Molecular fingerprints of socio-economic experience

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Health inequalities between and within countries: male life expectancy at birth

<table>
<thead>
<tr>
<th>Country</th>
<th>Male life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>40</td>
</tr>
<tr>
<td>UK, Glasgow (Calton)</td>
<td>54</td>
</tr>
<tr>
<td>India</td>
<td>62</td>
</tr>
<tr>
<td>US, Washington D.C. (Black)</td>
<td>63</td>
</tr>
<tr>
<td>Bolivia</td>
<td>64</td>
</tr>
<tr>
<td>Lithuania</td>
<td>65</td>
</tr>
<tr>
<td>Mexico</td>
<td>72</td>
</tr>
<tr>
<td>United States</td>
<td>75</td>
</tr>
<tr>
<td>Cuba</td>
<td>76</td>
</tr>
<tr>
<td>Switzerland</td>
<td>79</td>
</tr>
<tr>
<td>US, Montgomery County (White)</td>
<td>80</td>
</tr>
<tr>
<td>UK, Glasgow (Lenzie N.)</td>
<td>82</td>
</tr>
</tbody>
</table>

Sources: WHO, World Health Statistics 2008; Hanlon, Walsh & Whyte 2006; Murray et al. 2006
Educational inequalities in mortality in Europe

Education and cumulative mortality in Europe (EPIC, 371,295 participants, 9 countries)

Mortality rate by educational level (Swiss National Cohort, 1990-2000)

Socioeconomic status and premature mortality

Population attributable fraction of selected risk factors (1.7 million participants in 7 countries)

- Hypertension: 10%
- High alcohol intake: 4%
- Physical inactivity: 26%
- Diabetes: 6%
- Current smoking: 29%
- Low socioeconomic status: 19%

Causal explanations for social inequalities in health

**SES**
- Education
- Income
- Occupation
- Wealth

**ENVIRONMENTAL EXPOSURES**
- Pollution, toxics, carcinogens
- Neighbourhood-community characteristics
- Living and working conditions

**PSYCHOSOCIAL EXPOSURES**
- Cognitive and emotional
- Social relationships/support
- Stress exposure (at home/work)

**BEHAVIOURAL EXPOSURES**
- Smoking
- Diet and physical activity
- Drug/alcohol use

**ACCESS TO/USE OF HEALTH CARE**

**HEALTH**
- Mental health
- Functioning
- Physical health
- Mortality
The lifecourse perspective
## Socioeconomic status and biomarkers

<table>
<thead>
<tr>
<th>System</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamic-pituitary-adrenal axis</strong></td>
<td>Cortisol - Saliva, urine</td>
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<tr>
<td></td>
<td>Dehydroepiandrosterone sulfate - Blood</td>
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<tr>
<td><strong>Sympathetic neuro-hormonal system</strong></td>
<td>Norepinephrine/Epinephrine - Urine</td>
</tr>
<tr>
<td></td>
<td>Alpha-amylase - Saliva</td>
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<tr>
<td><strong>Parasympathetic neuro-hormonal system</strong></td>
<td>Heart rate variability - Pulse rate recording</td>
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<tr>
<td><strong>Inflammatory/Immune system</strong></td>
<td>C-reactive protein - Blood</td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate - Blood</td>
</tr>
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<td></td>
<td>Interleukins - Blood</td>
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<tr>
<td></td>
<td>Lymphocyte number and function - Blood</td>
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<tr>
<td></td>
<td>Circulating serum albumin - Blood, saliva</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td>Diastolic/systolic blood pressure</td>
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<td></td>
<td>Resting heart rate</td>
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<tr>
<td><strong>Glucose metabolism</strong></td>
<td>Fasting glucose - Blood</td>
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<tr>
<td></td>
<td>Glycosylated hemoglobin - Blood</td>
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<td></td>
<td>Fasting insulin - Blood</td>
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<tr>
<td><strong>Lipid metabolism</strong></td>
<td>Cholesterol and lipoprotein fractions - Blood</td>
</tr>
<tr>
<td></td>
<td>BMI, waist to hip ratio</td>
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<tr>
<td></td>
<td>Total body fat - DXA scan</td>
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<tr>
<td><strong>Hematological</strong></td>
<td>Serum hemoglobin - Blood</td>
</tr>
<tr>
<td></td>
<td>Clotting factors and clotting time - Blood</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Creatinine - Serum or 24h urine</td>
</tr>
<tr>
<td></td>
<td>Urine albumin leakage - Urine</td>
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<tr>
<td></td>
<td>Cystatin C - Serum or dried blood spot</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Circulating serum albumin - Blood, saliva</td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td>Serum testosterone/estradiol - Blood</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Follicle-stimulating hormone - Blood</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>Arterial oxygen saturation - Pulse oximeter</td>
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<tr>
<td></td>
<td>Peak expiratory flow - Spirometer</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td>Bone density - DXA scan</td>
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<tr>
<td></td>
<td>Bone turnover markers - Blood, fasting urine</td>
</tr>
<tr>
<td><strong>DNA</strong></td>
<td>Skeletal muscle mass - DXA scan, body impedance</td>
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<tr>
<td></td>
<td>Grip strength - Dynamometer</td>
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<td></td>
<td>Epigenetic markers</td>
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</tbody>
</table>

Socioeconomic status and HPA-axis dysregulation

Mean saliva-free cortisol sampled on waking up, 30 minutes later, and then at 2-hour intervals

Whitehall II Study

SES and immune system biomarkers

Lifecourse SES and CRP and IL-6 concentration

Whitehall II Study

SES and neural structure

60 typically developing, native English speaking children (US)

Stressful events in early life generally related to lower hippocampal and higher amygdala volume

Preterm birth and telomere length

T/S ratio = Telomere to single-gene copy ratio. Preterm = gestational age <37 weeks. The horizontal bars represent the mean values.

Source: Smeets et al. PLOS ONE 2014.
Occupational exposures and oxidative stress
Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling.

Social environment is associated with gene regulatory variation in the rhesus macaque immune system.

Socio-economic status is associated with epigenetic differences in the pSoBid cohort.
SES and gene regulation

EXPOSURES

MEDIATING FACTORS

OUTCOMES

Lifecourse SES

LIFESTYLE FACTORS

GENE REGULATION

Inflammation

Inflammation-related diseases

Genomic
Epigenetic
Transcriptomic, etc.
Dominance rank and proinflammatory genes expression (macaques)

Socioeconomic status and DNA methylation

- **Population**: prospective cohort study of 857 individuals, sampled from the 47'749 participants of the EPIC-Italy study
- DNA extracted from white blood cells
- SES in early and adult life + lifecourse SES trajectories
- Genome wide methylation data available (450K)
- 17 genes (403 CpG sites) chosen on the basis of their involvement in SES-related inflammation in previous studies
Main results: household’s occupation and DNA methylation

B

Household's highest occupational position

Mean methylation difference (low vs high SES)

Source: Stringhini S, …Vineis P. IJE 2015
SES trajectory e DNA methylation of proinflammatory genes

EPIC ITALY

Life-course SES trajectory

Δ DNA Methylation (%)

NFATC1
IL1A
GPR132

High-High = 0
High-Low
Low-High
Low-Low

Low-High
High-Low
High-High = 0
Low-Low

Source: Stringhini S, ...Vineis P. IJE 2015
Conserved transcriptional response to adversity (CTRA)

Neurobiological activation of leukocyte inflammatory genes and inhibition of innate antiviral genes in response to subjectively experienced physical or social threat

Historically associated with wounds and infection

PROINFLAMMATORY SKEWING OF LEUKOCYTE BASAL TRANSCRIPTOME

Socio-environmental conditions associated with hundreds of «socially-sensitive» genes
- urbanity
- low socioeconomic status
- social isolation
- social threat
- low or unstable social status

Majority of studies examined leukocytes or diseases tissues
Other examples of biological embedding

Source: Rook et al. Clinical and Experimental Immunology 2014
Other examples of biological embedding

- High socioeconomic-status related to alpha-diversity of both the colonic sigmoid mucosa and fecal microbiota (possibly through diet) (Miller et al. 2016)
- C-section related to « less healthy » microbiome, C-section related to SES
- Other examples: exposure to environmental toxics during life in utero
Why this is important?

Exploring the molecular fingerprints of social factors may:

- Allow “tracing” exposures down at molecular level and clarify pathways leading from the social environment to health outcomes
- Identifying the link between social factors and early markers of disease
- Identifying optimal windows for interventions (pregnancy?, early life?, adolescence? Etc)
- Provide new tools for interventions
Challenges

- Few studies with biomarkers, fewer with repeated measures of biomarkers, very very few with epigenetics and/or transcriptomics measures with good exposure data

- When data exist, sample is small and not always exposure data is good enough (ie: SES indicators poorly collected)

- Concerning SES-epigenetics:
  - Need to replicate results on larger studies
  - Test whether SES differences in methylation translate into differences in gene expression and circulating molecules
  - Test whether this can partly explain social differences in health
  - Explore link between SES and gene-regulation in other tissues

- At this stage, policy implications of this research debated if not for identification of exposures and of critical time windows
Conclusions

- Social factors are integrated biologically from birth (or earlier)
  - Various pathways of integration
  - Various windows of integration → of intervention?
  - Exposures from conception to old age

- Need better data and more interdisciplinary research

- Public health impact as well as philosophical/ethical implications not clear
Thank you for your attention!
Box 2 | The ecology of socioeconomic status

In addition to parenting quality and the *in utero* and home environments, there are other factors that may mediate the effects of socioeconomic status (SES) on neural development. These factors include:

- **Toxin exposure**: low-SES children show increased levels of lead in the blood. Lead is a neurotoxin that affects IQ, school achievement, particularly reading ability.

- **Nutrition**: nutrients and caloric intake influence the neural mechanisms that subserve cognition and emotion. Lower-SES families have less access to healthy foods and are more likely to experience food insufficiency and nutritional deficiency.

- **Prenatal drug exposure**: there is little evidence that prenatal drug exposure is a major contributor to the SES disparities noted in this article. Although alcohol and drug use during pregnancy is related to SES, the direction of the relationship varies by substance, and alcohol use in particular is less common in pregnant women of low SES. Furthermore, the effects of prenatal cocaine exposure seem to be relatively small when the effects of other factors, such as the home environment, are controlled for.

- **Stress**: stress affects family relationships, including relationships with children. Low-SES families experience increased stress related to social rank, difficulties in providing for the family’s needs, living in dangerous neighbourhoods and other factors. This can lead to chronic stress and thereby affect child development. There is some evidence from research in animals and humans that stress specifically impairs attentional control, and that indicators of chronic stress exposure mediate the relationship between childhood SES and working memory.
Epigenetics – DNA methylation