



## The Biomes of Frailty

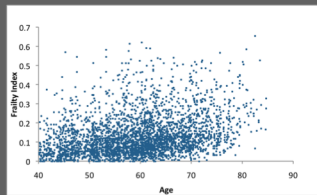
Claire Steves  
MA MBBS MRCP PhD  
Geriatrician and clinician scientist  
Guys and St Thomas's Trust  
King's College London

## To be frail or not to be frail



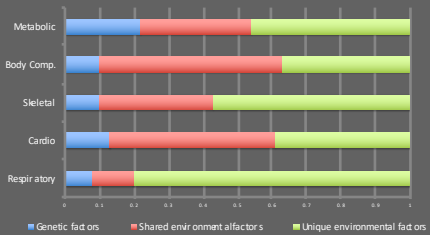
22% of the population will be over the age of 65 years by the year 2050

## Variability in health increases with age



By understanding sources of variance could we unlock a demographic dividend??

## Variance in ageing trajectories are substantially environmental



Moayyeri 2015 TRHG  
DOI:10.1017/thg.2015.100

## What environment??

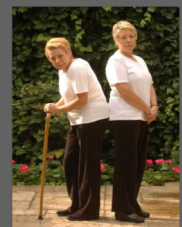
... by which biological mechanisms?



## Ageing in identical twins

Two roads diverged  
in a wood, and I -  
I took the one  
less traveled by,  
And that has made  
all the difference.

Robert Burns



## TwinsUK.ac.uk - a nationwide bioresource population

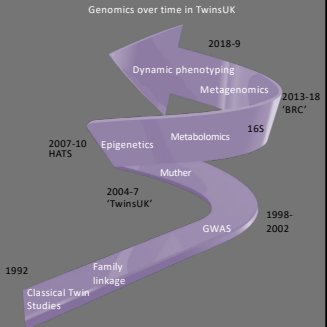



## Cohort description

Twin volunteers, aged 18 -97

Recruited through national media campaigns

13000 individuals on register  
3853 (2871 active) complete MZ pairs  
2727 (1690 active) complete DZ pairs  
>8000 visited, >80% female



Genomics over time in TwinsUK

2018-9: Dynamic phenotyping, Metagenomics, Metabolomics, 16S

2013-18: 'BRC'

2007-10: HATS

2004-7: 'TwinsUK'

1998-2002: GWAS

1992: Family linkage, Classical Twin Studies

twinsUK

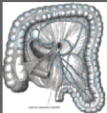
## Lecture objectives

- Give you a new perspective on who you are, and who your patients are!
- Consider how a “new organ” – the gut microbiome - might relate to
  - the development of frailty
  - acute presentations in the elderly
- Introduce a potential role of oral and urinary microbes in geriatric syndromes
- Consider the impact of your prescriptions in light of current understanding.

## Mr George M-B.

- 88 year old man
- Presented with a fall to AE
- Weight loss and “change in bowel habit”
- Mild mixed anaemia and chronically raised inflammatory markers
- CT enema – fat stranding in colonic mesentery ? Inflammation
- Colonoscopy negative but faecal calprotectin up.
- Lands on elderly care ward, frail, reduced mobility, overflow constipation, intermittent delirium

## The gut microbiome – the internal environment




The gut is the largest interface with the external world, with a surface area of 30 m<sup>2</sup>


More microbial cells than human cells  
360 times more genes

The ‘Microbiome’ is the sum total of those genes

70% of the body's lymphocytes reside in the MALT




## Who are you?



For every 100,000 genes in your body, there are 100 million microbial genes.

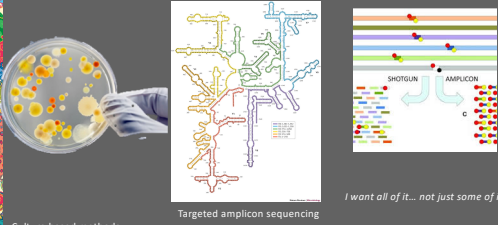
- 100 trillion bacteria and archaea
- 500 trillion viruses (phages)
- Plus fungi and protists
- Producing thousands of chemical metabolites
- The main driver of our immune system and control of digestion



## Who is your patient!?



## Measuring microbes – a new science



1900s 2000s 2012 HMP 2014

*I want all of it... not just some of it...*

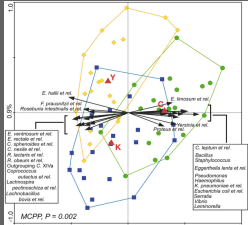
## Who is Mr G. M-B?

Comparing “nursing” and “residential” patients in a care home in Groningen, Netherlands

Frail ones had substantially different microbiomes

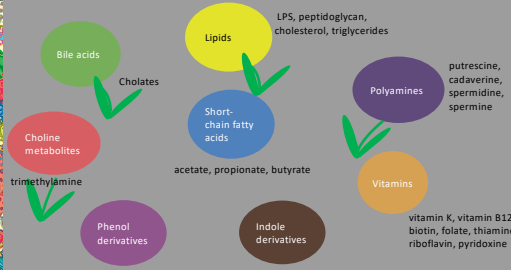
Perhaps not quite so super then...

van Tongeren, S.P., et al. Appl Environ Microbiol, 2005



Blagi E, PLoSOne 2010

## Metabolic capability of the gut microbiome



Bile acids  
Cholates  
Choline metabolites  
trimethylamine  
Phenol derivatives  
hippuric acid, tyrosine, phenylalanine

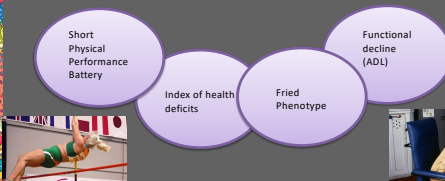
Lipids  
LPS, peptidoglycan, cholesterol, triglycerides  
Short-chain fatty acids  
acetate, propionate, butyrate

Polyamines  
putrescine, cadaverine, spermidine, spermine  
Vitamins  
vitamin K, vitamin B12, biotin, folate, thiamine, riboflavin, pyridoxine

Indole derivatives  
N-acetyltryptophan, Melatonin, Serotonin

## Frailty: “ageing” that matters

Vulnerability to stressors underpinned by homeostasis



## What is Mr G. M-B’s internal garden like?



Why is it like that???

What are the effects?

What can we do about it?

## Why is it like that???

Host health

Diet

Medication

Location

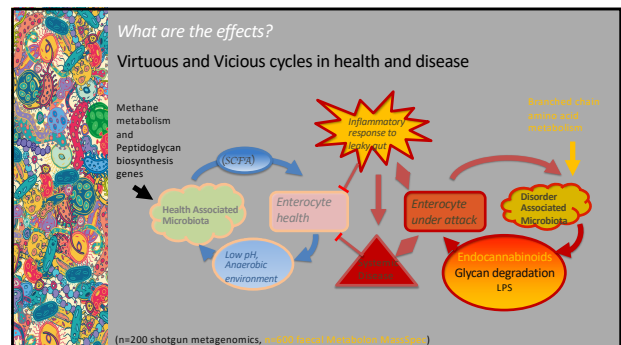
### Gut microbiota composition correlates with diet and health in the elderly

Signatures of early frailty in the gut microbiota

Use of dietary indices to control for diet in human gut microbiota studies

Proton pump inhibitors alter the composition of the gut microbiota

Gut microbiota associations with common drug and prescription medications in a population cohort



## Animal transplantation experiments:

Old phenotypes transmitted...

Old secret: Germ free mice actually live longer than those with a microbiome

Increased inflammation  
Increased gut permeability in GF mice given old vs young transplants

Fransen, Frontiers Immunobiology 2017  
doi: [10.3389/fimmu.2017.01111](#)

Killifish rejuvenation

Smith Elife 2017

## Types of intervention

- Prebiotic – whole food, constituent, targeted
- Probiotic – selected, consortia, FMT
- Synbiotic – combined synergistic preparation
- Not giving gut altering drugs!

## Pre- & Probiotics & polyphenols

## Trials in older people

Galacto-oligosaccharides (GOS) – found in legumes

Vulevik 2015, doi: [10.1017/S0007114515001889](#)

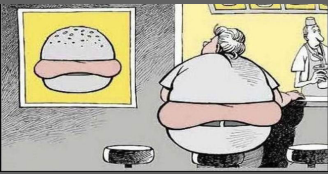
Bulgues 2016 doi: [10.1017/S0007114516000024](#)

Inulin & fish oils – showing promise in new study

Bamberger et al, Nutrients 2018. Shift in microbiota after 8 weeks of 43g walnuts a day



**"You are what you eat"**



Food isn't fuel its fertiliser

Medications can be modulators

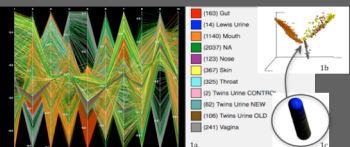
**Mrs Ursula M-B**

- 80 year old lady
- Seen in A&E with new onset confusion and incontinence
- "Off legs"
- Urinary dipstick shows + leucocytes + nitrites +protein
- Admitted and treated for UTI by medical team

- MSU comes back with mixed growth, no significant wcc

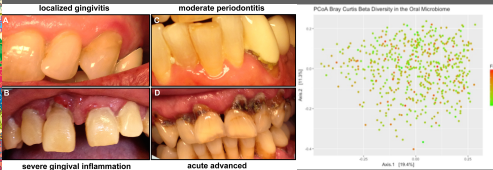
**CDRF**

**Different biomes in different body sites**



- Urine is not sterile in apparently well older adults
- The urinary microbiome in older people is almost as diverse as the gut
- Urine microbiome patterns associate with recurrent UTI history and frailty
- Could this explain our the confused ?UTI story

**The oral microbiome**



localized gingivitis moderate periodontitis

severe gingival inflammation overlying chronic periodontitis acute advanced periodontitis

PCoA Bray Curtis Beta Diversity in the Oral Microbiome

SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

***Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors**

Stephan L. Denney<sup>1,2</sup>, Casey Lynch<sup>1,2</sup>, Roshan Umesh<sup>1</sup>, Malgorzata Renczyk<sup>1,2</sup>, Agata Marczyn<sup>1,2</sup>

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**Thanks to everyone!**

**wellcome**trust

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