

# Collaborative Models for Biomarkers Development

Vincent Mooser, MD  
Medical Genetics/Clinical Pharmacology  
And Discovery Medicine  
GlaxoSmithKline

Coronary artery disease and  
cardiovascular risk factors  
are relatively heritable  
and have a complex genetic basis

→ Opportunities :

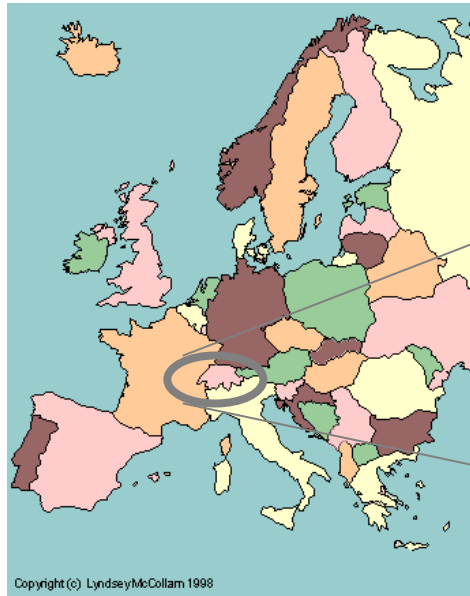
New drug targets

Target validation in humans.

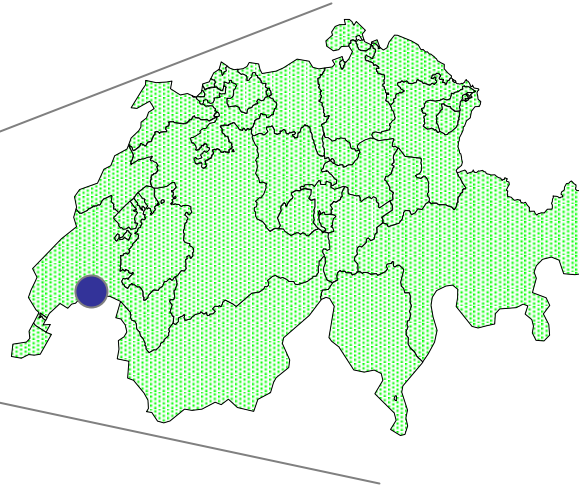
# Our Approach

- Portfolio of large-scale family-based + case-control + population-based studies
- Collaboration with Academia
- Extensive and cohesive phenotype
- Genome-wide association analyses
- IP to inventors, support for publications

# Europe



# Switzerland



# Lausanne



# Lausanne : Phenotypes

n = 6205

n = 4000  
(by 4Q07)

## Hypertension

Systolic BP  
Diastolic BP  
Heart rate  
Creatinine  
Urinary Creatinine  
Micro-albuminuria

## Dyslipidemia

Total Chol  
Triglycerides  
HDL-C  
LDL particle size

## Diabesity

Body weight  
Height  
BMI  
Waist  
WHR  
Leptin  
Glucose  
Insulin  
Adiponectin  
Bioimpedance

## Others

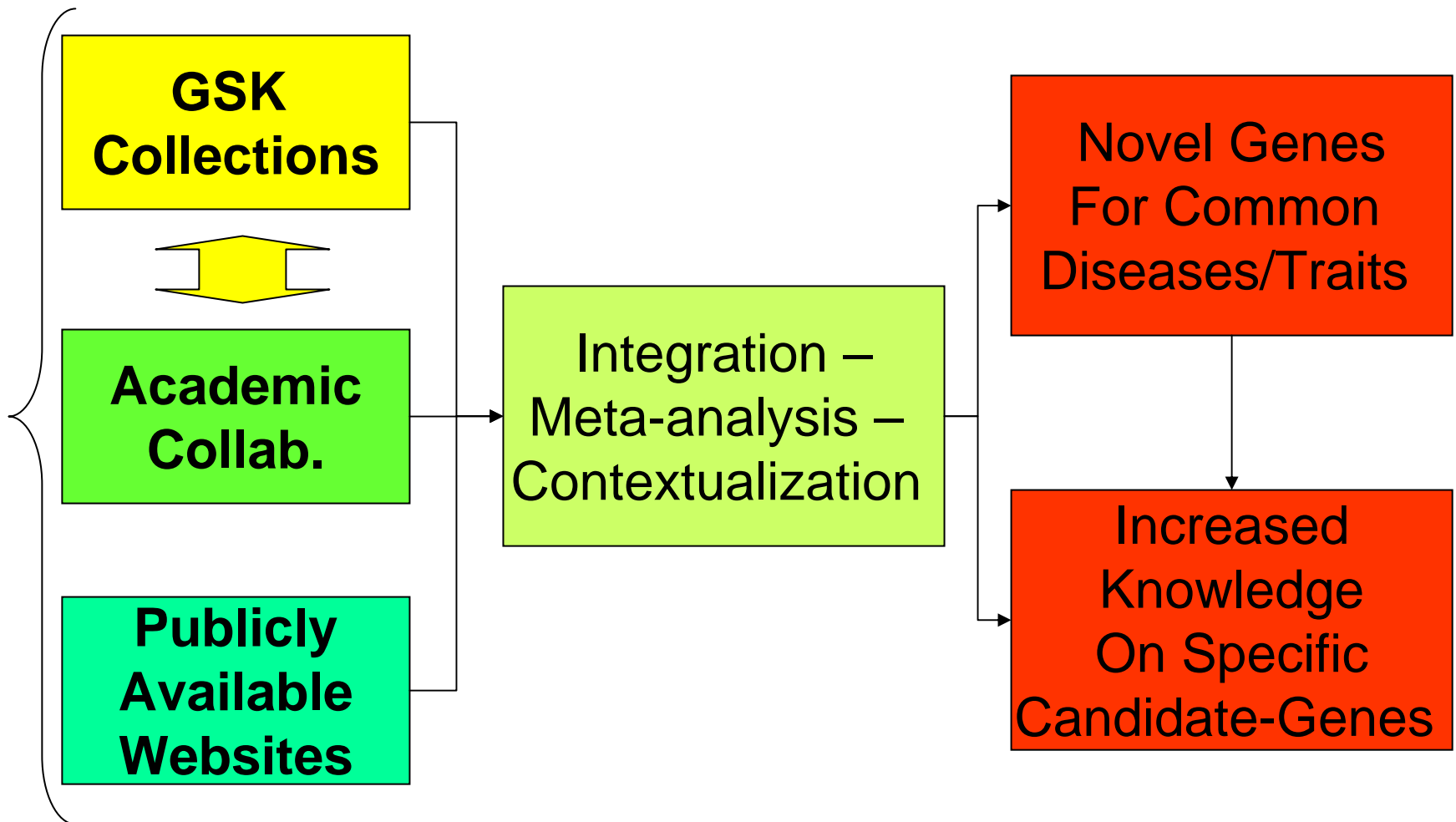
Transferrin  
LFTs, HCy  
Grip strength  
MMSE (> 65)  
  
HS-CRP  
  
Ca, Prot,  
Albumin  
Baldness

## Psychiatry

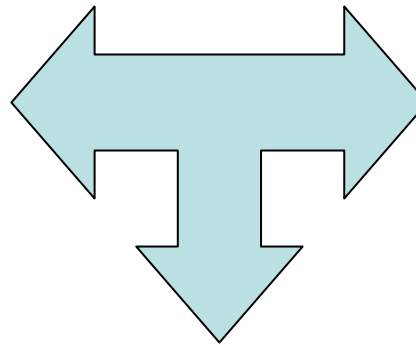
Careful  
assessment of  
all common  
conditions, in  
particular :  
  
Anxiety  
Depression  
Addiction  
Migraine

**Genotypes : Affymetrix 500K SNP chip on n = 6000**

# Integrating and Coordinating Genetic Initiatives



# The MRC Cambridge – Lausanne – GSK Collaboration



# Example : Height

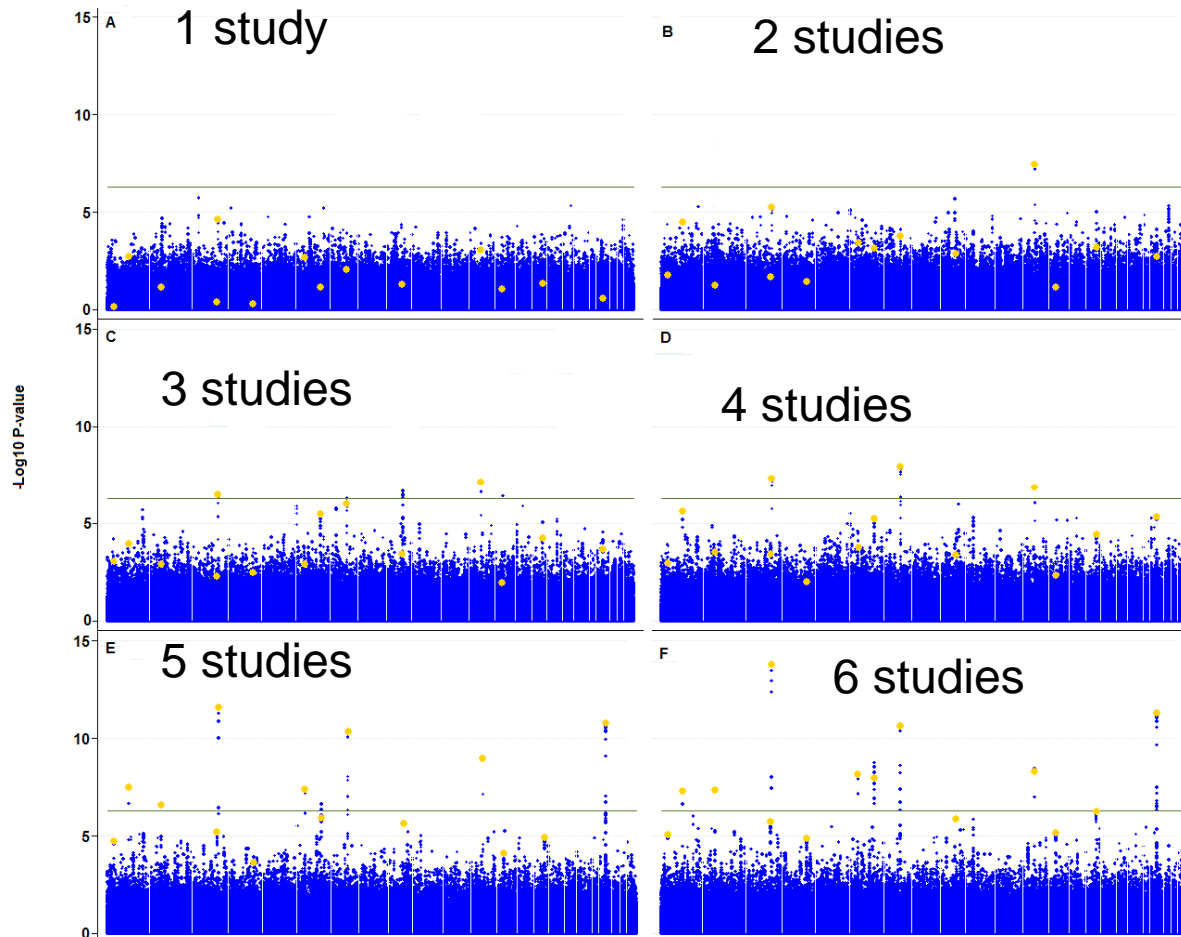
- Highly heritable ( $> 90\%$ )
- Genetically complex
- Reliable phenotype
- Large datasets available for collaborative work

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# A common variant of *HMGA2* is associated with adult and childhood height in the general population

Michael N Weedon<sup>1,2,21</sup>, Guillaume Lettre<sup>3,4,21</sup>, Rachel M Freathy<sup>1,2,21</sup>, Cecilia M Lindgren<sup>5,6,21</sup>, Benjamin F Voight<sup>3,7</sup>, John R B Perry<sup>1,2</sup>, Katherine S Elliott<sup>5</sup>, Rachel Hackett<sup>3</sup>, Candace Guiducci<sup>3</sup>, Beverley Shields<sup>2</sup>, Eleftheria Zeggini<sup>5</sup>, Hana Lango<sup>1,2</sup>, Valeriya Lyssenko<sup>8,9</sup>, Nicholas J Timpson<sup>5,10</sup>, Noel P Burt<sup>3</sup>, Nigel W Rayner<sup>6</sup>, Richa Saxena<sup>3,7,11</sup>, Kristin Ardlie<sup>3</sup>, Jonathan H Tobias<sup>12</sup>, Andrew R Ness<sup>13</sup>, Susan M Ring<sup>14</sup>, Colin N A Palmer<sup>15</sup>, Andrew D Morris<sup>16</sup>, Leena Peltonen<sup>3,17,18</sup>, Veikko Salomaa<sup>19</sup>, The Diabetes Genetics Initiative, The Wellcome Trust Case Control Consortium, George Davey Smith<sup>10</sup>, Leif C Groop<sup>8,9</sup>, Andrew T Hattersley<sup>1,2</sup>, Mark I McCarthy<sup>5,6,21</sup>, Joel N Hirschhorn<sup>3,4,20,21</sup> & Timothy M Frayling<sup>1,2,21</sup>

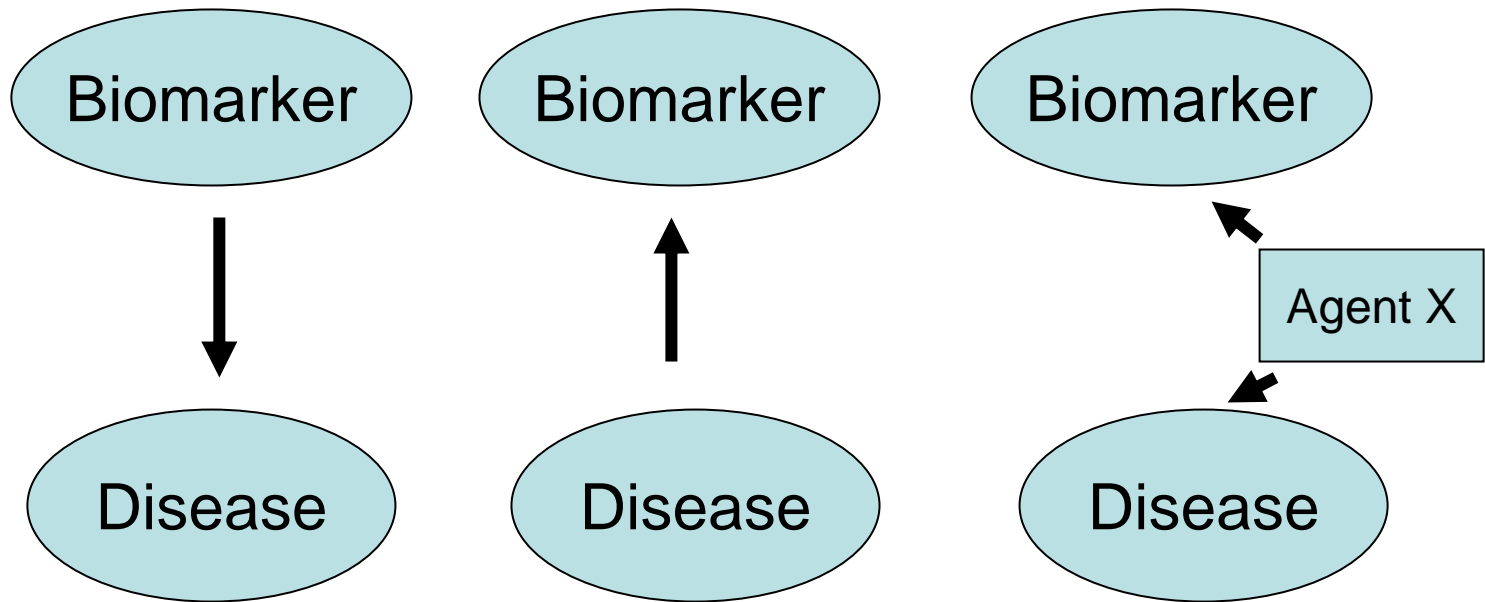
# Manhattan Plot for SNPs Associated with Height by Adding More Studies



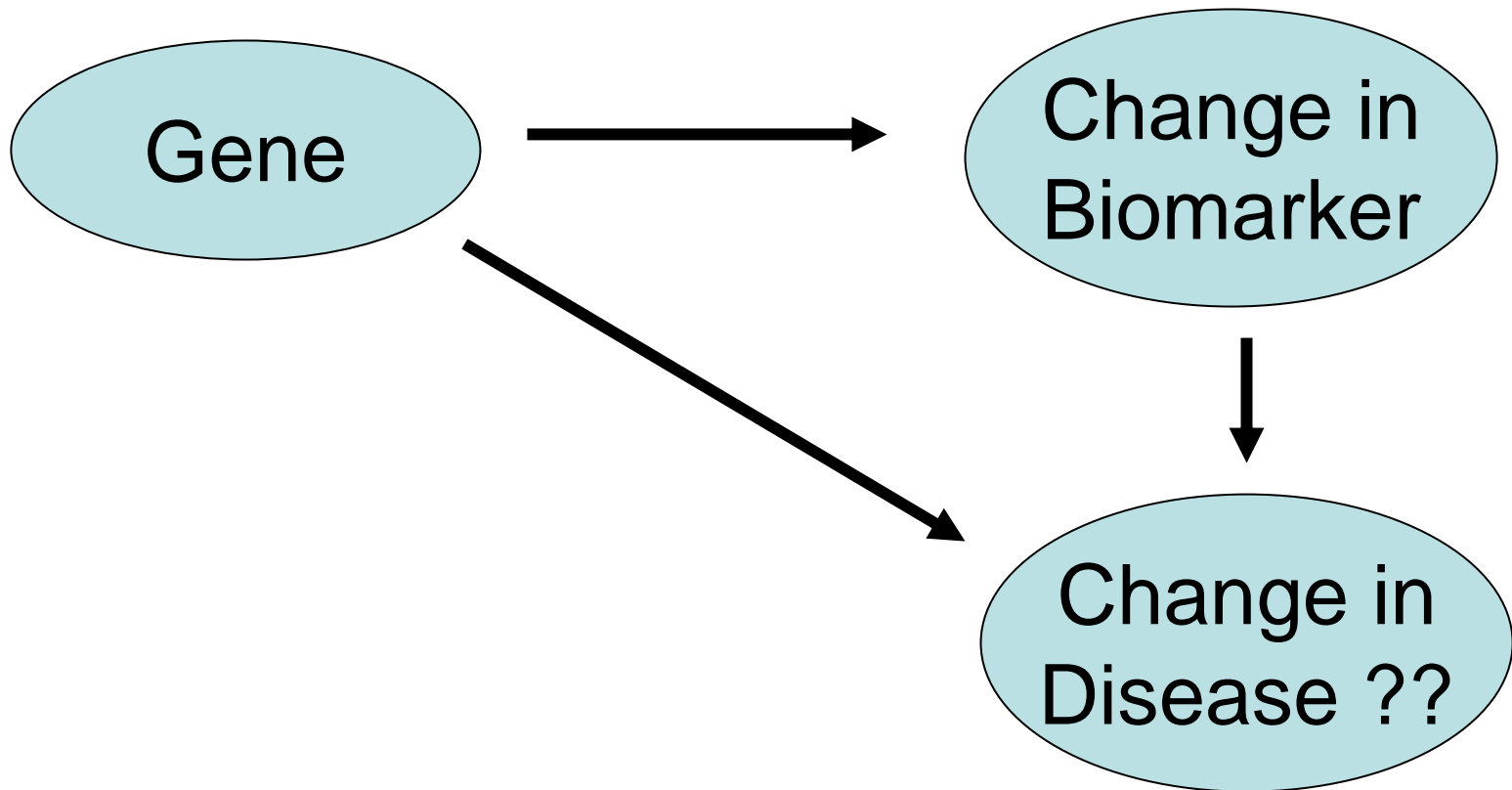
## A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

Timothy M. Frayling,<sup>1,2\*</sup> Nicholas J. Timpson,<sup>3,4\*</sup> Michael N. Weedon,<sup>1,2\*</sup> Eleftheria Zeggini,<sup>3,5\*</sup> Rachel M. Freathy,<sup>1,2</sup> Cecilia M. Lindgren,<sup>3,5</sup> John R. B. Perry,<sup>1,2</sup> Katherine S. Elliott,<sup>3</sup> Hana Lango,<sup>1,2</sup> Nigel W. Rayner,<sup>3,5</sup> Beverley Shields,<sup>2</sup> Lorna W. Harries,<sup>2</sup> Jeffrey C. Barrett,<sup>3</sup> Sian Ellard,<sup>2,6</sup> Christopher J. Groves,<sup>5</sup> Bridget Knight,<sup>2</sup> Ann-Marie Patch,<sup>2,6</sup> Andrew R. Ness,<sup>7</sup> Shah Ebrahim,<sup>8</sup> Debbie A. Lawlor,<sup>9</sup> Susan M. Ring,<sup>9</sup> Yoav Ben-Shlomo,<sup>9</sup> Marjo-Riitta Jarvelin,<sup>10,11</sup> Ulla Sovio,<sup>10,11</sup> Amanda J. Bennett,<sup>5</sup> David Melzer,<sup>1,12</sup> Luigi Ferrucci,<sup>13</sup> Ruth J. F. Loos,<sup>14</sup> Inês Barroso,<sup>15</sup> Nicholas J. Wareham,<sup>14</sup> Fredrik Karpe,<sup>5</sup> Katharine R. Owen,<sup>5</sup> Lon R. Cardon,<sup>3</sup> Mark Walker,<sup>16</sup> Graham A. Hitman,<sup>17</sup> Colin N. A. Palmer,<sup>18</sup> Alex S. F. Doney,<sup>19</sup> Andrew D. Morris,<sup>19</sup> George Davey-Smith,<sup>4</sup> The Wellcome Trust Case Control Consortium,<sup>20</sup> Andrew T. Hattersley,<sup>1,2†‡</sup> Mark I. McCarthy<sup>3,5†</sup>

# Mendelian Randomisation



# Determining Causality : Mendelian Randomisation



# Homocysteine and stroke: evidence on a causal link from mendelian randomisation

Juan P Casas, Leonelo E Bautista, Liam Smeeth, Pankaj Sharma\*, Aroon D Hingorani\*

Summary

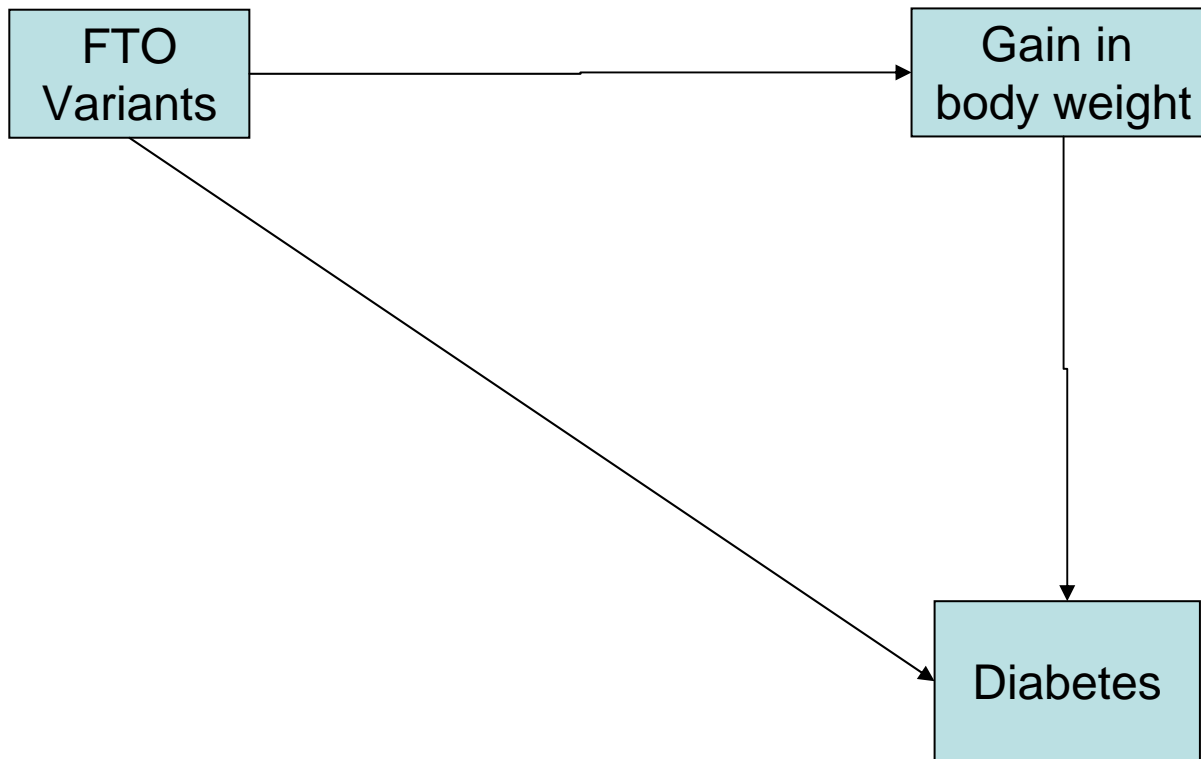
homozygous for the T allele of the *MTHFR* C677T polymorphism (the phenotype) than those with the CC genotype. Since this polymorphism is distributed randomly in the population, it is unlikely to be biased or confounded. We investigated the association between homozygotes, extrapolated from genotype-phenotype associations, and the risk of stroke. The expected odds ratio from a meta-analysis of genotype-disease association studies was 1.20 (1.10 to 1.31).

**Methods** We searched MEDLINE and EMBASE up to June, 2003, for all relevant studies on the association between homocysteine concentration and the *MTHFR* polymorphism, and until December, 2003, for those on the association between the polymorphism and the risk of stroke. Pooled odds ratios and 95% CI were calculated by random-effects and fixed-effects models. Consistency between expected and observed odds ratios was assessed by interaction test.

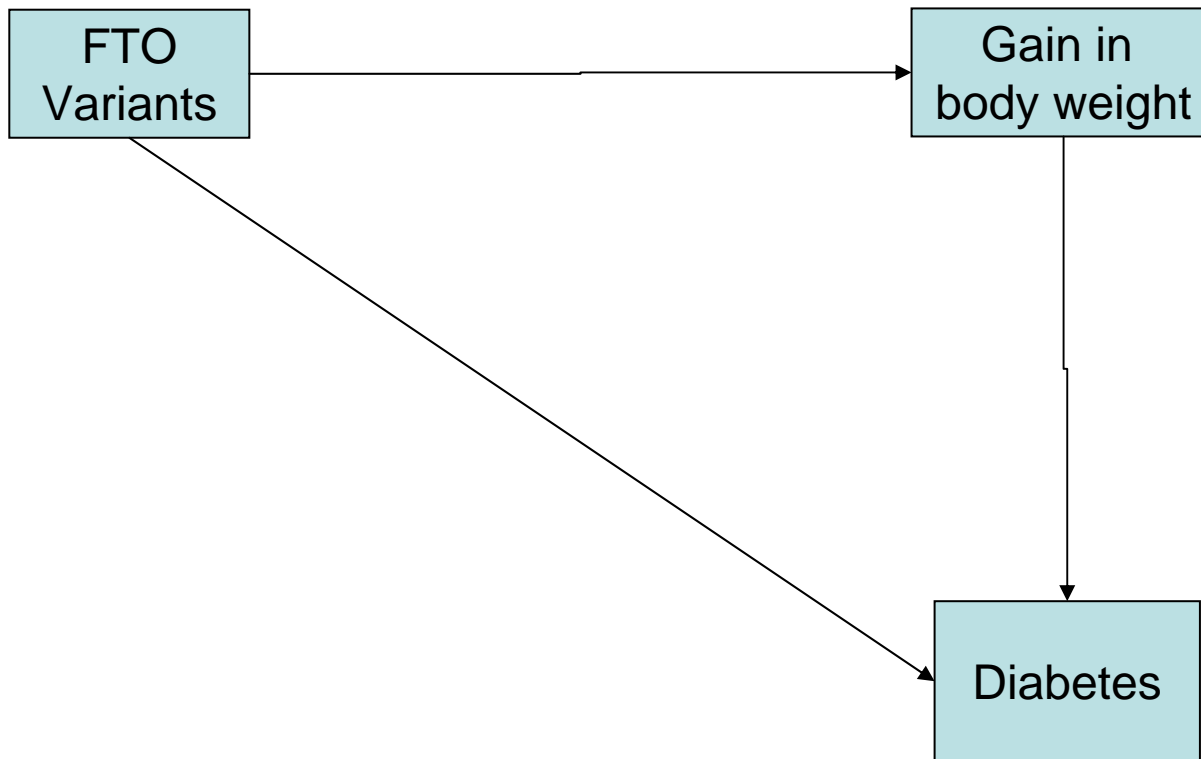
**Findings** 111 studies met the selection criteria. Among 15 635 people without cardiovascular disease, the weighted mean difference in homocysteine concentration between TT and CC homozygotes was 1.93  $\mu\text{mol/L}$  (95% CI 1.78 to 2.08). The expected odds ratio for stroke corresponding to this difference based on a meta-analysis of genotype-disease association studies was 1.20 (1.10 to 1.31). In our genetic meta-analysis (n=13 928) the odds ratio for stroke among TT versus CC homozygotes, similar to the expected odds ratio (p=0.29). Consistency between expected and observed odds ratios was preserved in analyses by age-group, ethnic background, and geographical location.

**Interpretation** The observed increase in risk of stroke among individuals homozygous for the T allele of the *MTHFR* C677T polymorphism is close to that predicted from the differences in homocysteine concentration between TT and CC homozygotes. This concordance is consistent with a causal relation between homocysteine concentration and the risk of stroke.

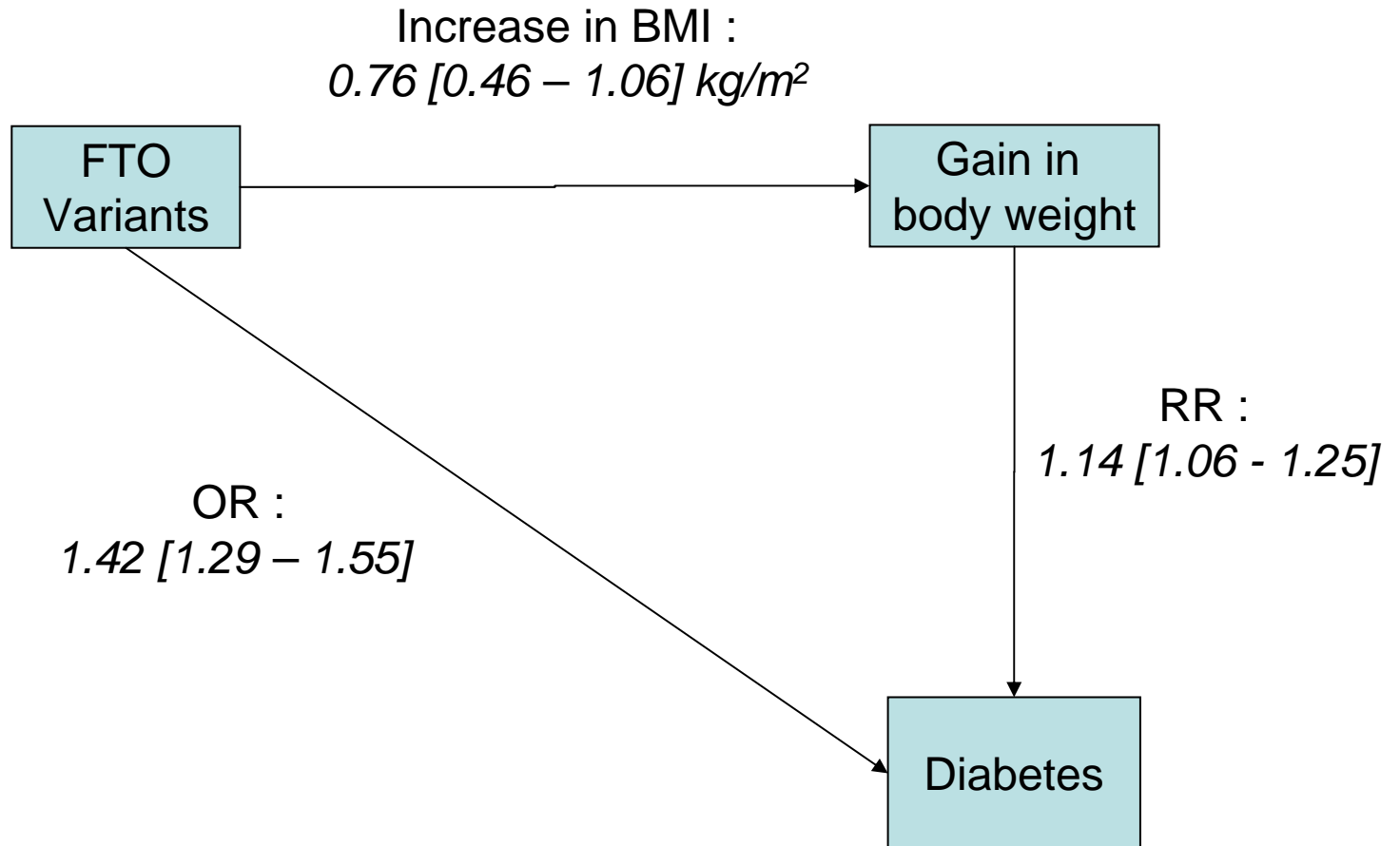
# Mendelian Randomisation



# Mendelian Randomisation



# Mendelian Randomisation



# Conclusion

- Identification of novel genes for common diseases/traits using WGAS in large, collaborative efforts
- Power of extensively phenotyped population-based studies to expand our knowledge on genes identified by case-control WGAS
- Identification of a SNP = beginning of a story

A Word of Wisdom by  
JL Goldstein and MS Brown (JCI 1997)



# A Word of Wisdom by JL Goldstein and MS Brown (JCI 1997)



CCGGAAAGGA ACCAGGCTCT ETGAGAAAT ACTTCAGGAG TAGRAAGRGG AAGCTAGAGG  
 UAGTTAUNNT ATGUTYAGAG UTGTAUTYAA UHAAACAAU TCTHGAATIG CATACGCCA  
 AGGAAACTC CAGCCGCTCT ATTACTAGAT AGCTTCCATC AACAGCTCAA AACCTACARA  
 AATTTGGTTT GGNCCGATG CCGATGAGCE TGCEAGETGA CAMTCTHAG CATGCGGAAA  
 TGGCCCTTTA TGTGAAGTAC CTGGTTTTTC CATTTCCTGT TTTACCRTAG GCCTAGTTC  
 VLATVUVAU AGATTAAAA AAAAGAAATL AHUGAGGLL RAGIGATIAA GCCTTCCTTA  
 AAGGTATTB AGTACRGAH AATGTCRAGH GAARTGGCTT ATTICTIATC CTATTTTTGA  
 TCTCCATCGA CTTCGCTCAG CTTTGGCCTG AAGCTATCTT YAAAGCTACC CTGTACAAGC  
 TCTTCGATTA GGACACATUP CAGTGGCAGH YAAACAGCAA ACPIATENTA TGTATCAAGC  
 CTCTTAAGAC TATAGCAATB TCTTCACCTG AAAAAGCCTT UTATATITTC TATUTAGAT  
 TRATCCACC TGGCTCTACR AAGCTAGTCT GGACAGCAT TTRACANTC ATCTCTTAA  
 AAAAAACAA GTGAGCAGCT CPTCTGTCT CACTCAATG ACCTAGACCA AAGGCTAGG  
 CAAATGAAT TCTTTGTAT ATGAGTGAH GCARACACTE TTTATTGAC AACTTGGGTG  
 AACGGITAGG TTGGAGTTH AGGTAGGAR GAARACCAA GGTAAAGRCC TCTTTCTG  
 TGTATAATTT GTAAAGCAT GGTGTGTTT GGTTTTTGTH TATHTUPLAG TLTAAAGAG  
 TTGACAGAT ATACCTCAGH GGTCTCAGC AGACCATAG CTTTCCCATC TTTCCCAFTA  
 GCAGACATCT CHTACCCDAA ATAGCTAATB TTTTGATAG TATGATCTG AAGGGCGAAA  
 TATATTTTAG GCCTTTCTCT TGGCAAGGAT GTTTGGTCAH GGGTTGGLAA AAATATGCT  
 CACCGAAGG TAGIAGHAC CCCCAGGAAH CARCTCTTG TCRAGAGTCA GACTRGTAC  
 CCTGGCCTAA CTAGCCTACI GAGCTGAGAG ATGTCRATT TCCGCCPAT ACACTBACCA  
 TTTCAATTC TAAACAAAT ATGTTAGTT GTAACATAA ATACCAGTAT ATAACAGTGT  
 ACCGACAGC ATGCTGTTAT CAGCCGCTB CTACCCAGG GCCTTGCAT GAGACAGCTC

*Ceci n'est pas un médicament.*

# Acknowledgments

## **GSK Management**

Allen Roses

Lefkos Middleton

Dan Burns

Eric Lai

Paul Matthews

## **Medical Genetics**

Dawn Waterworth

Chris Knouff

Kijoung Song

Xin Yuan

+ Heide Stirnadel (Epi)

+ Nicolas Guex (BIX)

+ Theo Danoff (CVU)

+ Tjerk Debruin (Met)

## **Pharmacogenetics**

Meg Ehm

Matt Nelson

Stephanie Chissoe

David Yarnall

Keith Nangle

Karen King

Scott Sundseth

+ Bill Caulkins

+ Derk Bergsma

+ Max Walker

+ many others

## **Lausanne Leadership Team**

Gerard Waeber

Peter Vollenweider

Daniel Hayoz

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Alain Pecoud

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