CCSR
The Cathie Marsh Centre for Census and Survey Research

The challenges and benefits of interdisciplinary working

Frailty, resilience and inequality in later life

MICRA PhD conference
Manchester
15th March 2013

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fRaill

Structure

1. What is interdisciplinary working and why do it?
2. Case study - Frailty, resilience and inequality in later life project
3. Risks and challenges
4. How to do it
5. Conclusions

What is interdisciplinary research?

- Interdisciplinary research integrates knowledge from two or more disciplines to solve a common research goal (sum is more than the parts.
- Multidisciplinary research is a non-integrative mixture of disciplines working in parallel or in sequence

- Many of the processes that we study are complex
- Necessitate an interdisciplinary approach that moves beyond traditional disciplinary (and multidisciplinary) approaches.

"We are not students of some subject matter, but students of problems. And problems may cut right across the borders of any subject matter or discipline." Karl Popper

Why do it?

Strategic motivations

- Funding opportunities
- Availability of new data or increasing computational capabilities
- Dissemination of research and research profile

Or something with intrinsic value

- The complexity/multidimensionality of processes cannot be grasped within single, or even multi-disciplinary perspectives.
- Leading to unique knowledge
- Placing complexity and a broad understanding at the centre of enquiry

Case study: Frailty, Resilience and Inequality in Later Life

- Concern with inequalities in later life, using concepts of frailty and wellbeing to understand the patterning and drivers of such inequalities.
- How to define and measure frailty and wellbeing
- Examine the contribution of a range of factors to wellbeing and frailty, and inequalities in these outcomes.
- **An interdisciplinary approach** to build an understanding of the connections between genetic, metabolic, biological, psychological and social factors.
- **A life-course approach**
- **A comparative approach**

fRaill team

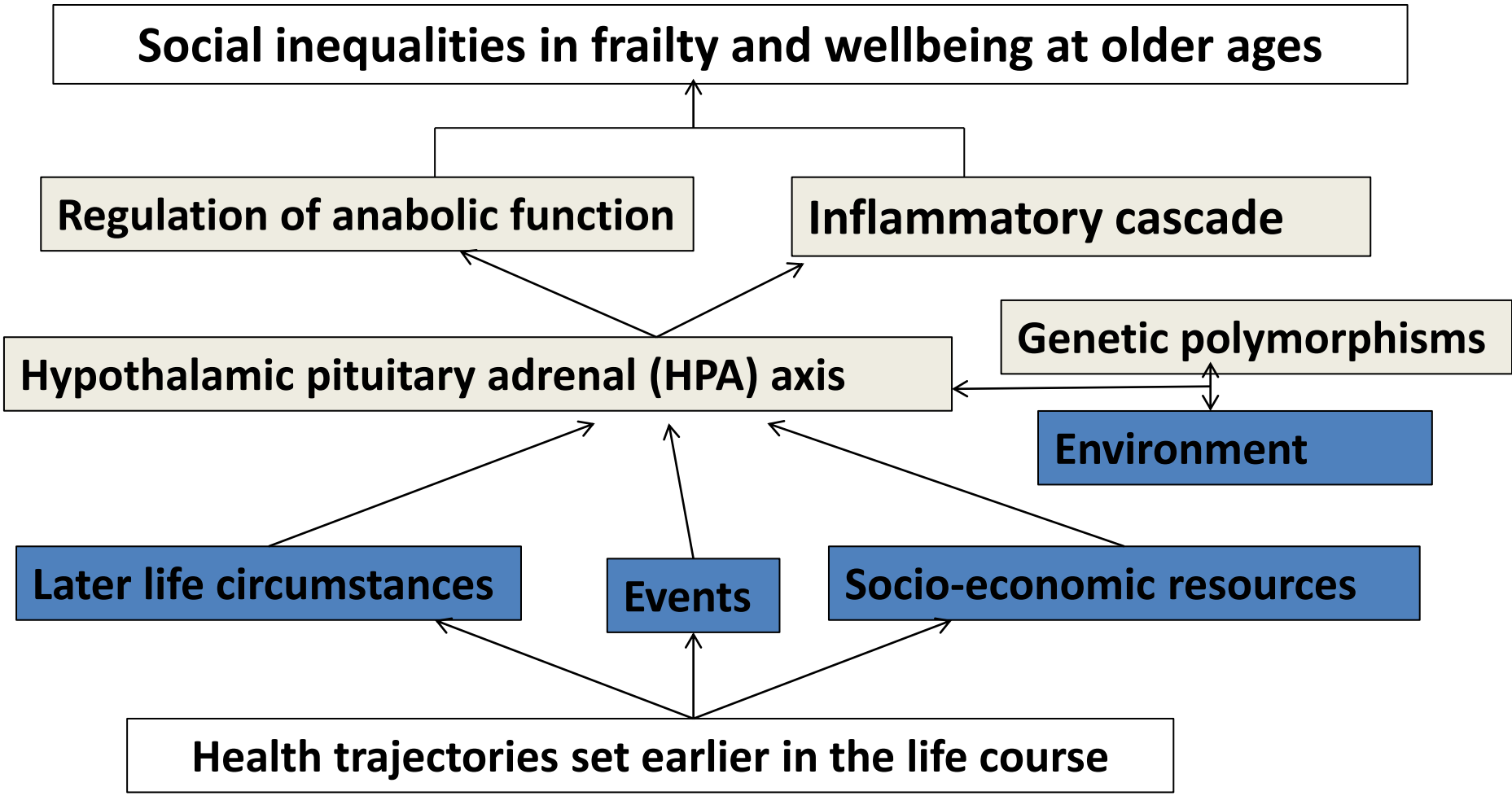
Principal investigators

- James Nazroo –Sociology
- Alistair Burns – Psychiatry
- Tarani Chandola – Medical Sociology
- Gindo Tampubolon – Social Statistics
- Neil Pendleton – Geriatric Medicine
- Frederick Wu – Medicine and Endocrinology
- Michael Horan – Geriatric Medicine

Researchers

- Alan Marshall – Social Statistics
- Kris Mekli – Genetics
- Bram Vanhoutte – Sociology

fRaill project - Core Hypotheses



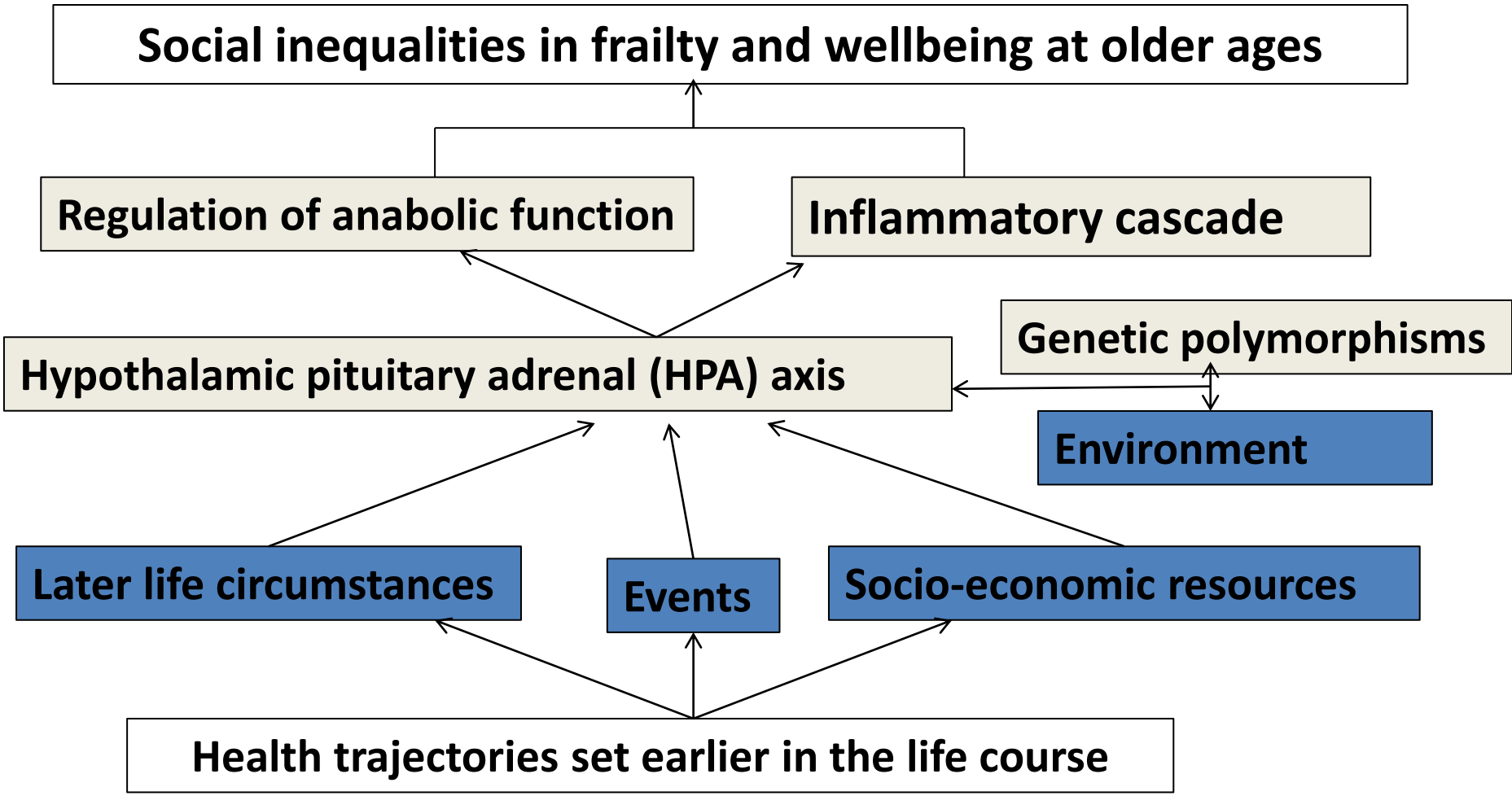
Research Methods

- English Longitudinal Study of Ageing as the core dataset

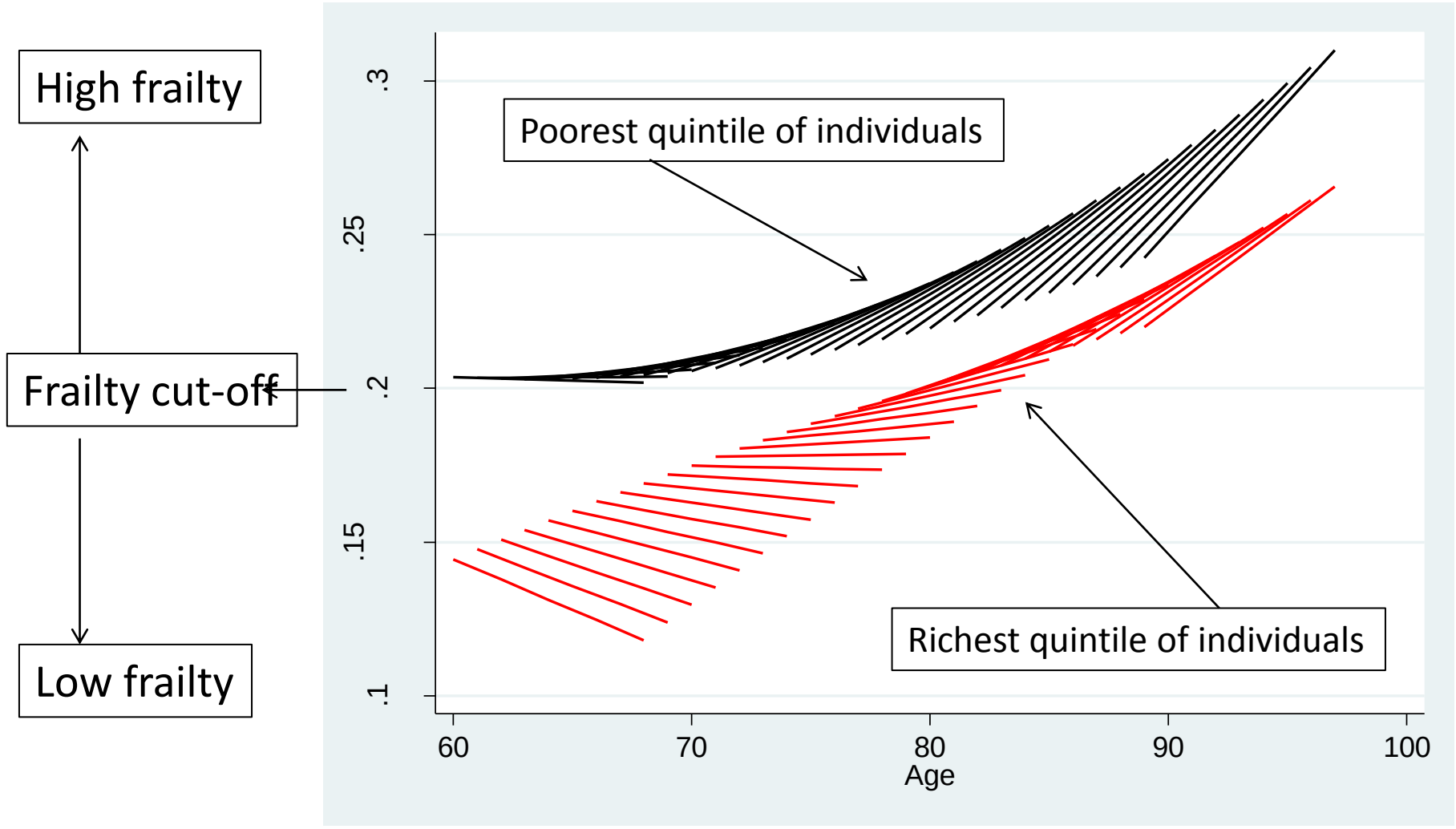
- Six waves of interview data (including HSE) covering: demographics, economics, physical health, cognitive function, mental health, wellbeing, participation in social, civic and cultural activities and social networks;
- Four waves with biomedical samples, include DNA collection and samples stored for further analysis (cortisol and sex hormones);
- Life history interview, using event history calendar approach.
- Multilevel approach to identify pathways – genes, metabolites, biomarkers, 'disease' phenotypes

- But placing this within a social and economic context

fRaill project - Core Hypotheses



Frailty growth curves by wealth



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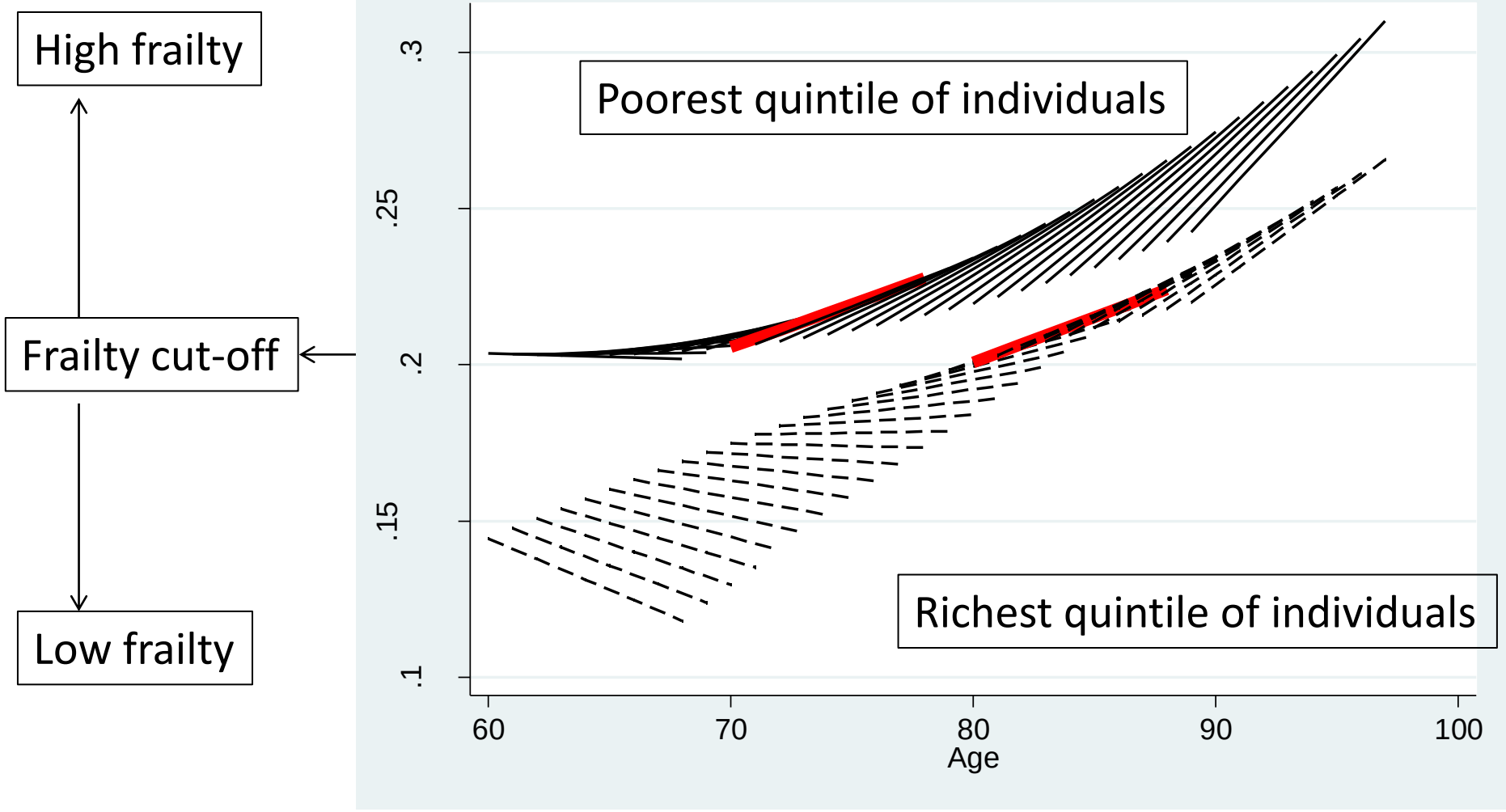
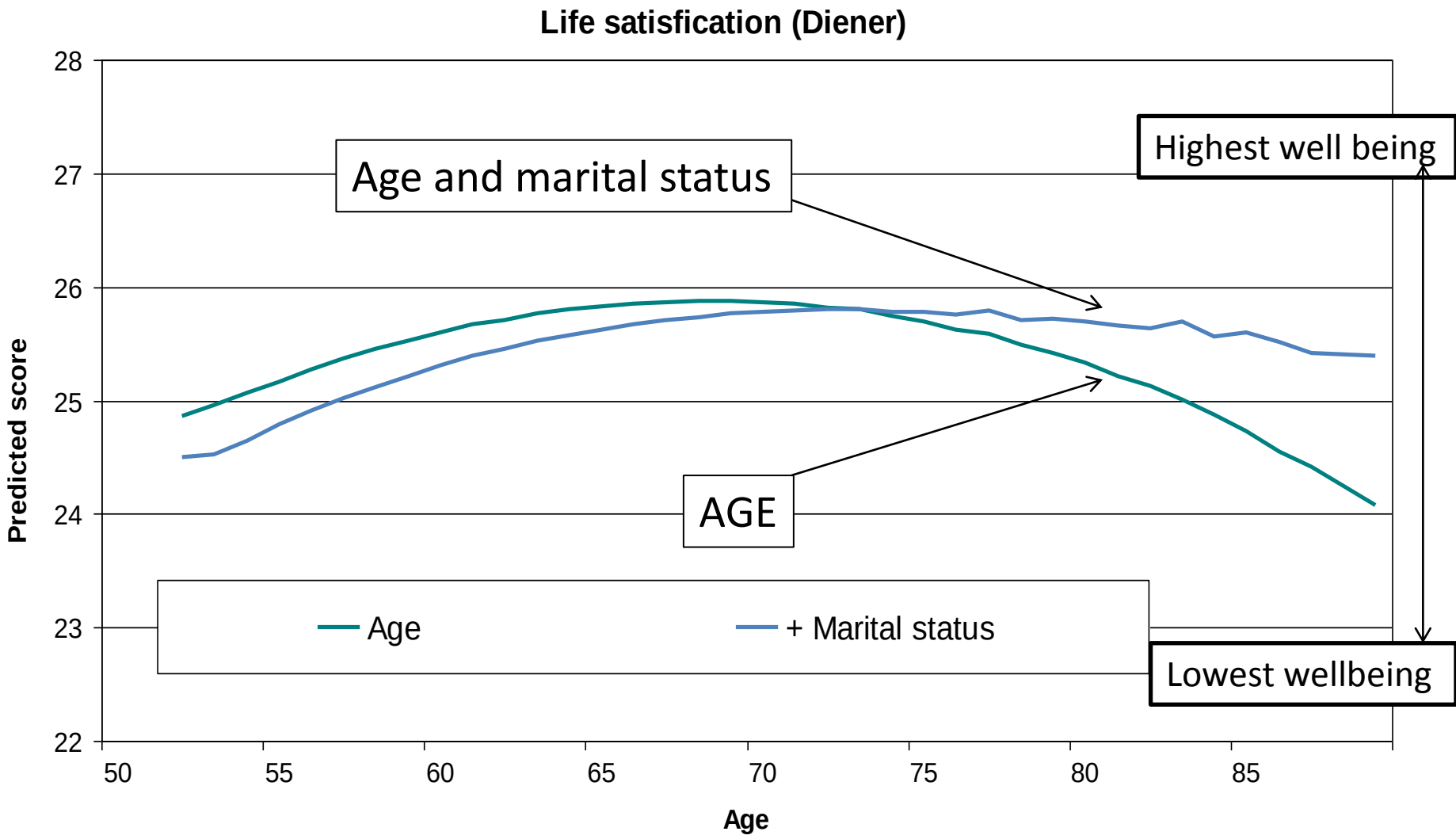


Wellbeing: explaining the U-shaped relationship with age



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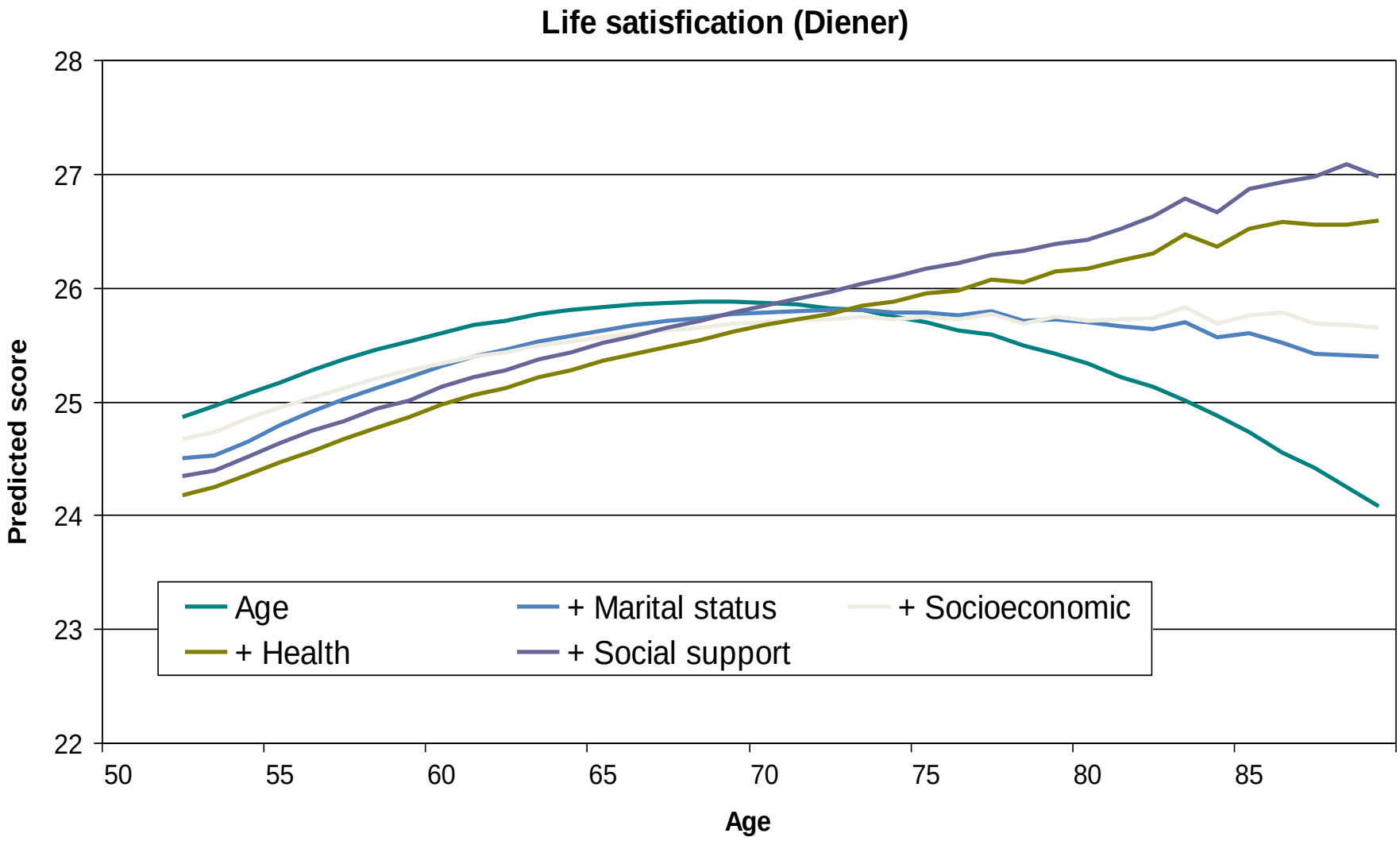
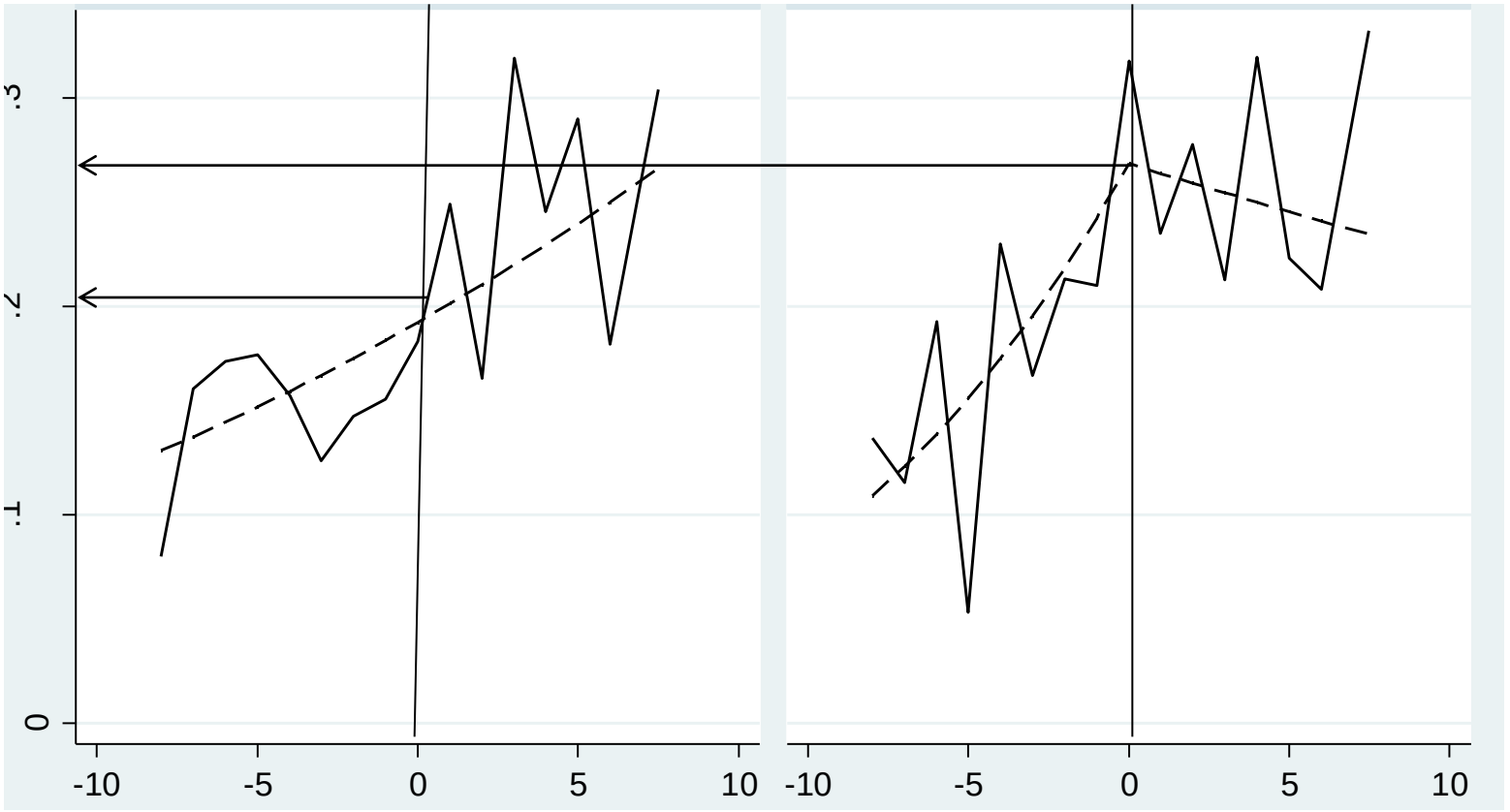


Events: Retirement trajectories in self-reported health

Managerial and professional

Routine occupations



Time to retirement (years)

Summary of social influences

- Our research shows social factors contribute to inequalities in later life wellbeing and frailty:
- Gradient in frailty and wellbeing across individual wealth and differences according to circumstances (e.g. social support and marital status)
- Events – retirement, death of a spouse, divorce

- But why are some people particularly resistant or susceptible to the onset of frailty or declines in wellbeing as they age?
- Genetic and biological factors might offer further explanation

Genetics of frailty

Frailty is a state, reflecting age-related multi-system physiological change and leading to increased risk of adverse outcomes
Research question: what causes frailty from the biological side?

Frailty measures

- Comprehensive measure including a wide range of conditions:
  health problems, physical activity level, mood, problems in everyday activities
  (~ 70 variables)
  Rockwood Index

- Performance-based measure:
  A few specific criteria is applied (~ 5 variables)
  Fried Frailty Phenotype
    - fRaill study started with this measure
    - Easier to develop
    - Closer to biological pathways

Paper: Fried *et al*. 2001 Frailty in Older Adults:
Evidence for a Phenotype J Gerontol; 56(3):M146-M156.

Aim: to establish a standardized definition of frailty

Method:

- population: from the Cardiovascular Health Study (CHS)
  5,317 individuals (2,240 men and 3,077 women)
  65 years and older
- phenotype: questionnaires and physical examination
  5 items:
  - sarcopenia
  - exhaustion
  - low physical activity
  - slowness
  - weakness

Outcome
Robust: positive for 0 item
Pre-frail: positive for 1-2 items
Frail: positive for 3-5 items

Frailty in the English Longitudinal Study of Ageing

5 items

Nurse data

- sarcopenia replaced with unintentional weight loss [measured, kg], positive if over 8% bodyweight
- slowness: timed walk over 8 feet (~ 2.5 m) [measured, sec] positive for the slowest 20% of population
- grip strength: using a dynamometer [measured, kg] positive for the weakest 20% of population

Core dataset

- exhaustion: questionnaire [self-reported] '*everything they did during the past week was an effort*' and '*could not get going much of the time during the past week*' positive if answer is yes to both question
- low physical activity [self-reported] positive if respondent does not work and takes part in no other physical activities

Outcome:

Robust: positive for 0 item

Pre-frail: positive for 1-2 items

Frail: positive for 3-5 items

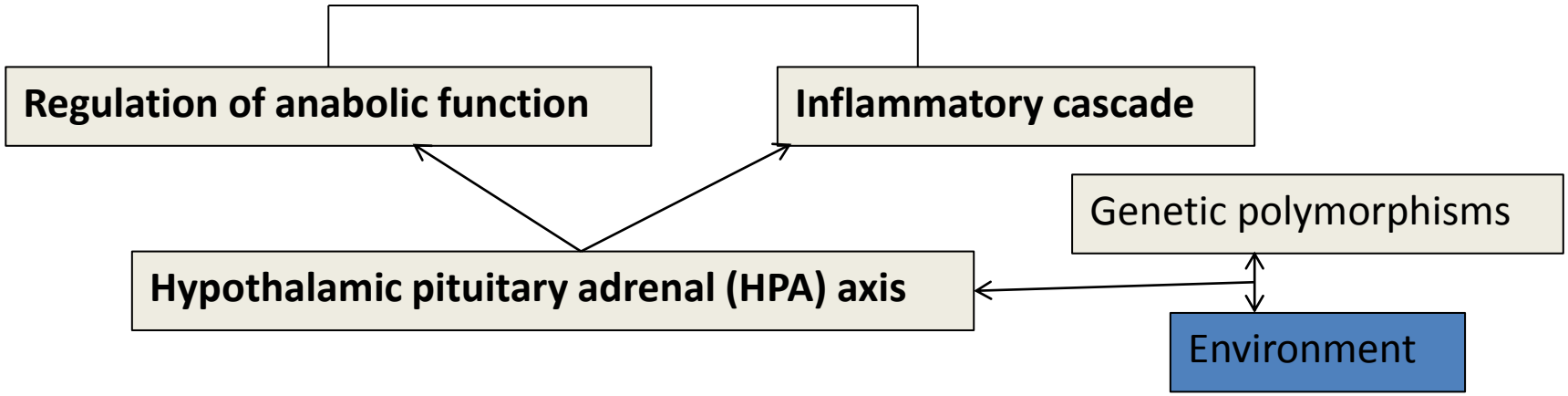
Phenotypic results in ELSA

	Frailty category	CHS	W2 (=5,113)	W4 (=5,113)	W2 drop Out (=2,485)
All participants	Not frail (0-1 items)	78	83.68	83.32	78.38
	Pre-frail (2 items)	15	11.21	10.45	11.83
	Frail (3-5 items)	7.02	**5.10**	**6.23**	**9.79**
	Total	100.2	100	100	100
Males	Not frail (0-1 items)	81	85.28	84.16	78.99
	Pre-frail (2 items)	14	10.07	10.76	13.17
	Frail (3-5 items)	7.02	**4.65**	**5.08**	**7.84**
		102.2	100	100	100
Females	Not frail (0-1 items)	77	82.40	82.64	77.86
	Pre-frail (2 items)	15	12.12	10.21	10.69
	Frail (3-5 items)	8.1	**5.48**	**7.15**	**11.45**
		100.1	100	100	100

- the frailty phenotype is present in the ELSA dataset
- % of frail participants in waves increases with age
- highest percentage is present in the drop out population

The biological determinants of frailty

Hypothesis: HPA axis in the centre



Effects of HPA axis on

Anabolic function: HPA axis regulates the synthesis and secretion of steroid hormones (cortisol, testosterone, progesterone, aldosterone) in peripheral tissues

Inflammatory cascade: glucocorticoids have an immunomodulatory effect (cortisol is immunosuppressive)

Biomarker approach biomarker/metabolite → phenotype

• Inflammatory biomarkers: cytokine (IL-6) and CRP levels in frail individuals

In ELSA CRP level is not predictive for frailty

• Cortisol pathway hormones:

In ELSA DHEA-SO_4 level is not predictive for frailty

Other hormones (measurement in progress)

• testosterone and oestradiol

• cortisol (cortisol/DHEA-SO_4 ratio)

Candidate gene approach genotype → phenotype

selection of genes from the literature (cortisol and inflammatory pathways)

↓

identifying genetic variants

↓

determine association of genetic variants with the phenotype (frailty)

Genetic association analysis overview

Individual 1

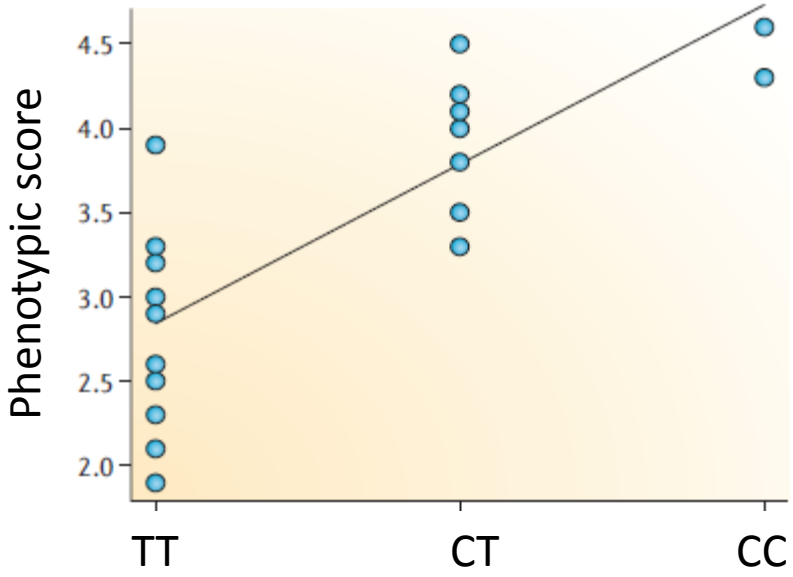
- - C A T G A T T G T G C C G - -

Gene of interest

Individual 2

- - C A C G A T T G T G C C G - -

SNP= Single Nucleotide Polymorphism



Example: in *CRP* gene
rs1800497 C→T (70-30%)
Glu (CTC) → Lys (TTC)

On a population level
↓
Linear or logistic regression

Adapted from: Balding DJ,
Nat Rev Gen, 2006, 7(10): 781-791.

Results

620 SNPs from cortisol and inflammatory pathways and over 3000 individuals

- cortisol: stress hormone, cortisol/DHEA-SO_4 ratio increases with ageing
- inflammation: elevated levels of inflammatory markers (IL-6 and CRP) have been previously associated with frailty

IL-6 and ***CRP*** variants: no significant association with frailty,
However, rs1800947 (in *CRP* gene) is significantly associated with CRP level
rs296368 (in *SULT2A1* gene) is with DHEA-SO_4 level

Significant association was observed between frailty status and genetic variants in
TNFα – pro-inflammatory cytokine, involved in regulation of many cellular processes, including apoptosis, lipid metabolism and coagulation
IFNγ – soluble cytokine, with immunoregulatory and anti-tumor properties
PTPRJ – protein-Tyr phosphatase, involved in signal transduction and downregulates T cell production
CYP1A1 – monooxygenase, involved in cholesterol and steroid synthesis

Conclusion

Frailty has genetic components (genes in inflammatory pathways and cholesterol synthesis) but SNPs only explain a small amount of phenotypic variance

Early stage of biomarker work

genotype → biomarkers/metabolites → phenotype

More genetic variants (in progress)

- GWAS: 2.5 million SNPs

More biomarkers to measure

- cortisol and sex hormones

Aim: multi-level approach to predict frailty

- environment, socio-economic factors, life history
- biomarkers (hormones, metabolites)
- genetics (susceptibility alleles/genetic variants)

Risks and challenges

- Different disciplines may favour different models and ideas of what is considered to be high quality research
- The threat to our academic position: from expert to novice.
- And Jack of all trades and master of none – losing your disciplinary grounding.
- Types of and routes of publication – which journals, value of monographs, book chapters, etc.
- Very varied authorship practices and rules.
- Difficulty of getting genuinely integrated publications (role of editors and reviewers).

How to do it?

- Team working
- Regular communication – findings, progress, expectations
- Learn other languages (methodological and disciplinary)
- Time and geographical proximity
- Partnerships, not subordinate disciplines.
- Should lead to integration of theory, methods, data and findings:
- Sometimes produced in tacit ways (implicitly drawing on alternative orientations and data) and invisible to those outside the research team.

Some concluding thoughts

- Interdisciplinary working provide new perspectives on complex problems that cut across disciplines
- fRaill project – considers drivers of inequalities at the older ages – social, genetic, metabolic, biological and psychological factors
- Challenges – adapting to different models and research methods, terminology and writing styles
- Meet regularly and plan early
- Not straightforward – be patient!
- Fraill project - http://www.ihs.manchester.ac.uk/MICRA/fRaill/