

Epigenetics, Inequality and the Biosocial Paradigm.

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The Age of Public Health Biology

Strategies to improve human health increasingly emphasise the importance of prevention, early detection and population stratification.

The effectiveness of these strategies relies on methodologies that can be used at population scale in real time and a deep understanding of the pathways of causality.

The contribution of genetics and epigenetics.



Evidence to inform public health nutrition policy

Randomised Control Trials

Plus: Clear result attributed to food or nutrient of interest.
 Minus: Often short duration, limited power (morbidity/mortality)



Prospective Cohort Studies

Plus: Realistic, large numbers, detect long term effects.
 Minus: Susceptible to confounding and reverse causality.



Genetic Studies

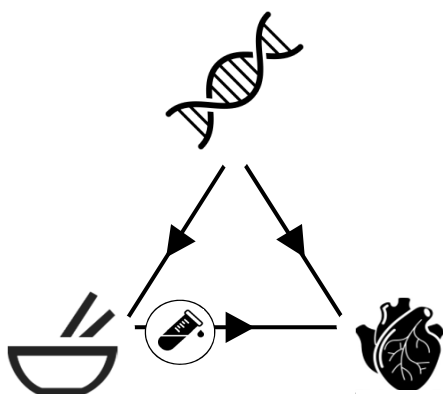
Plus: Realistic, large numbers, detect long term effects.
 Minus: interpretation (multiple gene effects, LD, timing)



Exploiting genetic effects: Mendelian Randomisation



MTHFR gene; base 677 can be C or T
 Possible genotypes; C677C C677T T677T

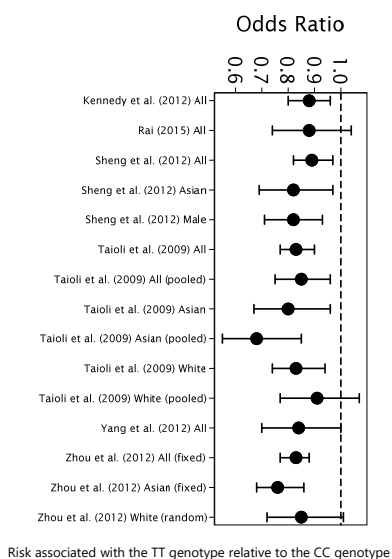


Blood status: MTHFR TT as % of CC

	Baseline	Restriction (-115 ug/d)	Supplement (+400 ug/d)
Serum	-20%	-28%	-18%
Plasma	-34%	-36%	
Erythrocyte	-18%	-18%	-14%
Erythrocyte/Hb	-44%	-55%	
Homocysteine	+13%	+18%	+24%

Shelnutt et al. J Nutr. 2003; Davis et al J. Nutr. 2005

MTHFR C677T polymorphism & colorectal cancer risk



The MTHFR TT genotype decreases blood folate.

Odds ratio less than 1.0 suggests that a high level of folate increases the risk of colorectal cancer.

The MTHFR genetic studies suggest that*:

↑ blood folate concentrations ↑ colorectal cancer risk.

Implications for other cancers

↑ blood folate concentrations ↑ prostate cancer risk
 ↑ blood folate concentrations ↓ breast cancer risk
 ↑ blood folate concentrations ↓ overall cancer risk.

*Inference based on a number of unproven assumptions.

Genetic evidence and public health nutrition policy

SACN report

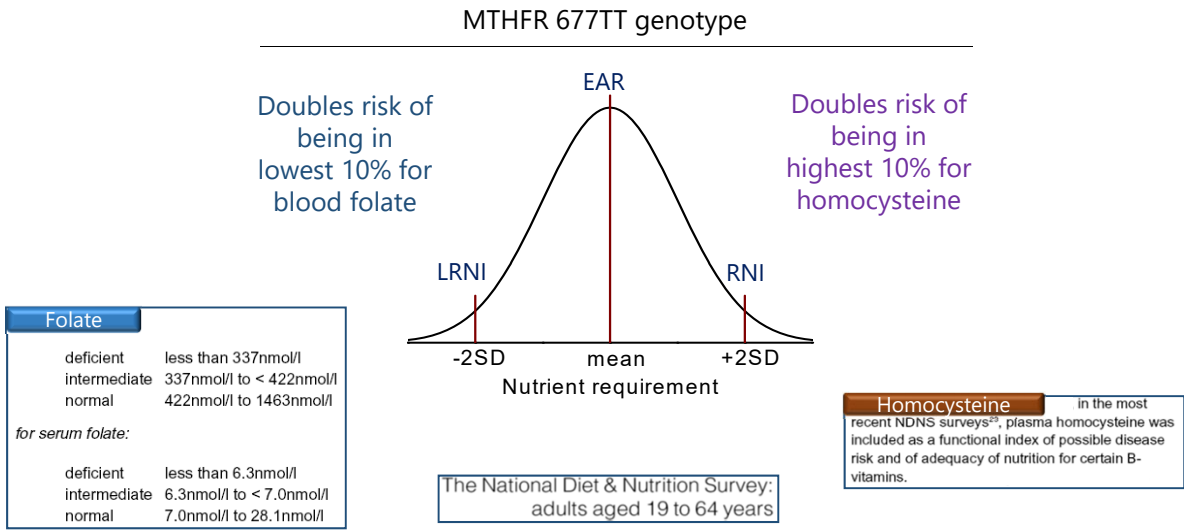
Iron and Health (2010);
 Selenium and Health (2013);
 Vitamin D and Health (2016);
 Update on folic acid (2017);
 Diet, cognitive impairment and dementia (2018);

Genotypes considered

HFE, TFR2; hemojuvelin; Hpcidin, Ferroportin 1
 unspecified
 CYP27B1, CYP2R1, VDR, DBP, NADSYN1/DHCR7
 MTHFR
 APOE

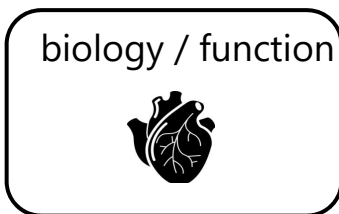
**Scientific Advisory
 Committee on Nutrition
 (SACN)**

Genetic effects complicate nutritional interpretation



Mendelian Randomisation (MR)

genetics



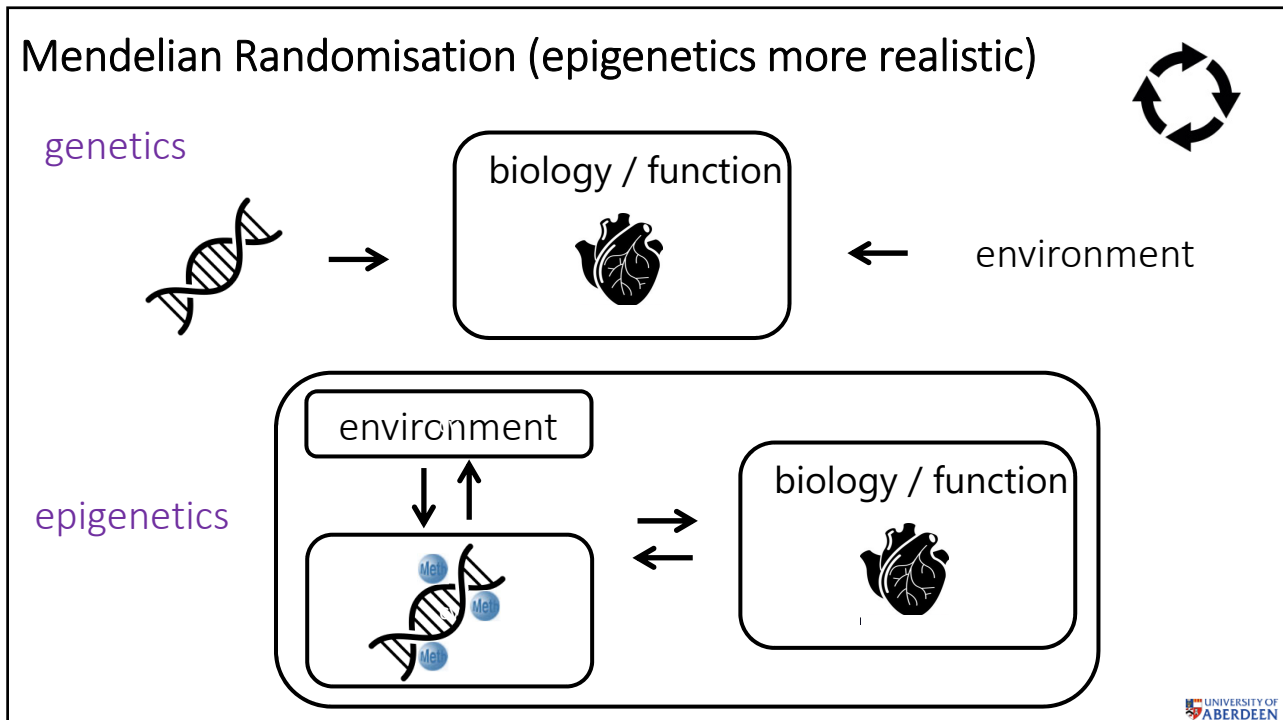
environment

MR doesn't fully take into account:

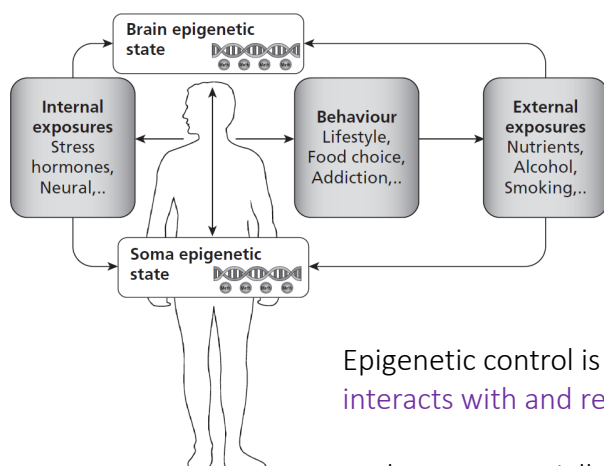
Time

Environmental feedback





Complexity of biological-environmental interactions



Epigenetic control is central to the way in which the **genome** interacts with and responds to the environment

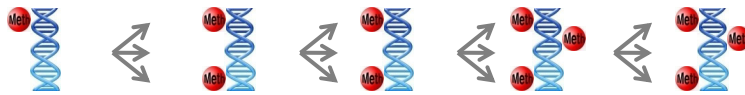
And even potentially the way in which the **genome** can influence its own environment via effects on behaviour.

How life gets under the skin

Health



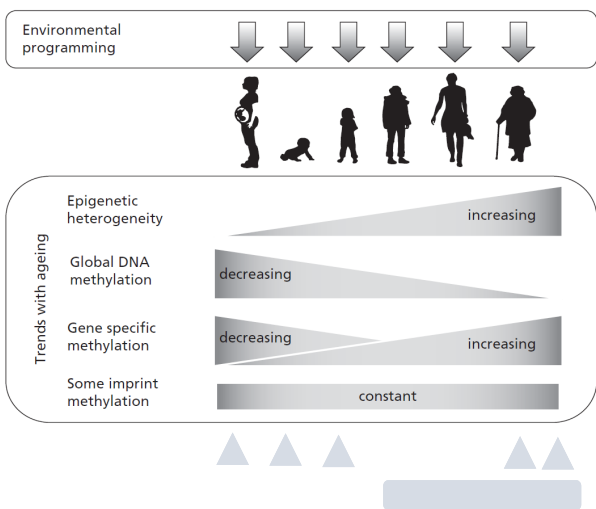
Cellular memory



Life!



Epigenetic focus: life-course, imprints, repeat elements



Paradigm

- Lifecourse

Epigenetic focus

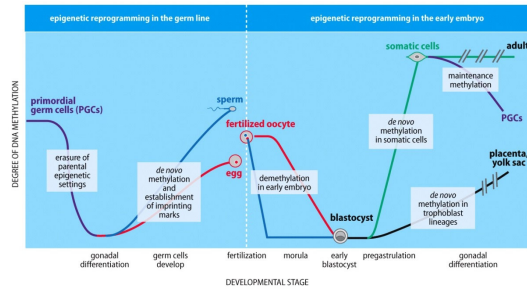
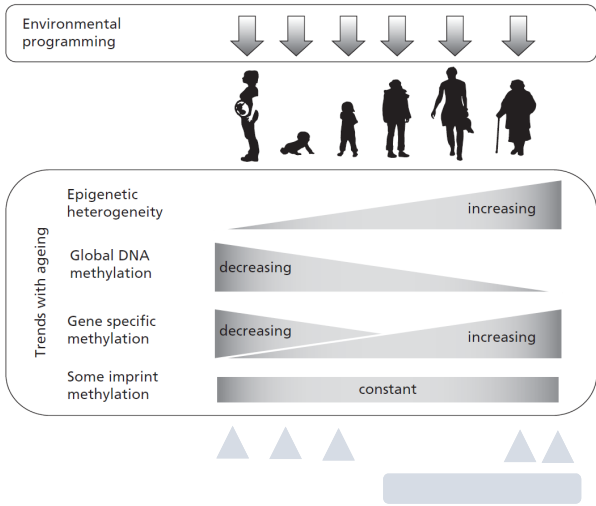
- Imprinted genes
- Repeat elements (LINE1, Alu, SAT α)
- Large scale genome

Methods

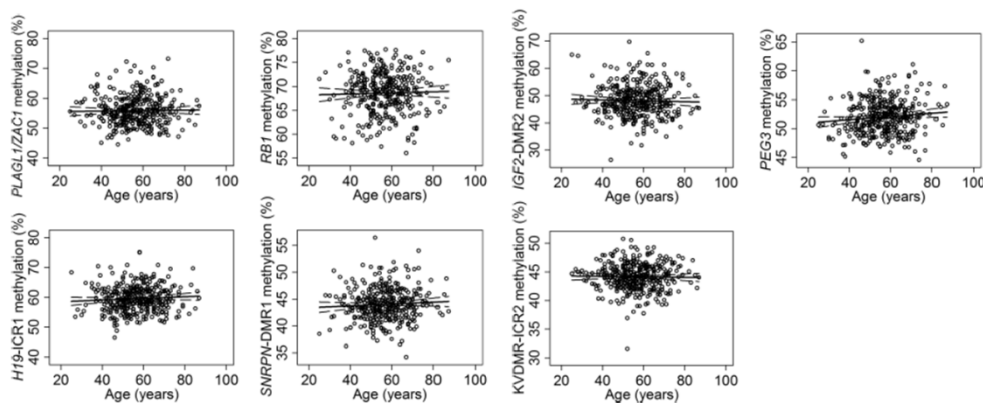
- Next Generation Bis-Sequencing
- Illumina Array
- Pyrosequencing



Epigenetic focus: life-course, imprints, repeat elements

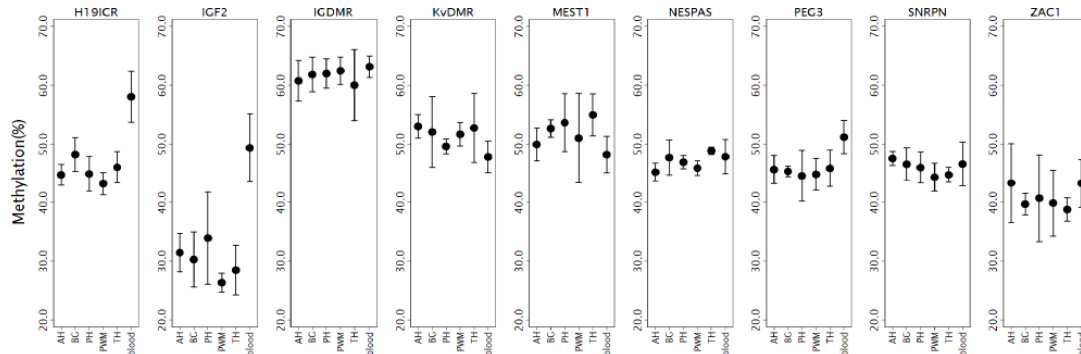


Epigenetic focus: Stability of imprinting methylation with age



Imprints variable between individuals but stable with age (cross-sectional)

Epigenetic focus: Imprinting across tissues



AH: Anterior Hippocampus
 BG: Basal ganglia
 PH: Posterior Hippocampus
 PWM: Periventricular white matter
 TH: Thalamus

Lorgen-Richie et al (2019) Imprinting methylation in SNRPN and MEST1 in adult blood predicts cognitive ability. PLoS One, 14, e0211799



Early life nutrition and offspring imprinting



Maternal folic acid supplement use in pregnancy after 12 weeks is associated with epigenetic changes in the offspring:



INSULIN-LIKE GROWTH FACTOR II; IGF2 (chr 11p)

Implicated in growth, IUGR, overgrowth syndrome, BWS, SRS, Wilms Tumour, obesity, metabolic syndrome.



PATERNALLY EXPRESSED GENE 3; PEG3 (chr 19q)

Regulator of TNF response. Implicated in tumour development.



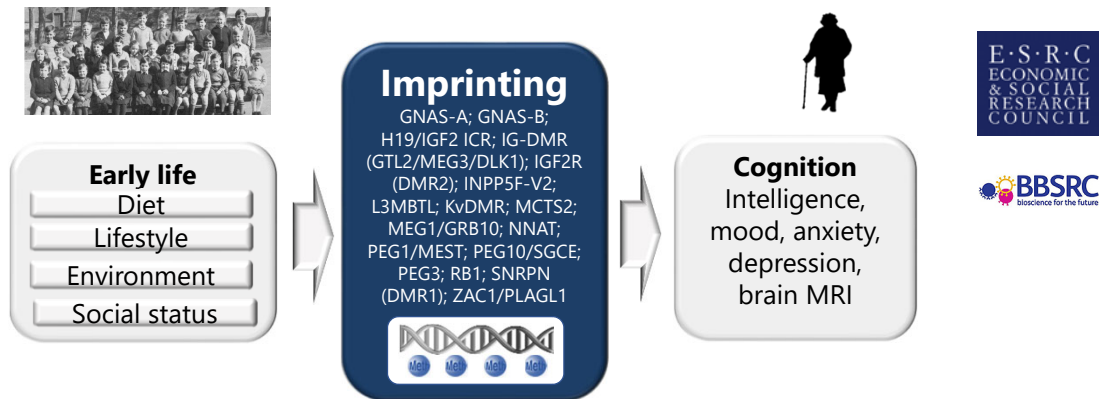
LINE1 RETROTRANSPOSABLE ELEMENT (genome wide)

Implicated in chromatin structure, gene expression, mutation.

Haggarty P, Hoad G, Campbell DM, Horgan GW, Piyathilake C, & McNeill G (2013). Folate in pregnancy and imprinted gene and repeat element methylation in the offspring. Am J Clin Nutr 97, 94-99.



Early life effects on cognition and mood (biosocial research)



Imprinting methylation; early life influences and later cognition and mood. P Haggarty, A Murray, L Phillips, R Staff, A Ferguson-Smith, M Richards.
University of Aberdeen, University of Cambridge, University College London.



Early life effects on cognition and mood

Cognitive Ability

Moray House Test (MHT) - childhood cognitive ability
National Adult Reading Test (NART) – adult crystallised ability
Raven's Progressive Matrices – adult fluid ability

Mood and Personality

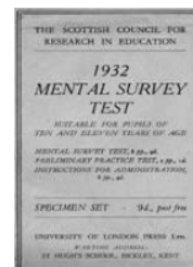
Hospital Anxiety and Depression Scale (HADS)

Big Five Personality Traits;

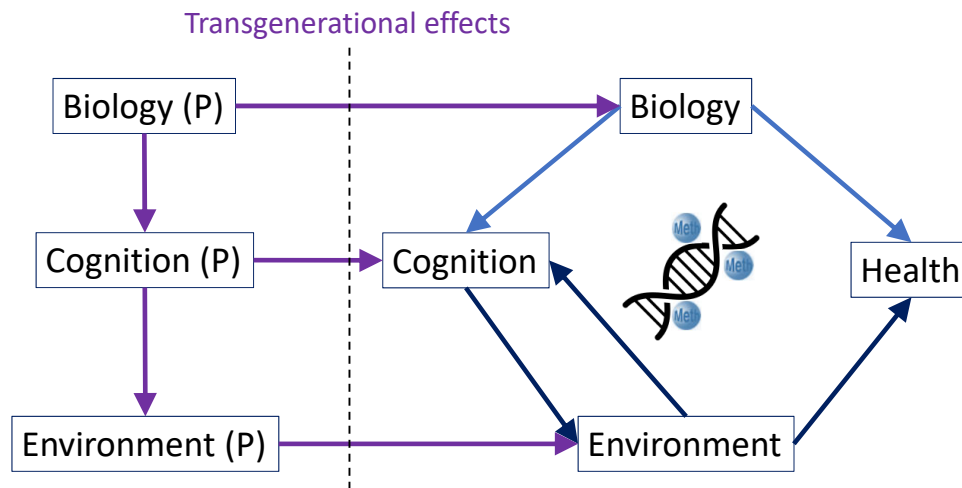
- Agreeableness
- Conscientiousness
- Extraversion
- Neuroticism
- Openness Brain Imaging

Brain

- Hippocampal volumes
MRI hyperintensities in different brain regions;
- Deep white matter
 - Periventricular white matter
 - Grey matter
 - Infratentorial
 - Hippocampal grey matter



Possible interpretations of cognitive findings



P=Parental influences (potentially separate pathways for mother and father).

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