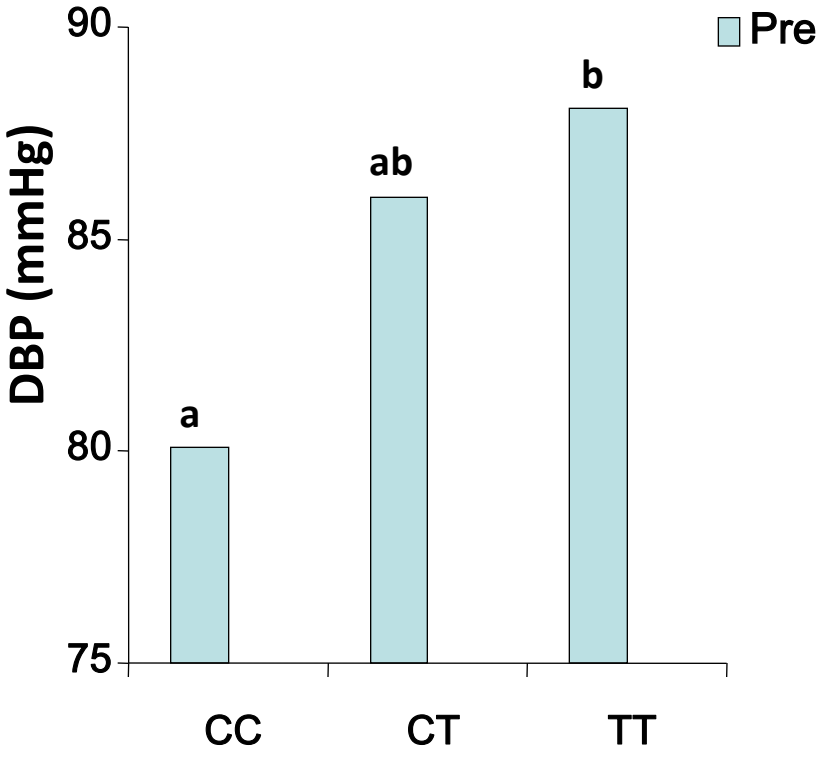
Genome-wide association study identifies eight loci associated with blood pressure

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.

This gene-nutrient interaction may have a novel role in BP





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

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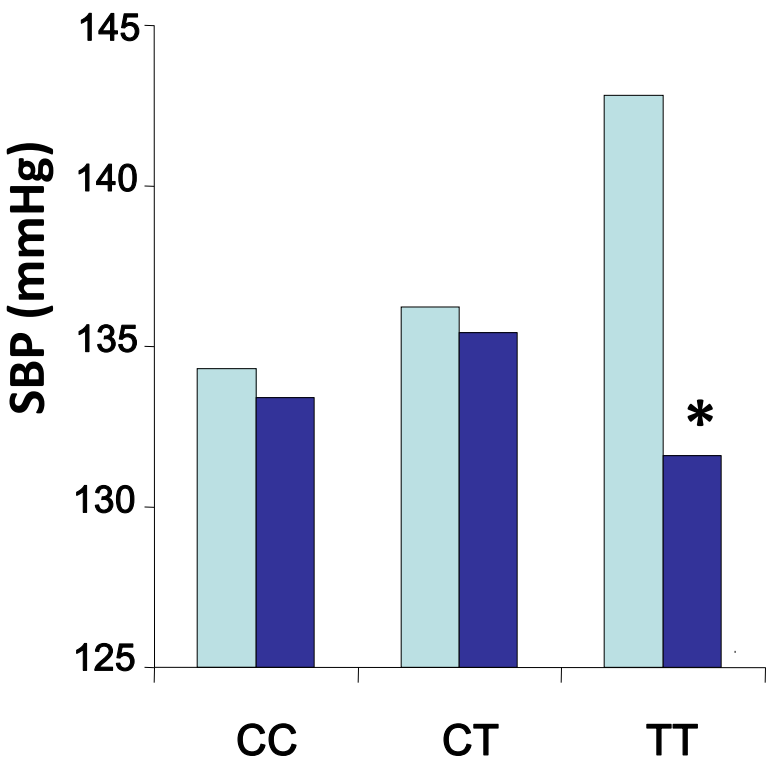
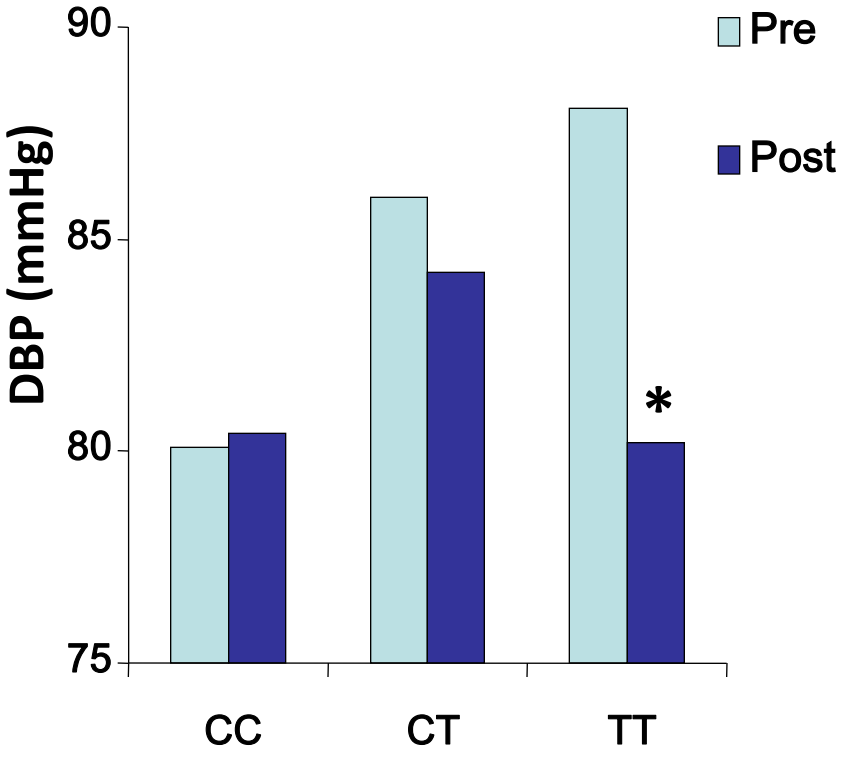
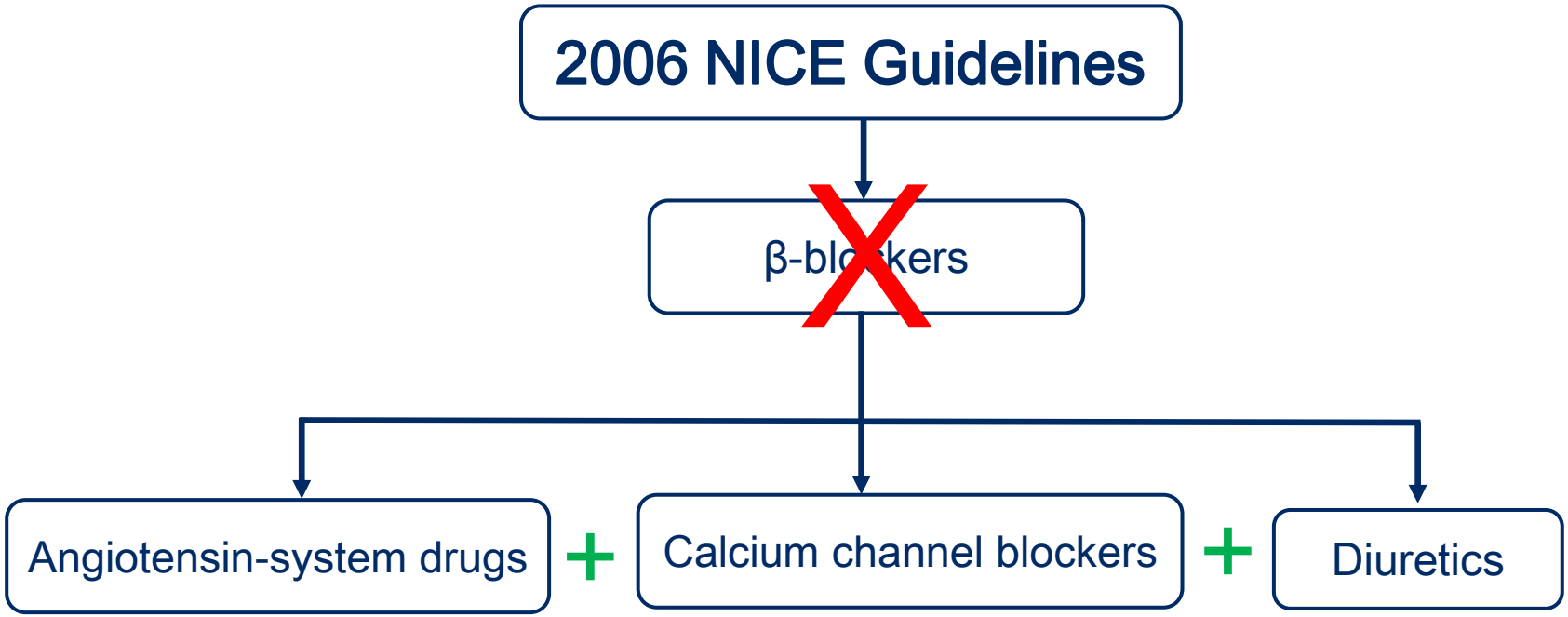




Horigan *et al.* 2010 *Journal of Hypertension;* **28:** 478-486.

BP medication changes



- Two major changes occurred:
  - β-blockers omitted
  - Shift from monotherapy to polytherapy

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

Role of this novel gene-nutrient interaction in hypertensive individuals generally (no overt CVD):

TUDA Participants pre-screened for MTHFR genotype

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 treated hypertensive individuals with the MTHFR 677TT genotype (recruited to the TUDA Ageing Study) showed a significant BP-lowering response to riboflavin**

Wilson CP, McNulty H, Ward M, Strain JJ et al (2013) *Hypertension*, **61**: 1302-1308.

Genetic risk and a novel gene-nutrient interaction in BP

Some unanswered questions

- What are the determinants of blood pressure in Irish 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 diet matter?

Genetic risk and a novel gene-nutrient interaction in BP

Some unanswered questions

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- **The JINGO project (through combined analysis of NANS and TUDA cohorts) provided a unique opportunity to address these key questions**

Summary of preliminary findings (unpublished)

- Total potential sample (NANS/TUDA): 6706 Irish adults aged 18+ years

- Well known causes of hypertension such as increasing age and overweight/obesity were evident

- Apart from well known causes, more than 1 in 10 Irish adults are genetically at-risk of developing high blood pressure; their higher blood pressure is evident by aged 18 years
  - This risk is evident regardless of whether blood pressure-lowering drugs are being taken
  - A good riboflavin status appears to protect against the development of hypertension in this genetically at-risk group.

MTHFR 677 TT genotype and BP

In people with TT genotype, MTHFR enzyme less active

↓ ***higher riboflavin status***

MTHFR enzyme more active
(5 methyl THF increased)

↓ **Plasma Homocysteine Decreased**

↓ **Blood Pressure Decreased**

↓ **Blood Pressure Decreased (? Nitric oxide implicated; smooth muscle cell vasodilation)**

MTHFR 677 TT genotype and BP

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MTHFR enzyme more active

(5 methyl THF increased)

↓

Plasma Homocysteine

Decreased

↓

Blood Pressure

Decreased

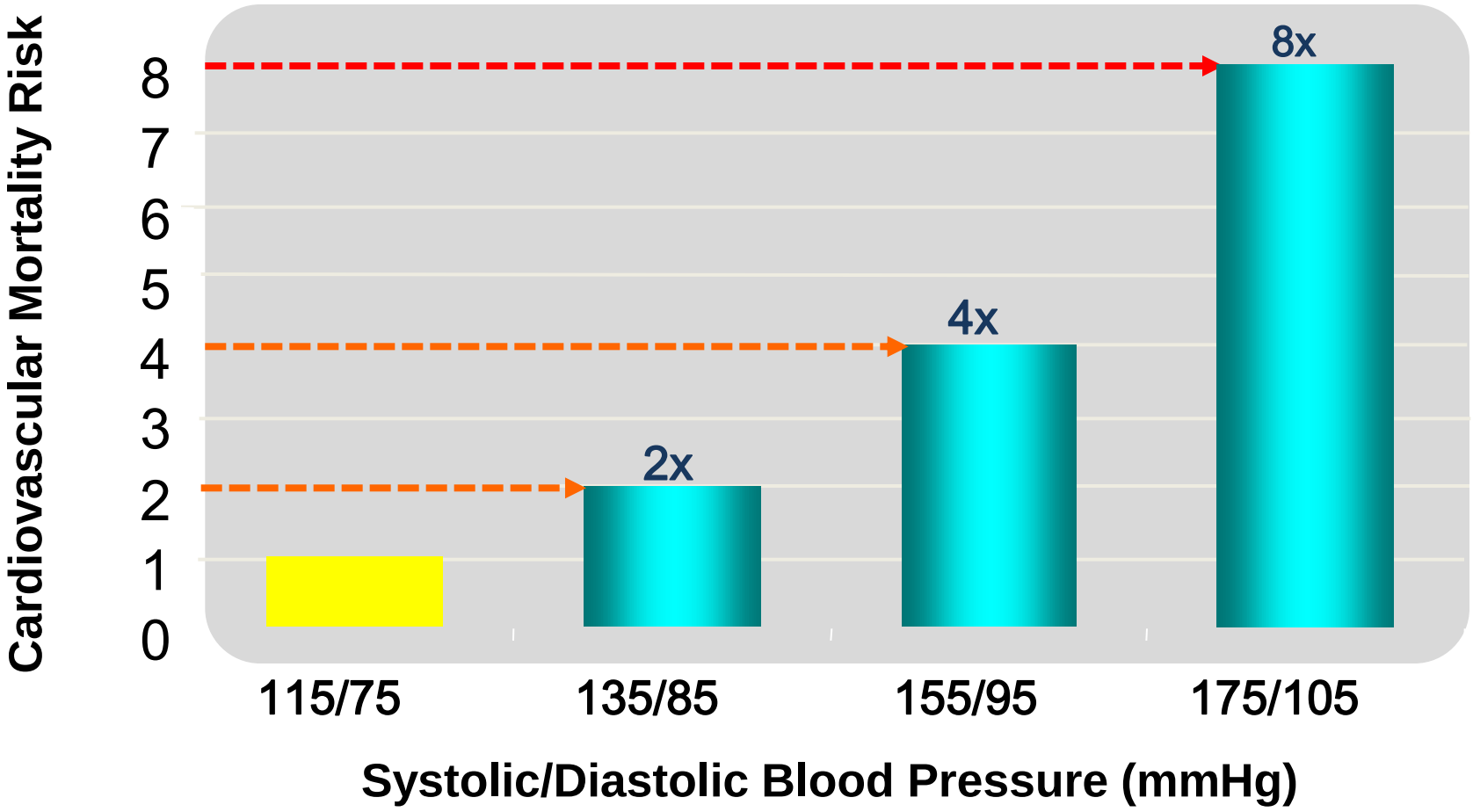
↓

Blood Pressure

Decreased (? Nitric oxide implicated; smooth muscle cell vasodilation)

Impact

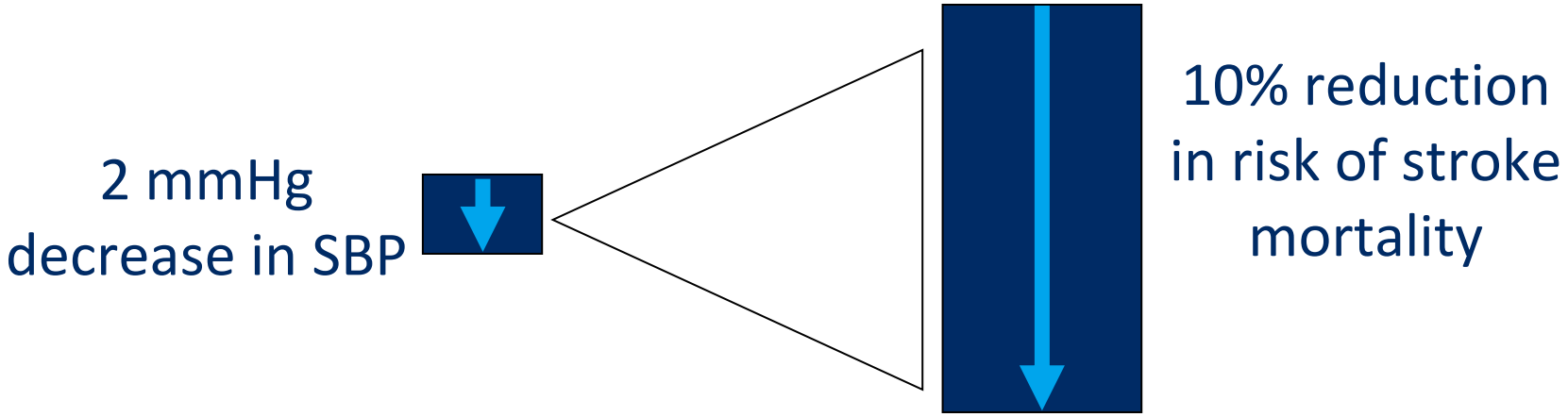
CVD mortality risk increases as BP rises



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

Impact of BP reduction

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



- Potential public health significance of this gene-nutrient interaction on BP

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

Lifestyle factors targeted 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

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

A novel gene-nutrient-nutrient interaction in BP

Take-home messages

- The ***MTHFR* 677TT genotype** increases the risk of developing hypertension

- **Riboflavin** can play an important preventative role against hypertension *specifically* in people with the TT genotype
  - Independent of current antihypertensive therapy
  - Increased riboflavin intake in this genetically at-risk group may offer a 'personalised' non-drug approach to preventing/treating hypertension.

- **Future work**
  - Targeted randomised trials in individuals pre-screened for MTHFR genotype
  - Confirmation of these results in other populations in the world

My thanks to…….

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Adrian McCann

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Conal Cunningham
Miriam Casey

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Carol Wilson (2010)
Rosie Reilly (current)
Emma Hughes (current)

Clinical Collaborators

Maurice O'Kane
Tom Trouton
John Purvis

DSM
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