# A conceptual basis for life course biology

Sir Peter Gluckman FRS

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Singapore Institute for Clinical Sciences

Chief Science Advisor to the Prime Minister of New Zealand

LIGGINS INSTITUTE
THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

# Some core issues

- Life course studies have tended to be very siloed
  - Biological
  - Clinical
  - anthropological
  - educational
  - sociological
  - Economic

- Humans are animals that live in a (changing) ecological context where change is driven by the technological capacity of our species, yet the speed of biological change is limited

- When studying multiple aspects of the human condition evolutionary biology provides the one integrating principle on which to integrate biology, behaviour, physical and social environments and take into account the dimension of development

# Fundamental principles of evolutionary medicine (1)

- Our history, as a species, through our particular lineage and through our development, influences our *susceptibility* to disease.
- Selection operates to maximise fitness
- Selection does not operate to maximise health or longevity.
- Fitness is particularly affected by life history traits (eg age of maturation)
- Average human longevity has increased due to techno-cultural factors

# Fundamental principles of evolutionary medicine (2)

- Humans now live in very different ways and in different environments to those where the majority of selective processes affecting the modern human phenotype operated.
- The constraints on evolutionary processes (the speed, substrate or direction of selection, or the scope of plasticity) in the presence of environmental novelty, often of human origin, can lead to ill health.
- Definitions of normality, abnormality and disease are not absolute and are influenced by the environmental context of the individual and the individual variation in phenotype.

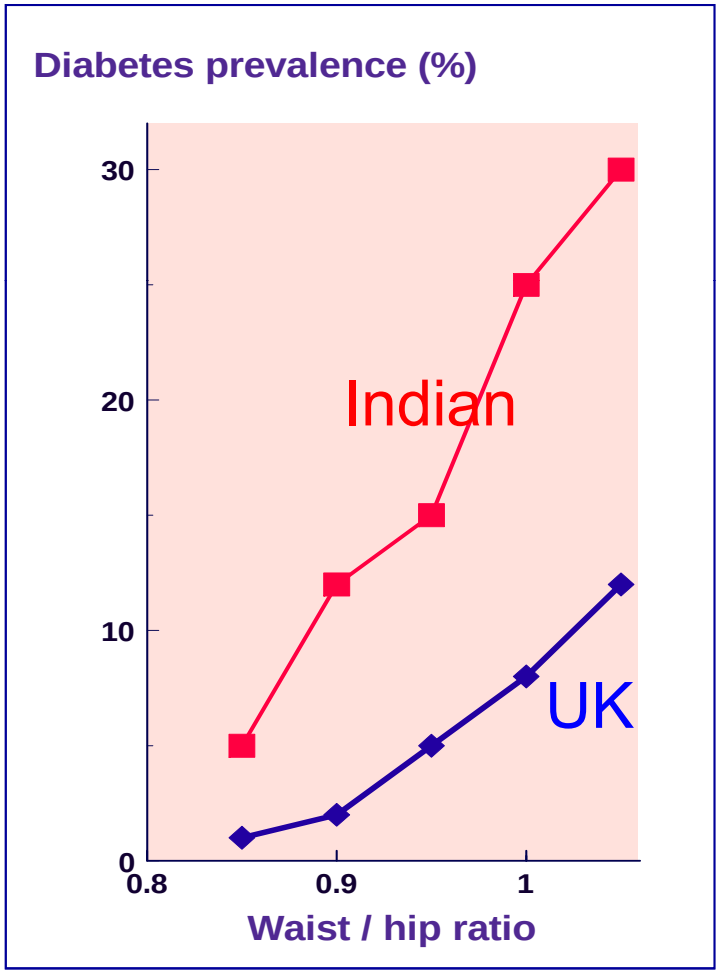
# Context specific definition of normality

- Until 10,000 years ago no human lived on cows milk (in Australia only 250 years ago)
- The C→T mutation appeared 13.4 kb 5' to the start site of the lactase gene in Europeans about 8000 years ago which matches the archaeological evidence for the date of adoption of dairy farming in Europe
- If a person from a non-milk rearing ancestry stays away from milk then they are symptom free
- If however they consume large amounts of milks they feel unwell – they do not have a disease - they are *mismatched* to their (nutritional) environment
- So should we talk about people from the developing world as having lactase deficiency (ie a disease) or should we see them as the "normal" and we as the "abnormal"?
- Adapted and maladapted depend on the circumstance – not on normal or abnormal physiology

# Variable vulnerability

- We all now live in obesogenic environments; the level of change in the environment possible will not take many people (at least in Asia) below the point of metabolic compromise

- There is considerable individual and population variation in sensitivity : why?



# Variable responses to an obesogenic environment

- **Evolutionary reasons** – body weight is defended, time preferences are short for those at risk
- **Differential sensitivity – genetic**
- **Differential sensitivity – developmental**
  - **epigenetic / programming**
  - **hard wiring of appetite control, resting energy expenditure, willingness to exercise**
  - **set points for body weight control**
- **Cultural and societal factors** influencing behaviour

# DOHAD – difficulties in overcoming conventional wisdom

- Three major issues have delayed acceptance of the DOHAD model
  - The focus on birth weight
  - The need for a biologically plausible mechanism
  - Demonstrating the importance of the process

  - All these issues have been addressed
    - It is not about birth weight
    - It involves epigenetics
    - Development is critical

# Responses of the developing organism to environmental cues

- Disruptive to the developmental programme (teratogensis)

- Adjust the developmental programme (developmental plasticity)

  – Potentially adaptive (ie promote fitness) – but can have maladaptive consequences
  – Responses to cues such as altered nutrition

- **Trade-off with immediate benefit:**
  - early adaptive advantage with potentially longer term consequences

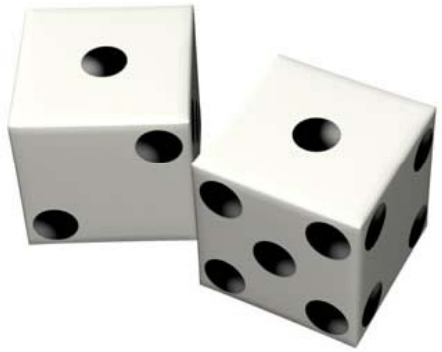
# Changed developmental strategy with delayed but no obvious immediate benefit

- Altered developmental trajectory for potential fitness benefit in later life
- Very common phenomenon across taxa
- Underpinned by epigenetic processes

- The fitness cost of error in prediction is not symmetrical

  - To predict a high nutrition environment and end up in a low nutrition environment will have a greater fitness cost than predicting a low nutrition environment and ending up in a high prediction environment
  - Hence humans have evolved with bias in prediction which is reinforced by the phenomenon of maternal constraint

# Anticipation vs. bet-hedging



- Bet-hedging is a phylogentically old adaptive response to variable environments for organisms which have high reproductive outputs
- Bet-hedging organisms produce multiple offspring with a range of fixed phenotypes, some of which will be well adapted to the future environment
- An asymmetric fitness environment (where the cost of being mismatched varies between environments) favours anticipation (PARs) rather than bet hedging
- Anticipation need not be accurate to be the selected mechanism
- Anticipation is the only possible strategy in monotocous slow producers where each pregnancy represents a high proportion of lifetime reproductive effort

# Developmental pathways to obesity and metabolic disease

- There are three major classes of developmental pathway to an increased risk of adiposity.

  These pathways can coexist especially in developing world

  - **The mismatch pathway**: primed by a less than optimal early life environment

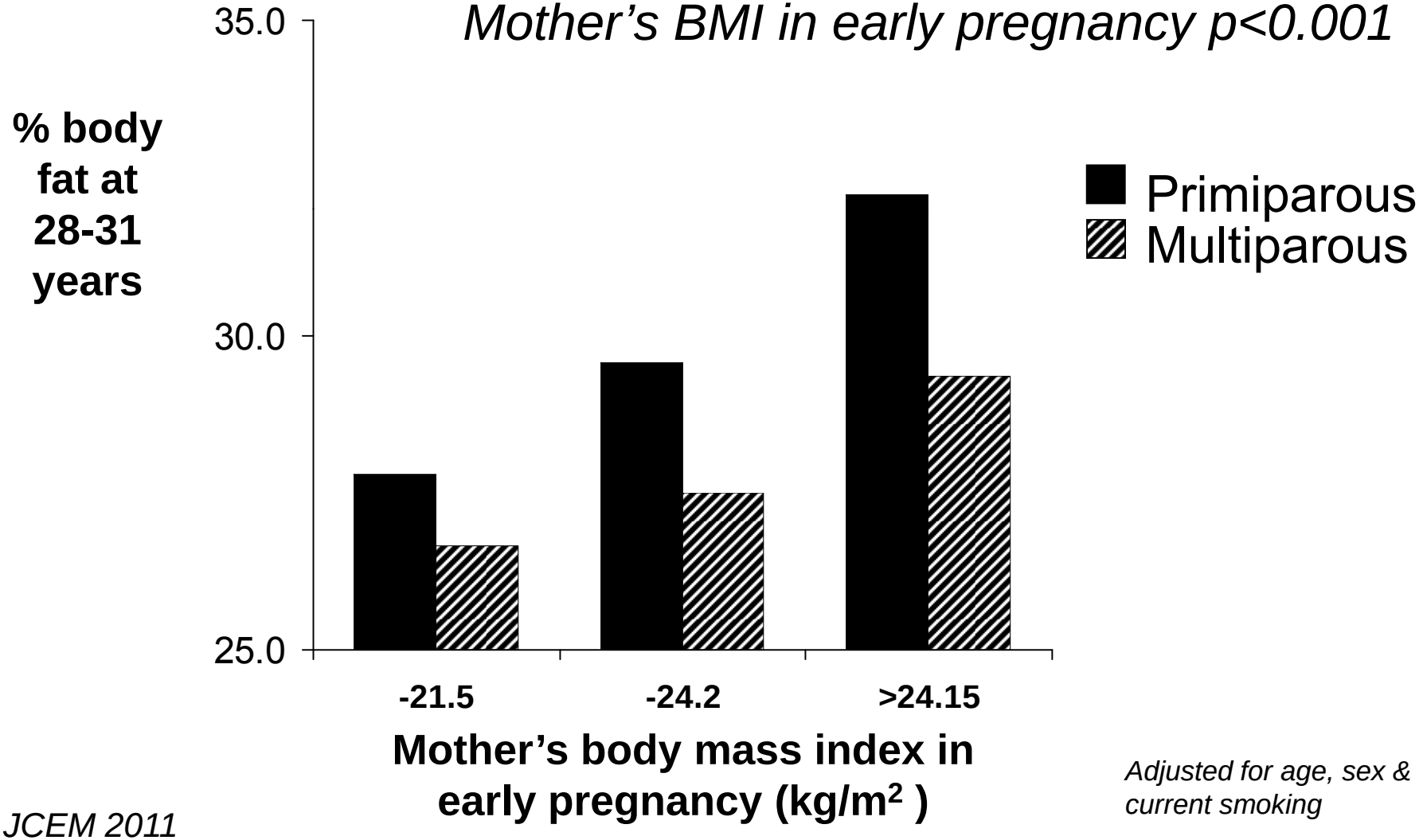
  - **Pathways arising from maternal or infant nutrient excess**
    - Maternal obesity, early formula feeding

  - **Pathways arising from fetal hyperinsulinemia**
    - Gestational diabetes

# The impact of parity

*Parity p=0.004*

*Mother's BMI in early pregnancy p<0.001*




*Adjusted for age, sex & current smoking*

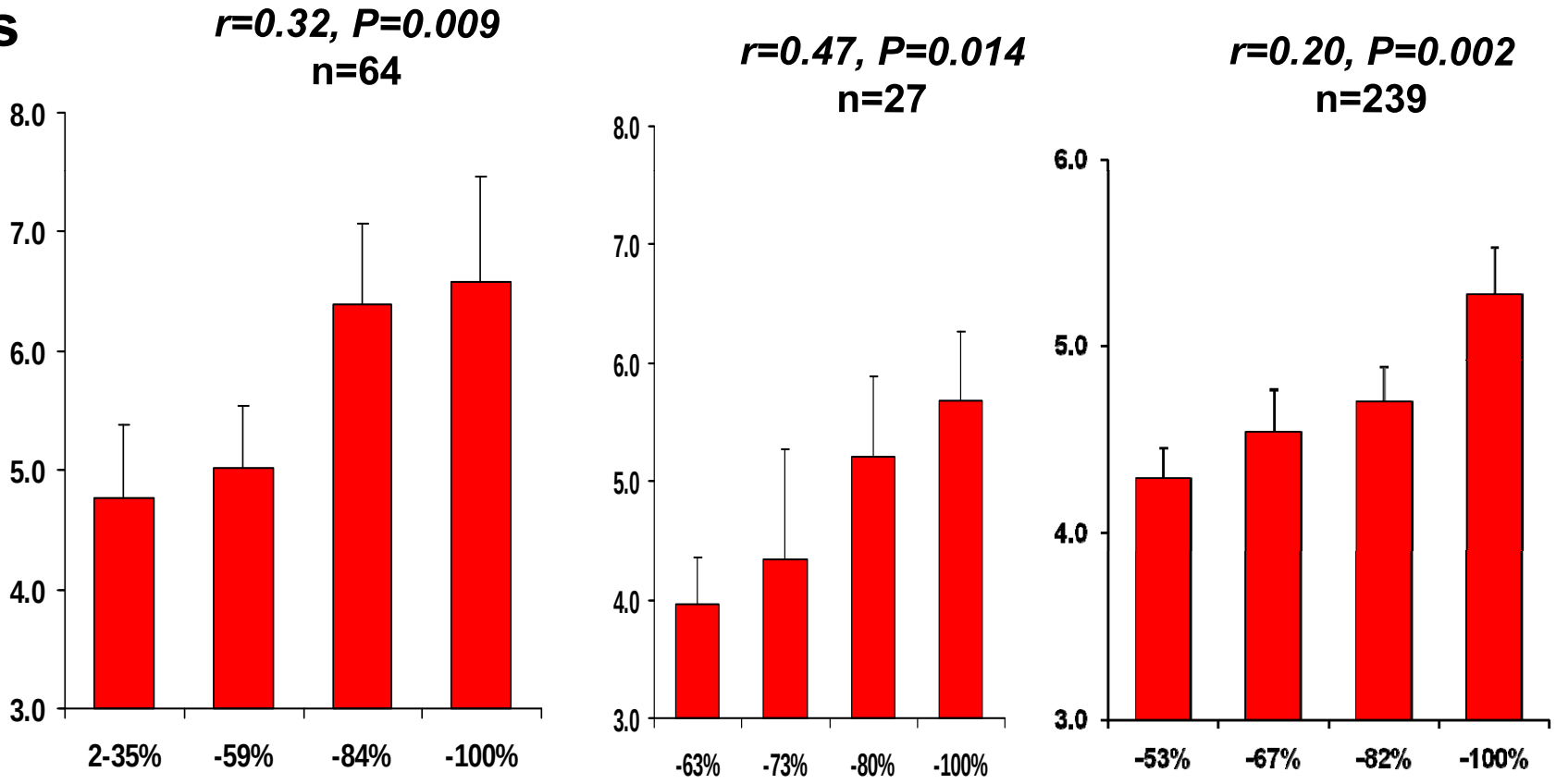
*JCEM 2011*

# Epigenetic state at birth predicts body composition in childhood

**Child's fat mass** (kg)

PAH study children aged 9 years

SWS children aged 6 years



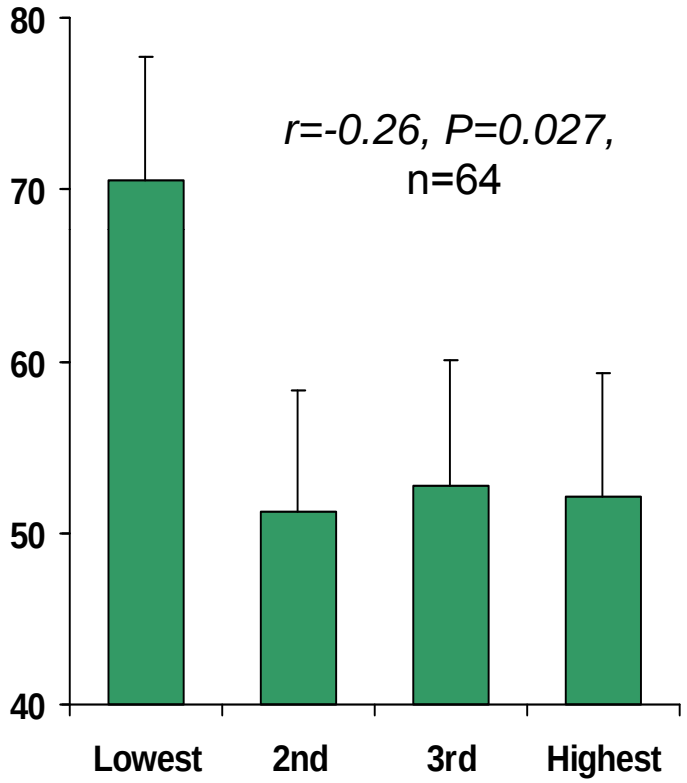

**Umbilical cord RXRA Methylation CpG 2/13**

Godfrey at al 2011

*Values are means + SEM*

# Low maternal carbohydrate intake in early pregnancy associated with higher RXRA gene promoter methylation

Umbilical cord RXRA: methylation CpG 2/13




Maternal carbohydrate intake in early pregnancy (quartiles)

*N.B. No association with mother's BMI or offspring birthweight*

Godfrey at al 2011

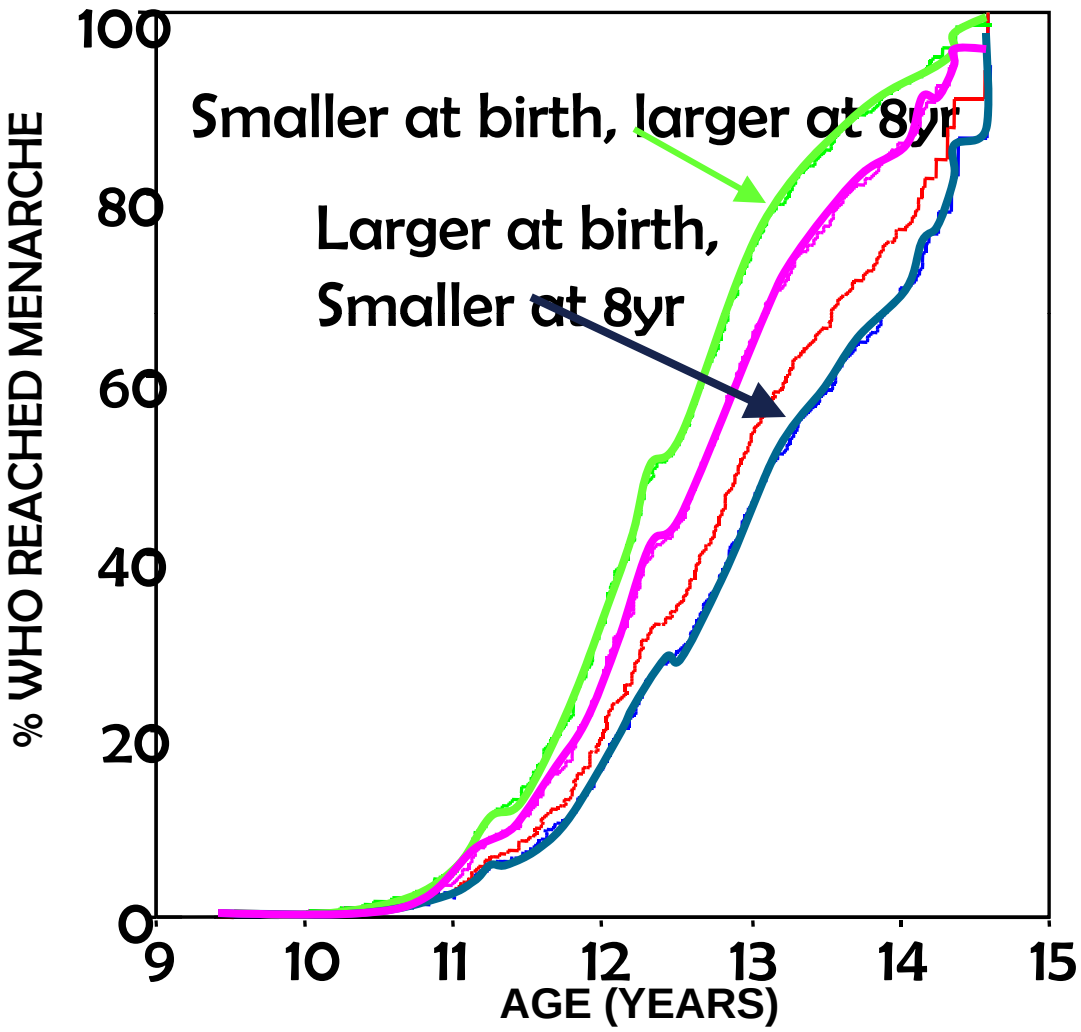
# Girls who were smaller at birth but larger at 8 years reach menarche earliest

*Smaller* at birth
Larger at 8yr

*Larger* at birth
Larger at 8yr

*Smaller* at birth
Smaller at 8yr

*Larger* at birth
Smaller at 8yr

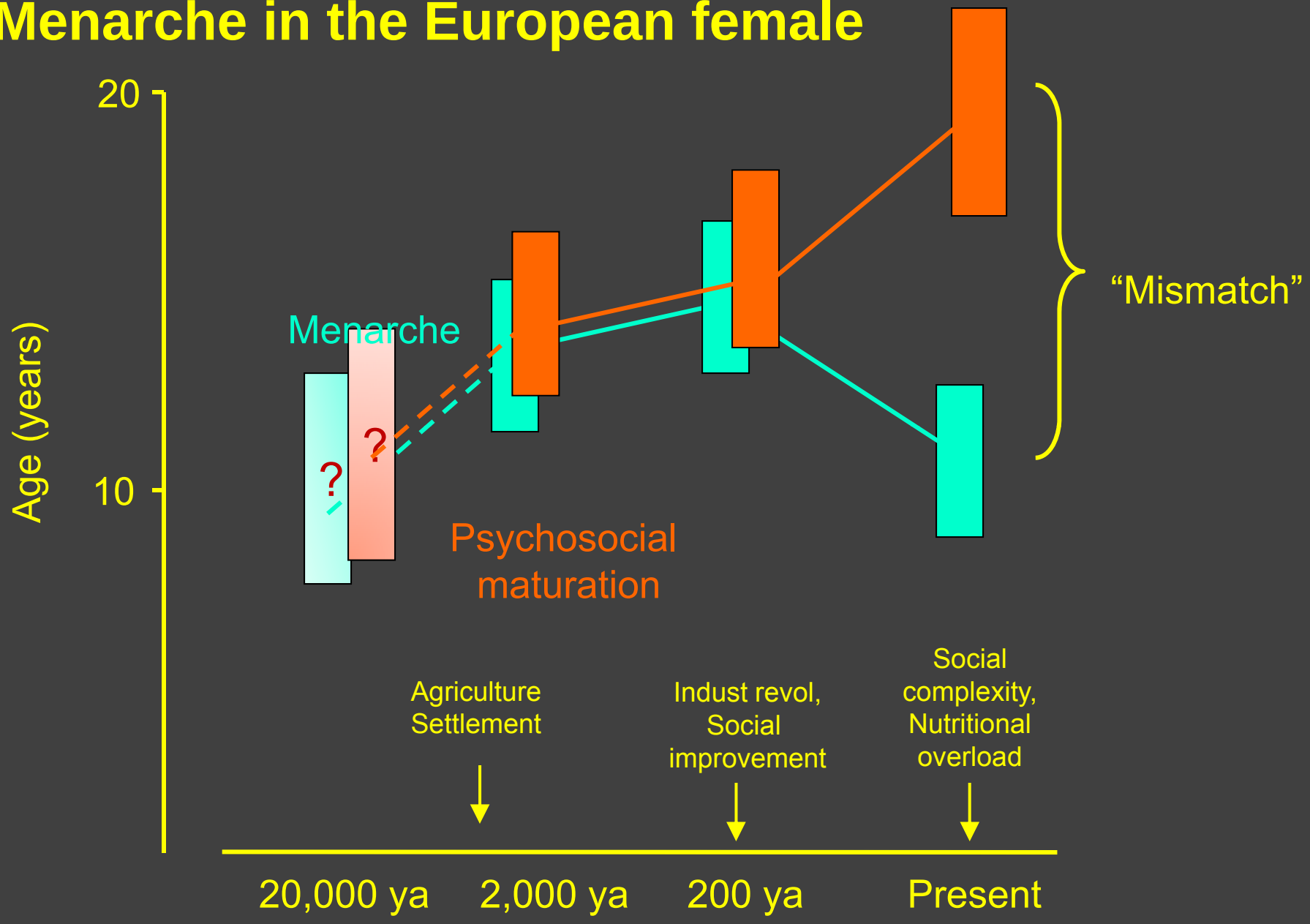



From Sloboda et al. J Clin Endocrinol Metab 2007; 92:46-50

# Post-pubertal adolescence is an evolutionary novelty

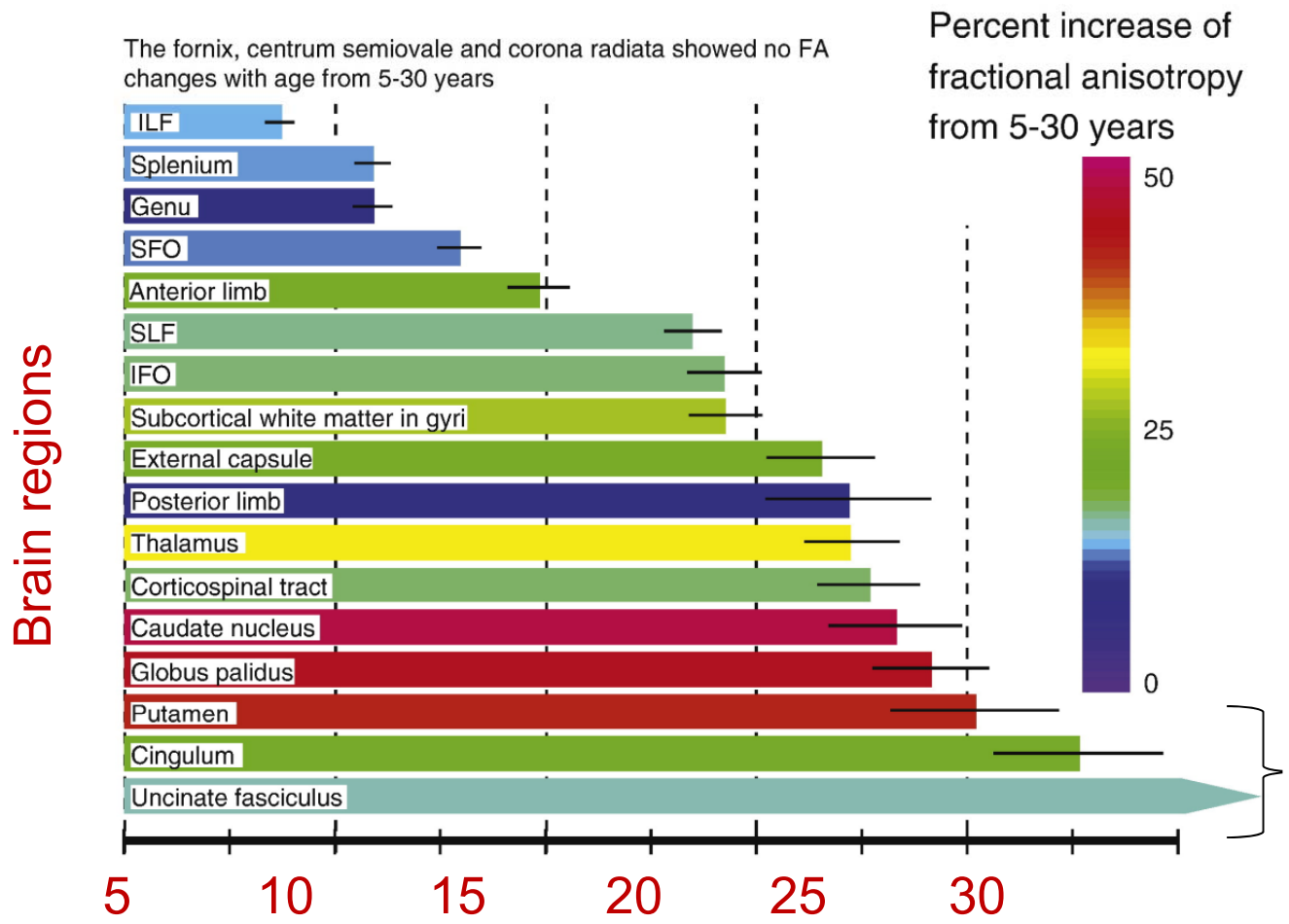
- Puberty is the process of biological maturation
- Adolescence is the process of attaining social recognition as an adult
- Prolonged post-pubertal adolescence is a novel phase of life

# Menarche in the European female




*Gluckman & Hanson (2006) Trends Endocrinol Metab*

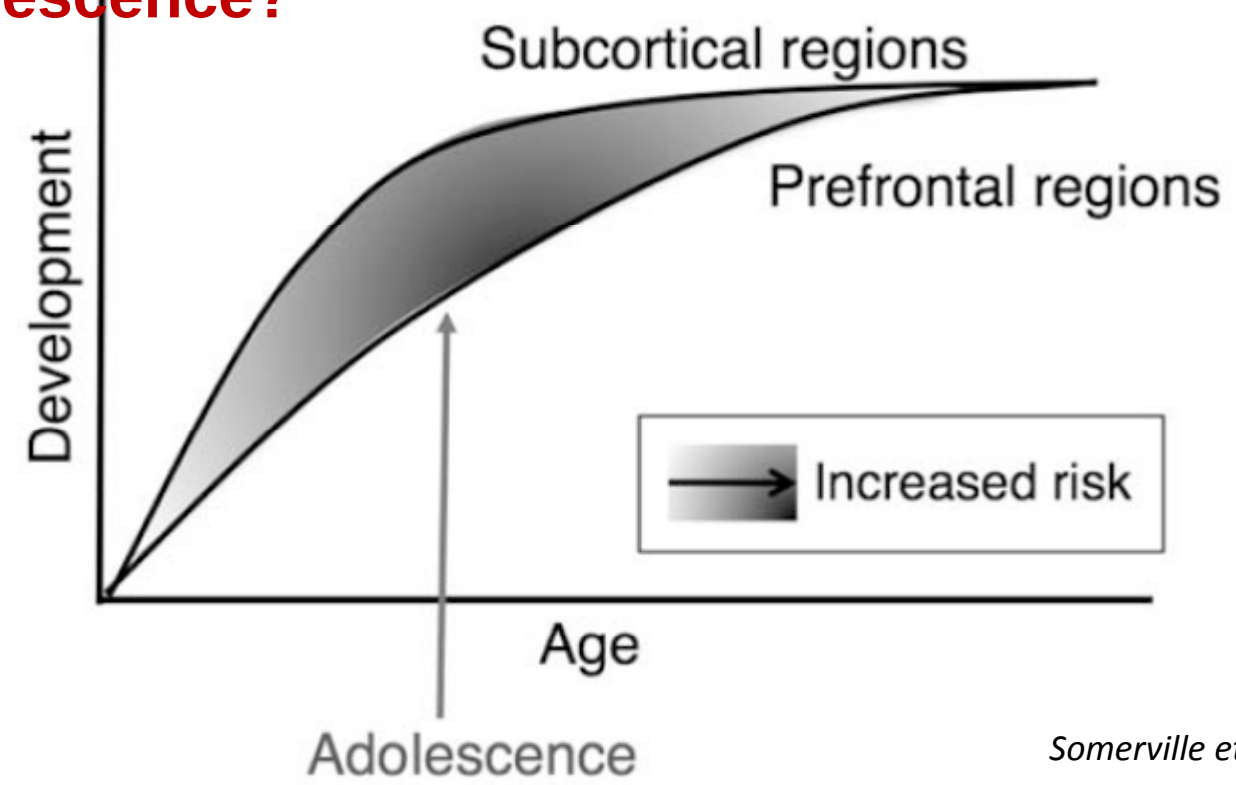
# White matter and axonal organisation




Frontothalamic pathways

*Lebel et al. (2008) NeuroImage*

# What are the consequences of a longer adolescence?




*Somerville et al. 2010 Brain Cognition*

- Subcortical regions modulating emotions mature earlier than prefrontal regions mediating cognitive/impulse control
- Imbalance is thought to account for the biased emotional and incentive-based behaviour of adolescence

# Possible explanations

- Brain maturation has always taken that long – but advanced skills not relevant in a simpler society – an exposed mismatch
- Takes longer to learn
- Cultural practices have slowed brain maturation

# Males – early versus average

| | |
|---|---|
| • Bad health | 1.9 times higher |
| • Functional symptoms | 2.2 times higher |
| • Victimisation | 1.7 times higher |
| • Sexually active | 1. 8 times higher |
| • Smoking | 1.8 times higher |
| • Drunk in last 6 months | 1.4 times higher |
| • Cannabis | 1.8 times higher |
| • Illegal drugs | 2 times higher |
| • Depression | 2.1 times higher |
| • Suicide attempts | 4.9 (3.0-8.1) times higher |

All $p<0.001$

SMASH study: Michaud et al 2001

# Contingent developmental cues

- Critical window effects mean that cues may have different implications at different stages in development
  - Nutrition and longevity
  - Nutrition and puberty
  - Stress and puberty

- Because the phenotype is dependent on past experience, past experience may change the magnitude, direction of effect and significance of a later environmental exposure

  - acting through epigenetic mechanisms, directly or indirectly

# Epigenetic effects on phenotype

- **Within the life course**
  - Particularly induced in early life
  - Often induced by maternal state (parental effects)
    - direct induction
    - recreation of inducing niche

- **Across generations**
  - Trans-meiotic epigenetic inheritance ?
  - Grand- maternal effect (the gamete of $F_2$ is exposed to the environment created by $F_0$)

# The evolution of epigenetics

The same biochemical mechanisms (DNA methylation, histone modifications etc) are co-opted by evolution for multiple mechanisms

- Gene dosage control – prokaryotic fusion
- Transposon silencing – eukaryotes
- Cell differentiation – essential for metazoan development
- Developmental plasticity – insects to mammals
  - Polymorphisms (discontinuous phenotypes eg female bee worker/queen)
  - Continuous phenotypes in response to developmental cues (the reaction norm)
- Chromosomal sex determination – birds, mammals
- Parental imprinting – eutherian mammals and marsupials

# The role of epigenetics in evolution

- Evolutionary transitions
  - complexity – metazoa
- **Handle variable environments**
  - Polyphenisms
  - **Adaptive developmental plasticity**
- ? handle genetic variation - canalisation
- ? biased mutation
  - role in genetic accommodation

# Multiple systems of inheritance need to be incorporated into population studies

- Genomic
- Cultural
  eg shared environment, assortitive mating
- Trans-meiotic – epigenetic inheritance
  eg microRNAs ??
- Parental effects mediated through epigenetic change
- Grandparental effects mediated through epigenetic change
- Niche reconstruction leading to regeneration of the developmental cue and thus of the epigenetic change in next generation

# Beyond the gene-environment interaction

- The concept of genotype-environmental interaction is rendered problematic by understandings of developmental plasticity, phenotypic determination and epigenetics.

- The environment interacts with the whole organism's phenotype which is informed by the developmental history and epigenotype

- A new phenotype - environment model needs to be developed taking into account multiple forms of inheritance and different types of epigenetic induction, the latent effect of epigenetic change and the changing significance of the environment across the life course

- The concept of genotypic driven evolution is now being supplemented by the evo-devo model of phenotypic driven evolutionary processes
  - Choice driven selection (including sexual selection), Baldwin effects, genetic accommodation, epigenetic bias in mutation

# Dying young and living fast: variation in life history across English neighborhoods

**Daniel Nettle**
Centre for Behaviour and Evolution, Institute of Neuroscience, Newcastle University, Henry Wellcome Building, Framlington Place, Newcastle, NE2 4HH, UK

Where the expected reproductive life span is short, theory predicts that individuals should follow a "fast" life-history strategy of early reproduction, reduced investment in each offspring, and high reproductive rate. I apply this prediction to different neighborhood environments in contemporary England. There are substantial differences in the expectation of healthy life between the most deprived and most affluent neighborhoods. Using data from the Millennium Cohort Study ($n = 8660$ families), I show that in deprived neighborhoods compared with affluent ones, age at first birth is younger, birthweights are lower, and breastfeeding duration is shorter. There is also indirect evidence that reproductive rates are higher. Coresidence of a father figure is less common, and contact with maternal grandmothers is less frequent, though grandmaternal contact shows a curvilinear relationship with neighborhood quality. Children from deprived neighborhoods perform less well on a verbal cognitive assessment at age 5 years, and this deficit is partly mediated by parental age and investment variables. I suggest that fast life history is a comprehensible response, produced through phenotypic plasticity, to the ecological context of poverty, but one that entails specific costs to children. *Key words:* birthweight, breastfeeding, grandmothering, humans, life-history theory, parental investment, reproductive strategies. *[Behav Ecol 21:387–395 (2010)]*

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