UNCOVERING THE MULTIVARIATE GENETIC ARCHITECTURE OF FRAILTY USING GENOMIC STRUCTURAL EQUATION MODELLING

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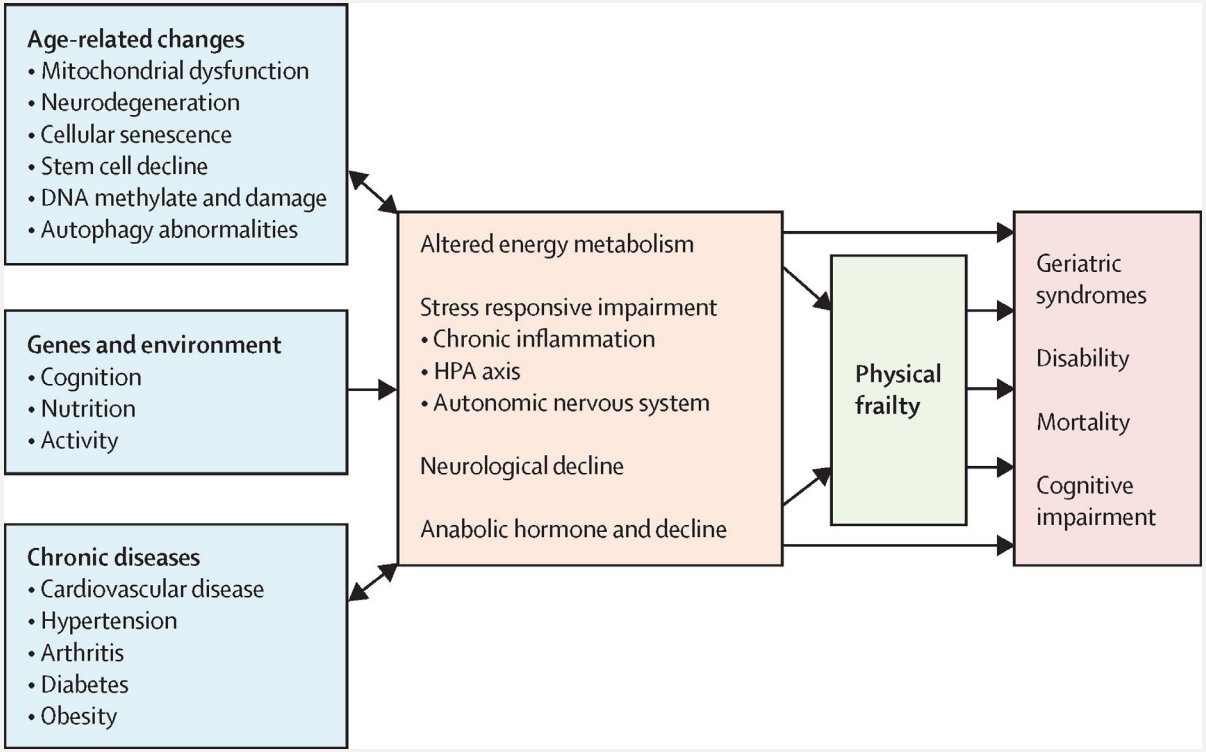
WHAT IS FRAILTY?

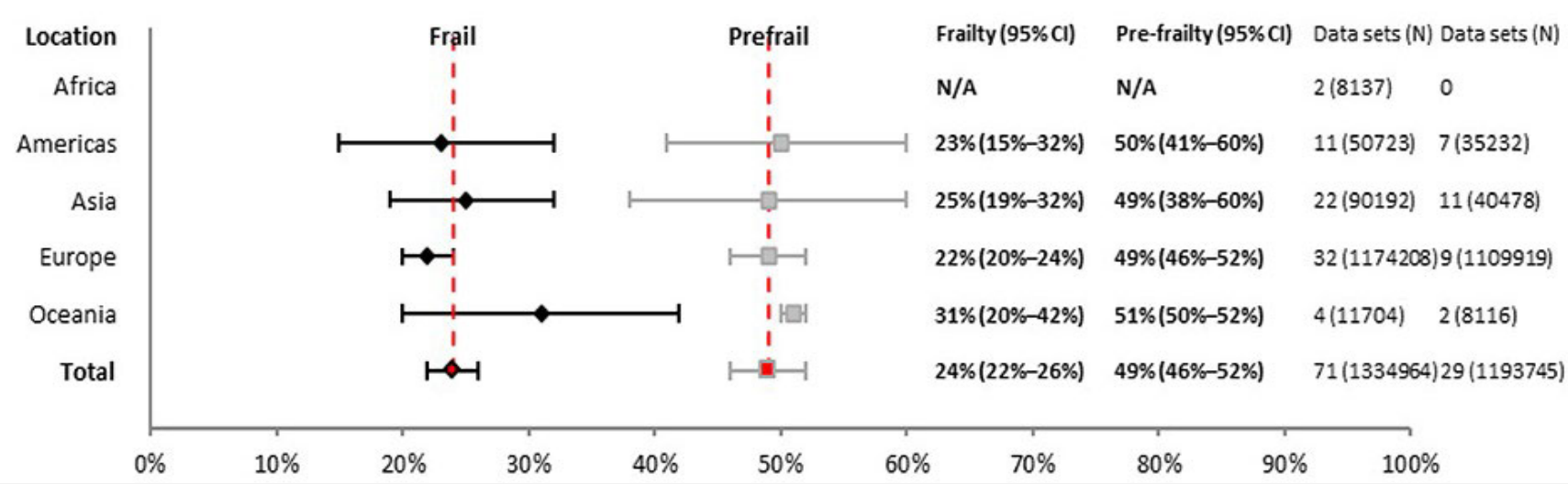
Frailty is a multifactorial clinical state characterized by decline in functioning across multiple body systems and increased vulnerability to external stressors.



Dent et al., 2019

FRAILTY PREVALENCE

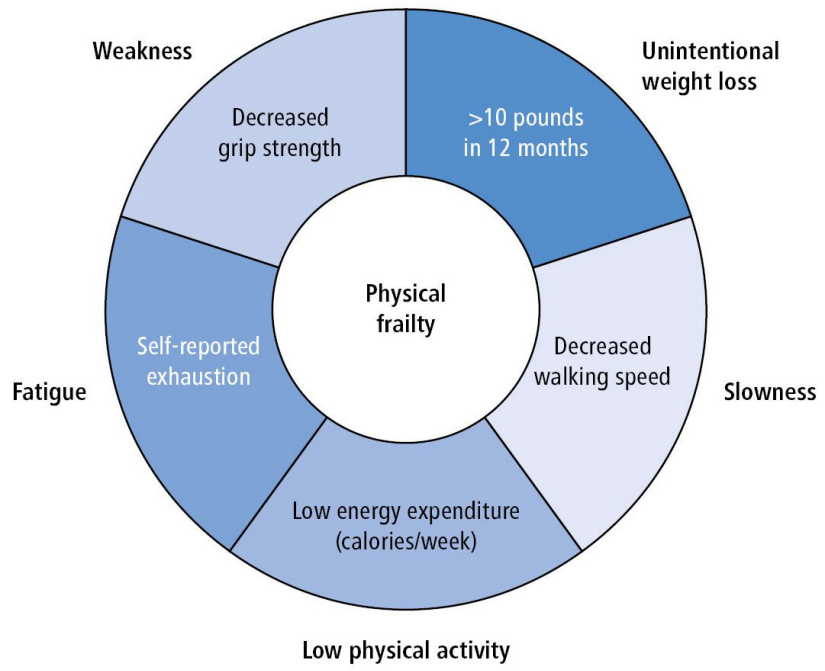
Frailty prevalence ~25% in over 50s, but prevalence increases dramatically with age with prevalence in individuals aged 90+ at >50%.



O'Caoimh et al., 2020

FRAILTY PHENOTYPES

The 'Frailty' Phenotype:



Fried et al., 2001

The Frailty Index:

Proportion of deficits a person has from a set of >30 traits (Rockwood & Mitnitski, 2001).

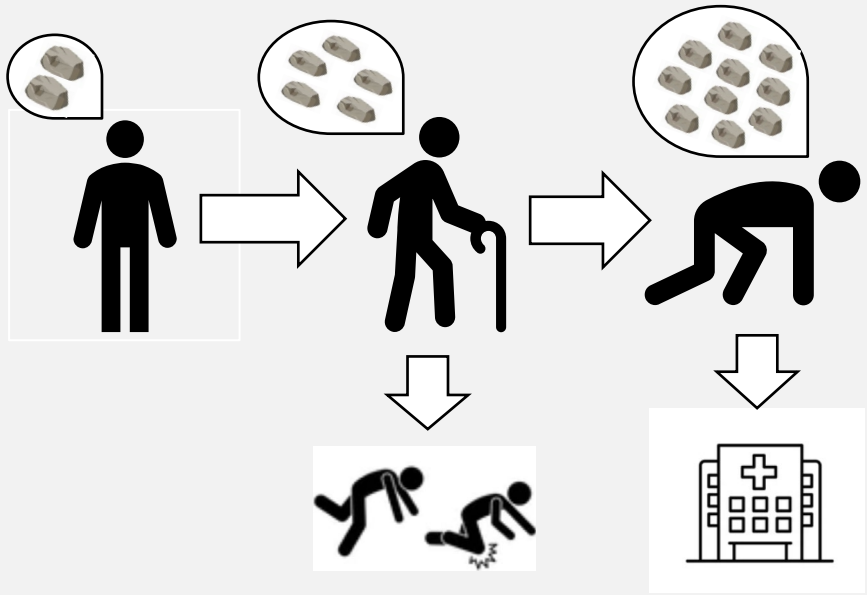
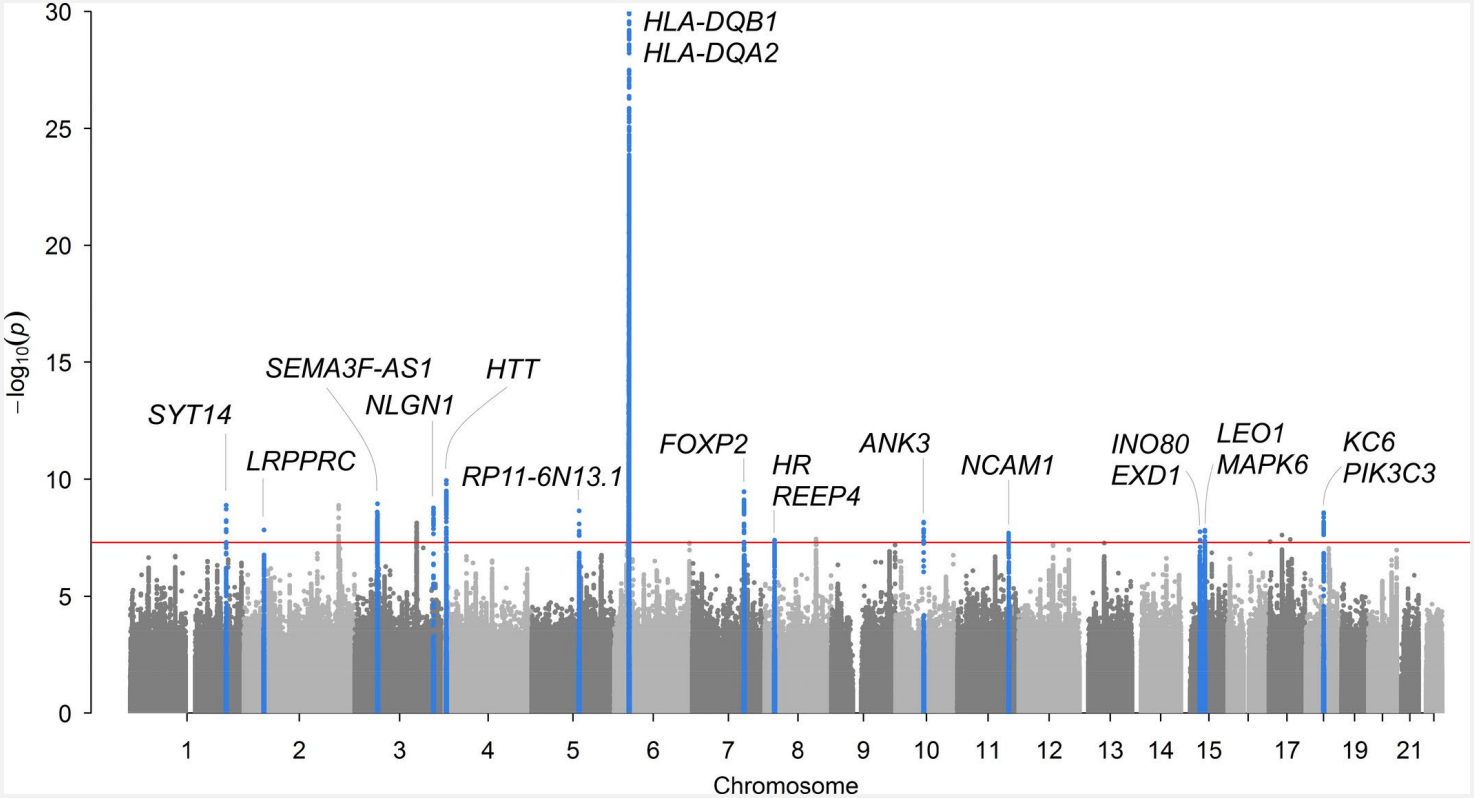


Image courtesy of: J P Flint, Advanced Care Research Centre (2023); L Johnson (2023). Cumulative Deficit Model of Frailty Metaphor

GENETICS OF FRAILTY

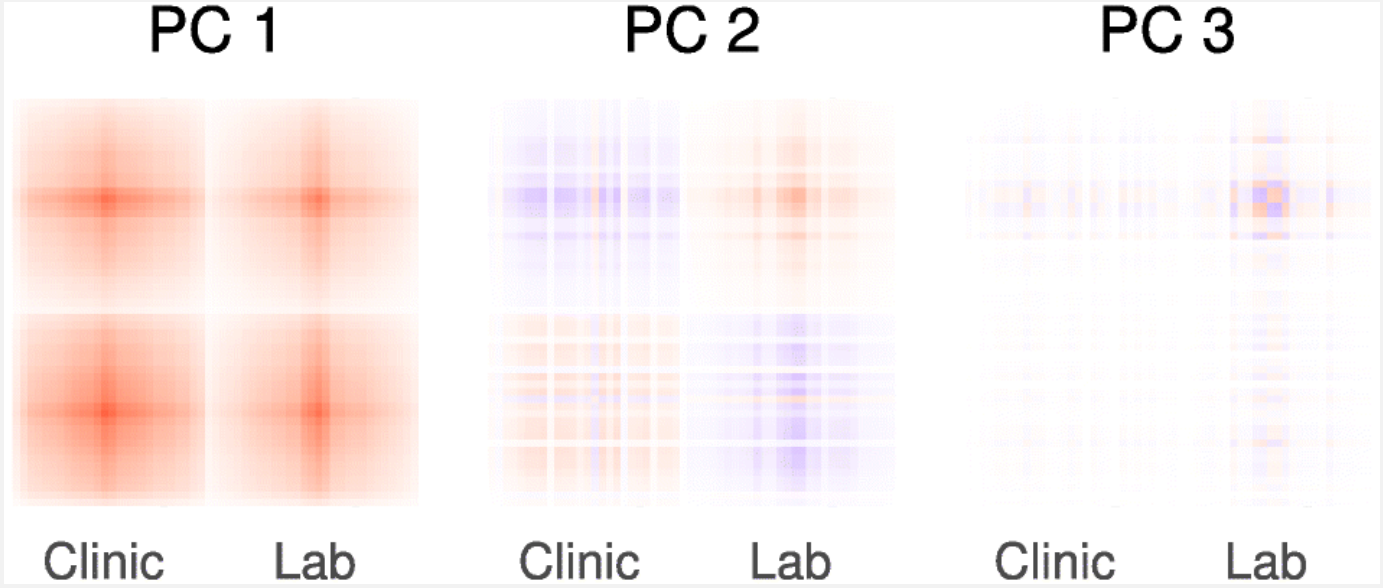
14 loci associated with Frailty Index; 11% SNP-based heritability



Atkins et al 2021

FRAILTY AS A MULTIVARIATE PHENOTYPE

26 clinical predictors, 29 lab predictors, 47 outcomes, and 7 demographical variables



NHANES data: *N* = 1872, aged >60 years

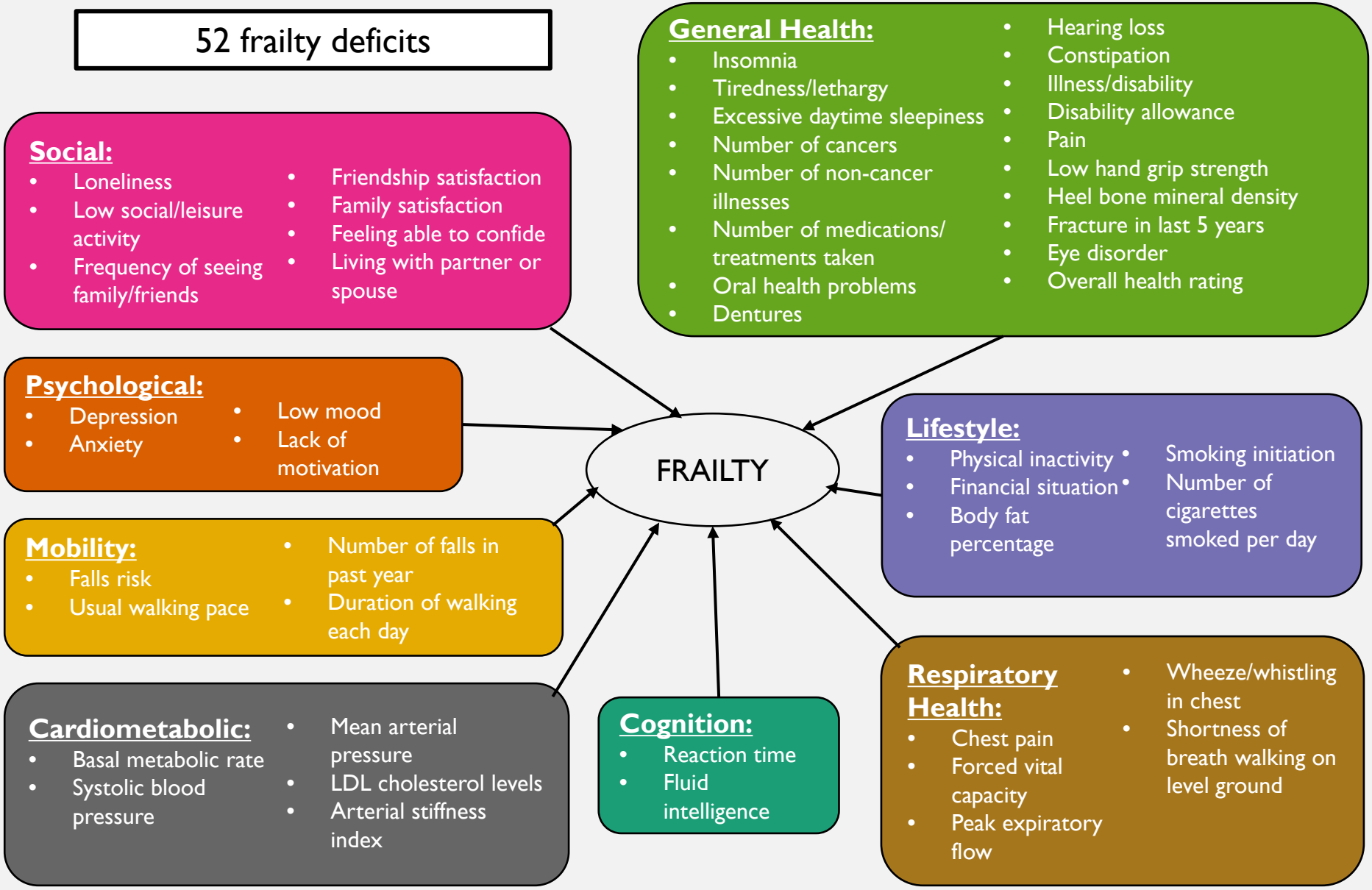
Adapted from Pridham et al 2023

CURRENT STUDY AIMS

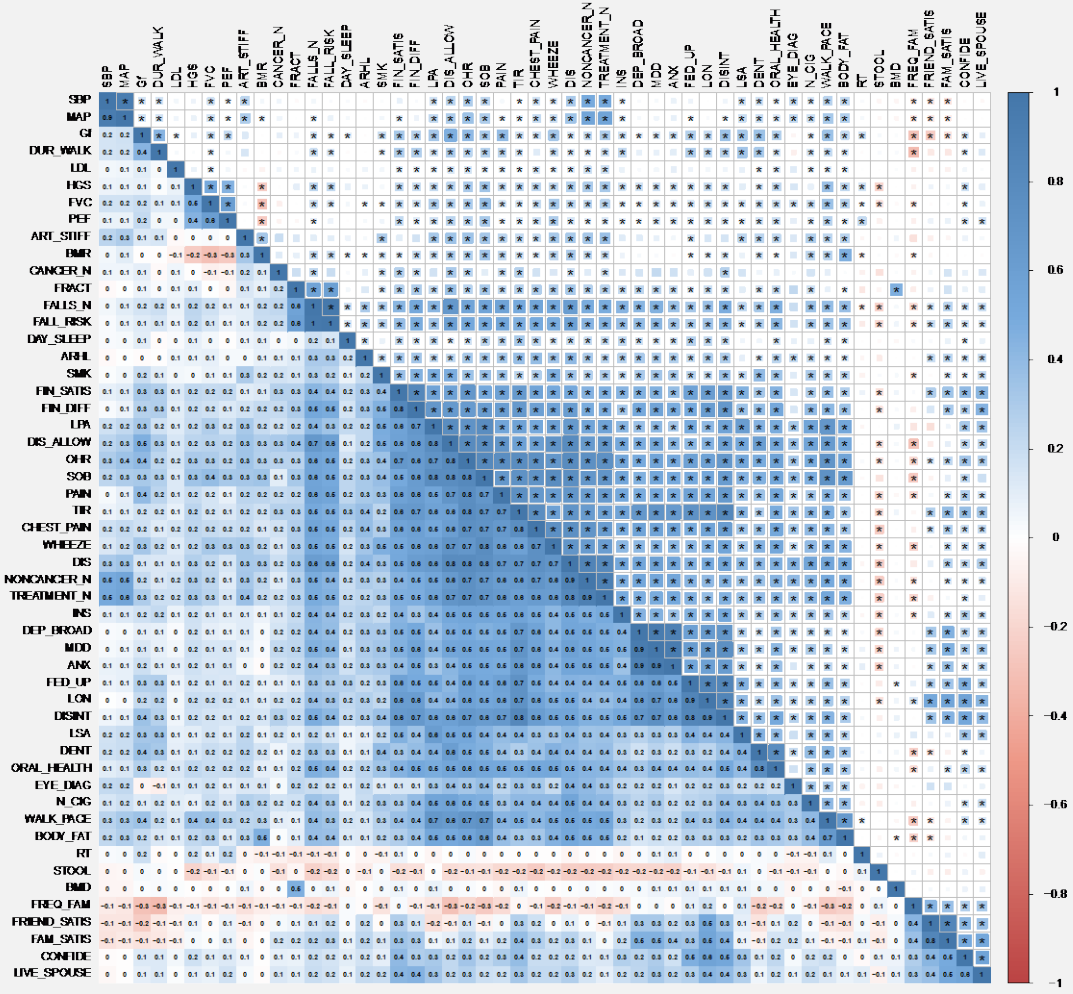
1. To use genomic SEM to model the genetic overlap between common deficits from the Frailty Index

2. To conduct multivariate GWAS to identify genetic risk variants that are significantly associated with each of these latent frailty constructs

3. To assess the biological significance of each frailty latent cluster and their effects on other outcomes of aging (e.g. dementia)


52 frailty deficits
General Health:
Insomnia
Tiredness/lethargy
Excessive daytime sleepiness
Number of cancers
Number of non-cancer illnesses
Number of medications/ treatments taken
Oral health problems
Dentures
Hearing loss
Constipation
Illness/disability
Disability allowance
Pain
Low hand grip strength
Heel bone mineral density
Fracture in last 5 years
Eye disorder
Overall health rating
Social:
Loneliness
Low social/leisure activity
Frequency of seeing family/friends
Friendship satisfaction
Family satisfaction
Feeling able to confide
Living with partner or spouse
Psychological:
Depression
Anxiety
Low mood
Lack of motivation
FRAILTY
Lifestyle:
Physical inactivity
Financial situation
Body fat percentage
Smoking initiation
Number of cigarettes smoked per day
Mobility:
Falls risk
Usual walking pace
Number of falls in past year
Duration of walking each day
Cardiometabolic:
Basal metabolic rate
Systolic blood pressure
Mean arterial pressure
LDL cholesterol levels
Arterial stiffness index
Cognition:
Reaction time
Fluid intelligence
Respiratory Health:
Chest pain
Forced vital capacity
Peak expiratory flow
Wheeze/whistling in chest
Shortness of breath walking on level ground

GENETIC CORRELATION



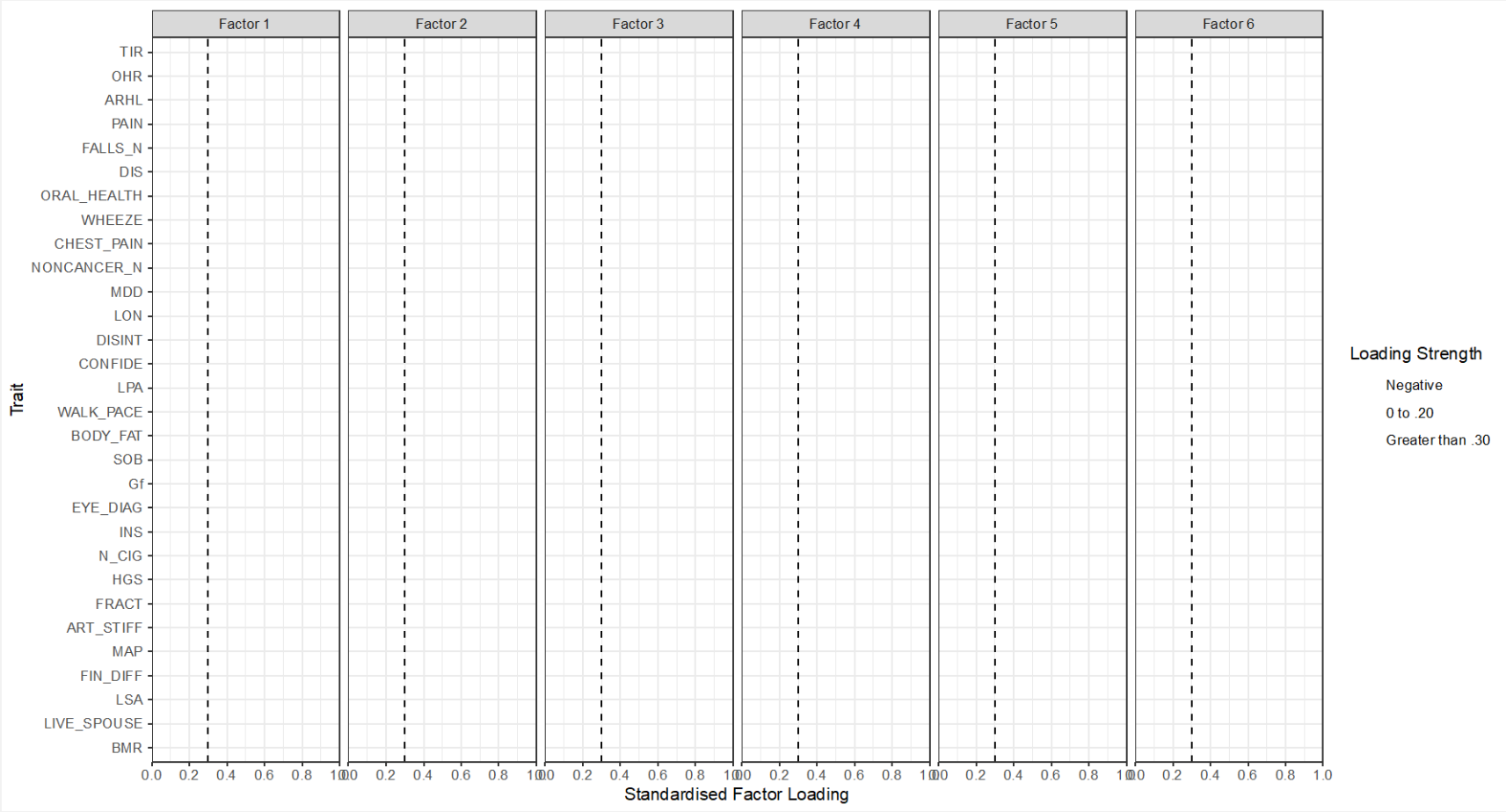
TRAIT REMOVAL

22 traits removed from final model – 30 taken forward

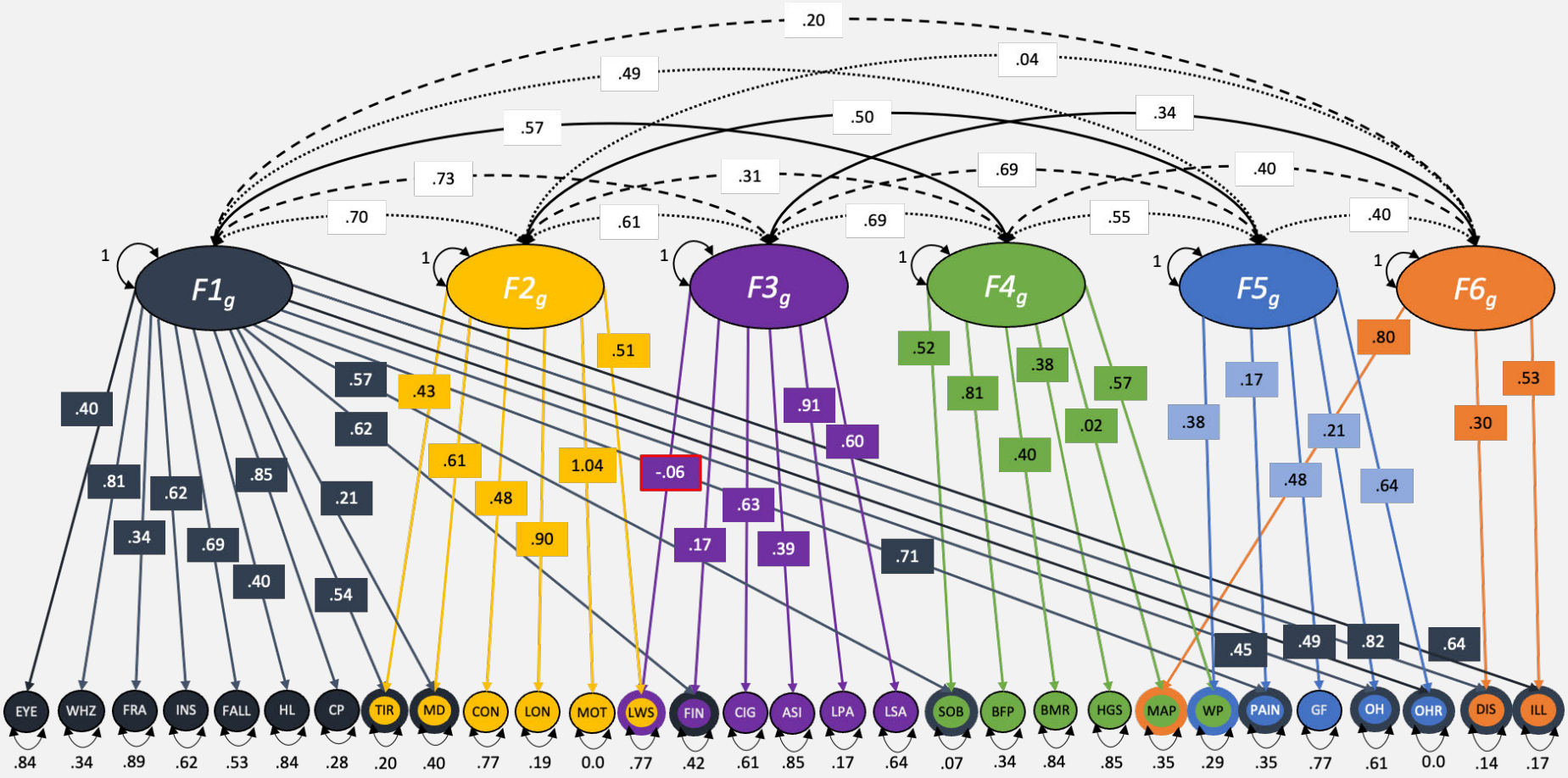
Reasons for removal:

- *Low heritability* – number of cancers (0.8%)
- *High multicollinearity* ($r_g \geq .9$) – broad depression; anxiety; falls risk; SBP; number of treatments/medications taken
- *Low mean genetic correlation (*mean $r_g \leq 10\%$*)* – reaction time; bone mineral density; LDL cholesterol; constipation; freq friends/fam visits
- *Low mean genetic correlation compared to similar trait* – excessive daytime sleepiness; low mood; smoking; duration of walking; disability allowance; dentures; FVC; PEF; financial satisfaction; friendship & family satisfaction

EXPLORATORY FACTOR ANALYSIS



CONFIRMATORY FACTOR ANALYSIS



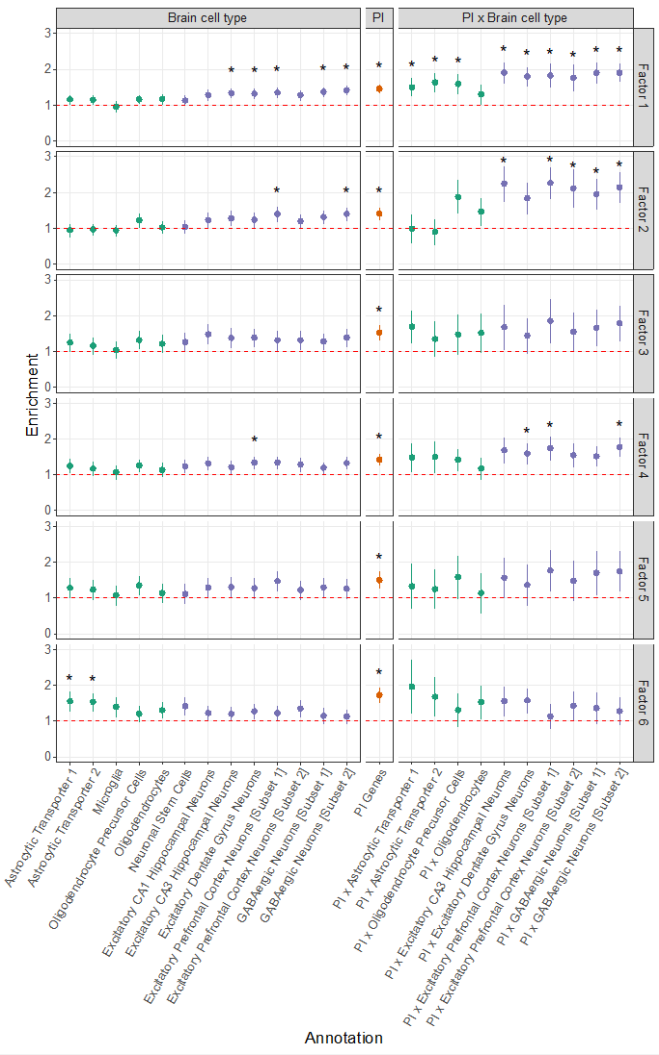
STRATIFIED GENOMIC SEM

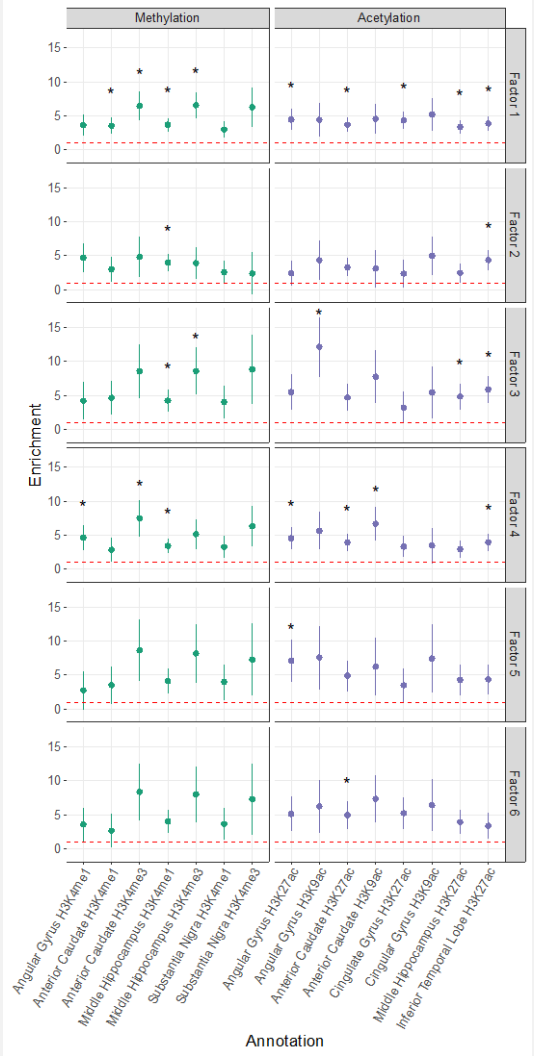
We used Stratified Genomic SEM to assess whether the shared genetics underlying the latent factors were enriched in gene sets or categories relevant to the brain.

Tested enrichment for 146 functional annotations including brain-relevant gene expression profiles and histone/chromatin marks using data curated from:

- 1000 Genomes Phase 3 BaselineLD v2.2 (original S-LDSC developers)
- Roadmap Epigenetics Project
- GTEx
- DEPICT
- gnomAD

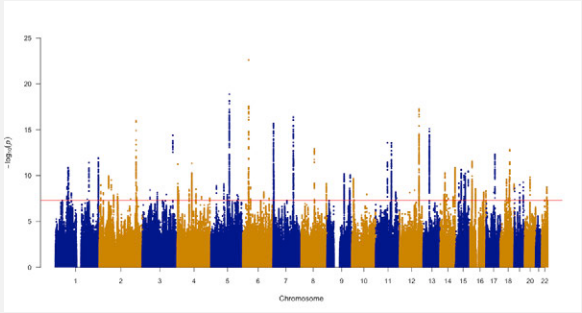
STRATIFIED GENOMIC SEM RESULTS



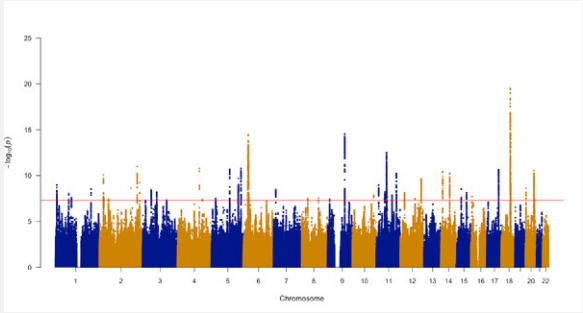


MULTIVARIATE GWAS OF FRAILTY

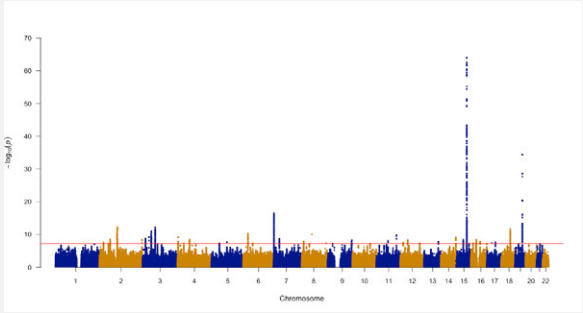
88 genomic loci for Factor 1
N = 1,808,850



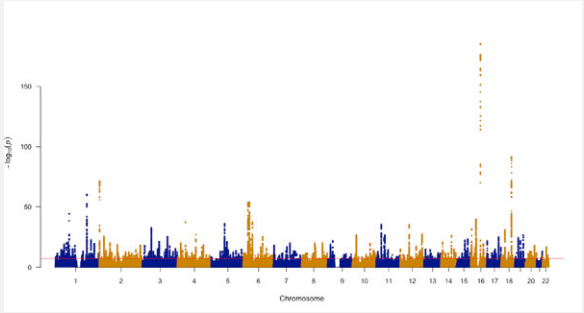
51 genomic loci for Factor 2
N = 706,221



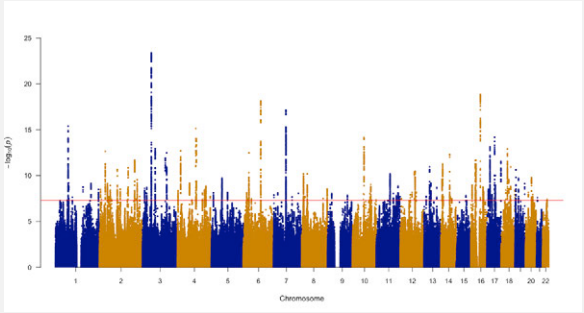
39 genomic loci for Factor 3
N = 182,208



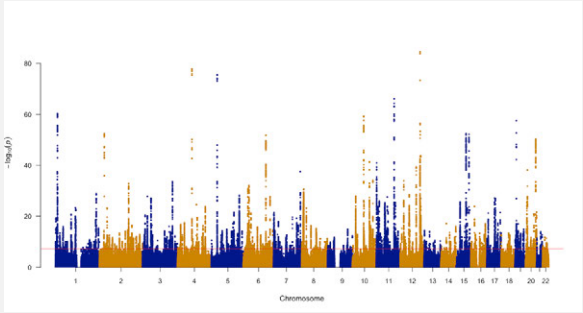
496 genomic loci for Factor 4
N = 384,934



123 genomic loci for Factor 5
N = 652,471



492 genomic loci for Factor 6
N = 420,670



CONCLUSIONS

Modelling frailty as multiple latent factors provides a more fine-grained picture of key frailty pathways than using a single aggregate phenotype.

Further analyses of the biology underlying each latent factor and their effect on other aging-related outcomes could help us understand how different components of frailty impact health.

ACKNOWLEDGEMENTS

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CNCR CTGLAB

biobank uk
Enabling scientific discoveries that improve human health

IBG

Pan-UK Biobank
Pan-ancestry genetic analysis of the UK Biobank

NIH National Institute on Aging

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