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

<table>
<thead>
<tr>
<th>Blood status:</th>
<th>MTHFR TT as % of CC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Serum</td>
<td>-20%</td>
</tr>
<tr>
<td>Plasma</td>
<td>-34%</td>
</tr>
<tr>
<td>Erythrocyte</td>
<td>-18%</td>
</tr>
<tr>
<td>Erythrocyte/Hb</td>
<td>-44%</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>+13%</td>
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</tbody>
</table>

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.

Risk associated with the TT genotype relative to the CC genotype

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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; hemojuevelin; Hepcidin, Ferroportin 1 unspecified
- CYP27B1, CYP2R1, VDR, DBP, NADSYN1/DHCR7
- MTHFR
- APOE

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Scientific Advisory Committee on Nutrition (SACN)
Genetic effects complicate nutritional interpretation

MTHFR 677TT genotype

Doubles risk of being in lowest 10% for blood folate

Doubles risk of being in highest 10% for homocysteine

<table>
<thead>
<tr>
<th>Nutrient requirement</th>
<th>MNT</th>
<th>RNI</th>
<th>EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+2SD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Folate
- deficient: less than 3.57 nmol/l
- intermediate: 3.57 nmol/l to < 4.22 nmol/l
- normal: 4.22 nmol/l to 14.63 nmol/l

Homocysteine
- double risk of being in highest 10% for homocysteine

The National Diet & Nutrition Survey; adults aged 19 to 64 years

Mendelian Randomisation (MR)

MR doesn’t fully take into account:
- Time
- Environmental feedback

genetics → biology / function → environment
Mendelian Randomisation (epigenetics more realistic)

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, SATα)
- 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


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.

Early life effects on cognition and mood (biosocial research)

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
Hippocampal volumes
MRI hyperintensities in different brain regions;
• Deep white matter
• Periventricular white matter
• Grey matter
• Infratentorial
• Hippocampal grey matter
**Early life effects on cognition and mood**

**Aberdeen Birth Cohorts: ABC21 and ABC36**
- Local survivors of the Scottish Mental Surveys of 1932 and 1947
- All sat the Moray House Test No. 12 at age 11
- Later recruited into longitudinal studies of health and cognitive ageing

Chromosomes: 4, 6, 7, 11, 14, 15, 19, 20
DMRs: 13
Amplicons: 71
Bases: 16,177
CpGs: 1010

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**Imprinting methylation and cognitive ability**

Early life  \[\downarrow\]

![DNA](image)

SNRPN and MEST1 methylation in ABC cohorts and childhood cognitive ability measured at age 11 using the Moray House Test (MHT). Adjusted for sex, adult socioeconomic circumstance (index of multiple deprivation decile).

Possible interpretations of cognitive findings

Transgenerational effects

Biology (P) → Cognition (P) → Environment (P) → Biology

Cognition → Health

Environment

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

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