The biological consequences of social inequalities
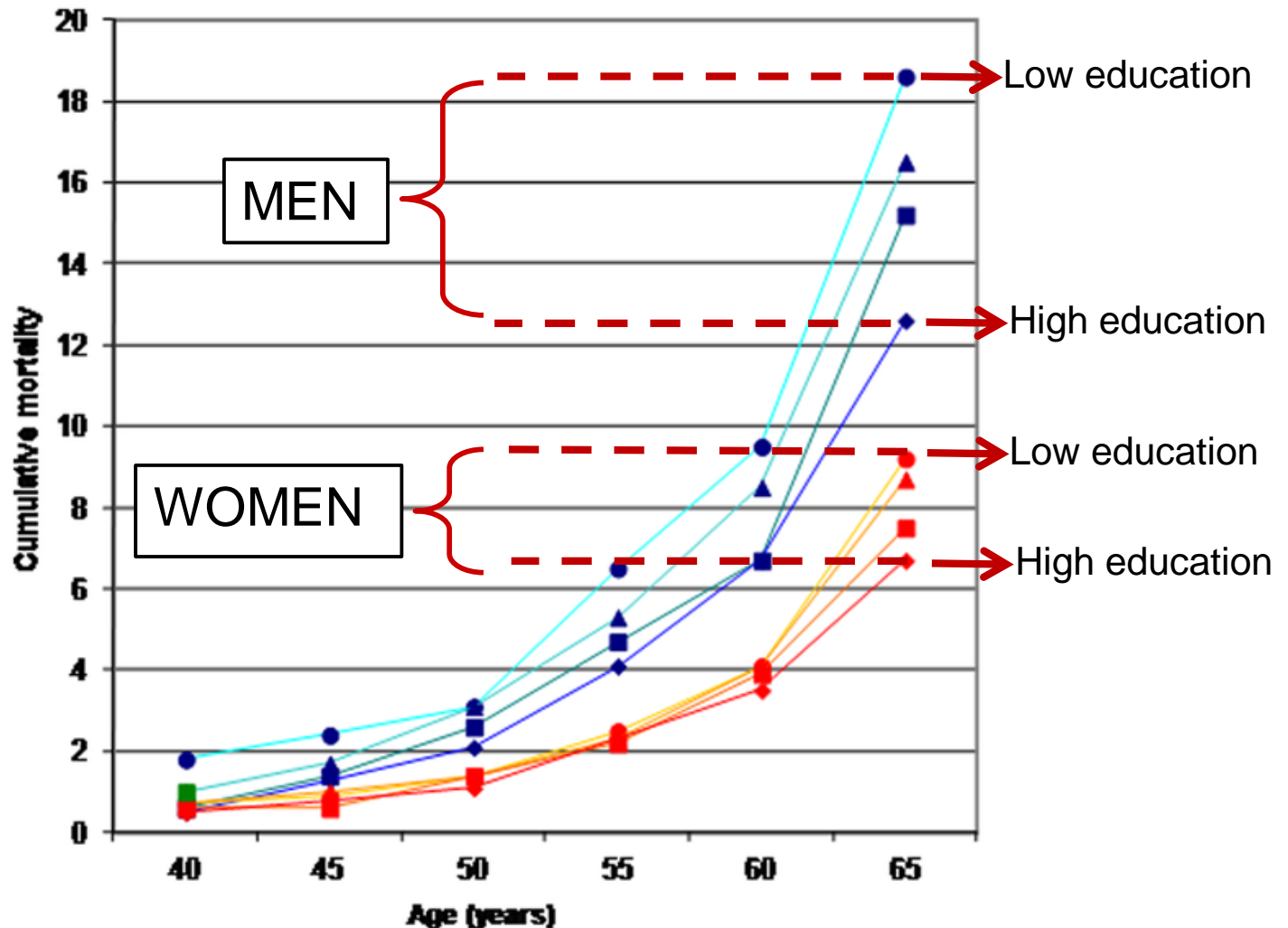
Dr. PD Silvia STRINGHINI
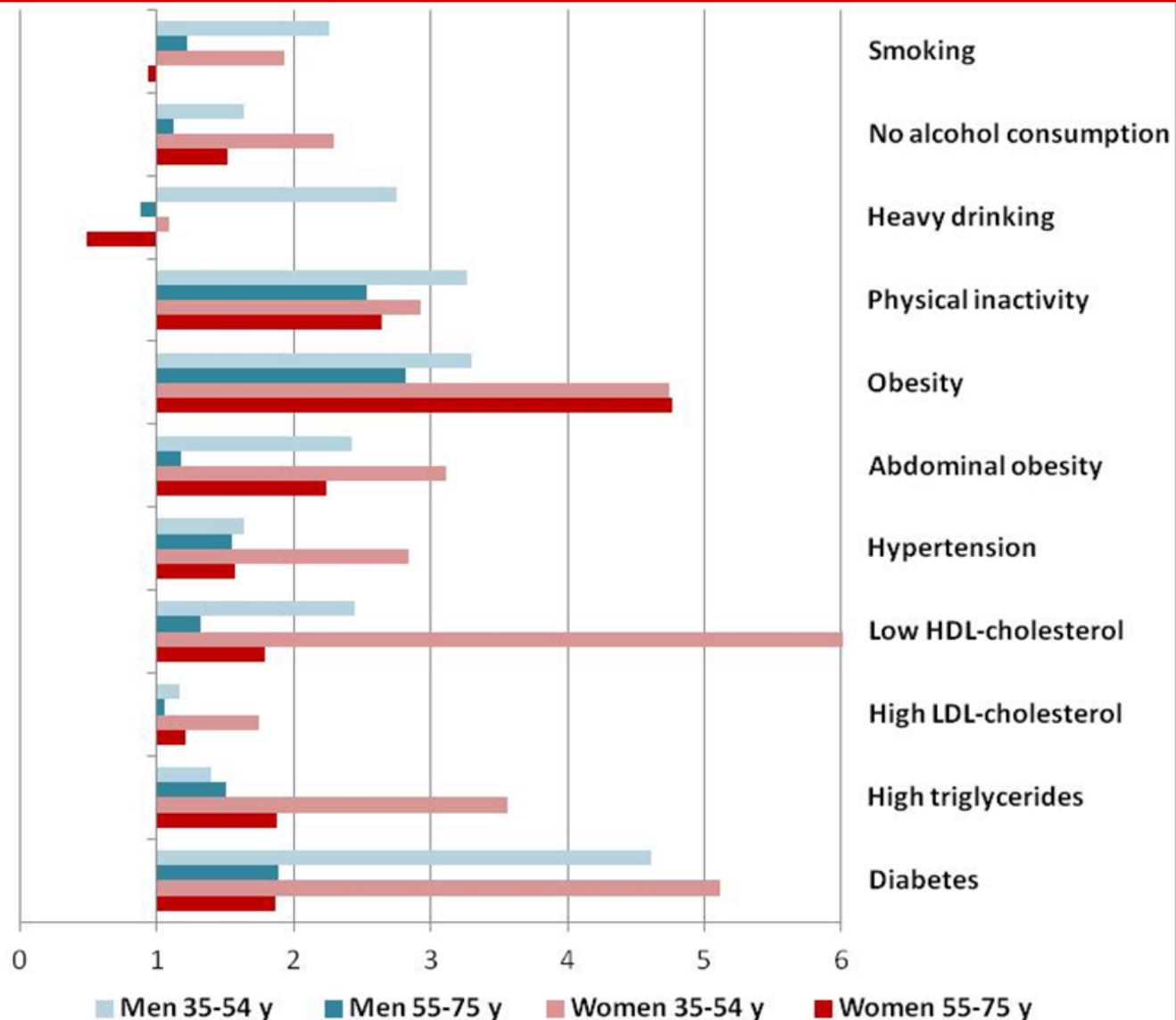
Research Director
Geneva University Hospital/ Geneva University

Educational inequalities in mortality

Education and cumulative mortality in Europe (EPIC, 371,295 participants, 9 countries)
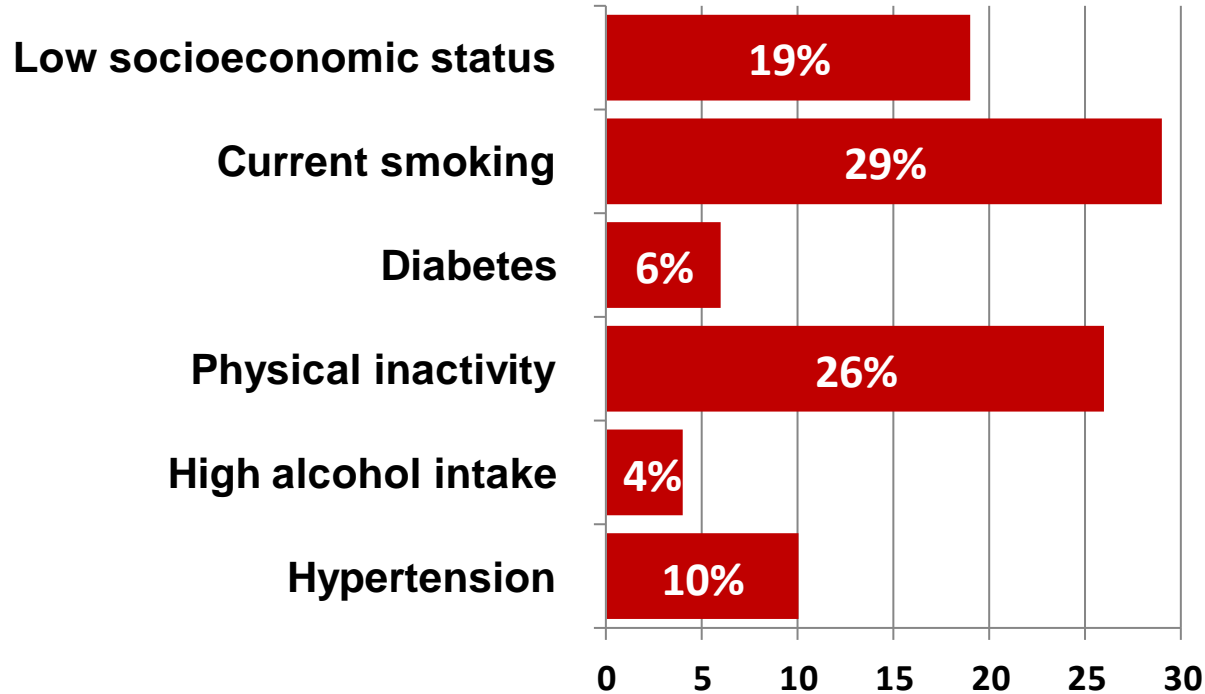
Educational inequalities in cardiovascular risk factors

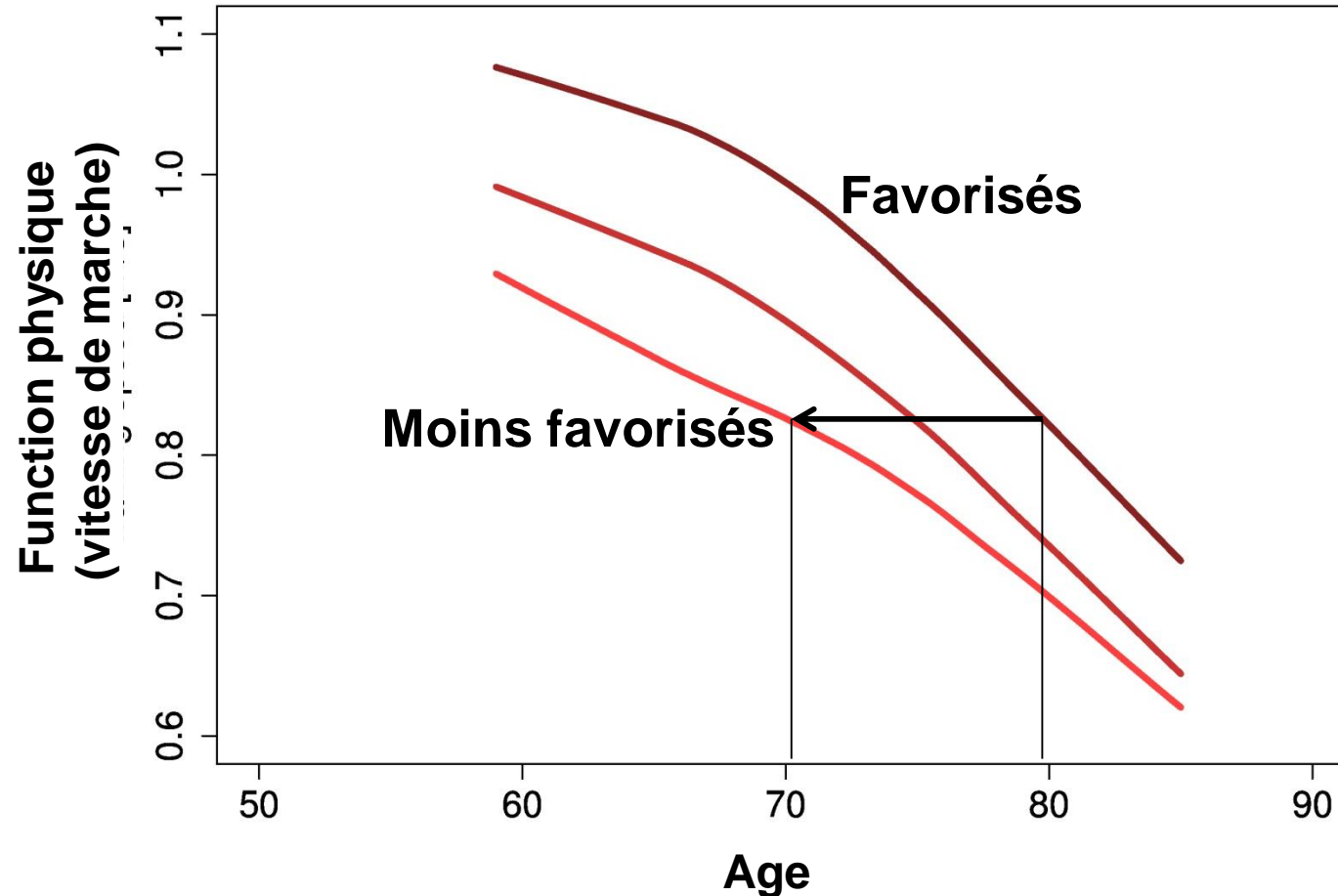# Impact of social factors on premature mortality

Risque attribuable dans la population à des facteurs de risque sélectionnées
(1.7 million de participants en 7 pays)
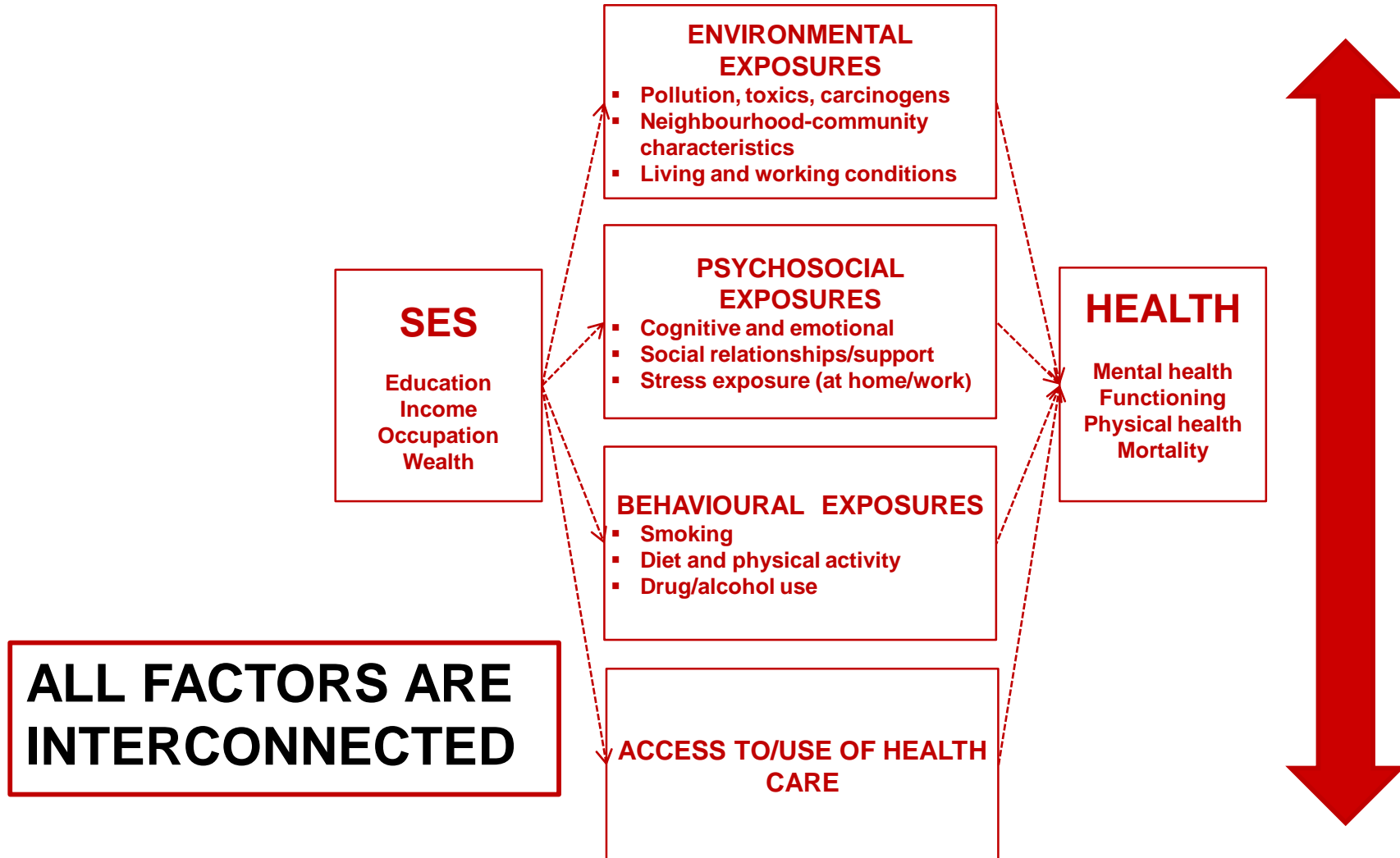

Stringhini S et al. *The Lancet*, 2017.

Social factors and trajectories of physical functioning
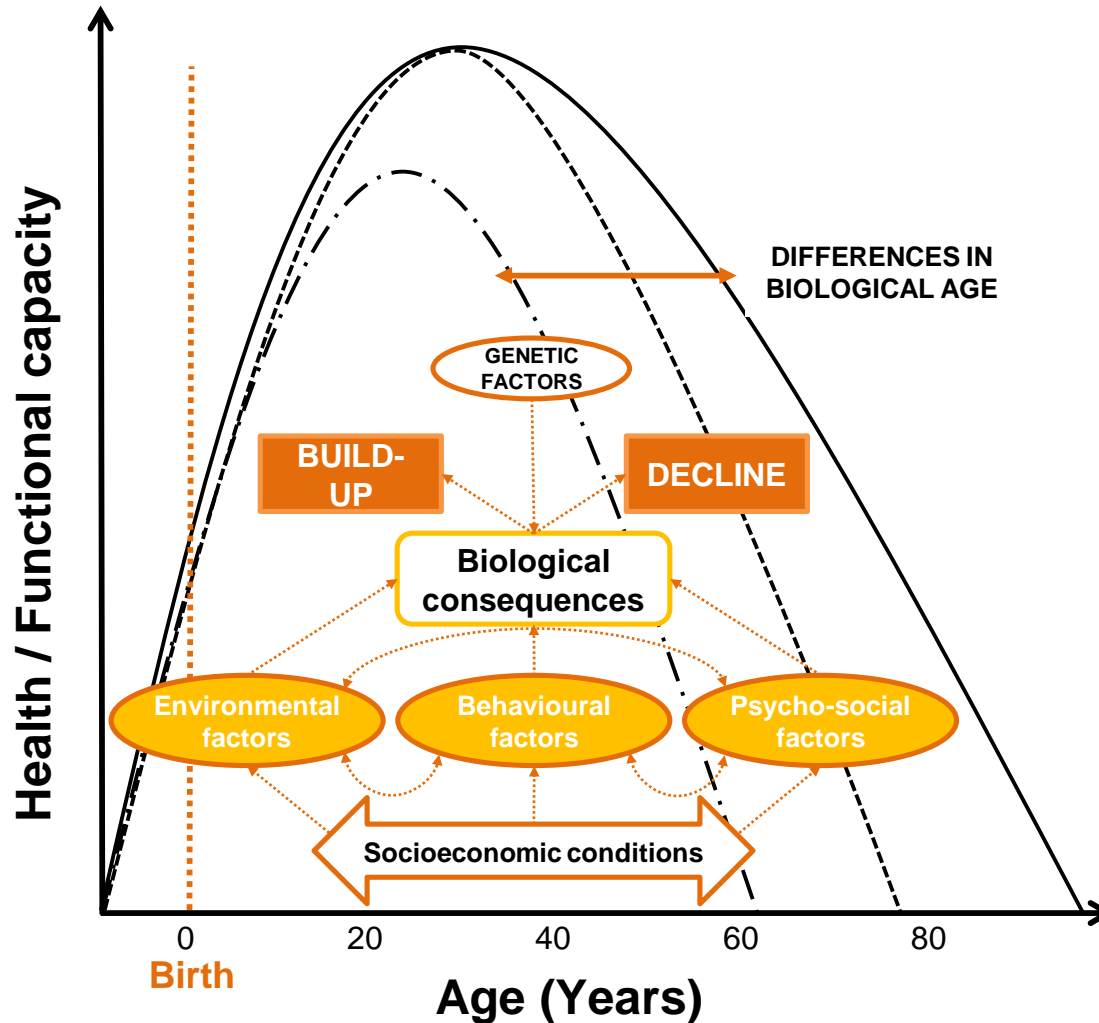
English Longitudinal Study of Ageing

Stringhini S et al., BMJ 2018

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

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

Embodiement

"we literally incorporate, biologically, the material and social world in which we live, from in utero to death; a corollary is that no aspect of our biology can be understood absent knowledge of history and individual and societal ways of living."

Nancy Krieger JECH 2001

SES and biomarkers

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

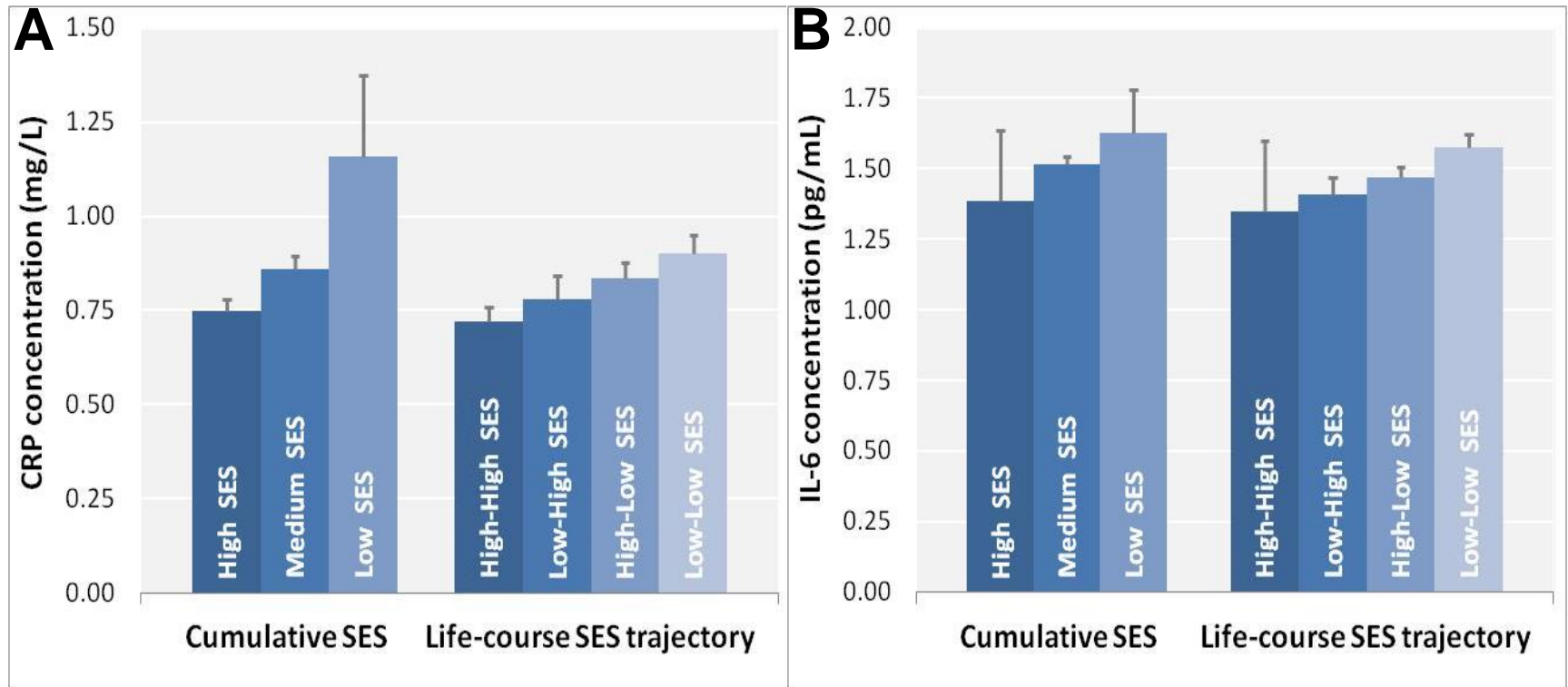Source: Wolfe B, Evans W, Seeman T. The biological consequences of health inequalities (2012).

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

Legend: ●—● High SES   ▲ Low SES
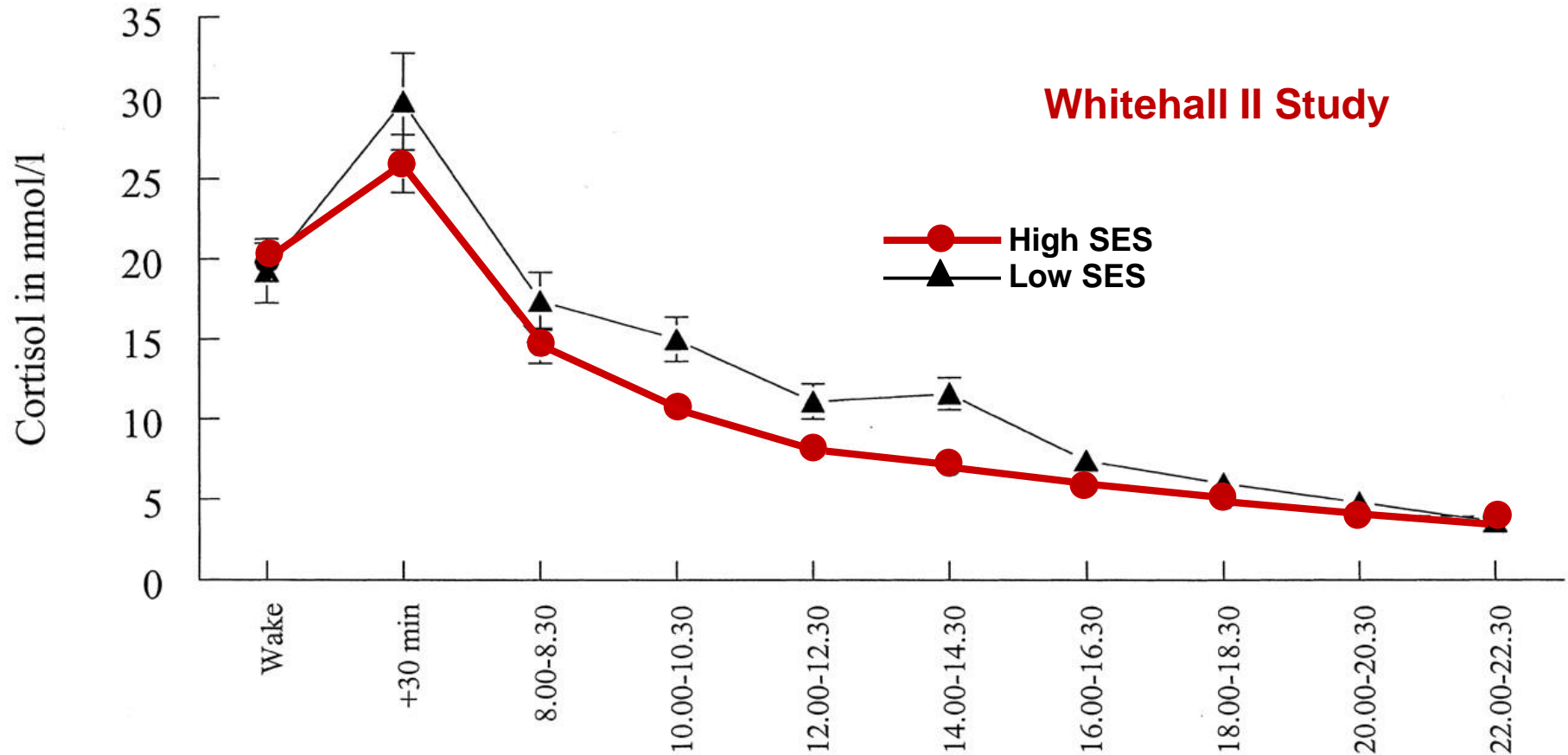
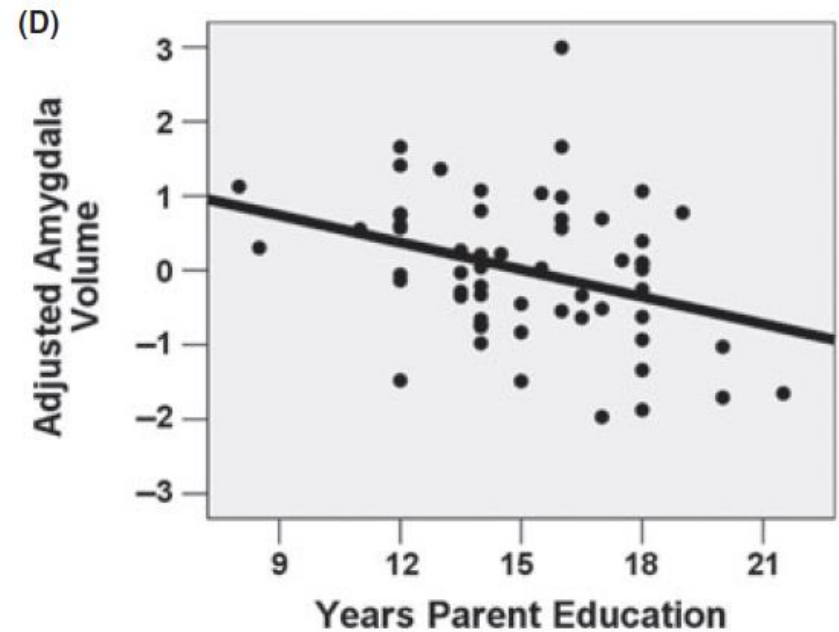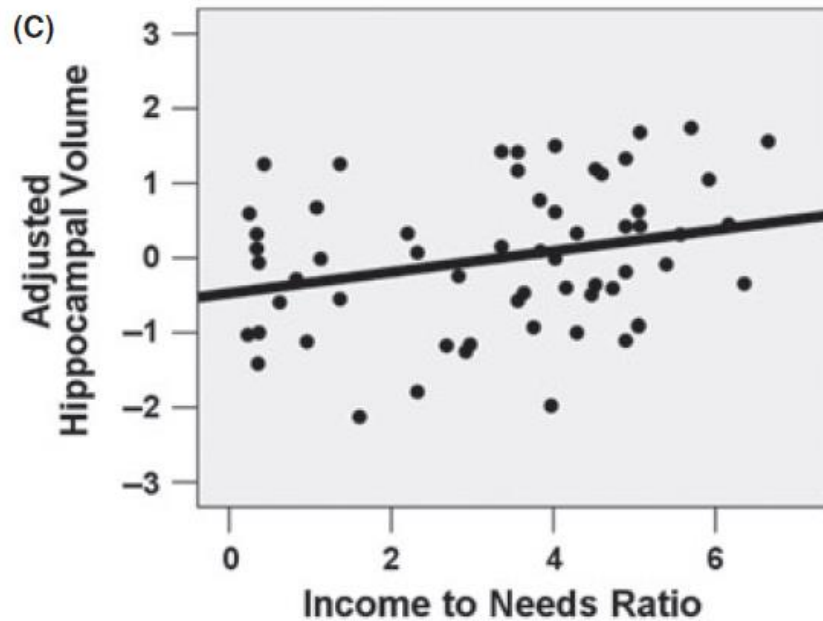# SES and immune system biomarkers

Lifecourse SES and CRP and IL-6 concentation
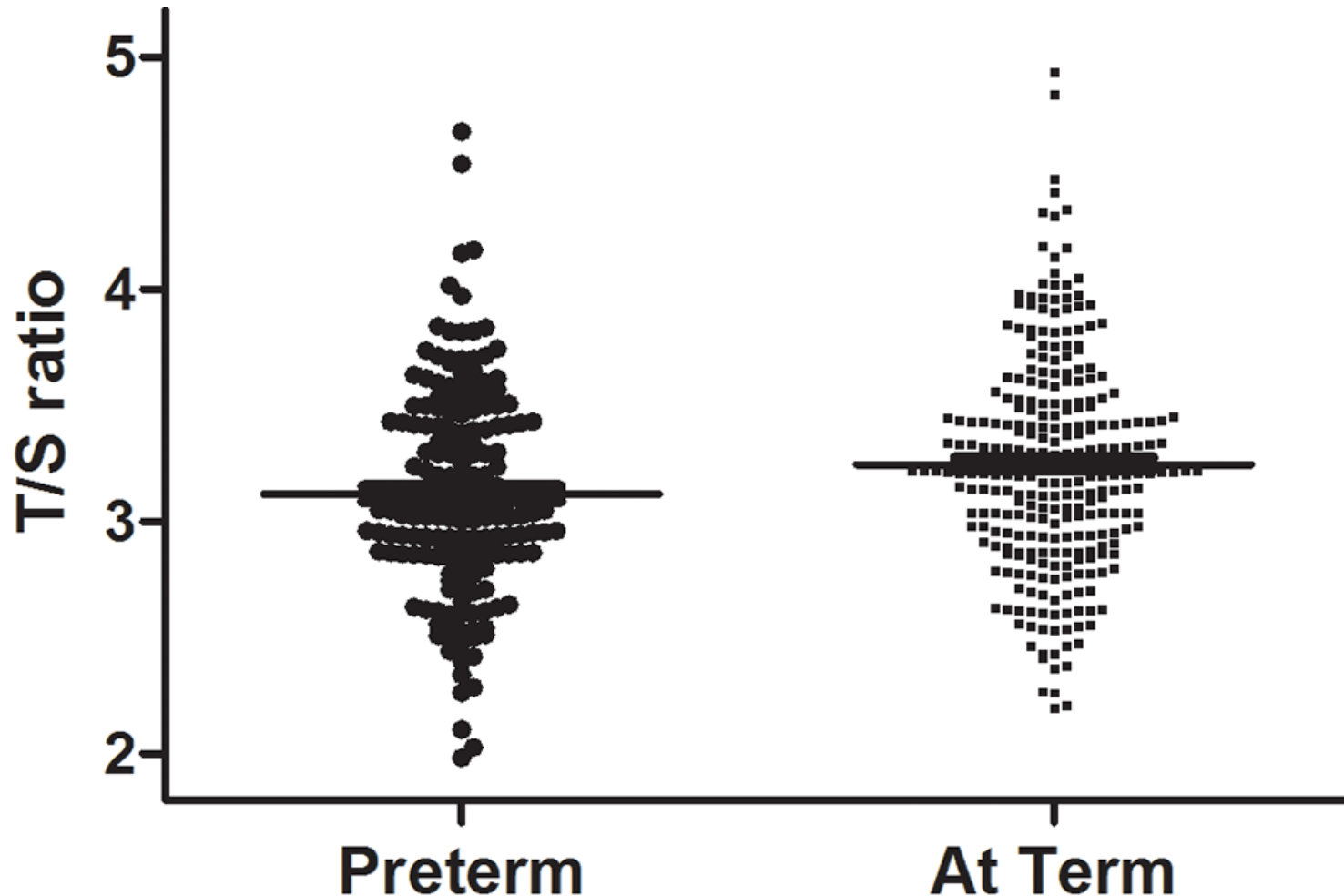

Whitehall II Study

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
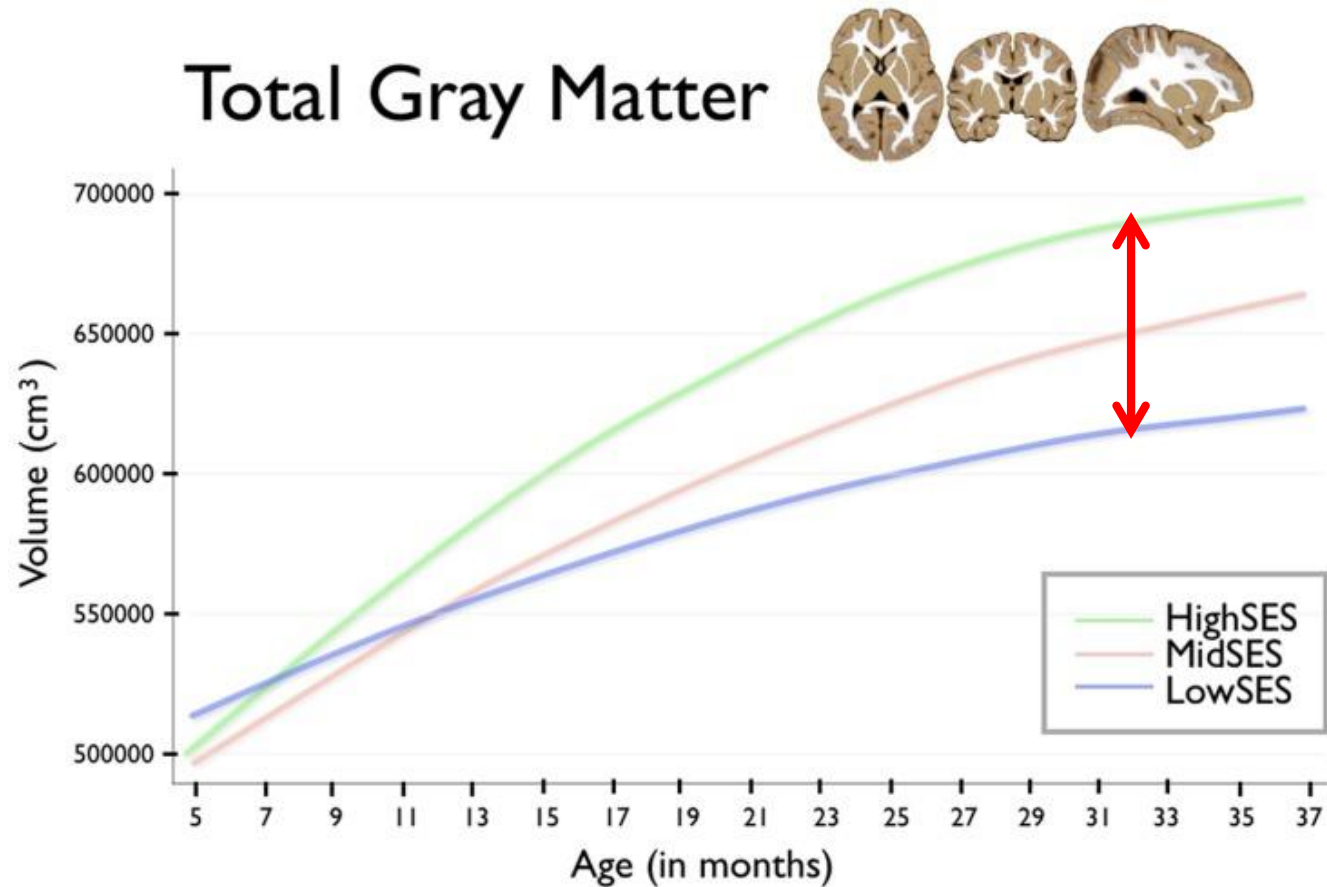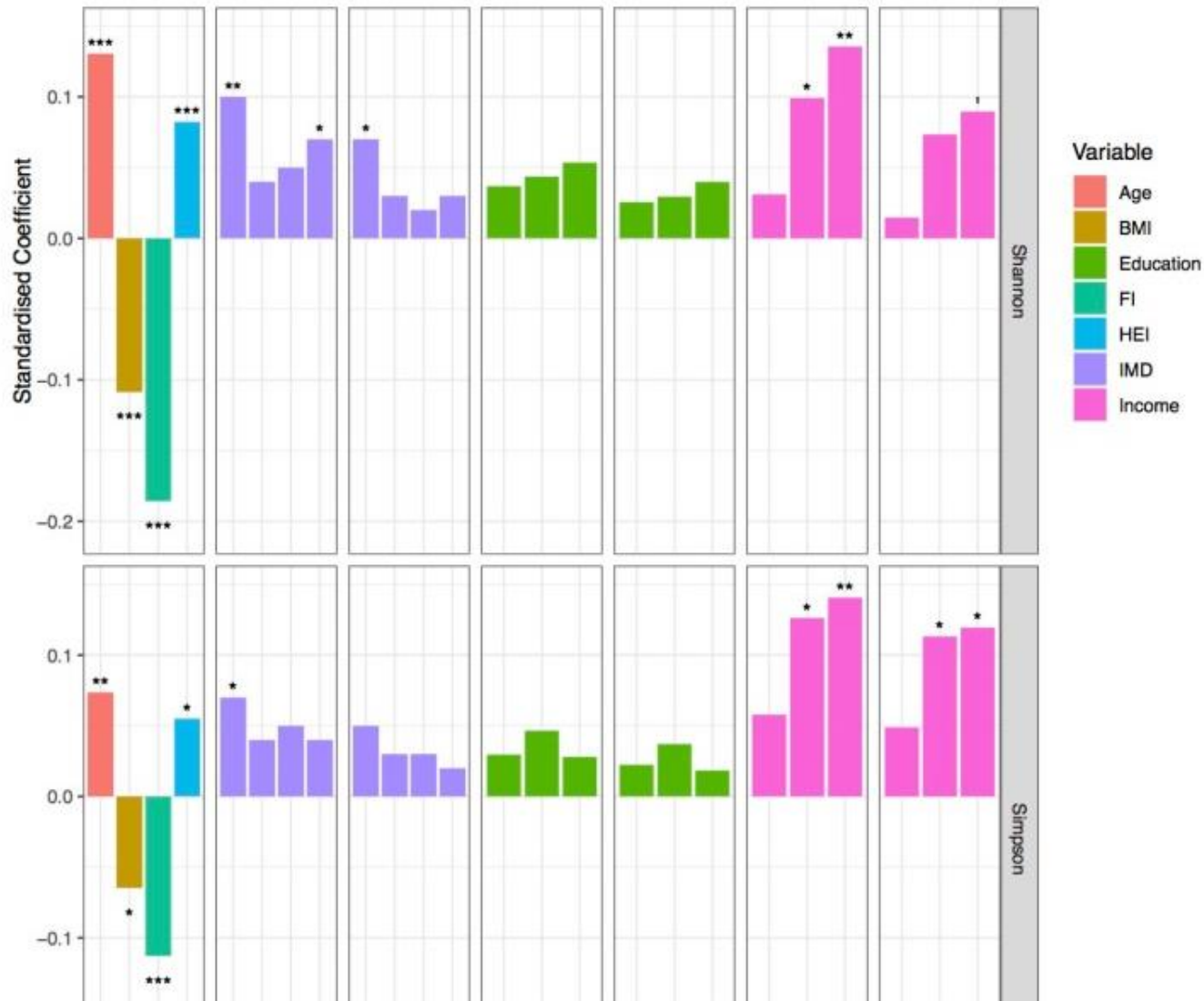
Preterm birth and telomere lenght

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

Social factors and brain development

Total Gray Matter

Social factors and gut microbiome

SES and gene regulation

Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling

Socia

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ty,[3]

Social Determinants

Life-course socioeconomic status and DNA methylation of genes regulating inflammation
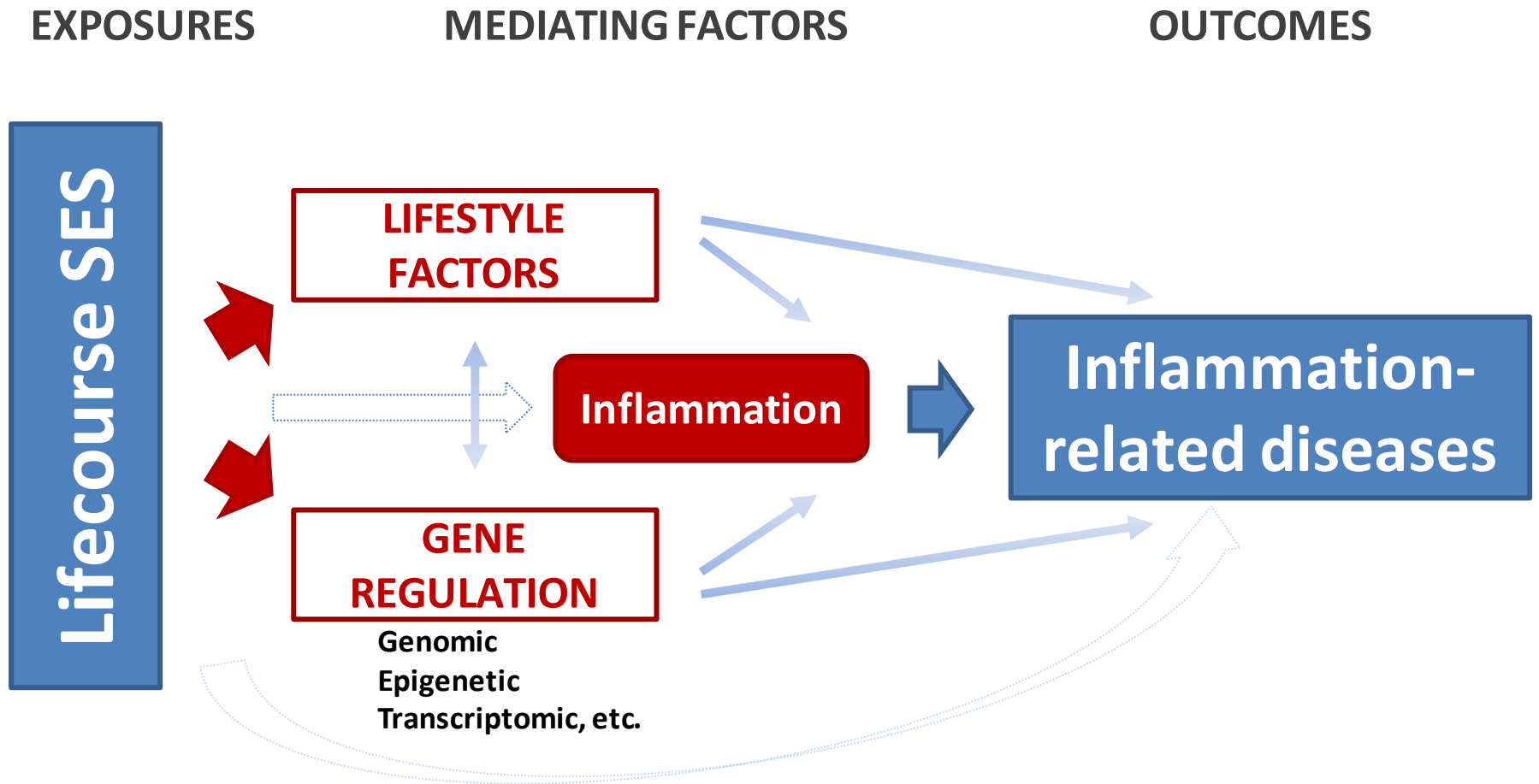
Silvia Stringhini,[1]*[†] Silvia Polidoro,[2][†] Carlotta Sacerdote,[2] Rachel S Kelly,[3,4] Karin van Veldhoven,[2,3] Claudia Agnoli,[5] Sara Grioni,[5] Rosario Tumino,[6] Maria Concetta Giurdanella,[6] Salvatore Panico,[7] Amalia Mattiello,[7] Domenico Palli,[8] Giovanna Masala,[8] Valentina Gallo,[9,10] Raphaële Castagné,[3] Fred Paccaud,[1] Gianluca Campanella,[10] Marc Chadeau-Hyam[3] and Paolo Vineis[2,3]

[1]Institute of Social and Preventive Medicine, University Hospital Centre, Lausanne, Switzerland,

SES and gene regulation
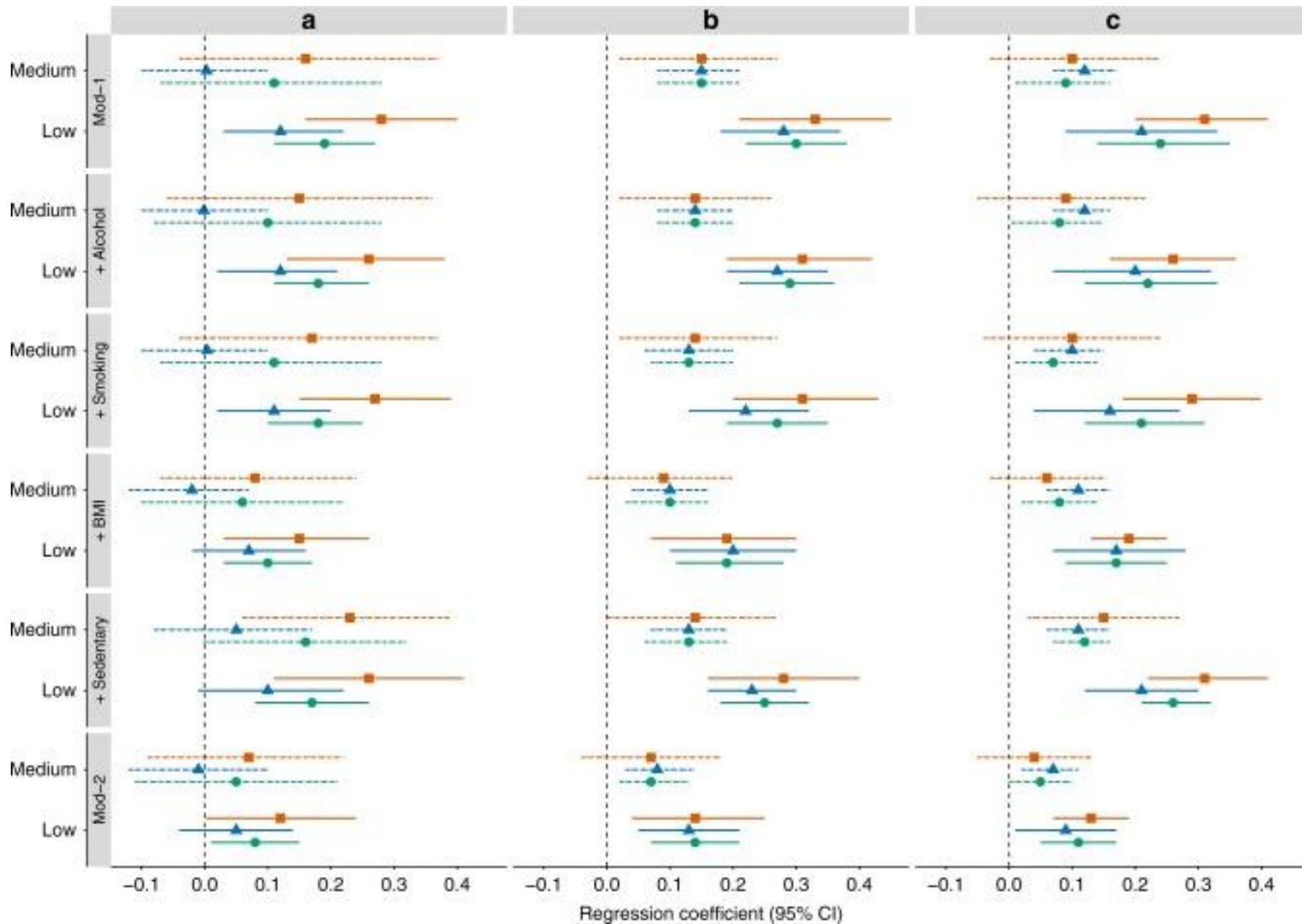

EXPOSURES   MEDIATING FACTORS   OUTCOMES

Lifecourse SES

LIFESTYLE FACTORS

Inflammation

GENE REGULATION

Genomic
Epigenetic
Transcriptomic, etc.

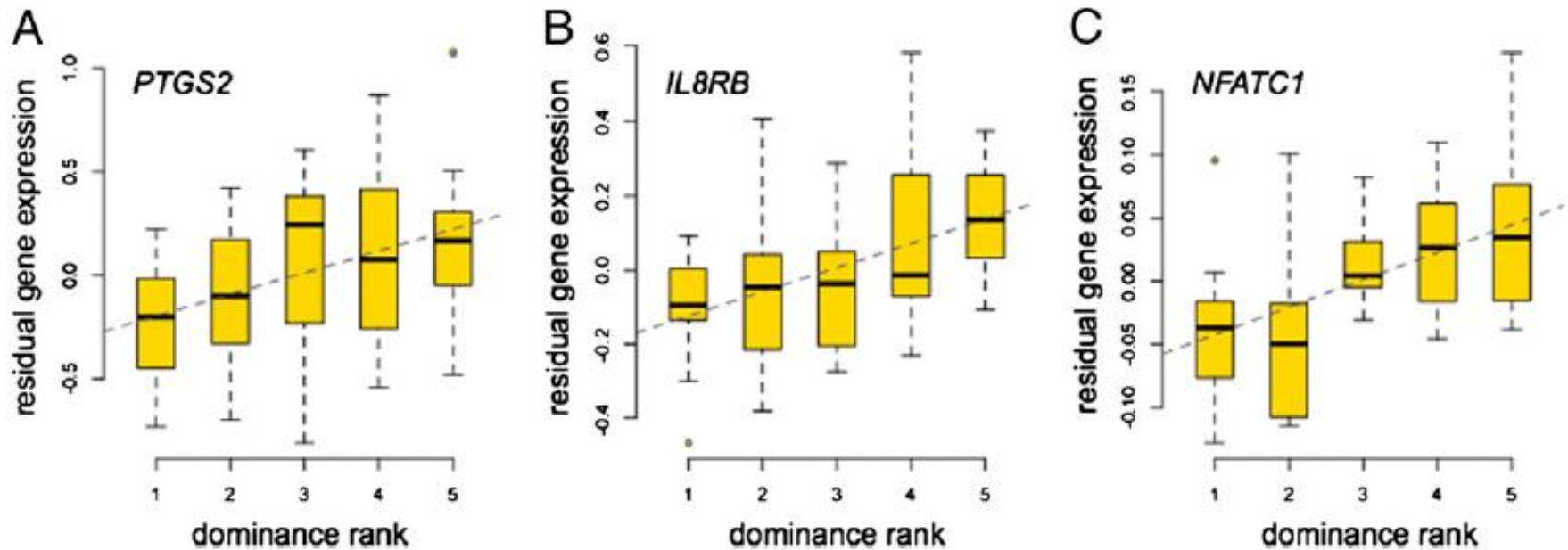**Inflammation-related diseases**

SES and inflammation

SES across the lifecurse and CRP among 23'000 participants in 6 cohorts
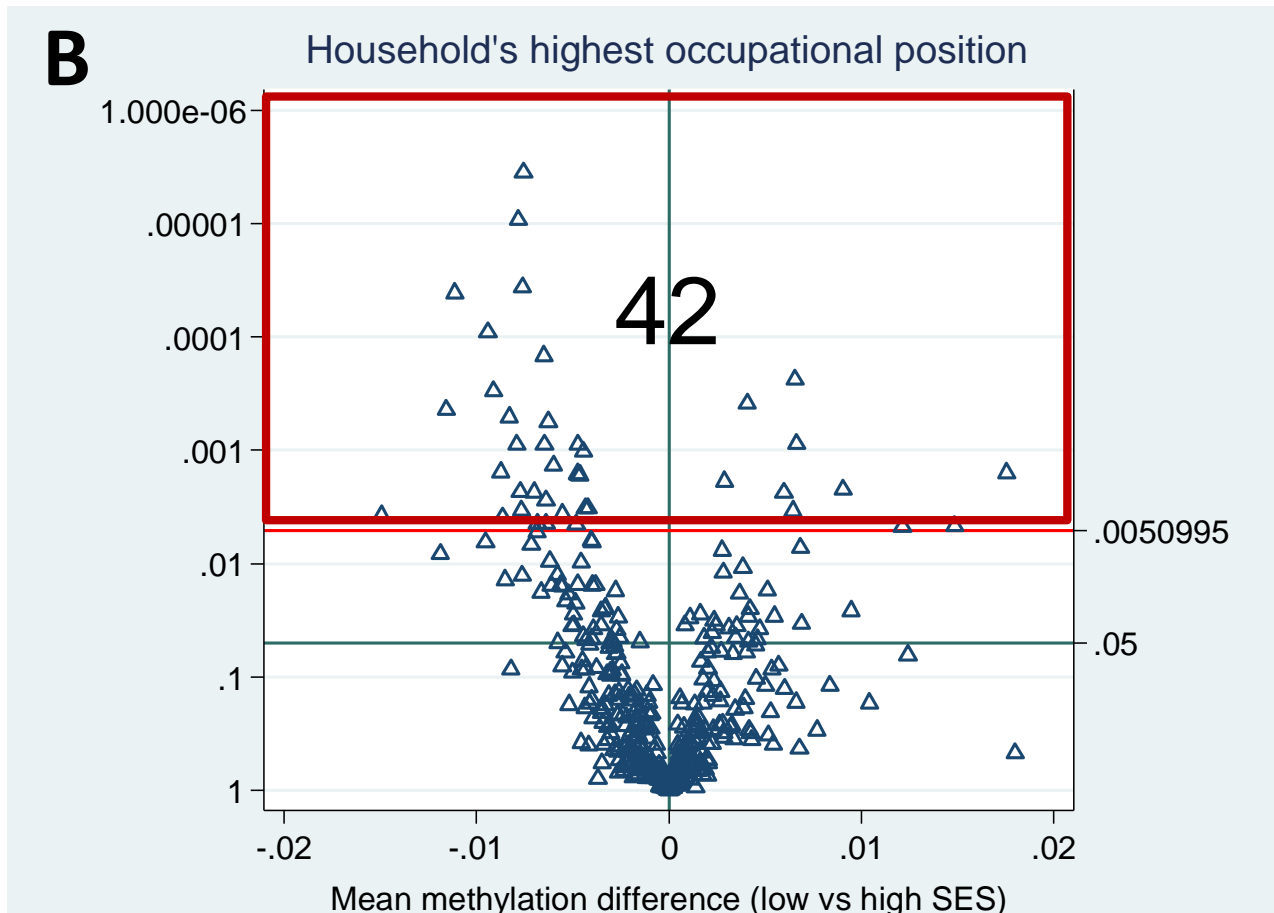
Dominance rank and proinflammatory genes expression (macaques)
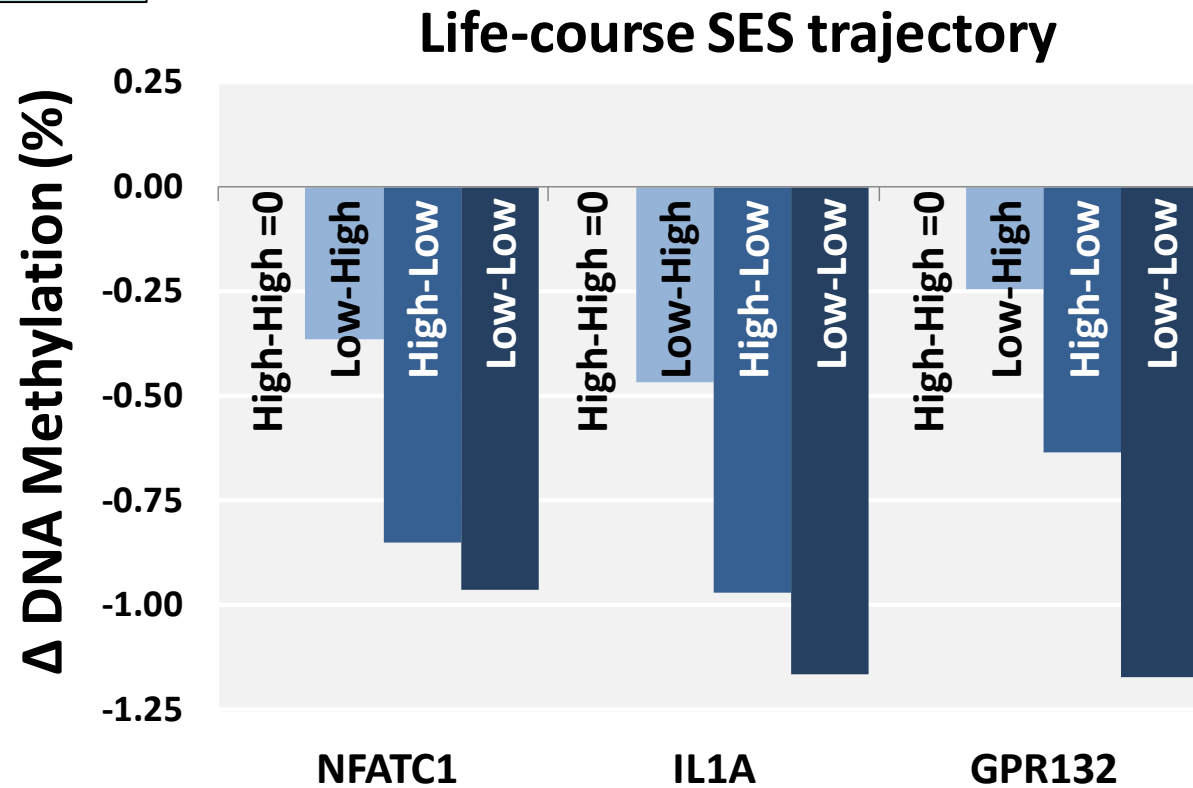
Socioeconomic status and DNA methylation

- **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

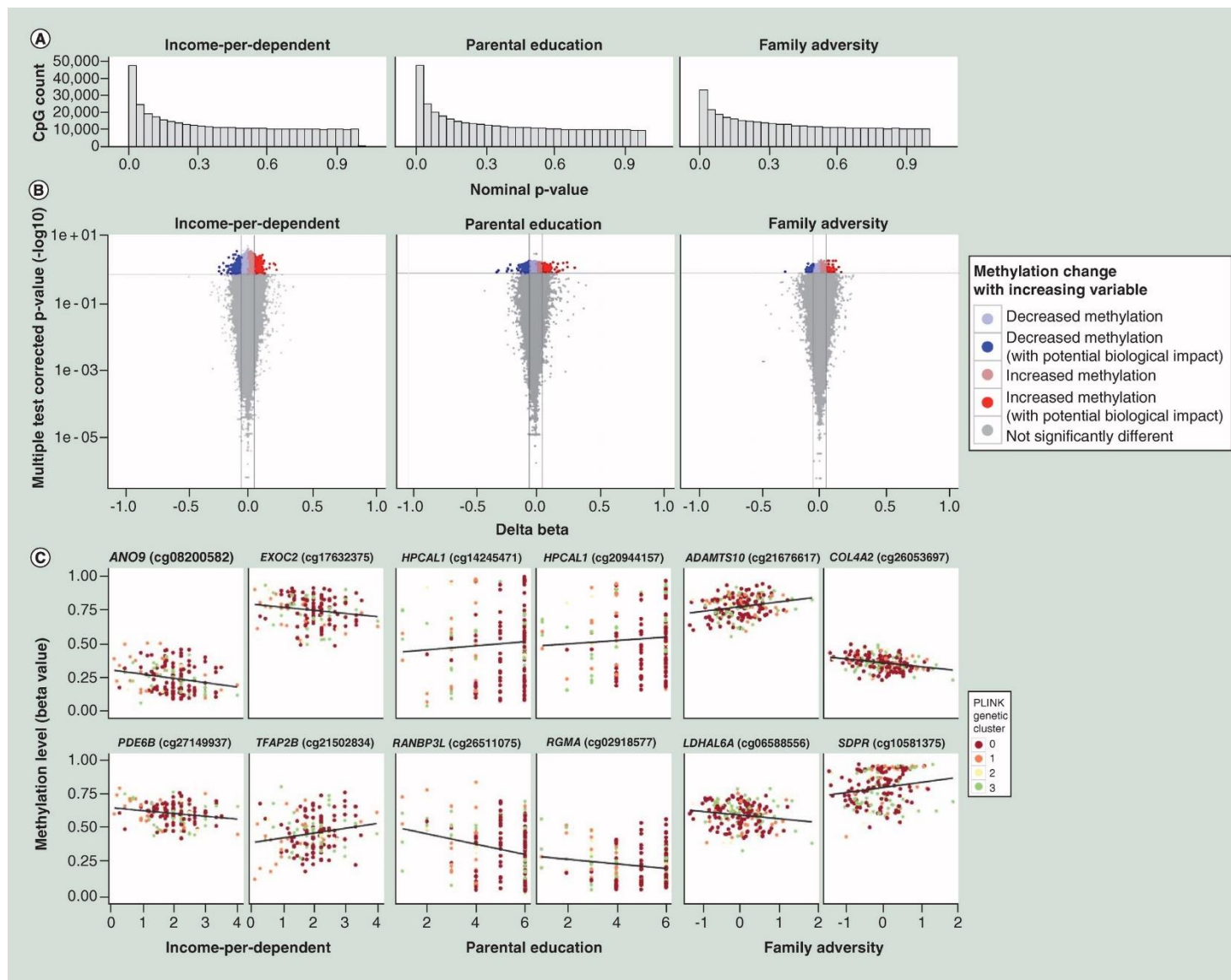

Household's highest occupational position

42

y-axis (top to bottom): 1.000e-06, .00001, .0001, .001, .01, .1, 1

Right side labels: .0050995, .05

x-axis: Mean methylation difference (low vs high SES)
x-axis values: -.02, -.01, 0, .01, .02

SES trajectory e DNA methylation of proinflammatory genes

EPIC ITALY

Life-course SES trajectory

Δ DNA Methylation (%)

NFATC1 — High-High =0, Low-High, High-Low, Low-Low
IL1A — High-High =0, Low-High, High-Low, Low-Low
GPR132 — High-High =0, Low-High, High-Low, Low-Low

SES trajectory e DNA methylation of proinflammatory genes

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
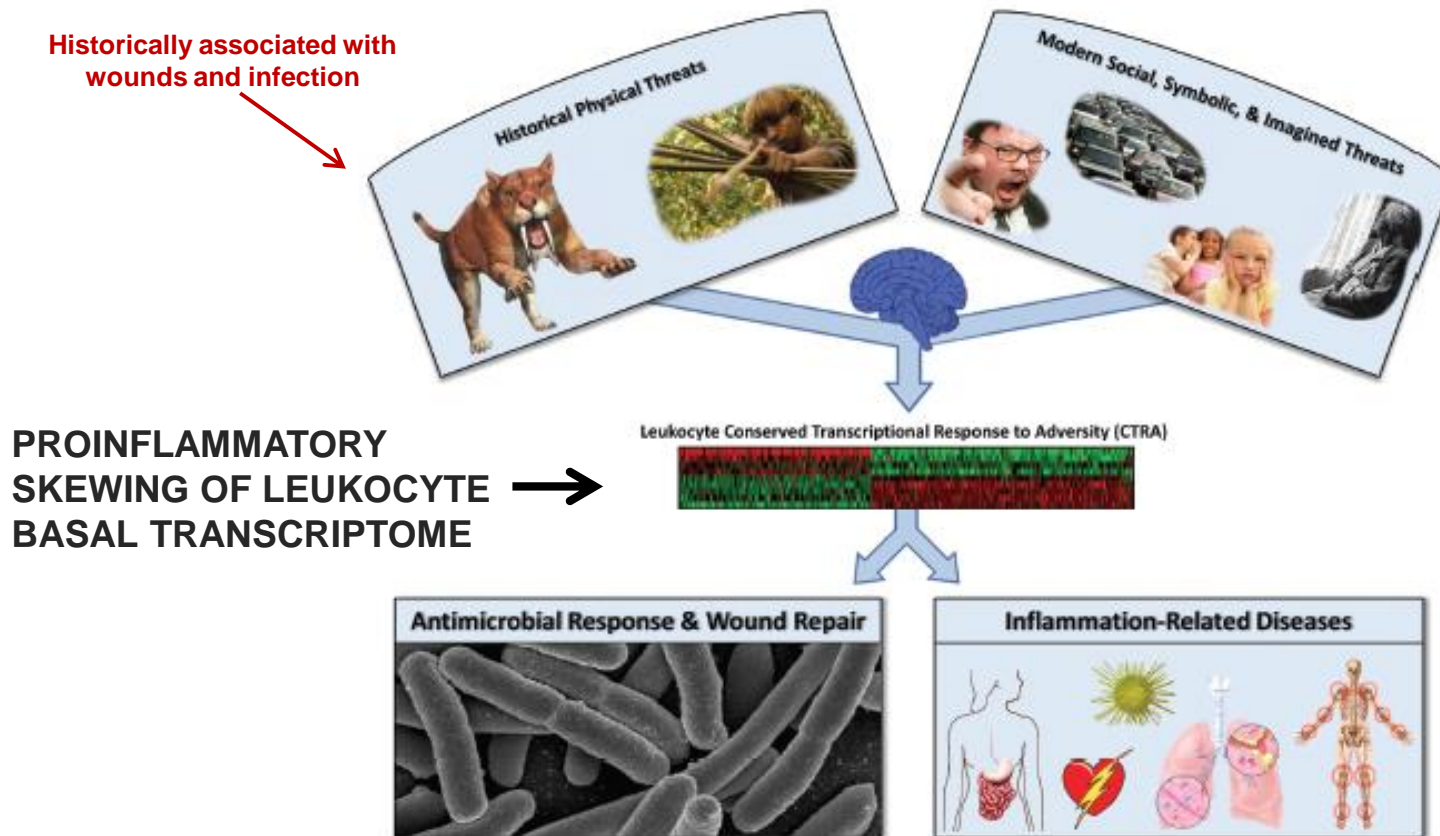
Human Social Genomics

- 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

Concept of the reactive genome

- Genes are unfolding in specific social and historical *milieu→ change in paradigm where DNA not anymore the master of the cell but "*sometimes comes to look like a servant, serving the proteins by being their memory" (Morange, 2001, Shapiro, 2002)

- Heritability of non-genetic features (ie. Transgenerational transmission of epigenetic traits)

- Nature and nurture no longer understood as dichotomous elements

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 identyfication of exposures and of critical time windows
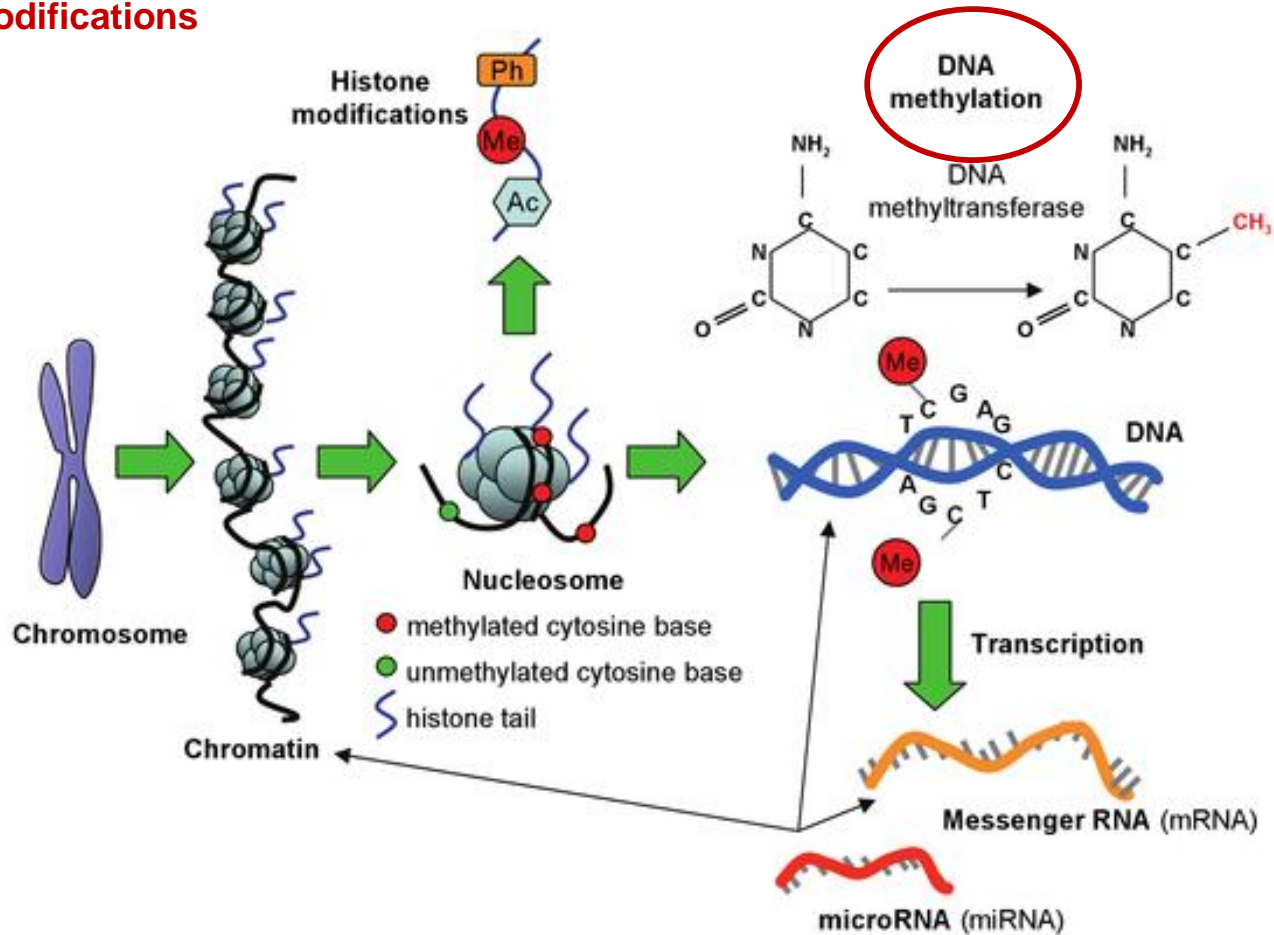
Conclusions

- 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 phylosophycal/ethical implications not clear

Thank you for your attention!

Epigenetics – DNA methylation

Epigenetic modifications