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**Imperial College London**

**The impact of socio-economic  
differentials and the environment on  
health: new technologies**

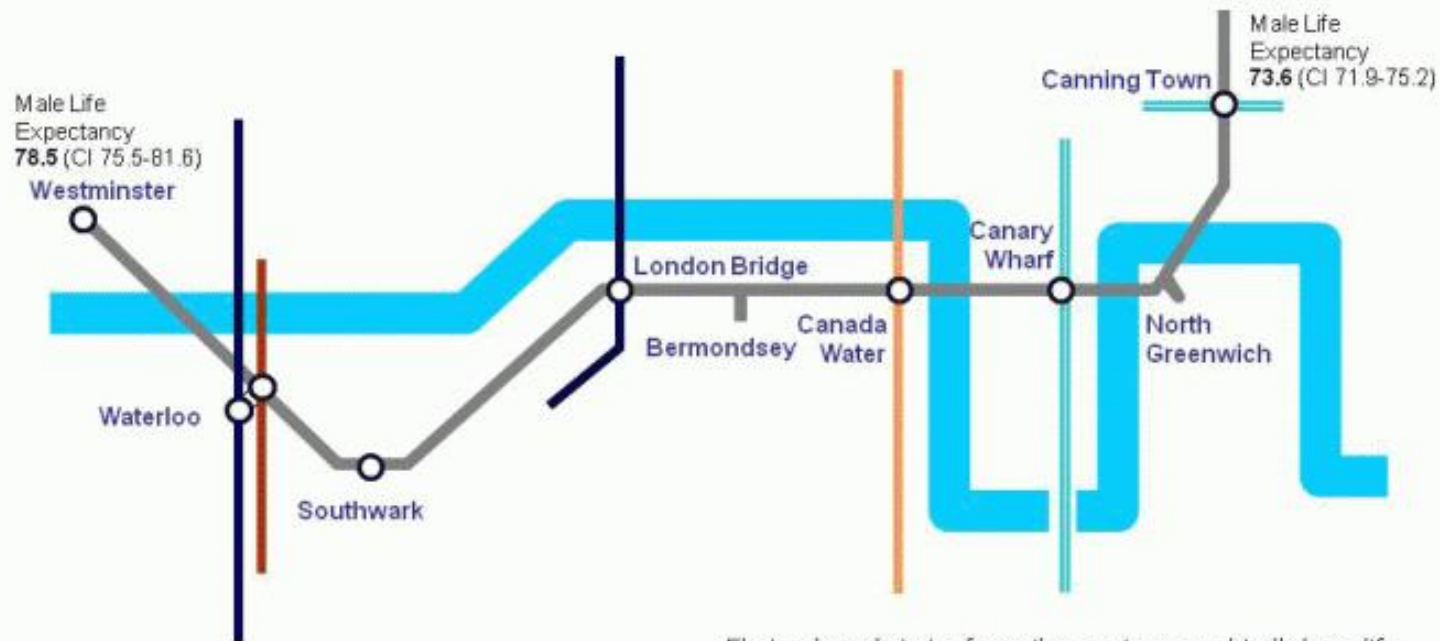
MRC-PHE  
Centre for Environment & Health



# Social inequalities in health

## Differences in Male Life Expectancy within a small area in London

Travelling east from Westminster, every two tube stops represent over one year of life expectancy lost – Data revised to 2004-08

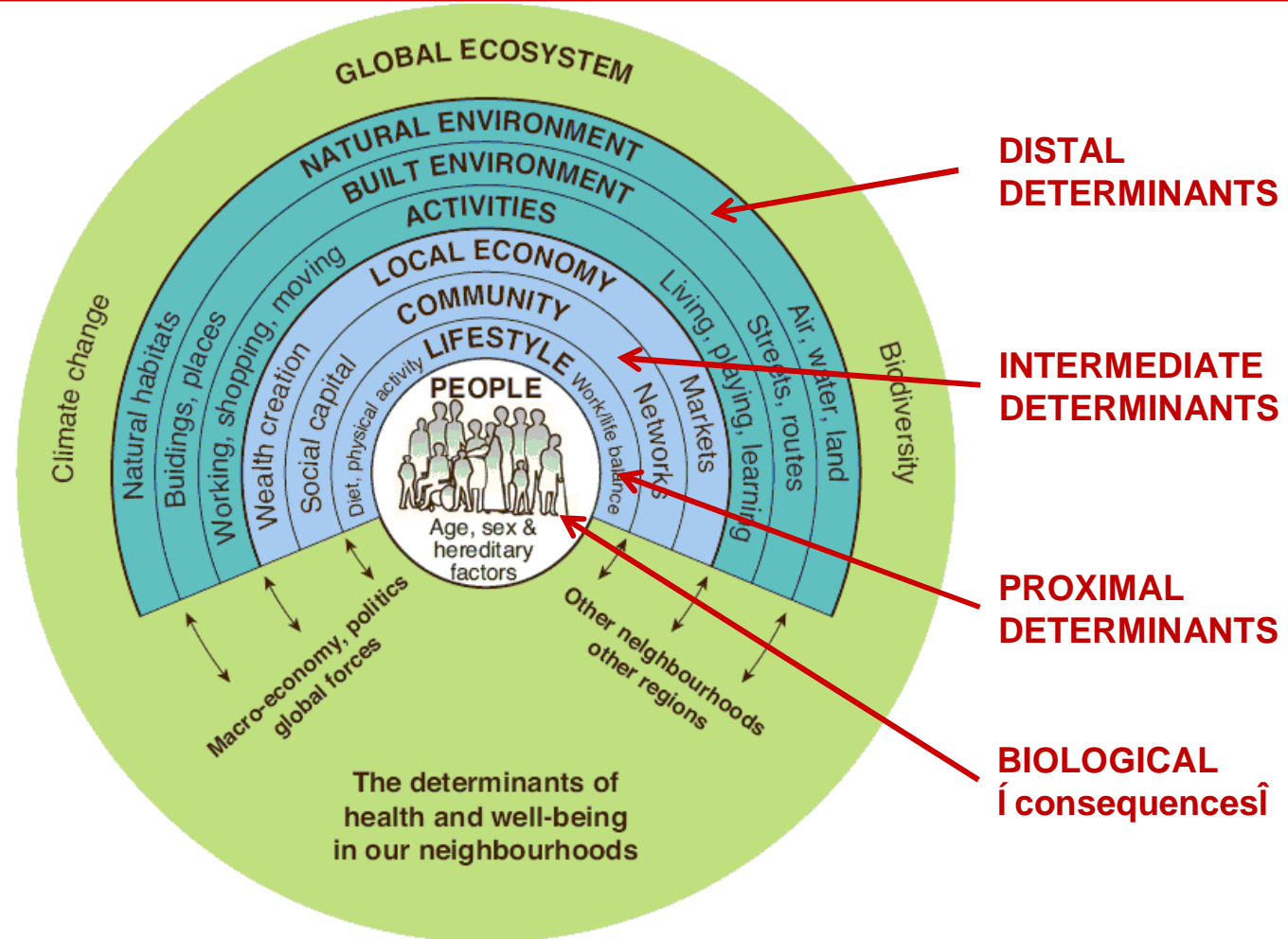


London Underground Jubilee Line

Electoral wards just a few miles apart geographically have life expectancy spans varying by years. For instance, there are eight stops between Westminster and Canning Town on the Jubilee Line – so as one travels east, every two stops, on average, mark over a year of shortened lifespan. <sup>1</sup>

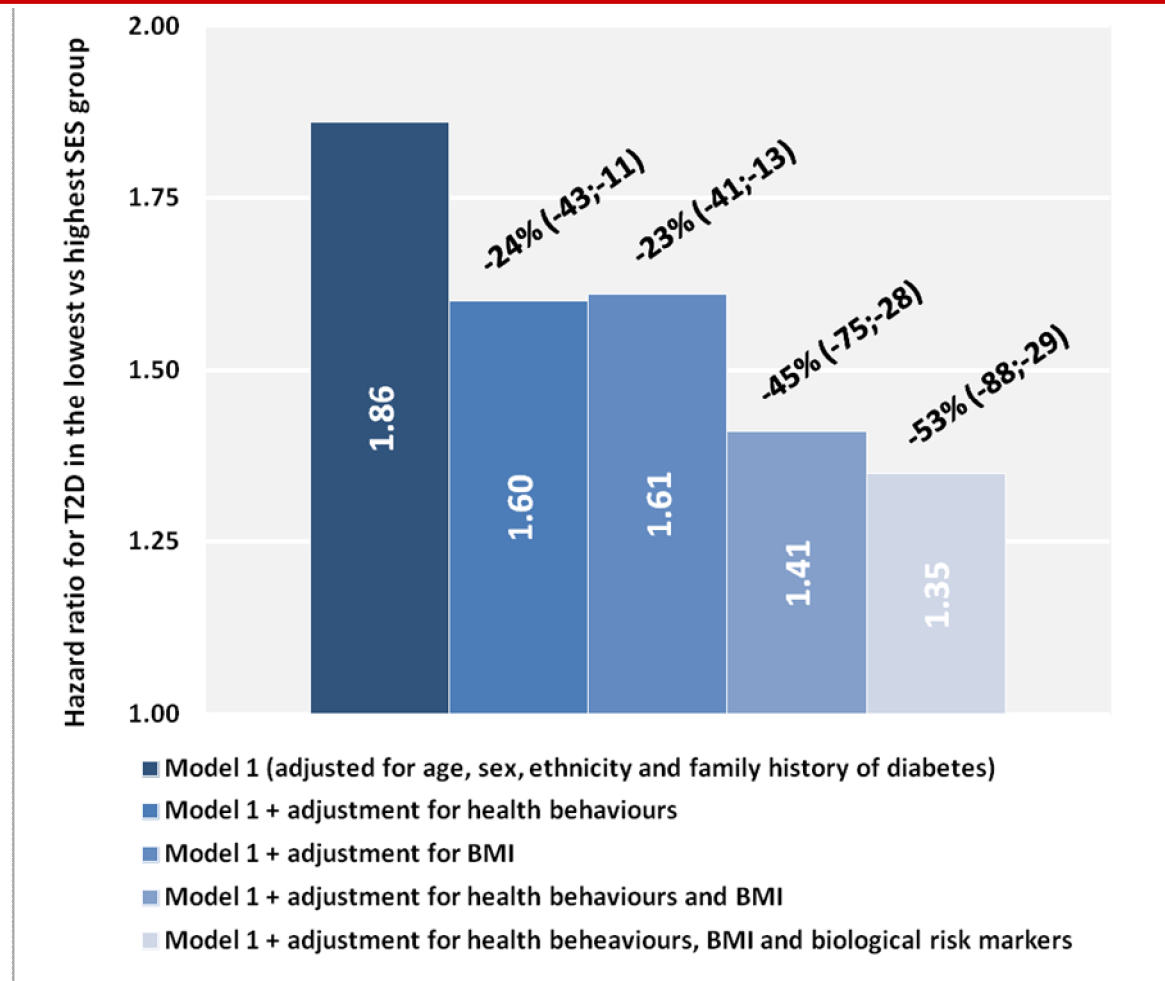
<sup>1</sup> Source: Analysis by London Health Observatory of ONS and GLA data for 2004-08. Diagram produced by Department of Health

# Explaining social inequalities in health



Barton H, Grant M, (2006). A health map for the local human habitat. *Journal of the Royal Society for the Promotion of Health*. 126 (6), p. 252-3.

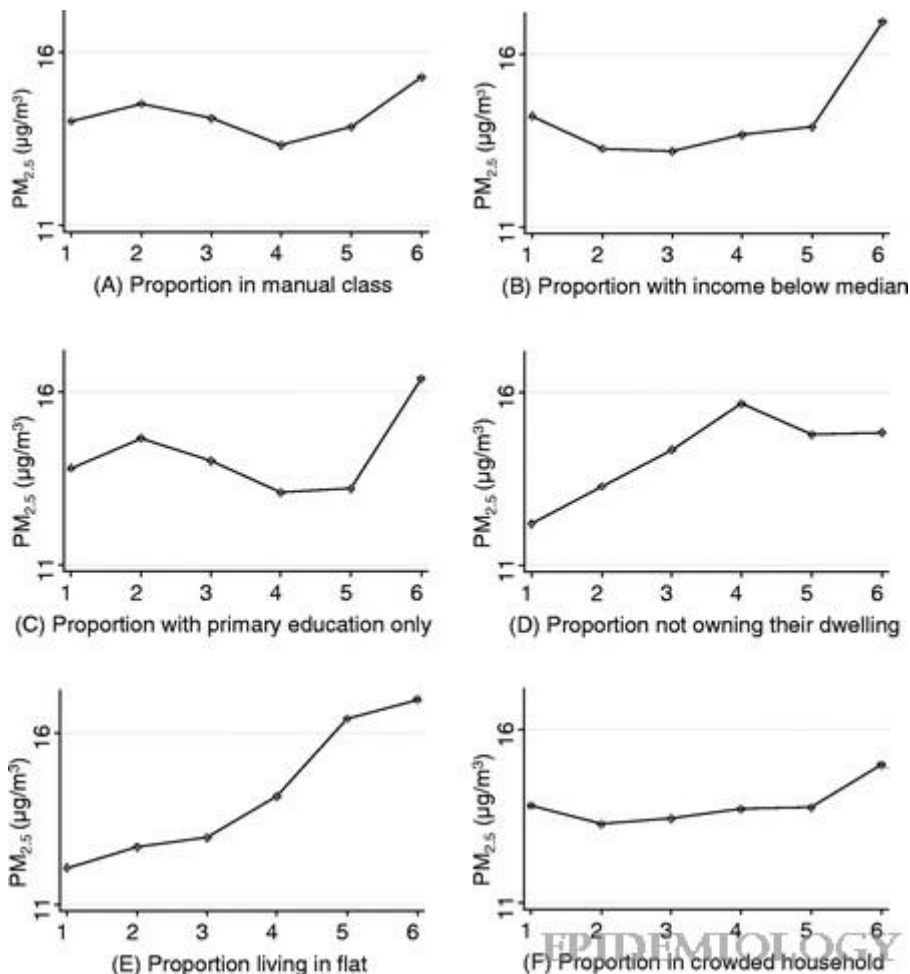
# Behavioral factors and social inequalities in health



Stringhini et al. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. *BMJ* 2012; 345 .

# Environmental factors and social inequalities in health

Concentration of PM<sub>2.5</sub> at place of residence (estimated at neighborhood level) by 6 quantiles of neighborhood level proportion in manual class (A), with income below median (B), with primary education only (C), not owning their dwelling (D), living in flat (E), and in crowded household (F).



# SES and biomarkers

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

Source: Wolfe B, Evans W, Seeman T. The biological consequences of health inequalities (2012). Russel Sage Foundation, New York

# SES and immune system biomarkers

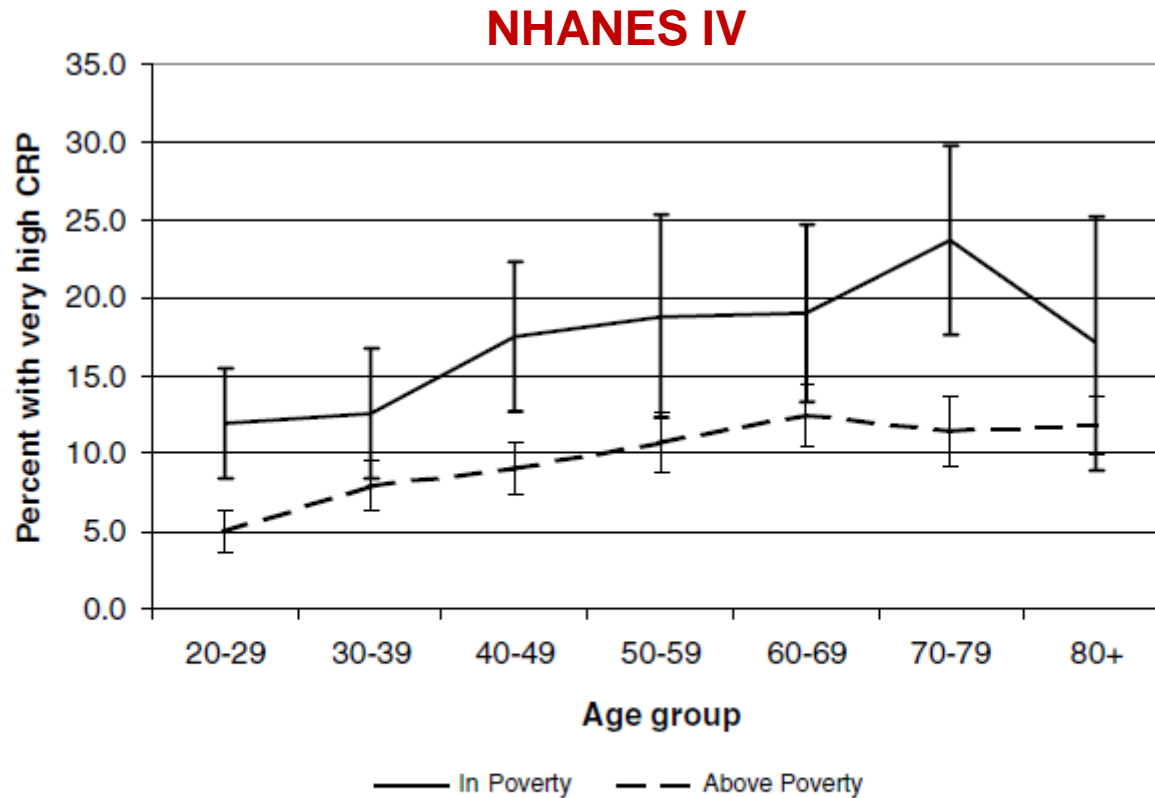
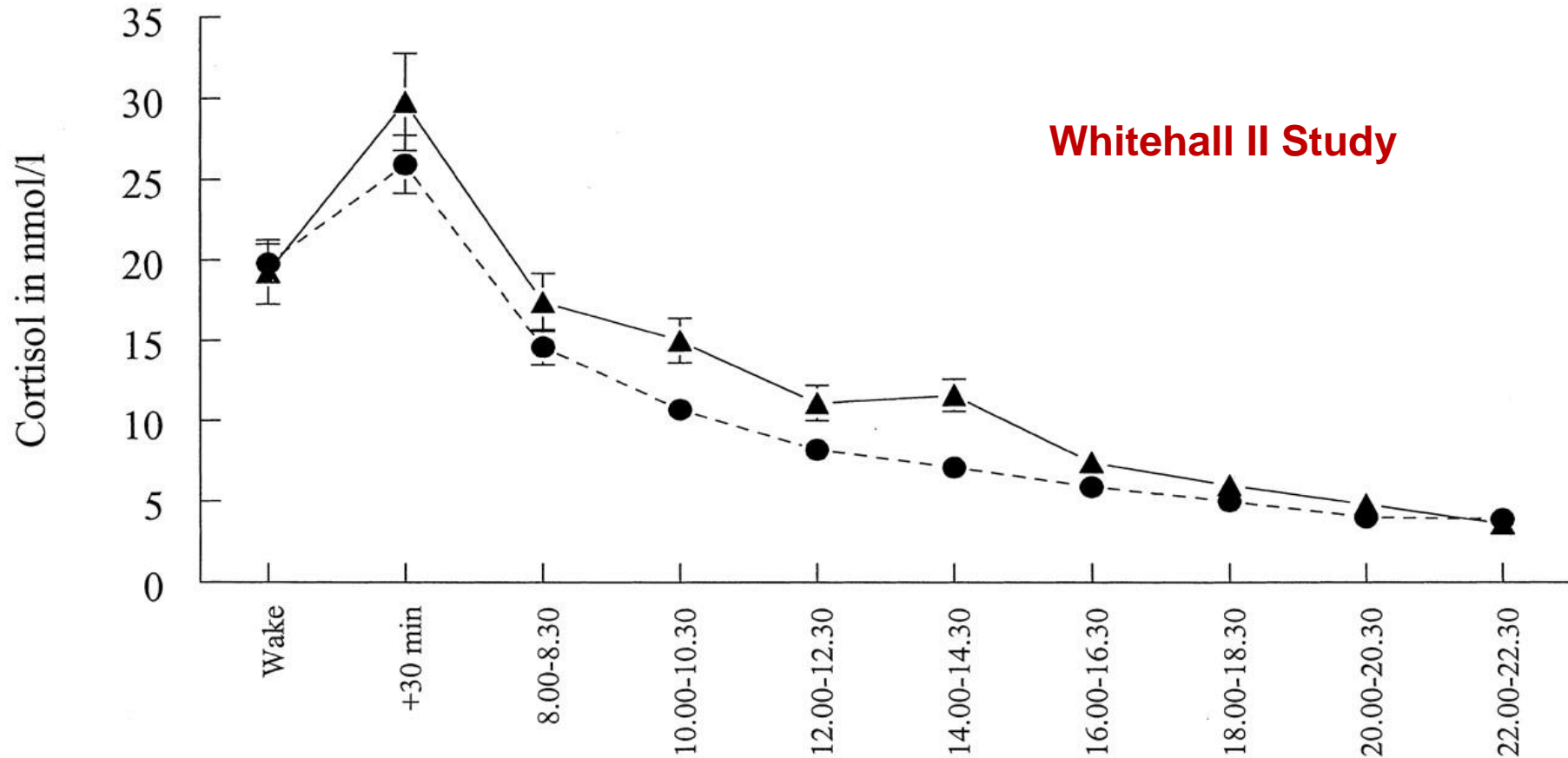


Fig. 1. Prevalence of very high (10+ mg/L) CRP by age group and poverty status with 95% confidence intervals ( $N = 7634$ ).

# SES and neuroendocrine biomarkers

Mean saliva-free cortisol sampled on waking up, 30 minutes later, and then at 2-hour intervals in men from higher (i) and lower (▲) grades of employment. Error bars are SEM.



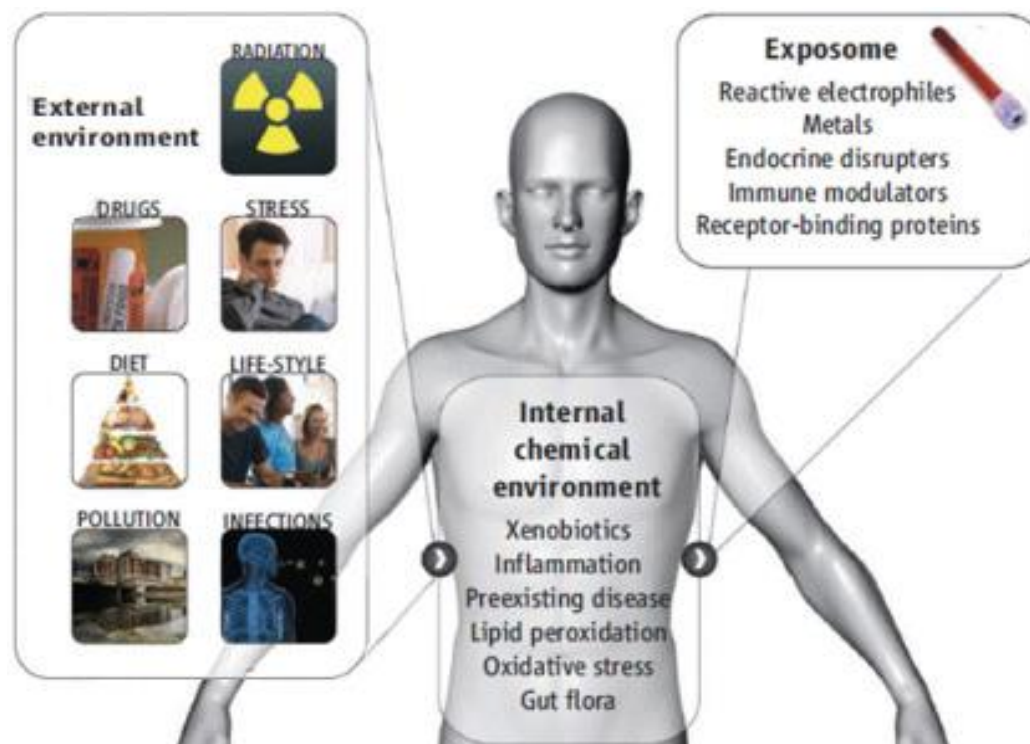
Stephens A et al. Socioeconomic Status and Stress-Related Biological Responses Over the Working Day. *Psychosom Med* 2003;65:461-470



**For >50% cancer the etiology is still unknown**

**How can we identify new risk factors? Relationships between macro-environment and micro-environment**

**The exposome changes paradigms for studying environmental causes of disease**



**S.M. Rappaport and M.T. Smith, Science, 2010: 330, 460-461**

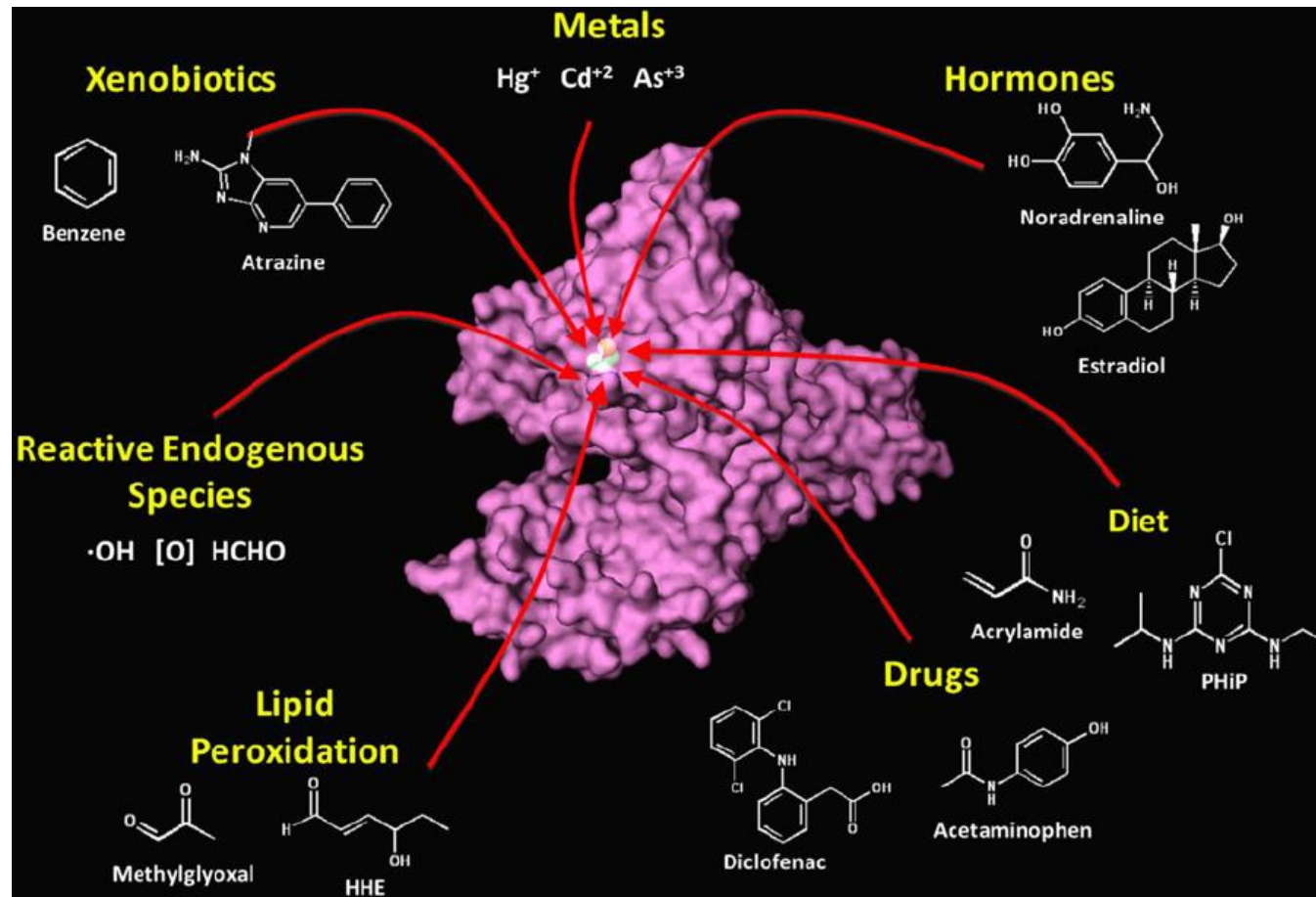
# A study on omics and air pollution - Oxford Street: high exposure, Hyde Park: low exposure

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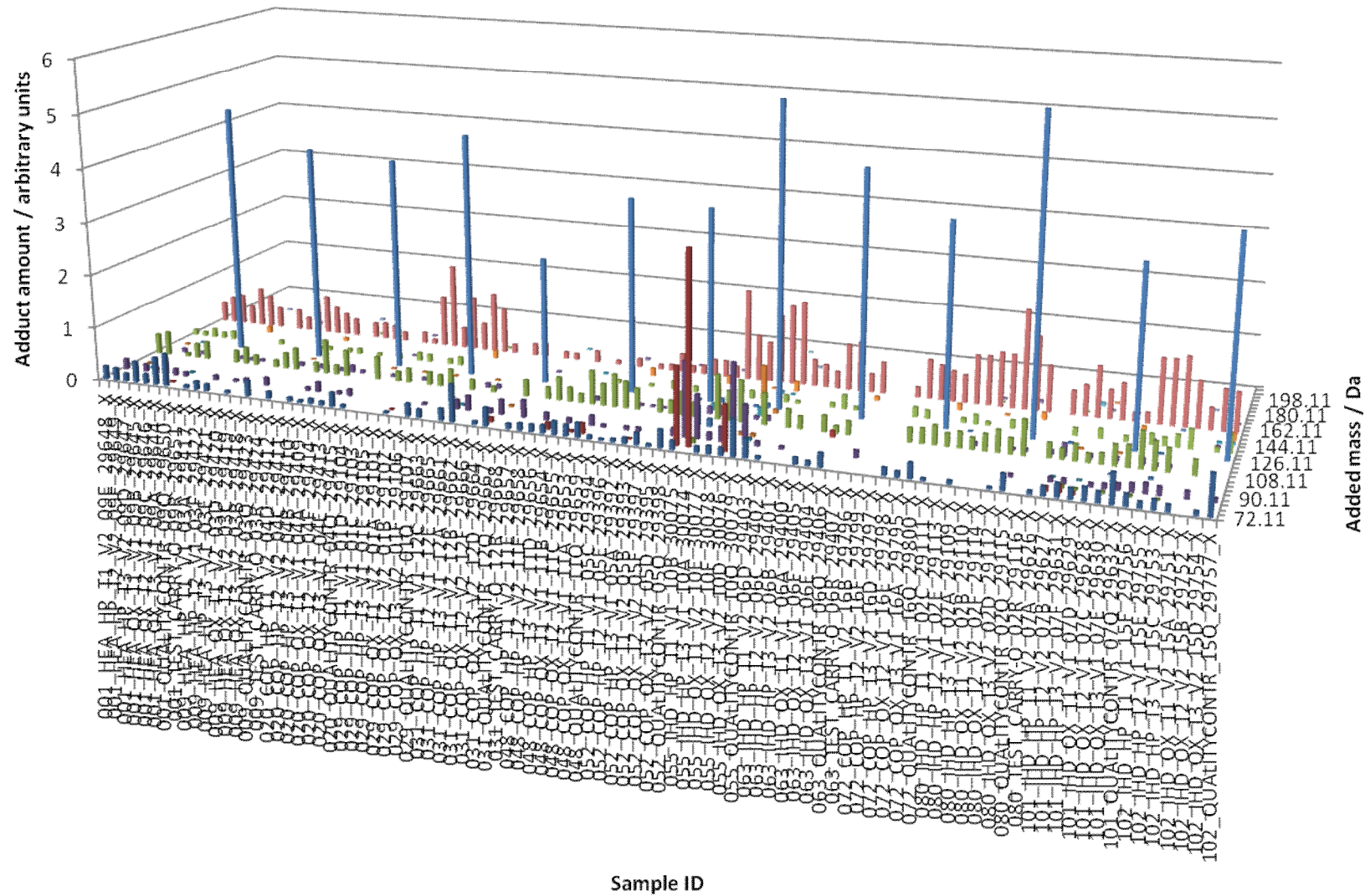
## Serum albumin adducts as biomarkers of exposure

Stephen Rappaport's group (UC Berkeley) have been profiling adducts of human serum albumin. Extended and adapted by David Phillips and George Preston at King's College

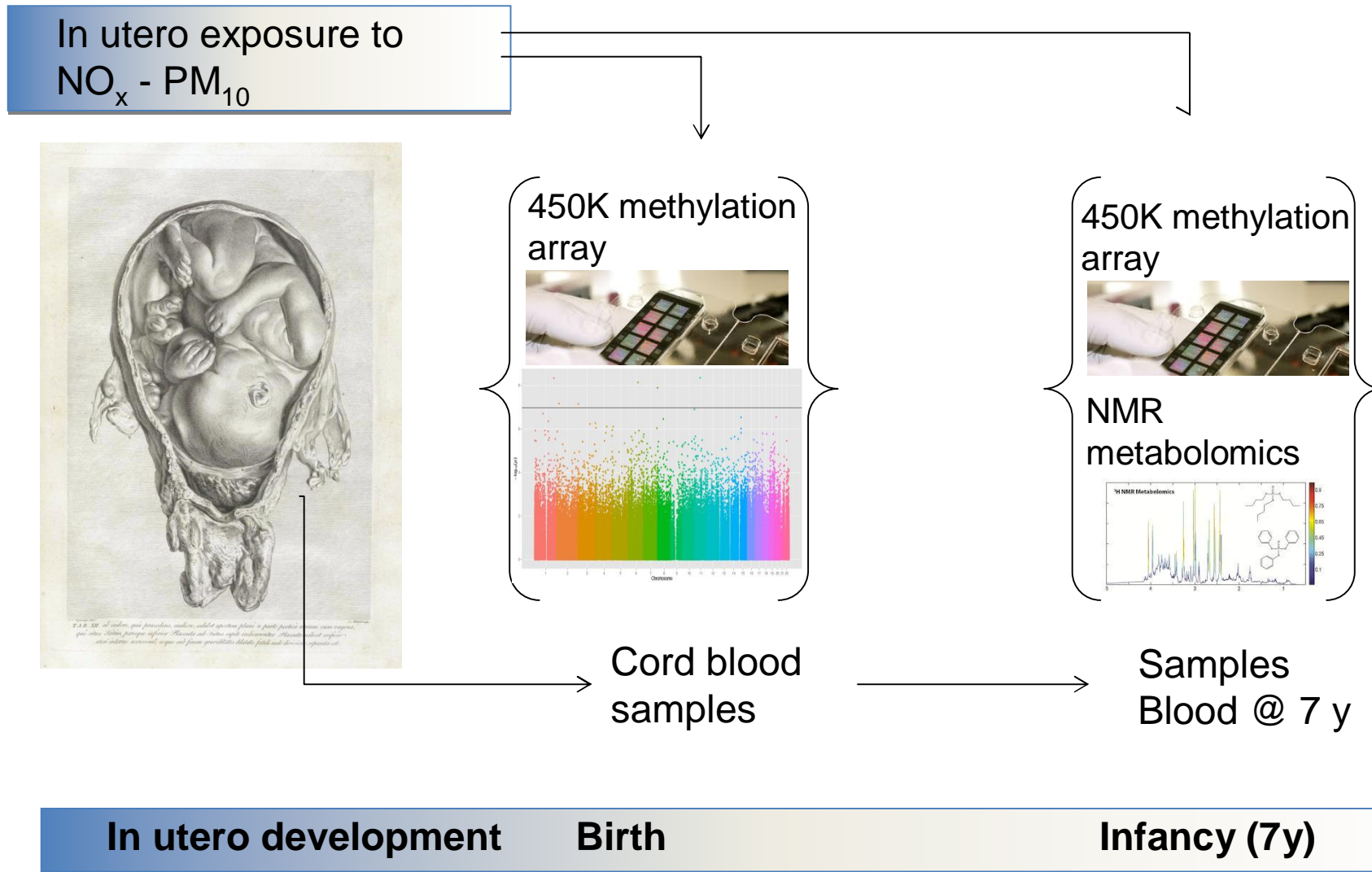


Rappaport, Williams *et al.*, *Toxicol. Lett.*, 2012, **213**, 83-90

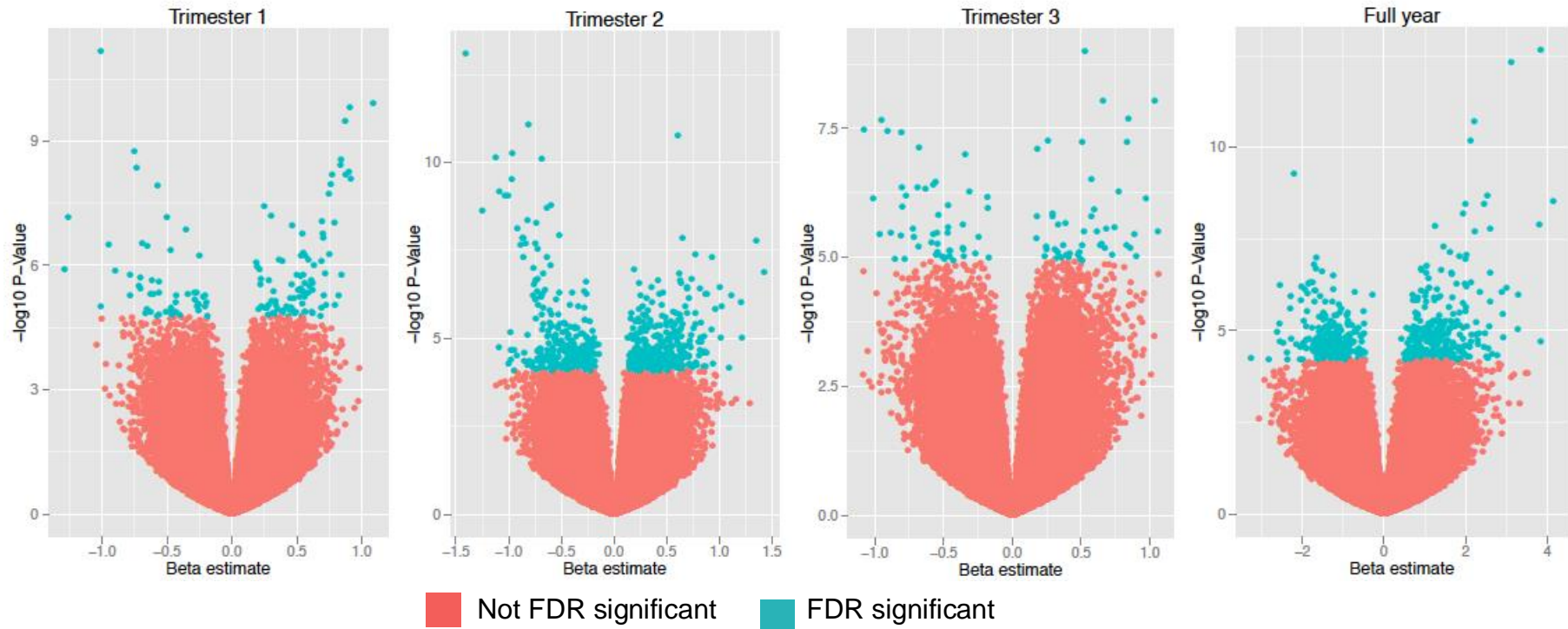
# Oxford Street: preliminary data (13 of 59 subjects)



# Epigenome wide association study of *in utero* exposure to air pollution in ALSPAC: design



## Epigenome wide association study PM10



Number of significantly differentially hypo (-) and hyper (+) methylated loci on the genome

+	93	318	49	228
-	53	369	49	300

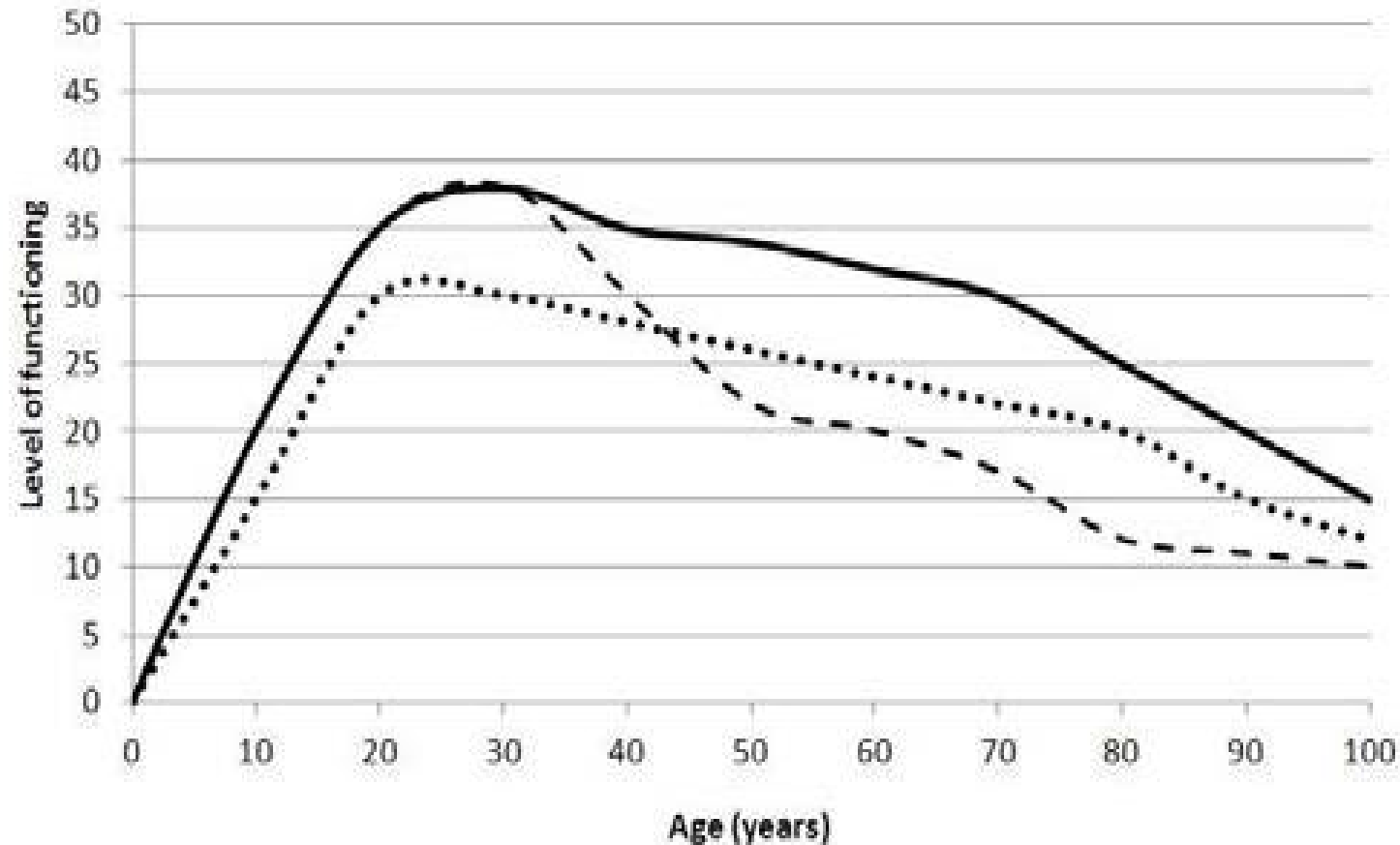
-> PM<sub>10</sub> exposure during trimester 2 shows many associations with methylation loci on the genome



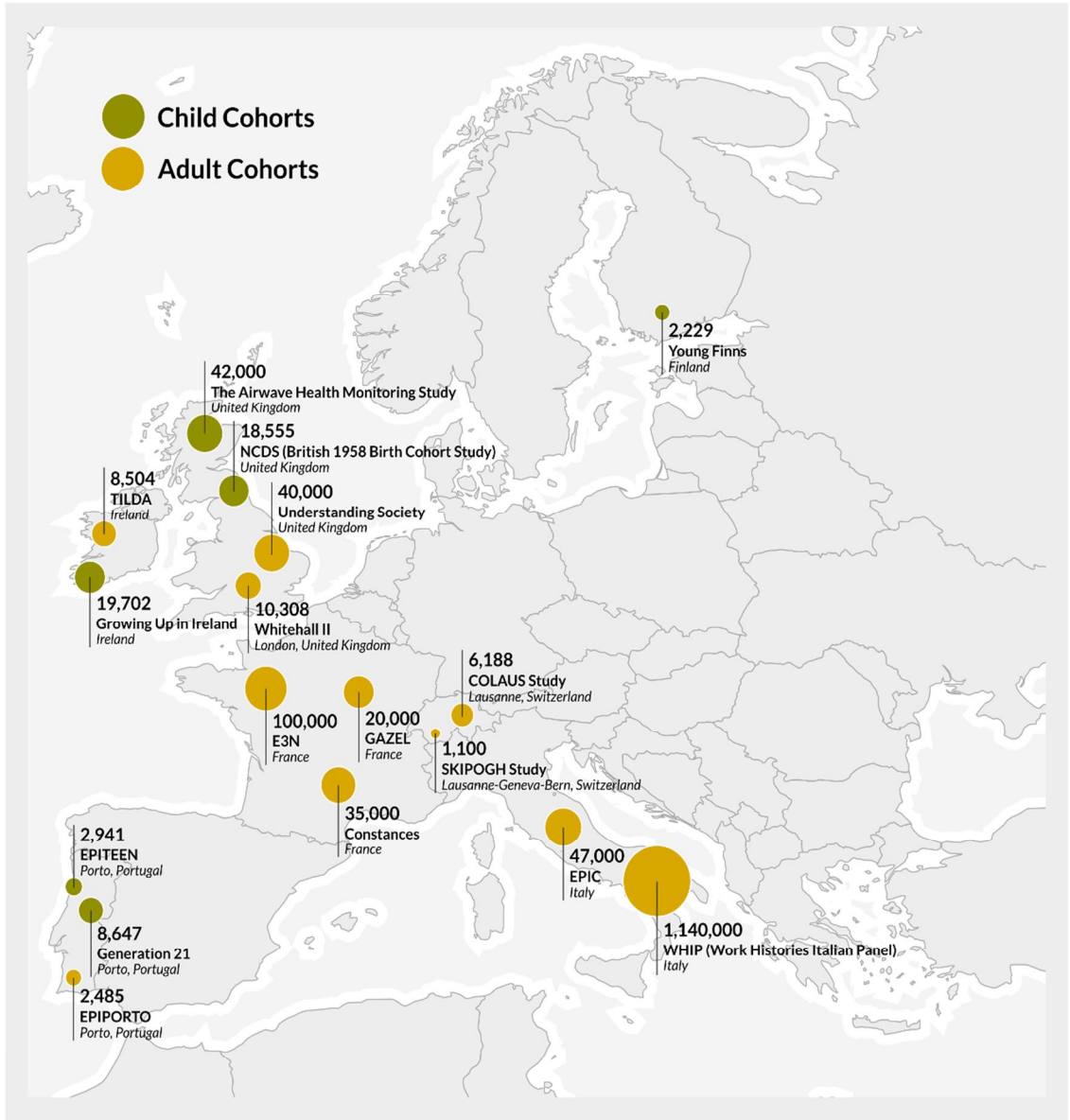
A «socio-molecular» study from  
existing cohorts:  
**LIFEPATH**



We use the revised Strachan-Sheikh (2004) model of life-course functioning (Kuh D 2007; Blane et al, 2013), to describe ageing across the life-course. This model presents ageing as a phenomenon with two broad stages across life: build-up & decline.







# Epigenetics – DNA methylation

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## Epigenetic modifications

Functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Examples of such modifications are DNA methylation and histone modification, both of which serve to regulate gene expression without altering the underlying DNA sequence.



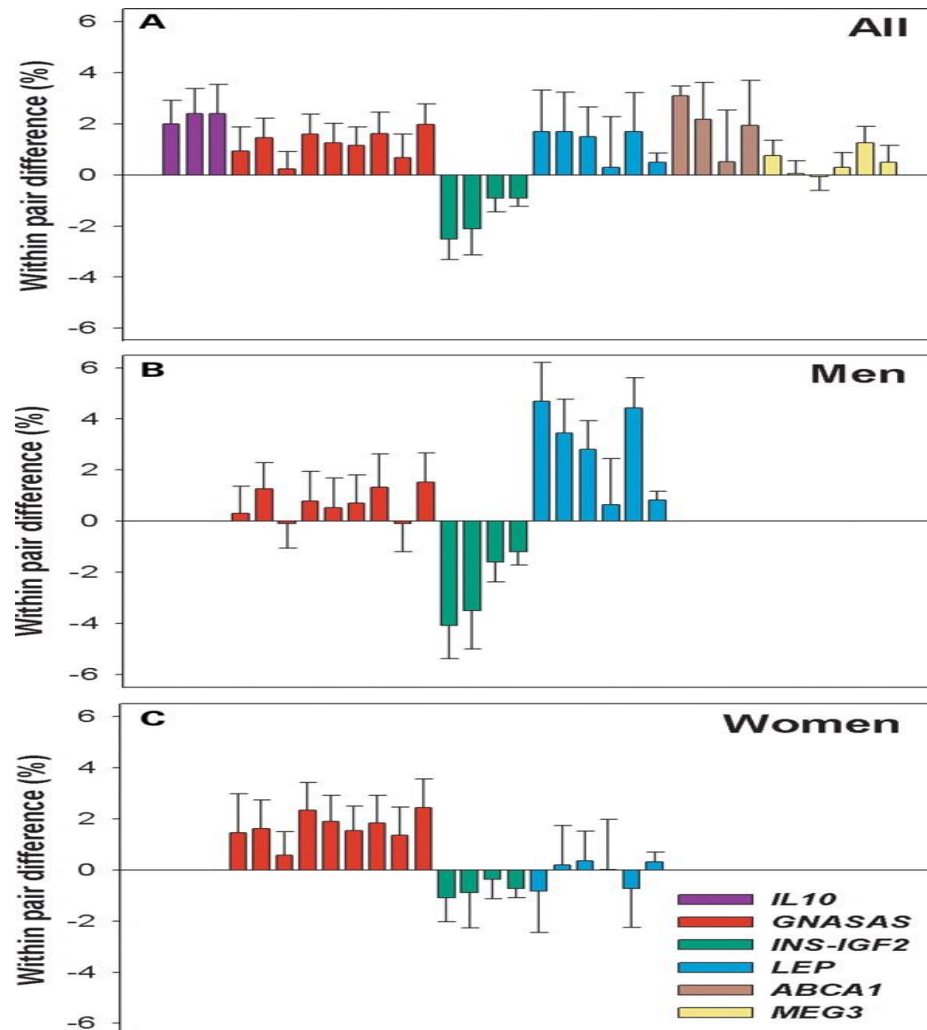
**Gene expression**



**Phenotype**



**Difference in DNA methylation of CpG dinucleotides in siblings discordant for periconceptual exposure to Dutch famine in 1944.**



*“60 individuals pre-natally exposed to famine compared with matched, unexposed siblings*

*“Investigated several genes involved in metabolism*

*“Positive difference indicates higher methylation level among exposed individuals*

# Dominance rank and expression level of pro-inflammatory genes (macaques)

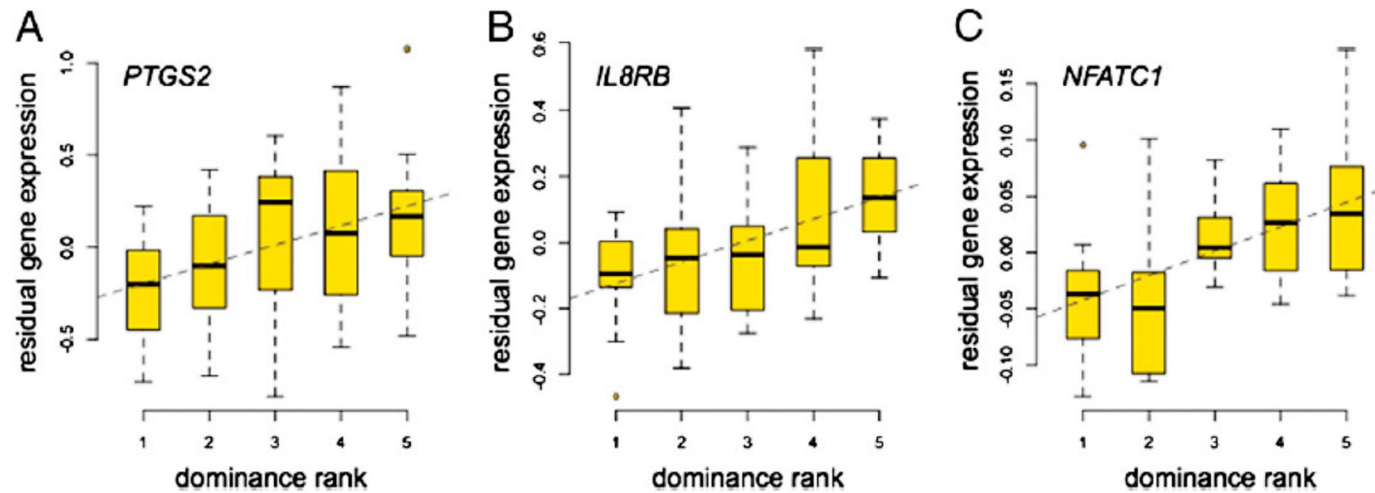


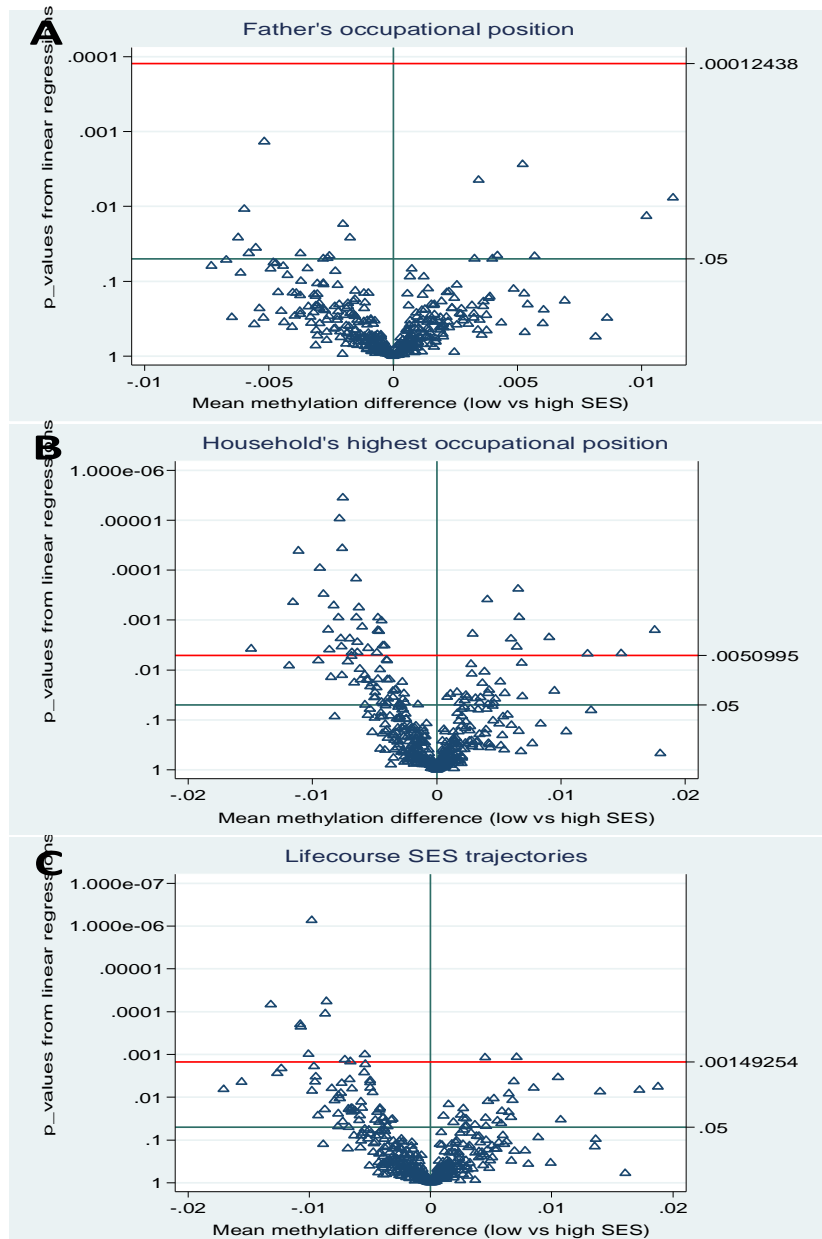
Fig. 2. Rank-gene expression associations among inflammation-related immune genes. Low-ranking females tend to overexpress inflammation-related genes: (A) *PTGS2* ( $P = 0.004$ ); (B) *IL8RB* ( $P = 0.003$ ); and (C) *NFATC1* ( $P < 10^{-3}$ ).

Tung et al. Social environment is associated with gene regulatory variation in the rhesus macaque immune system. *Proc Natl Acad Sci U S A.* 2012 Apr 24;109(17):6490-5.

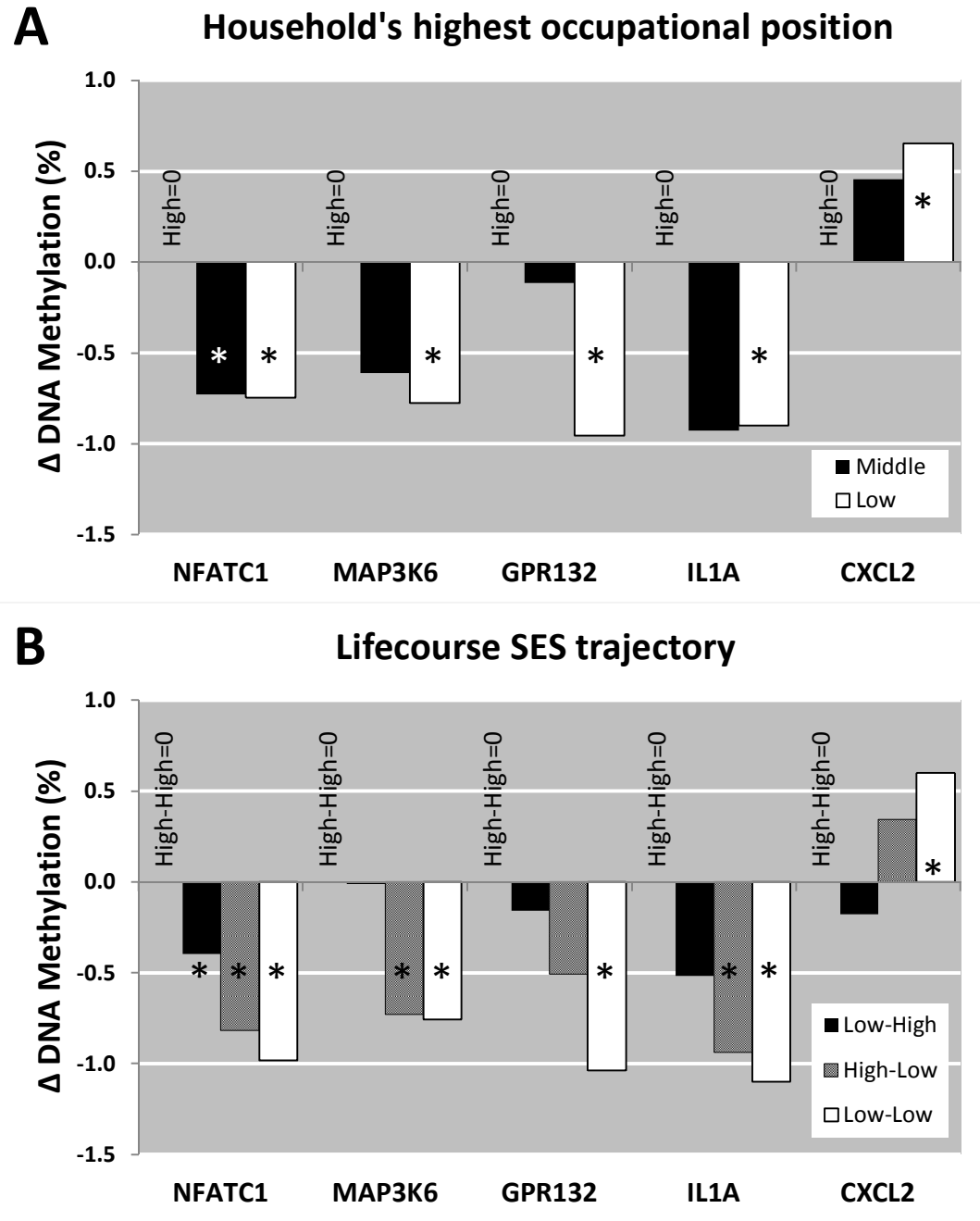
## SES and DNA methylation – EPIC Turin

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- “ Selection of candidate genes based on literature review: NR3C1, IL1A, CCL2, CXCL2, CCL20, GPR132, ADM, OLR1, CREBZF, TNFRSF11A, PTGS2, CXCR2, NFATC1, SAT2, MTHFR, AHRR, IGF2
- “ A total of 599 CpG sites were examined.
- “ Several indicators of socioeconomic status across the lifecourse
- “ Adjustment for potential confounding from lifestyle factors



Indicators of socioeconomic status are associated with DNA methylation of candidate genes. The graphs represent the plot of beta coefficients and p-values from linear regression of CpG sites on socioeconomic indicators, adjusted for age, sex, season of blood collection and disease status. The red line represents the corrected overall critical p-value after a multiple-test procedure (FDR). Data points on or above the red line correspond to rejected null hypotheses (p-values that remained significant after multiple-testing). For household's highest occupational position (B) 26 data points are above the red line; for lifecourse socioeconomic trajectory (C), 7 data points.





## Conclusions

The challenges posed by socio-economic differentials and NCDs require new tools for epidemiology and public health (P Vineis, C Wild. [Global cancer patterns: causes and prevention](#). The Lancet 2014 Feb 8;383(9916):549-57) – we know the causes of less than 50% of cancers

Omic technologies allow us to investigate a range of hypotheses on disease in populations according to the paradigm of the exposome

First proof-of-principle suggests that the exposome approach can be successful in areas as diverse as the impact of SES and environmental pollution