



# *Use of Twin Studies for Genomic Medicine & pharmacogenomics*

Tim Spector

**Dept of Twin Research &  
Genetic Epidemiology  
St Thomas' Campus,  
Kings College London**

[tim.spector@kcl.ac.uk](mailto:tim.spector@kcl.ac.uk)


[www.twinsUK.ac.uk](http://www.twinsUK.ac.uk)

# TWINS: HOW MANY?

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- Overall 1 in 50 Europeans is a twin
- MZ rates constant 4/1000 births
- No clear effect of age or race
- DZ rates vary -

Europeans	8/1000
Asians	2/1000
Bl. Africans	15/1000

- DZ rates  with age: (4 fold age 37)
- Rates increasing due to infertility Rx

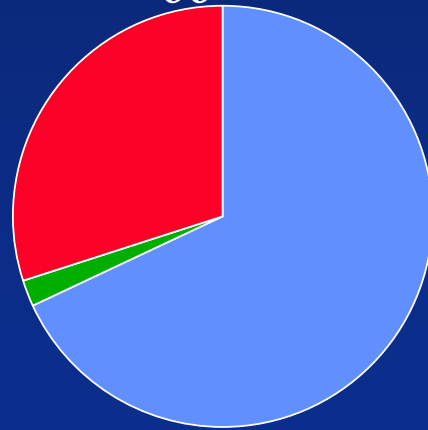
# POTENTIAL USE OF TWINS FOR GENETIC RESEARCH

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- Classical twin study - heritability
- Sib pair linkage studies
- Sib pair Association studies
- Gene- Environment interactions
- Gene Expression studies
- MZ discordant studies –CNV, epigenetics
- Aging Research
- Forensics
- Pharmaco-genomics

# HERITABILITY ESTIMATES

*“The proportion of differences between individuals explained by genetic differences.”*




■ genes 68%  
■ FAMILY ENVIRONMENT  
■ ENVIRONMENT

# TwinsUK Adult Twin Registry

- 11,000 Twin volunteers recruited through media campaigns
- Healthy Representative adult population 18-85
- 85% female
- 7500 –(3000 MZ and 4500 DZ) twins seen clinically with DNA
- 6000 have GWAS (317 or 610K)
- 1300 Stored PBLs
- LCL GW expression on 1200 twins, 850 fat, 850 skin, 100 muscle ongoing.
- Longitudinal DNA, serum & urine stored
- 1000s of phenotypes - longitudinal

# HERITABILITY OF COMMON TRAITS

FRECKLES	90%	
Myopia	90	HIGH
ACNE	80	
HEIGHT	80	
OSTEOPOROSIS	75	
DIABETES	70	
OBESITY	70	
BLOOD CLOTTING	70	
BACK PAIN	65	
IQ	65	
ASTHMA , allergy	60	
ARTHRITIS (OA)	60	
CATARACT	60	
MOTION SICKNESS	60	
Naevus count	55	
Pain thresholds	55	
Migraine	50	
Varicose veins &HR	50	
Menopause	50	
Blood pressure	50 %	
Menarche	40%	LOW



# Heritability of blood levels- using TwinsUK

- CRP, IL-6 –40%
- Vitamin D –40%
- Factor V, VIII, XIII- 70%
- Collagen cross links-50%
- Alkaline phosphatase –75%
- Creatinine- 50%
- Platelet count- 65%
- CD4/CD8 ratios -60%
- White Cell apoptosis rates 65%
- Platelet counts- 50%
- Leptin - 70%
- Glucose 51%
- Insulin 60%
- HOMA 57%
- HbA1c 60%
- T4, T3 63%
- Telomere length 40%
- HbF – 50%
- WCC- 55%

# HOW HERITABLE IS CANCER?

<b>PROSTATE CANCER</b>	<b>40 %</b>
<b>BREAST CANCER</b>	<b>25</b>
<b>LUNG CANCER</b>	<b>25</b>
<b>OVARIAN CANCER</b>	<b>22</b>
<b>CERVIX CANCER</b>	<b>0%</b>
<b>WOMB CANCER</b>	<b>0%</b>
<b>KIDNEY CANCER</b>	<b>0 %</b>

Lichtenstein et al 2000 – Joint Scandinavian twin registries

# Personality traits

OCEAN

40-50% H2

<10% C

- Obsession
- Conscientiousness
- Extroversion
- Anxiety
- Neuroticism

# Genetics of taste and smell

h<sup>2</sup>

Bitter taste – PTC	100%	Drayna 2003
Food neophobia	65%	Knaapila 2007
Emotional eating <sub>(TFEQ)</sub>	44%	Knaapila 2007
Sweet taste pref	53%	Keskitalo 007
Androstenone perception	28%	Knaapila 2008
Fruit and Veg diet	49%	Teucher 2008
Garlic eating	48%	Teucher 2008
Coffee	41%	Teucher 2008
Red meat	39%	Teucher 2008

# Non Heritable traits

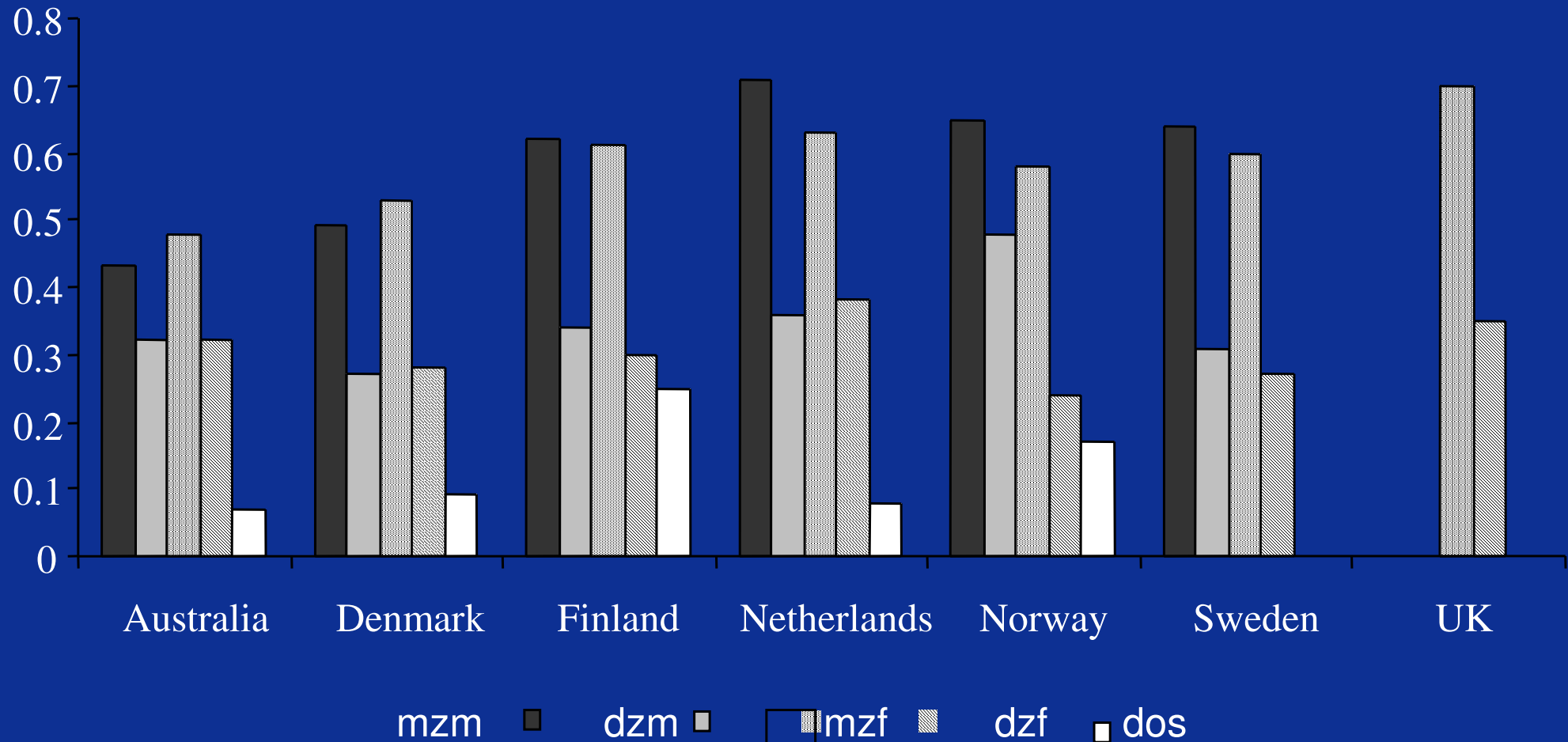
	H2
Church attendance	0
Milk Chocolate preference	<10
Football team support	<10
Liking mister Bean	0
Miscarriage rates	0

# SOCIO-SEXUAL TRAITS FOUND TO BE GENETIC

- Divorce
- Jealousy
- Infidelity
- Male homosexuality
- Female homosexuality
- Libido
- Promiscuity
- Female orgasm
- Body odour

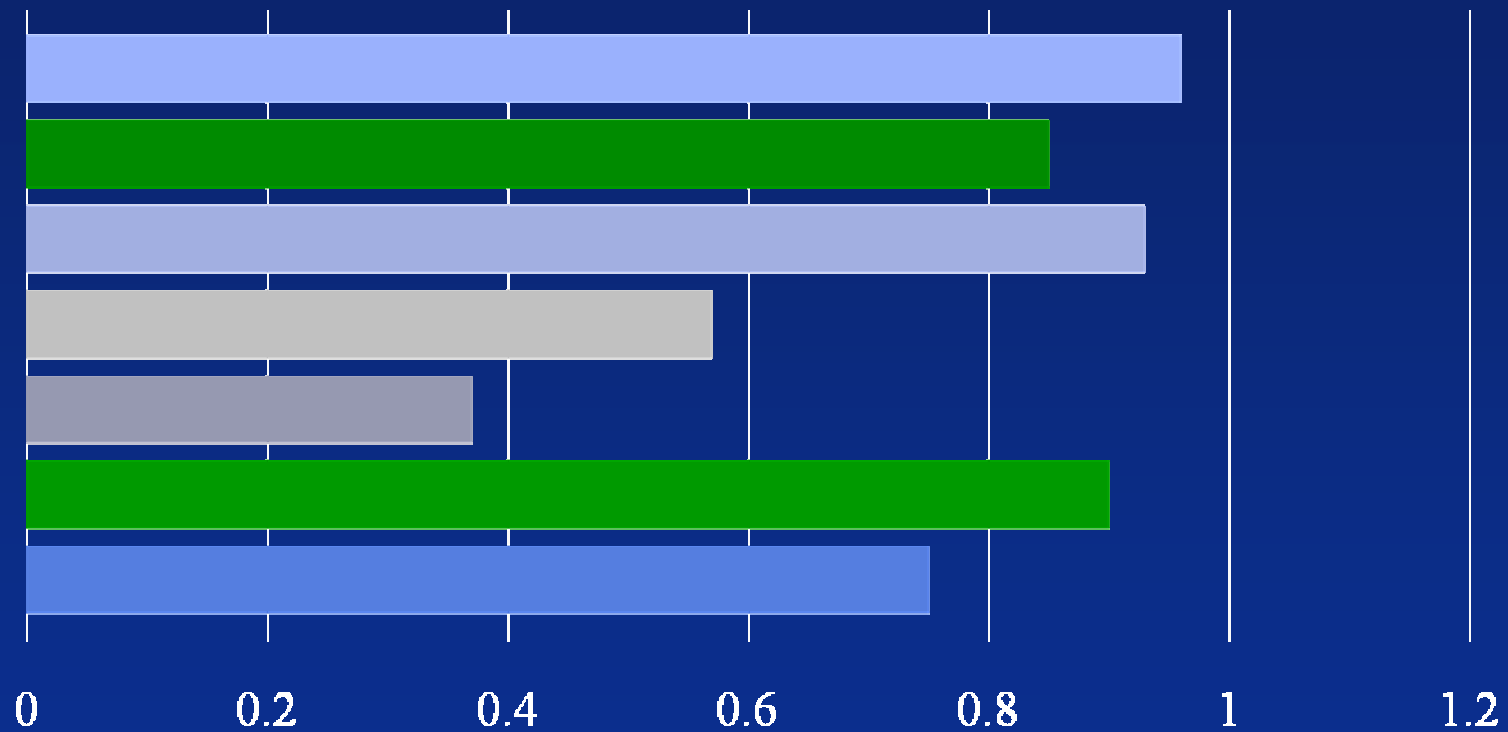
# EXERCISE AND GENES

Twin correlations for exercise participation by country and zygosity group (GenomEUtwin)



deGeus 2007

# Heritability of Drug Half-lives or serum levels



■ phenylbutazone ■ lithium ■ isoniazid ■ ethanol  
■ halothane ■ dicumarol ■ aspirin

## Heritability of drug related situations

- Nausea post general anaesthetic 60%
- Travel sickness 65%
- Pain tolerance 45-60%
- Placebo response 40%

# 'Environmentally' Genetic Traits

- Exercise
- Smoking
- Alcohol
- Occupation
- Social class
- Marital Status
- Food Preference - taste
- Dietary habits

# Genome-wide expression- A new phenotype?

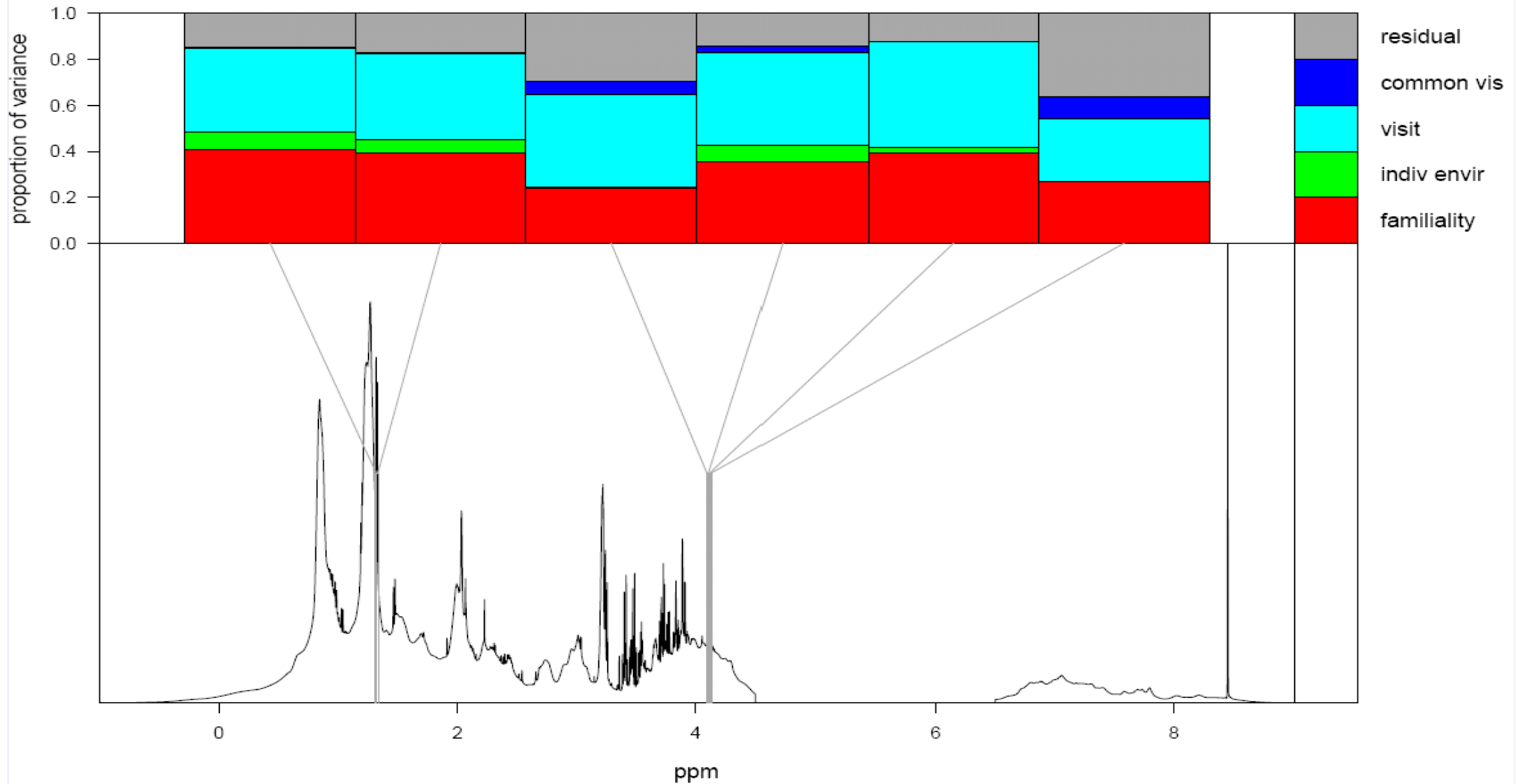
- Dixon et al (Nature Genetics 2007)
  - Goring et al - Nat Gen 2007
  - Valur et al - Nature 2008
  - Min et al – in preparation
1. Approx 30% of expressions heritable
  2. Wide variation in genetic influence
  3. The more heritable the more eQTLs associated
  4. The more heritable the more pleiotropy between tissues

# Metabolomics in 150 twins

lactate

nmr moltwin plasma, 1d pulse sequence

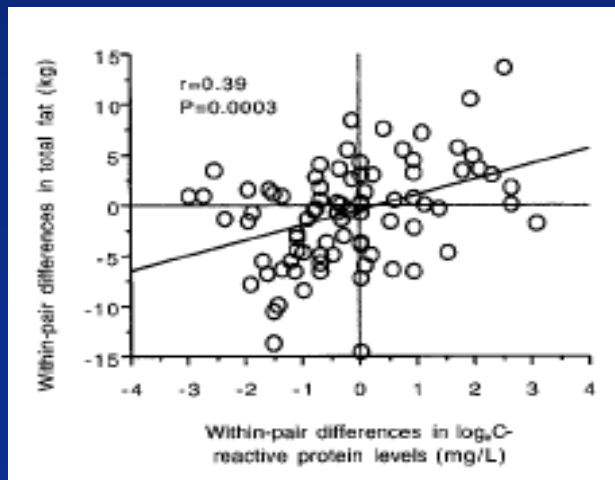
moltwin variance components



# Discordant Birthweight Twins.

- **Lipids**- Negative Association between twin pairs only and not within pairs -Suggests that shared influences on the maternal environment important  
*Skidmore et al. (2006)*
- **BP** - negative association within twin pairs –suggesting fetal malnutrition may be important.  
*Poulter et al 2000*

# The Association Between C-Reactive Protein and Obesity/central fat in MZ Female Twins



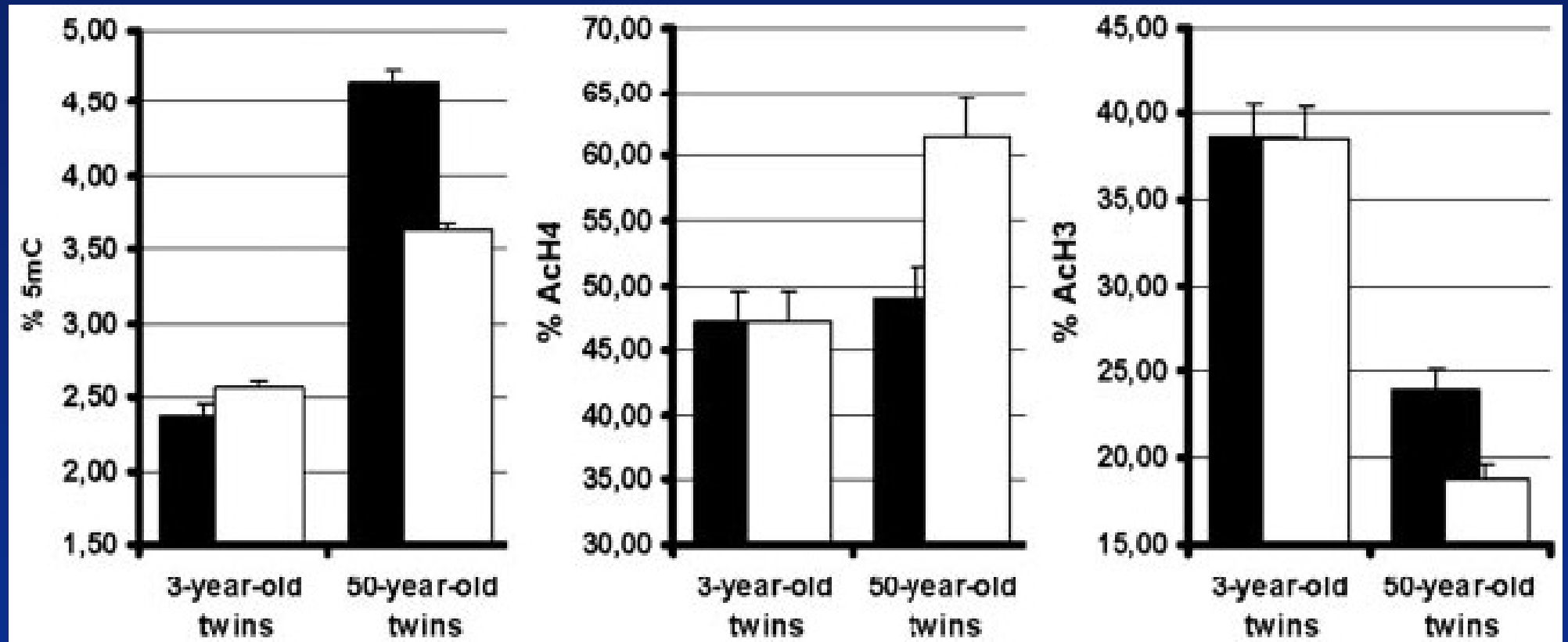
CRP was strongly related to total and central abdominal obesity, lipid levels and blood pressure **independent of genetic influences** (controlled for by MZ twin analysis).

So effect **not** cause

# Where is the missing heritability?

- GWAS hits explain 1-10% of genetic variance
- MZ Twin discordance unexplained by known environmental factors
- Could Epigenetic factors be responsible??

# Epigenetics in MZ twins



Fraga et al PNAS 2005

# Methylation in Twins

- MZ Twins show greater concordance for total methylation at different tissue sites, LCL, buccal, bowel.
- Areas under most genetic control are those close to promotor regions of functional importance.

Buccal:  
MZ= red, DZ= blue

– Kaminsky et al Nature Genetics 2009

# Copy Number Variation differences in MZ twins

- A study of 19 pairs of MZ twins showed a proportion with CNV differences

Any differences in the genetic makeup between twins derived from the same zygote represent an irrefutable example of somatic mosaicism..

Suggest that CNV analysis in phenotypically discordant monozygotic twins may provide a powerful tool for identifying disease loci.

Bruder et al AJHG 2008

# Forensics and twins

- Identical twins are identically innocent and guilty...march 2009
- Saved by their indistinguishable DNA, identical twins Hassan and Abbas O suspected in a \$5 mil jewelry heist have been set free. Neither could be exclusively linked to the DNA evidence.

# Getting to the Root of Hair loss

- Highly heritable >80%
- Common – 1 in 4 men early
- Collaborative study-
  - GSK, Decode, TwinsUk, Nijmegen
- Using 1,125 men identified a new locus at chr 20p11.22, confirmed in 3 independent cohorts (P $\times 10^{-14}$ )
- The one man in seven who harbours risk alleles at both 20p11.22 and AR has a sevenfold-increased odds of androgenic alopecia (OR 7.12)

Richards et al 2008 Nature Genetics

# Current Twin GWAS using 2000-6000 twins

- Bone Density and fracture – (Lancet 2008 & Nature Genetics 2009, Ann Int Med in press)
- Lipids- Nature Genetics 2008
- BMI, glucose, insulin (Nat Genetics 2009)
- Blood counts and platelet counts and CVD risk (Nat Genetics 2009 in press)
- HbF – Nature Genetics 2008
- Eyes –myopia (AJHG 2008)- cataract (Plos genetics 2009)
- Telomere length J med Genetics 2009
- Naevus counts and melanoma– Nature Genetics 2009 ( in press)
- Baldness (Nature Genetics 2008)
- OA (AJHG 2008 and 2009 submitted)
- Menopause (Nature Genetics 2009)
- Menarche – (Nature Genetics 2009)
- Blood pressure (Nature Genetics 2009)
- CD4 CD8 levels and immune disease (Nature Genetics in review)
- Metabonomic profiles (Nature Genetics in review)
- Height (Plos genetics 2009)
- Many others ongoing , muscle, pain,acne, eczema, adiponectin, Vit D, homocysteine, handedness, ECG, exercise, phosphate, thyroid, lung function, entrepreneurship, etc.

*The Times*

# UK-TWINBANK

March 31, 2009

## Search for a twin solution to matters of life and death

- 620,000 twin pairs identified since 1920
- 250,000 pairs recruitable to TwinBank
- Largest in world by 5-fold
- NHS record linkage possible
- Rare diseases and drug reactions could be studied in detail
- Large numbers of discordants
- Large scale epigenetics possible
- Synergy with UK Biobank

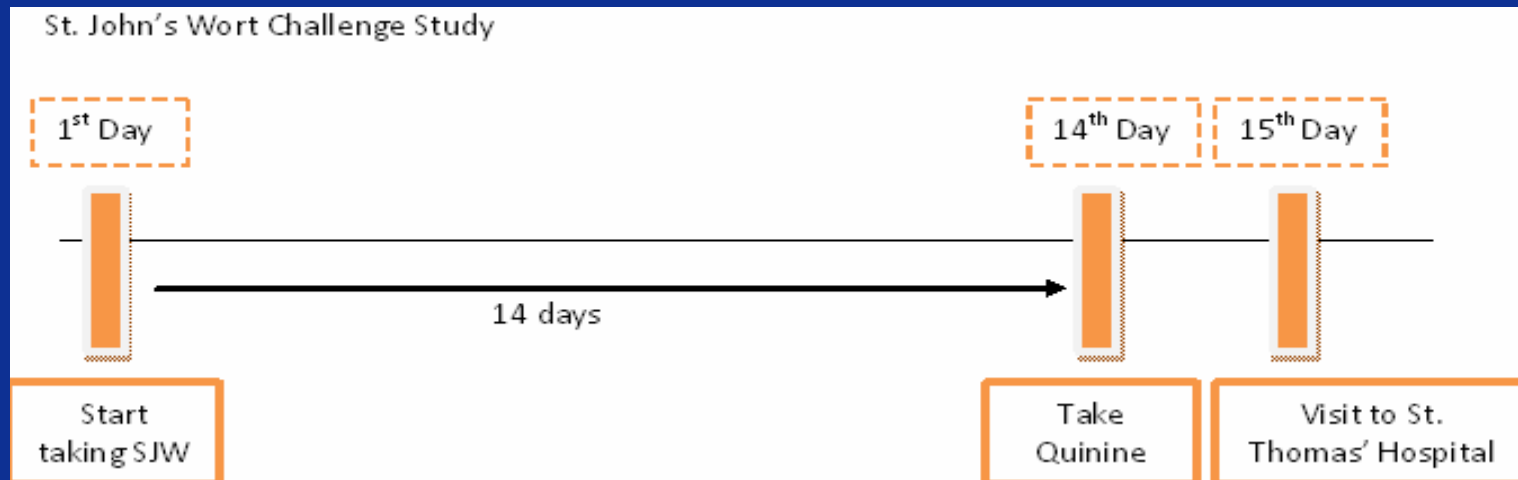
# Twin Pharmacogenetic studies

- 1. Vit D supplement study in 200 twins- no effect of vit D levels on BMD (Arden et al)
- 2. Folate supplementation in 150 twins via twin RCT –
- 3. St Johns Wort – in 400 twins

- **St. John's Wort** is a Mild, herbal antidepressant
- A very potent inducer of CYP3A4
- Daily Recommended Dose: one capsule 3 times a day
  
- **Quinine Sulphate** is an anti-malarial drug solely metabolised by CYP3A4. Hence used as a probe drug for CYP3A4 activity

Is induction variable & what epidemiological factors affect variation in CYP3A4 induction?

## Intervention Study



**Recruitment Goal:** 400 healthy individuals (100MZ:300DZ pairs)

- Phenotyped for baseline and induced CYP3A4 activity.
- St John's Wort 3 times a day for 14 days.
- Quinine tablet on day 14; metabolized exclusively by CYP3A4.
- Compliance; pill counting devices.

# St Johns Wort Side

## Effects

Dizziness (3)

Tiredness (8)

Abdominal pain (2)

Cramps in legs (1)

Cramps in stomach (1)

Headache (8)

Migraine (1)

Restless sleep (1)

Constipation (2)

Heart Palpitation (1)

Nauseated (2)

Irregular passing stool (3)

Spot on face (2)

Bumps on arms (1)

Aggravation of stomach (3)

De-motivation (1)

Metallic taste in mouth (3)

Dry mouth (2)

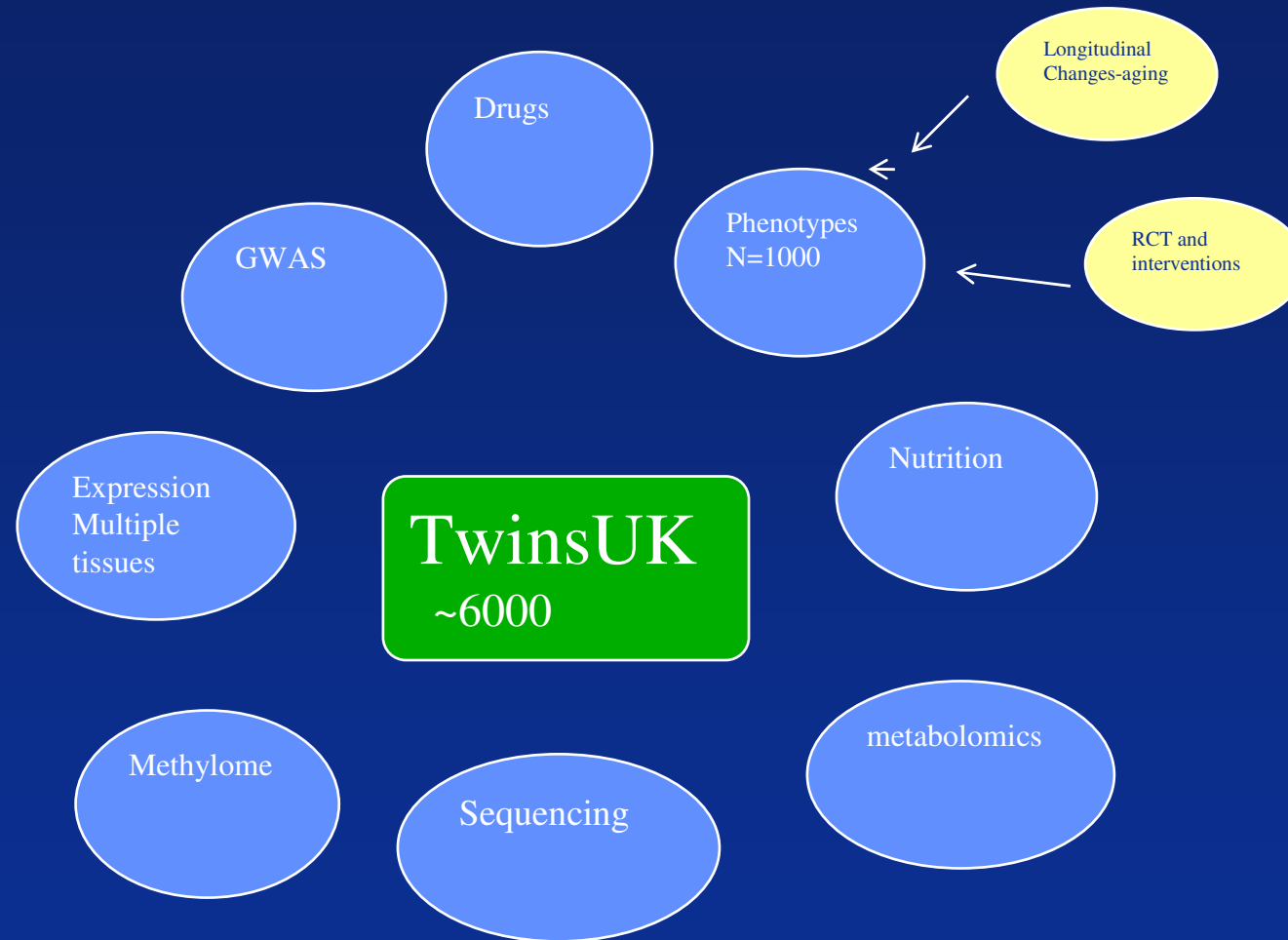
More dreams (1)

Bloatedly happy (4)

Energetic (1)

- 4 Individuals dropped out of the study due to severe side effects; Extreme anxiousness, sporadic fevers and skin sensitivity.

# Twins – a complete resource



# Conclusions

- Twins are a flexible and reliable research tool
- Virtually all traits (even ‘environmental’ ones are heritable —with common /family environment having minimal effect
- Twin studies can change perceptions
- Cohorts with multiple phenotypes will continue to be rich sources of gene discovery
- Twin Biobanks- allow a unique design adjusting for genetic effects-
  - Particularly useful for epigenetics, gene-age interactions and pharmacogenetic studies
- [www.TwinsUK.ac.uk](http://www.TwinsUK.ac.uk)

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## **DTR Analysis team**

Fran Williams  
Chris Hammond  
Veronique Bataille  
Mario Falchi  
Ana Valdes  
Kourosh Ahmadi  
Nilufer Rahmiooglou  
Ioana cotlarciuc  
Andrea Burri  
Bernet Kato  
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