L'incorporation biologique des différences socioéconomiques dans la santé

Dr. PD Silvia STRINGHINI

Research Associate (Maître Assistant)

IUMSP
Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne, Switzerland
Outline

- Social inequalities in health
- Mechanisms explaining social inequalities in health
  - Biological mechanisms linking the social environment to health outcomes
- Socioeconomic status and gene regulation of the immune function
  - The Human Social Genomics
- Perspectives
- Conclusions
Outline

- **Social inequalities in health**
  - Mechanisms explaining social inequalities in health
    - Biological mechanisms linking the social environment to health outcomes
  - Socioeconomic status and gene regulation of the immune function
    - The Human Social Genomics

- Perspectives

- Conclusions
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

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

Educational inequalities in cardiovascular risk factors

Figure 1. Relative educational inequalities by gender and age group.
Social inequalities in health

Cardiovascular disease mortality by smoking status and socioeconomic status (British Whitehall II cohort)

Outline

- Social inequalities in health
- **Mechanisms explaining social inequalities in health**
  - Biological mechanisms linking the social environment to health outcomes
- Socioeconomic status and gene regulation of the immune function
  - The Human Social Genomics
- Perspectives
- Conclusions
Causal explanations for social inequalities in health

**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

**HEALTH**
- Mental health
- Functioning
- Physical health
- Mortality

**ACCESS TO/USE OF HEALTH CARE**

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

**ALL FACTORS ARE INTERCONNECTED**
The lifecourse perspective
Models of lifecourse perspective

- **Latency model:**
  - Exposure to adverse SES in critical/sensitive periods alters biological parameters permanently (fetal programming; traumatic events during first year etc.)

- **Cumulation model:**
  - Cumulative effect of exposure to low SES (and its associated factors) across the lifecourse

- **Pathway model:**
  - Low SES in early life influence social mobility pathways and behaviours
Outline

- Social inequalities in health
- Mechanisms explaining social inequalities in health
  - Biological mechanisms linking the social environment to health outcomes
- Socioeconomic status and gene regulation of the immune function
  - The Human Social Genomics
- Perspectives
- Conclusions
<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>
</tr>
<tr>
<td><strong>Sympathetic neuro-hormonal system</strong></td>
<td>Dehydroepiandrosterone sulfate - Blood</td>
</tr>
<tr>
<td><strong>Parasympathetic neuro-hormonal system</strong></td>
<td>Norepinephrine/Epinephrine - Urine</td>
</tr>
<tr>
<td><strong>Inflammatory/Immune system</strong></td>
<td>Alpha-amylase - Saliva</td>
</tr>
<tr>
<td><strong>Heart rate variability</strong></td>
<td>Heart rate variability - Pulse rate recording</td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
<td>C-reactive protein - Blood</td>
</tr>
<tr>
<td><strong>Erythrocyte sedimentation rate</strong></td>
<td>Erythrocyte sedimentation rate - Blood</td>
</tr>
<tr>
<td><strong>Interleukins</strong></td>
<td>Interleukins - Blood</td>
</tr>
<tr>
<td><strong>Lymphocyte number and function</strong></td>
<td>Lymphocyte number and function - Blood</td>
</tr>
<tr>
<td><strong>Circulating serum albumin</strong></td>
<td>Circulating serum albumin - Blood, saliva</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Diastolic/systolic blood pressure</td>
</tr>
<tr>
<td><strong>Glucose metabolism</strong></td>
<td>Resting heart rate</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td>Fasting glucose - Blood</td>
</tr>
<tr>
<td><strong>Glycosylated hemoglobin</strong></td>
<td>Glycosylated hemoglobin - Blood</td>
</tr>
<tr>
<td><strong>Fasting insulin</strong></td>
<td>Fasting insulin - Blood</td>
</tr>
<tr>
<td><strong>Lipid metabolism</strong></td>
<td>Cholesterol and lipoprotein fractions - Blood</td>
</tr>
<tr>
<td><strong>BMI, waist to hip ratio</strong></td>
<td>BMI, waist to hip ratio</td>
</tr>
<tr>
<td><strong>Total body fat</strong></td>
<td>Total body fat - DXA scan</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td>Serum hemoglobin - Blood</td>
</tr>
<tr>
<td><strong>Clotting factors and clotting time</strong></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><strong>Urine albumin leakage</strong></td>
<td>Urine albumin leakage - Urine</td>
</tr>
<tr>
<td><strong>Cystatin C</strong></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>Follicle-stimulating hormone</strong></td>
<td>Follicle-stimulating hormone - Blood</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Arterial oxygen saturation - Pulse oximeter</td>
</tr>
<tr>
<td><strong>Peak expiratory flow</strong></td>
<td>Peak expiratory flow - Spirometer</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>Bone density - DXA scan</td>
</tr>
<tr>
<td><strong>Bone turnover markers</strong></td>
<td>Bone turnover markers - Blood, fasting urine</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td>Skeletal muscle mass - DXA scan, body impedance</td>
</tr>
<tr>
<td><strong>Grip strength</strong></td>
<td>Grip strength - Dynamometer</td>
</tr>
<tr>
<td><strong>DNA</strong></td>
<td>Epigenetic markers</td>
</tr>
</tbody>
</table>

SES 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.
Social factors and brain development

US NIH MRI Study of Normal Brain Development, N=55 healthy children

Occupational exposures and oxidative stress

A. Protein (mg/ml)

B. Superoxide Dismutase (U/mg protein)

C. Catalase (nkat/mg protein)

D. Glutathione Peroxidase (all NADPH oxidized/min mg protein)

E. Lipid Peroxidation (MDA/mg protein)

F. ROS (U/L)

Outline

- Social inequalities in health
- Mechanisms explaining social inequalities in health
  - Biological mechanisms linking the social environment to health outcomes
- **Socioeconomic status and gene regulation of the immune function**
  - The Human Social Genomics
- Perspectives
- Conclusions
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

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

Life-course SES trajectory

Δ DNA Methylation (%)

NFATC1       IL1A       GPR132

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

Source: Stringhini S, ... Vineis P. IJE 2015
Social inequalities in health

Mechanisms explaining social inequalities in health

- Biological mechanisms linking the social environment to health outcomes

Socioeconomic status and gene regulation of the immune function

- The Human Social Genomics

Perspectives

Conclusions
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

Human Social Genomics

- 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
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, no clear policy implications of this research 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 philosopohycal/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 and school achievement, particularly affecting 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.

- **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