La biologia delle diseguaglianze sociali legate all’invecchiamento.

Carlotta Sacerdote

XLIII Convegno AIE 2019
Aging

Aging is the progressive decline in physiological ability and loss of function with advancing age:

Chronological aging is a measure of age in years and occurs at a constant rate in all individuals.

Biological ageing is due to the accumulation of damage at cellular level and it is determined by both environmental and genetic factors (Adams, 2004).
Socioeconomic differences in health could be understood as due to differential exposure: mediation role of traditional risk factors.

- Relative importance of traditional risk factors is different in different populations
- Differential exposure to traditional risk factors do not explain the increased risk of diseases.
SEP and biological aging

Biological ageing: A fundamental, biological link between socio-economic status and health?

Article in The European Journal of Public Health - October 2004

La biologia delle diseguaglianze sociali legate all’invecchiamento
• **Lifepath Funder** – European Union H2020

• **Lifepath coordinator** – Paolo Vineis, Imperial College, London

• **Lifepath Collaborators**

  Rotterdam University - Johan Mackenbach  
  Lausanne University - Silvia Stringhini  
  IIGM (ex HuGeF) - Silvia Polidoro, Giovanni Fiorito  
  CPO - Carlotta Sacerdote  
  ICL - Marc Chadeau-Hyam, Paolo Vineis (coordinator)  
  KCL - Mauricio Avendano  
  Toulouse University - Michelle Kelly Irving  
  UCL - Michael Marmot, Mika Kivimaki  
  SEPI – Giuseppe Costa, Angelo D’Errico, Fulvio Ricceri  
  Zadig - Luca Carra

La biologia delle diseguaglianze sociali legate all’invecchiamento
The biology of inequalities in health: the LIFEPATH project

*Longitudinal and Life Course Studies 2017 Volume 8 Issue 4 Pp 417 – 439*
Biological aging

Imperfect operation of maintenance mechanisms and the resultant accumulation of cellular damage. The rate at which cellular damage accumulates is determined by the balance between damage and repair mechanisms.
Biomarkers of biological aging

Several biomarkers of biological aging have been proposed:

- Telomere length
- DNA methylation (epigenetic clock, epigenetic drift)
- Allostatic load
- …
Telomere length

Telomeres are the protective nucleoprotein structures capping the ends of eukaryotic chromosomes.

Telomeres length can be decreased by aging for the increasing rounds of cell division, but also by biochemical environment.

The telomere shortening has important functional consequences: short telomeres lead to genomic instability and cellular senescence (i.e. short telomeres in leucocytes lead to the secretion of pro-inflammatory cytokines).
Telomere length

Figure 3. Results from random-effects meta-analysis for the standardized mean difference (SMD) (i.e., effect size) between low and high education categories in the relation of socioeconomic status (SES) with telomere length (TL), ranked by weights applied in the analysis. Squares, SMDs for individual studies; diamond, overall SMD. Bars, 95% confidence interval (CI). (RPCI, Roswell Park Cancer Institute).

Epidemiol Rev 2013;35:98–111

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Epigenetic clock refers to specific CpG sites identified in specific DNA regions at which DNAm levels constantly increase (or decrease) during aging can be used to predict chronological age with high accuracy.

Three epigenetic clocks: Horvat, Hannum and Levine.

Epigenetic aging acceleration differences DNAm age and chronological age.
Epigenetic clock

Epigenetic aging acceleration has been associated with:

- Risk factors: obesity, poor physical activity, unhealthy diet, cumulative lifetime stress, infections.
- All causes mortality
- Diseases: cancer incidence, neurodegenerative disorders.
Age acceleration based on DNAm

Meta-analysis: EPIC Italy, MCCS and TILDA
Socio-economic rank: basic adjustments

Meta-analysis: EPIC Italy, MCCS and TILDA
Socio-economic rank: full model

Social adversity and epigenetic aging: a multi-cohort study on socioeconomic differences in peripheral blood DNA methylation

Giovanni Fiorito, Silvia Polidoro, Pierre-Antoine Dugué, Mika Kivimaki, Erica Ponzi, Giuseppe Matullo, Simonetta Guerrera, Manuela B. Assumma, Panagiotis Georgiadis, Soterios A. Kyrtopoulos, Vittorio Krogh, Domenico Palli, Salvatore Panico, Carlotta Sacerdote, Rosario Tumino, Marc Chadeau-Hyam, Silvia Stringhini, Gianluca

SCIENTIFIC REPORTS | 7: 16266 | DOI:10.1038/s41598-017-16391-5
Epigenetic drift represents the trend of increasing DNAm variability over time across the whole genome. Age related genomic instability and chromatin deterioration lead to increased variability of genome-wide DNAm levels at older ages.

Teschendorff: differential DNAm variability
Gentilini: stochastic epimutations
Stochastic epimutations

The number of stochastic epimutations (SEMs) increases exponentially with age although there is high variability within individuals of the same age. Higher number of SEMs is associated with:

- risk factors such as cigarette smoking, alcohol intake and exposure to toxicants
- Hepatocellular carcinoma tumor staging
Stochastic epigenetic mutations

Socioeconomic position, lifestyle habits and biomarkers of epigenetic aging: a multi-cohort analysis

Giovanni Fiorito, Cathal McCrory, Oliver Robinson, Cristian Carmeli, Carolina Ochoa Rosales, Yan Zhang, Elena Colicino, Pierre-Antoine Dugue, Fanny Artaud, Gareth J McKay, Ayoung Jeong, Pashupati P Mishra, Therese H Nast, Vittorio Krogh, Salvatore Panico, Carlotta Sacerdote, Rosario Tumino, Domenico Palii, Giuseppe
Epimutations, SES and unhealthy lifestyle habits: meta-analysis within Lifepath cohorts.

Methods

\[ \log\text{SEMs} \sim f(\text{age, sex, SES, lifestyle variables, technical covariates, cohort specific variables}) \].

Random effect meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>( \beta )</th>
<th>95% CI</th>
<th>weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS</td>
<td>624</td>
<td>-0.04</td>
<td>(-0.63 ; 0.55)</td>
<td>0.49%</td>
</tr>
<tr>
<td>TERRE</td>
<td>174</td>
<td>0.25</td>
<td>(-0.27 ; 0.77)</td>
<td>0.63%</td>
</tr>
<tr>
<td>Skipogh 1</td>
<td>250</td>
<td>0.07</td>
<td>(-0.23 ; 0.37)</td>
<td>1.84%</td>
</tr>
<tr>
<td>Young Finns</td>
<td>186</td>
<td>0.19</td>
<td>(-0.10 ; 0.47)</td>
<td>2.07%</td>
</tr>
<tr>
<td>EXPOsOMICS CVD</td>
<td>313</td>
<td>0.05</td>
<td>(-0.22 ; 0.31)</td>
<td>2.40%</td>
</tr>
<tr>
<td>Skipogh 2</td>
<td>451</td>
<td>0.13</td>
<td>(-0.11 ; 0.37)</td>
<td>2.85%</td>
</tr>
<tr>
<td>Rotterdam 2</td>
<td>730</td>
<td>0.17</td>
<td>(-0.06 ; 0.41)</td>
<td>2.92%</td>
</tr>
<tr>
<td>Rotterdam 1</td>
<td>720</td>
<td>0.05</td>
<td>(-0.17 ; 0.27)</td>
<td>3.36%</td>
</tr>
<tr>
<td>ESTHER 2</td>
<td>864</td>
<td>-0.02</td>
<td>(-0.24 ; 0.20)</td>
<td>3.38%</td>
</tr>
<tr>
<td>TILDA</td>
<td>490</td>
<td>0.04</td>
<td>(-0.18 ; 0.26)</td>
<td>3.42%</td>
</tr>
<tr>
<td>ESTHER 1</td>
<td>1,000</td>
<td>0.11</td>
<td>(-0.06 ; 0.28)</td>
<td>5.54%</td>
</tr>
<tr>
<td>EPIC Italy</td>
<td>1,803</td>
<td>0.01</td>
<td>(-0.14 ; 0.17)</td>
<td>6.45%</td>
</tr>
<tr>
<td>NICOLA</td>
<td>1,929</td>
<td>0.03</td>
<td>(-0.12 ; 0.19)</td>
<td>6.93%</td>
</tr>
<tr>
<td>AIRWAVE</td>
<td>1,127</td>
<td>0.04</td>
<td>(-0.06 ; 0.14)</td>
<td>13.92%</td>
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<tr>
<td>MCCS</td>
<td>2,817</td>
<td>0.13</td>
<td>(0.05 ; 0.21)</td>
<td>19.61%</td>
</tr>
<tr>
<td>KORA</td>
<td>1,727</td>
<td>0</td>
<td>(-0.07 ; 0.07)</td>
<td>24.18%</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td>15,205</td>
<td><strong>0.06</strong></td>
<td><strong>(-0.02 ; 0.10)</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>
Allostatic Load

McEwen and Stellar (1993): “wear and tear” on the body as a result of exposure to chronic stress.

Indexes constructed from biomarkers to assess the physiological deregulation of nervous, metabolic, immune, cardiovascular and endocrine system.
La biologia delle diseguaglianze sociali legate all’invecchiamento
Allostatic Load

La biologia delle diseguaglianze sociali legate all’invecchiamento
Conclusions

European Journal of Epidemiology
https://doi.org/10.1007/s10654-019-00539-w

Biography and biological capital

Paolo Vineis¹,² · Michelle Kelly-Irving³

La biologia delle diseguaglianze sociali legate all’invecchiamento
Grazie dell’attenzione!

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### Allostatic load and epigenetic clocks

Pearson correlations between age, epigenetic clocks and allostatic load

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Horvath’s clock</th>
<th>Hannum’s clock</th>
<th>Levine’s clock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horvath’s clock</td>
<td>0,74***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hannum’s clock</td>
<td>0,74***</td>
<td>0,92***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine’s clock</td>
<td>0,85***</td>
<td>0,66***</td>
<td>0,65***</td>
<td></td>
</tr>
<tr>
<td>Allostatic load</td>
<td>0,32***</td>
<td>0,26***</td>
<td>0,25***</td>
<td>0,38***</td>
</tr>
</tbody>
</table>

*** p<0,001

Mc Crory, 2019

La biologia delle diseguaglianze sociali legate all’invecchiamento
Telomere length and epigenetic clocks measures correlate close to zero. Are they measuring different age related processes?

Pearson correlations between Hannum epigenetic clock and telomere length

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>r (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave 1</td>
<td>920</td>
<td>0.063 (0.03)</td>
<td>0.05</td>
</tr>
<tr>
<td>Wave 2</td>
<td>290</td>
<td>0.006 (0.06)</td>
<td>0.92</td>
</tr>
<tr>
<td>Wave 3</td>
<td>273</td>
<td>-0.076 (0.03)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

SEM and Clocks

**Education (ref: High)**

- Medium
- Low

**Socioeconomic position, lifestyle habits and biomarkers of epigenetic aging: a multi-cohort analysis**

Giovanni Fiorito, Cathal McCrory, Oliver Robinson, Cristian Carmeli, Carolina Ochoa Rosales, Yan Zhang, Elena Colicino, Pierre-Antoine Dugué, Fanny Artaud, Gareth J McKeay, Ayoung Jeong, Pushpati P Mishra, Therese H Nast, Vittorio Krogh, Salvatore Panico, Carlotta Sacerdote, Rosario Tumino, Domenico Palii, Giuseppe