

A cross-national comparison of biomarkers of aging between Costa Rica and the United States

New Measures of Age and Ageing
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Background: Biomarkers of aging

"A biomarker of aging is a biological parameter of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age"

(Baker and Sprott, 1988, *Experimental Gerontology*)

Six characteristics of Biomarkers of aging (Baker and Sprott, 1988)

1. Rate of change of biomarker must reflect some measureable parameter which can be predicted at a later chronological age.
2. The biomarker should reflect some basic biological process of aging and **certainly not the predisposition toward a disease state** or some inborn error in metabolism.
3. The biomarker should have **high reproducibility in cross-species comparisons** of functional or physiological age versus chronological age, particularly within the same classes and certainly within the same families of species.
4. Biomarkers should change independently with the passage of time and reflect physiologic (functional) age.
5. Assessment of biomarkers should be nonlethal in animal systems and should cause minimal trauma in humans.
6. Biomarker should be reproducible and measureable during a relatively short time interval.

Background: Biomarkers of aging

Problem: We do not have a gold standard of aging.
While there is death, this is not aging per se.
Thus we must establish validity through other approaches – not a simple comparison to a gold standard.

Objective of this paper

Objective: Examine the age related dependence of potential biomarkers of aging.

We focus on whether potential biomarkers of aging are similar in subpopulations:

- 1) correlated with age **overall**
- 2) correlated with age differentially by **gender**
- 3) correlated with age differentially by **education**
- 4) correlated with age differentially by **place**

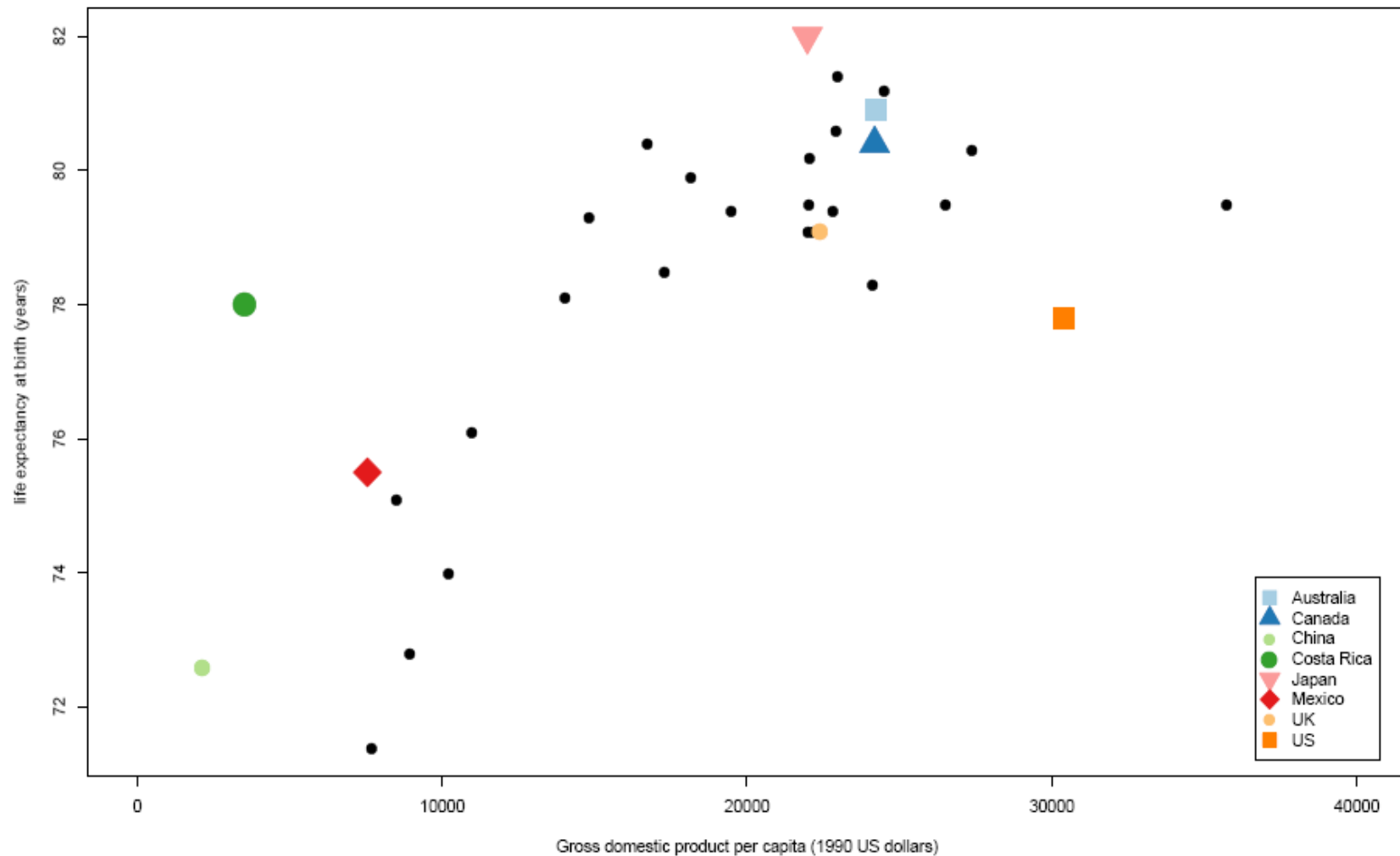
data

Costa Rica (Costa Rican Healthy Aging Study)
2000-2006, n = 3709, age 60-100

United States (National Health and Nutrition
Examination Survey)
1999-2004, n= 1196, age 60-84

United States (Health and Retirement Survey)
2006-2012, n=13,634, age 60-100

life expectancy vs. gross domestic product



12 biomarkers

Metabolic: HbA1c, Fasting glucose

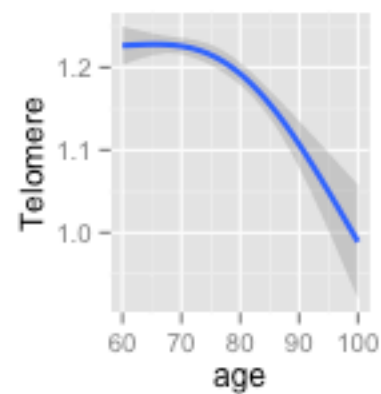
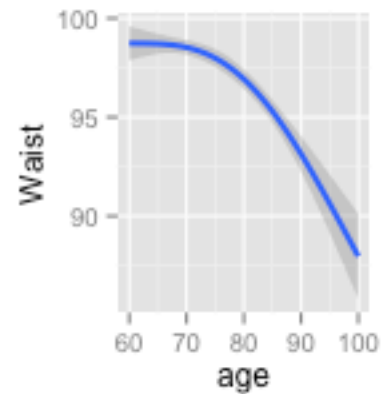
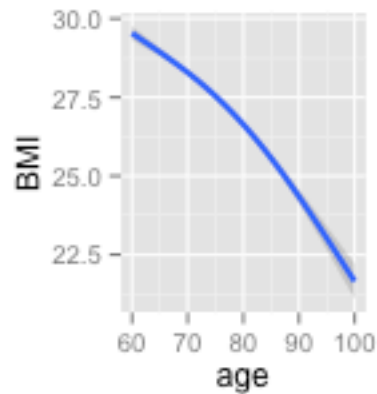
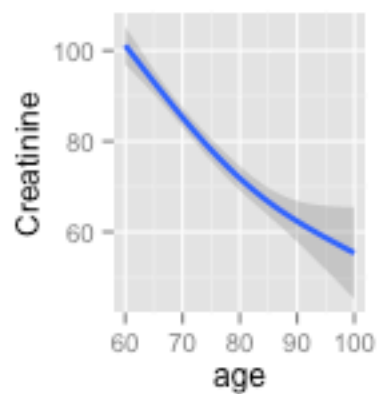
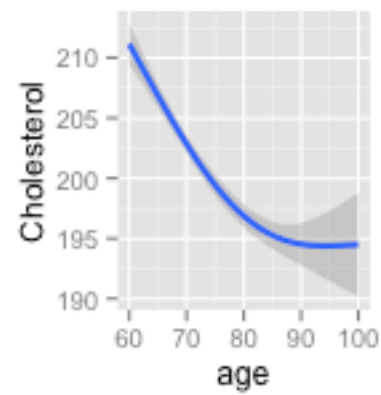
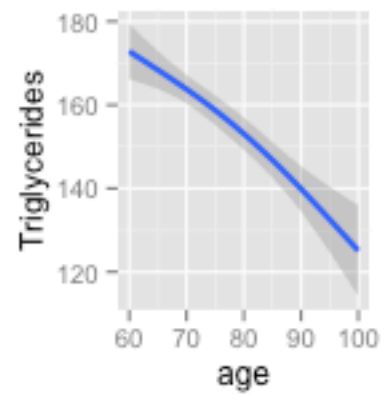
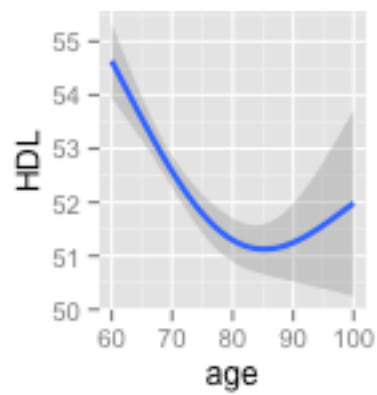
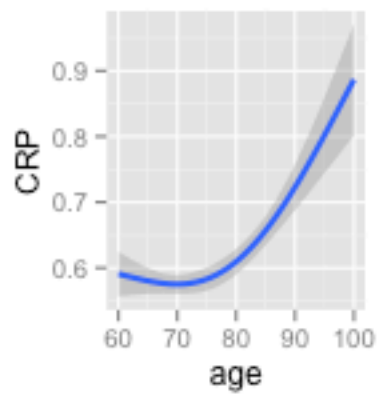
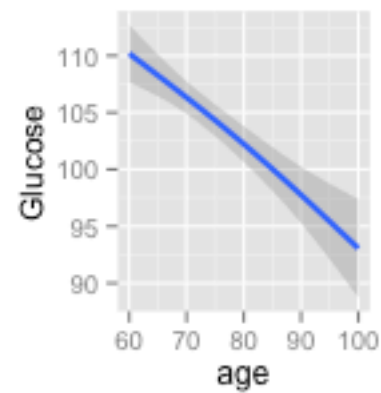
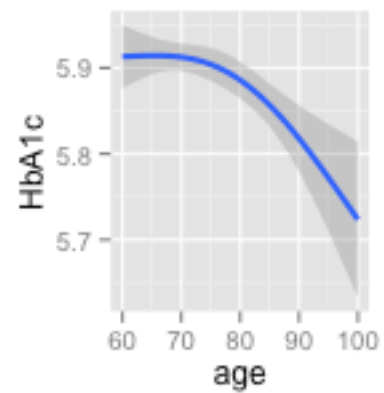
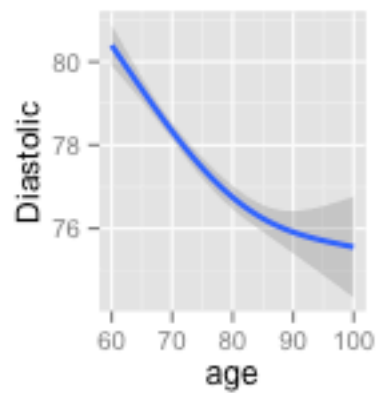
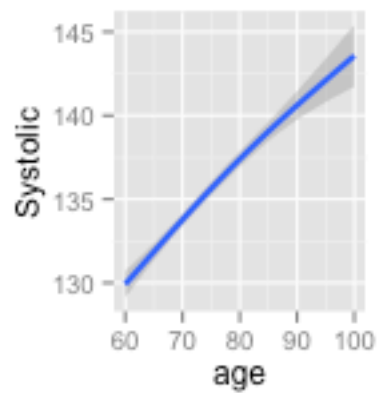
Cardiovascular: Systolic blood pressure, Diastolic blood pressure

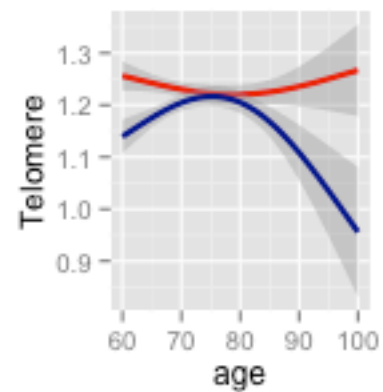
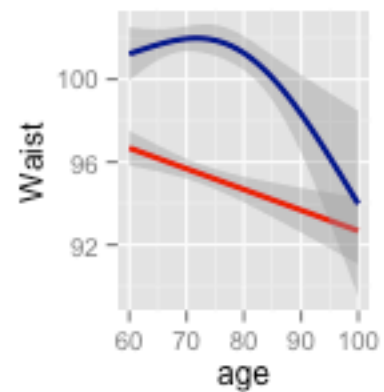
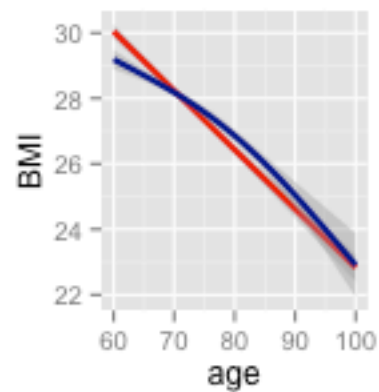
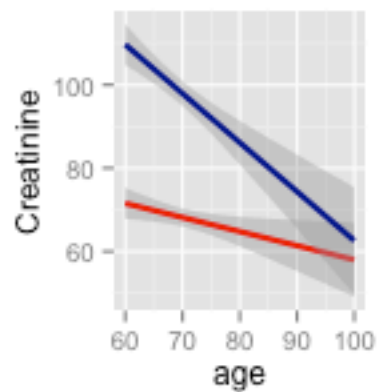
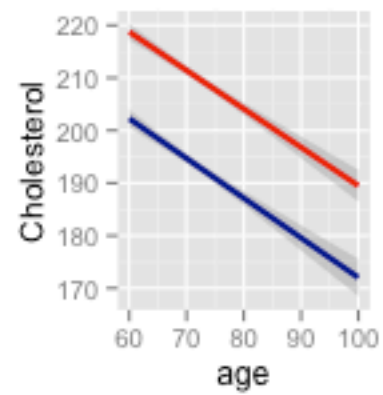
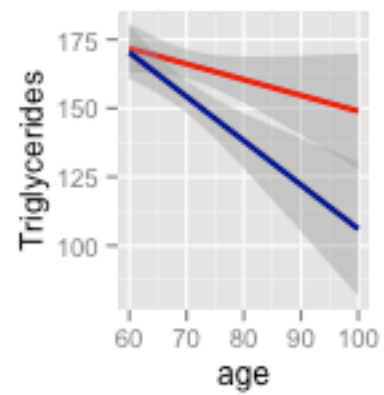
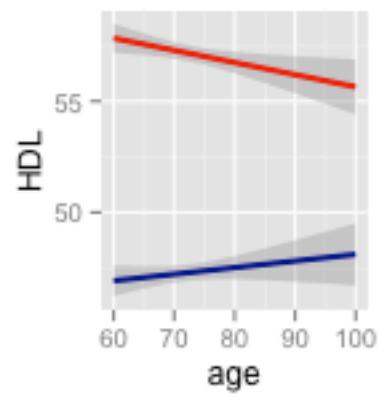
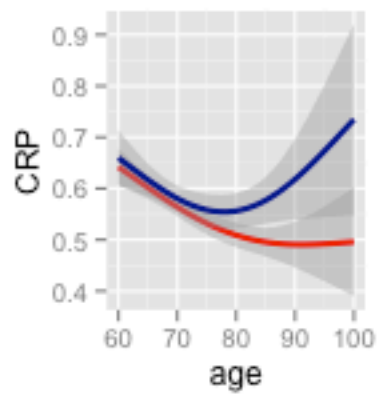
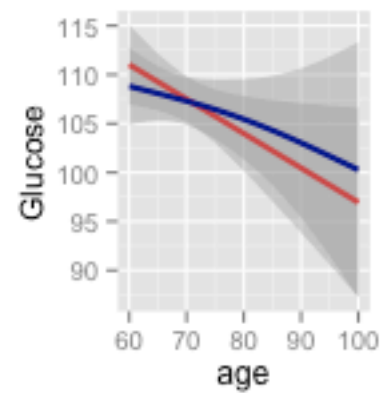
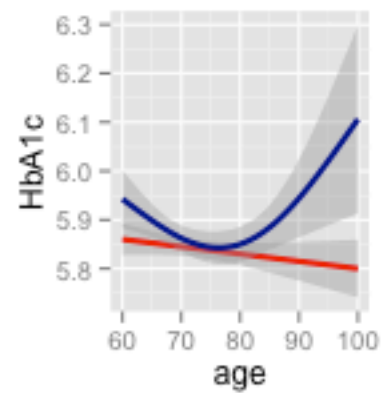
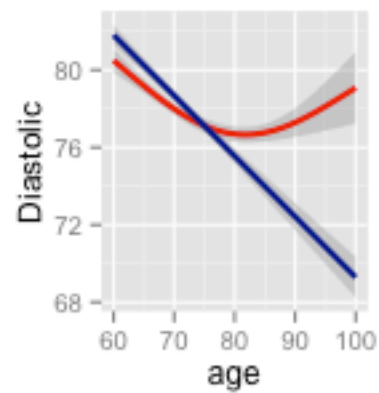
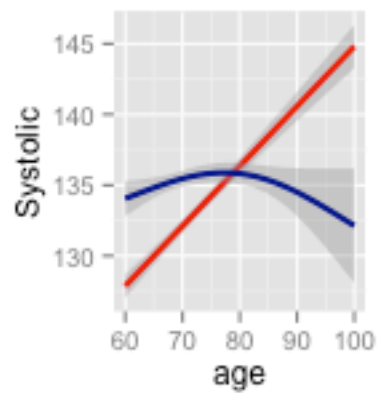
Lipids: Total cholesterol, HDL cholesterol, Triglycerides

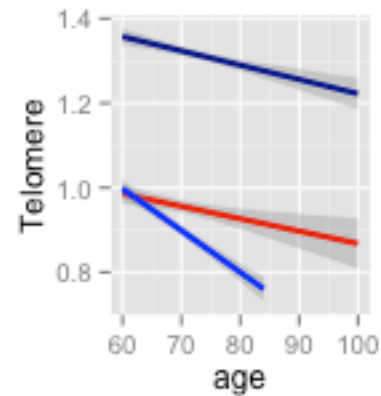
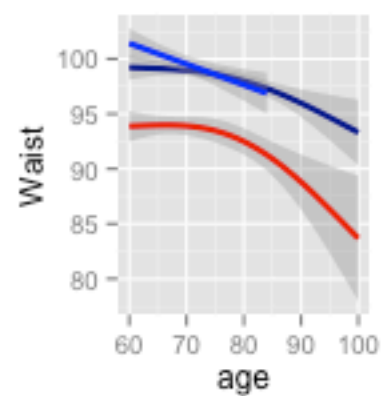
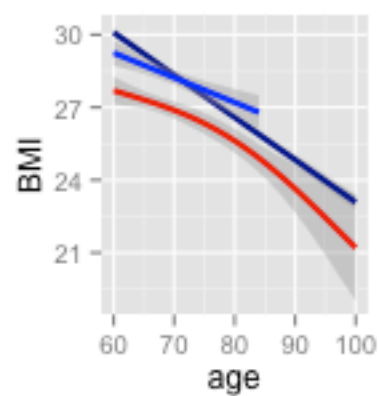
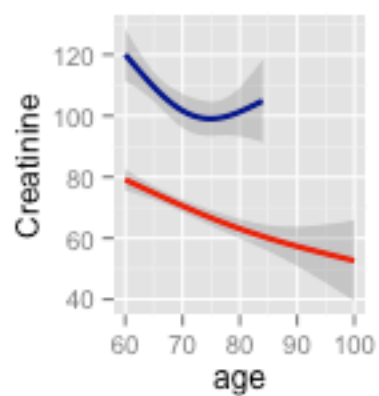
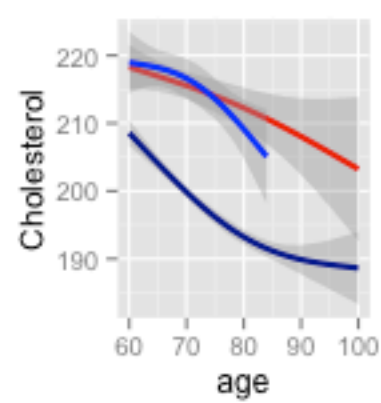
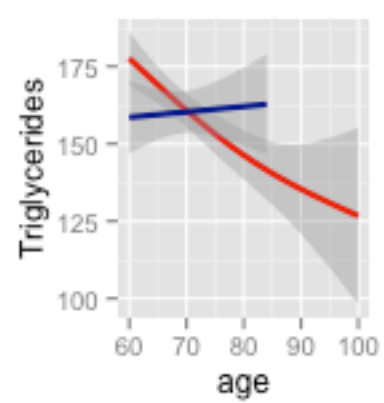
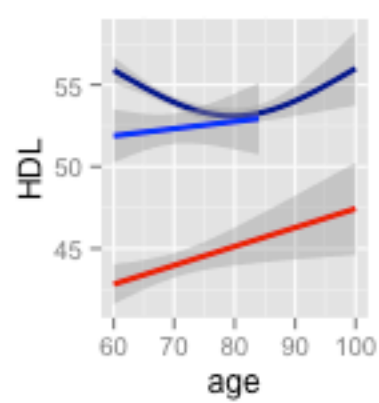
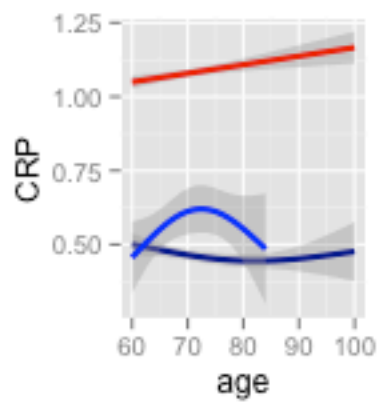
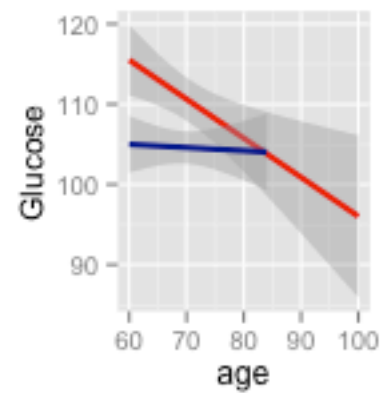
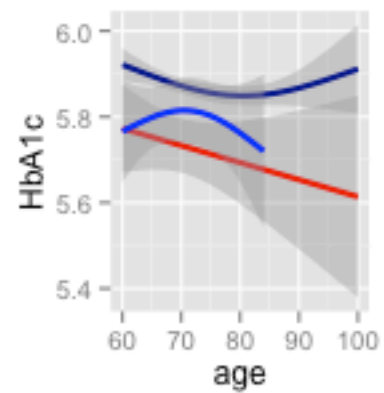
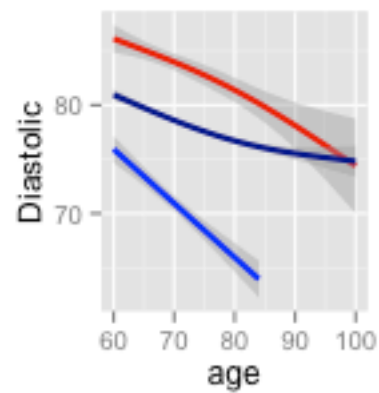
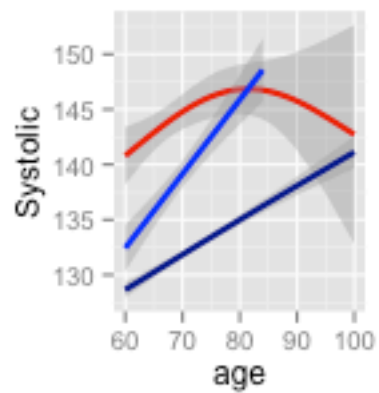
Immune system: C-reactive protein, Telomere length

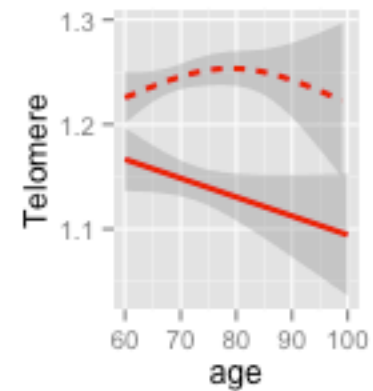
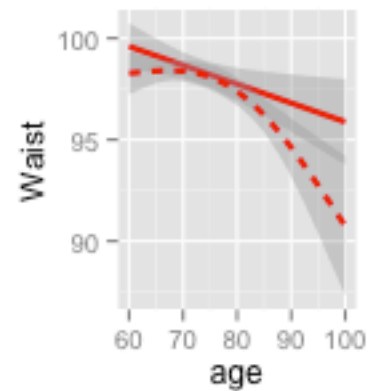
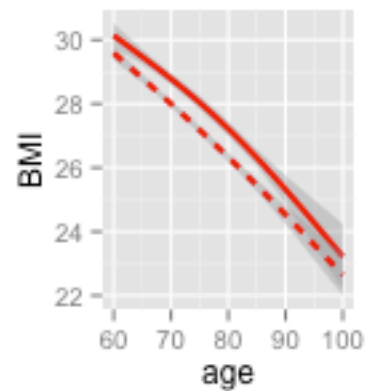
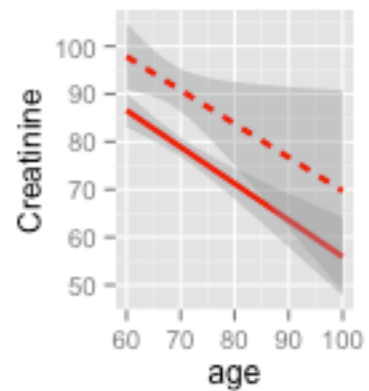
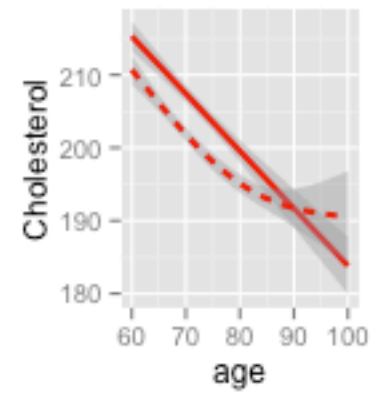
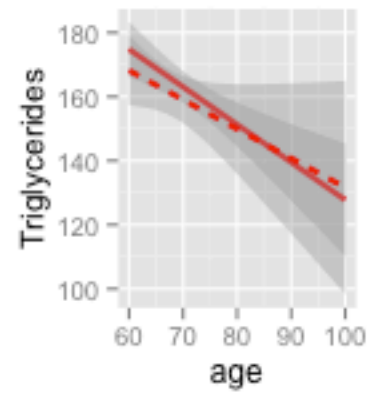
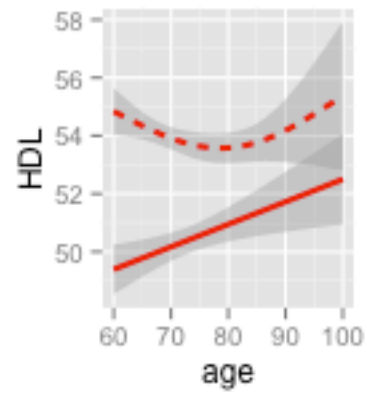
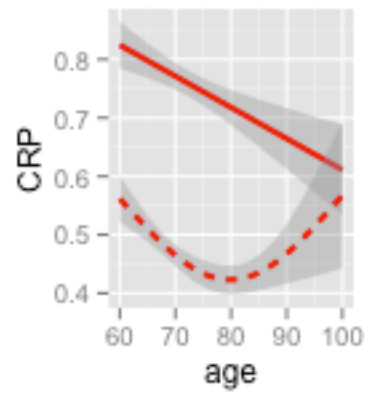
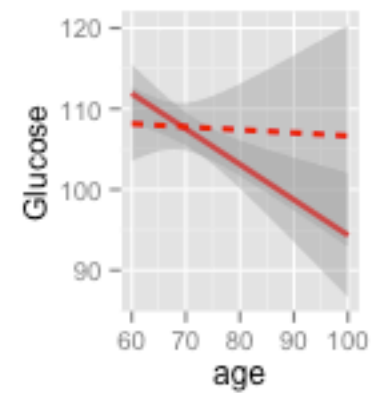
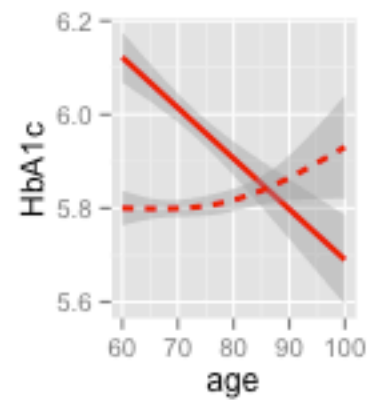
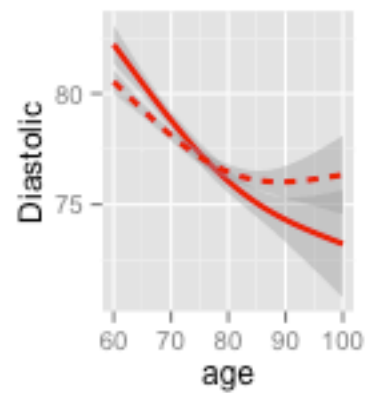
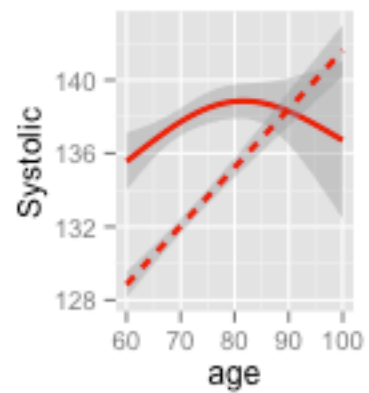
Organ specific function: Creatinine

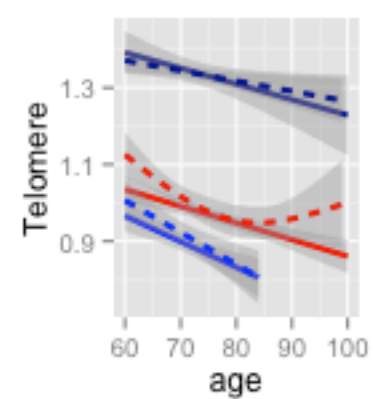
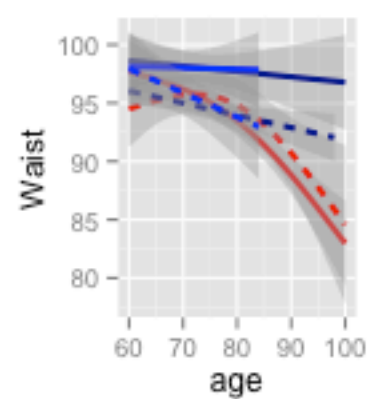
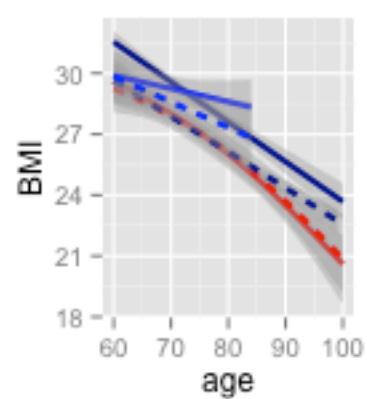
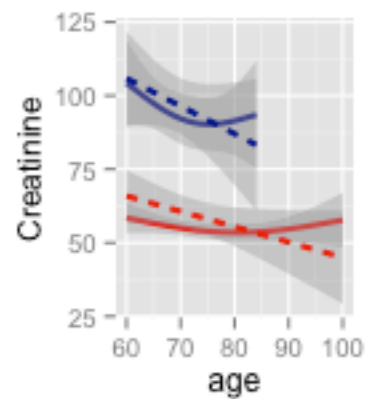
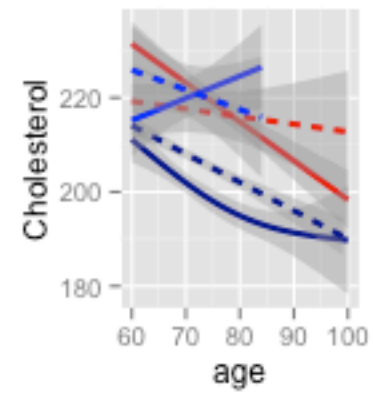
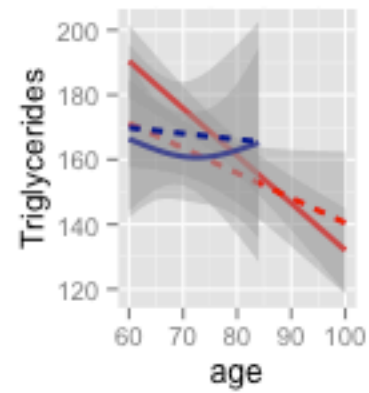
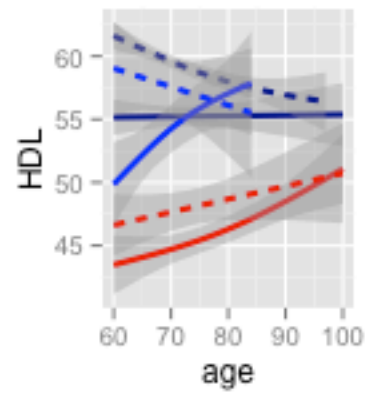
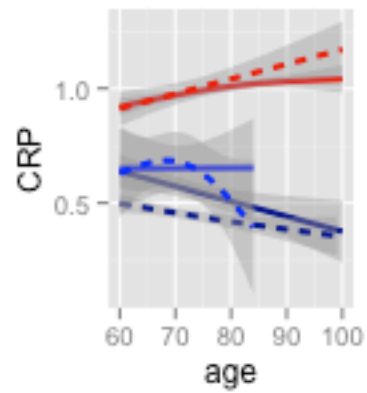
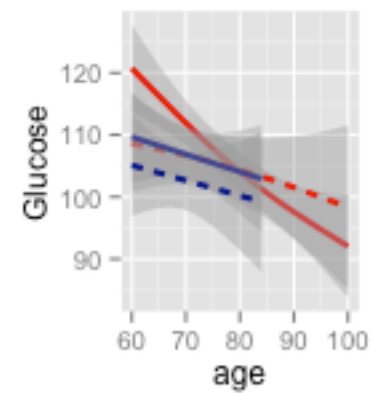
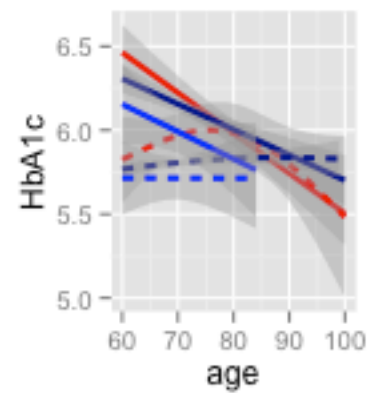
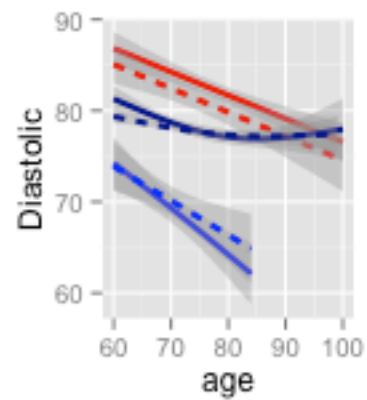
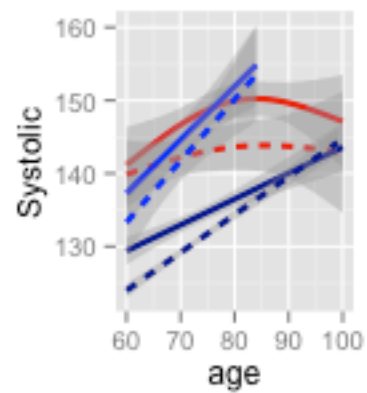
Anthropometric: Body mass index, Waist circumference

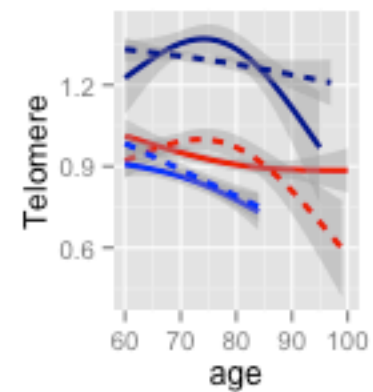
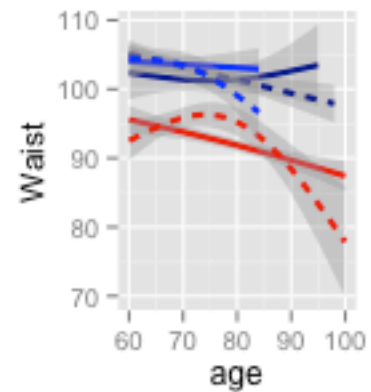
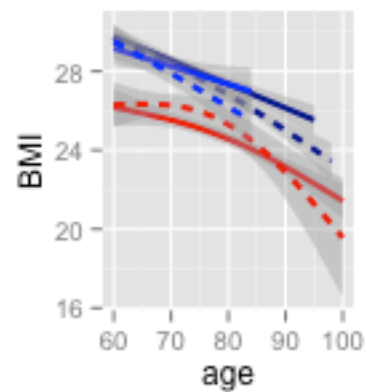
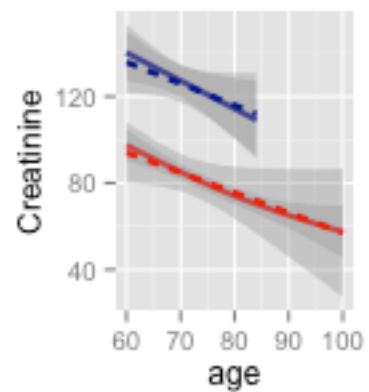
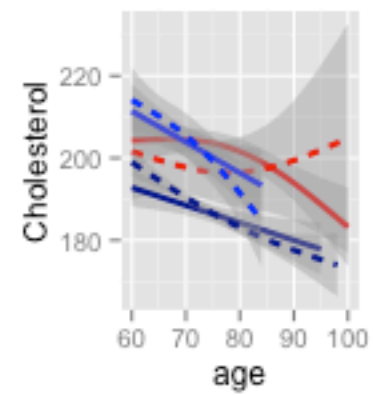
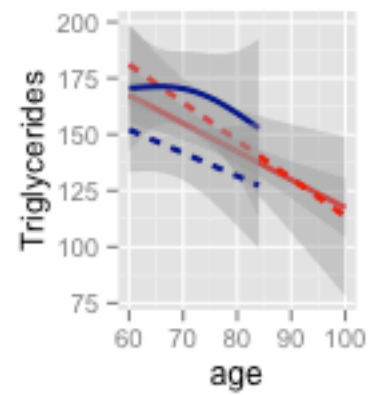
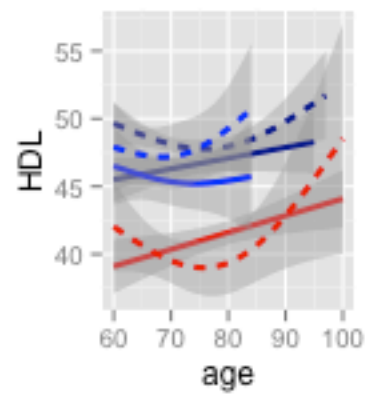
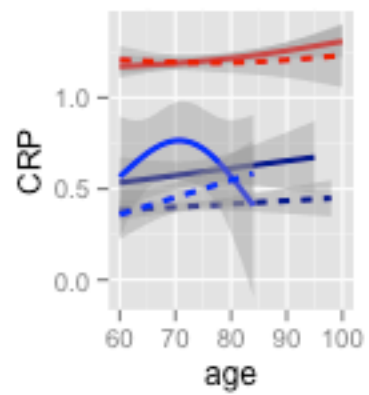
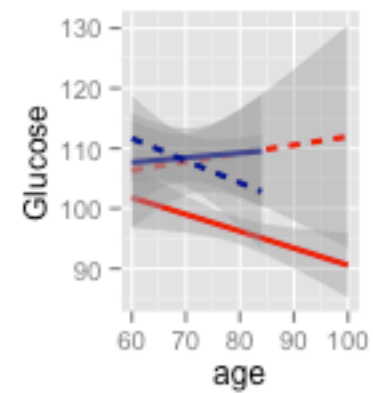
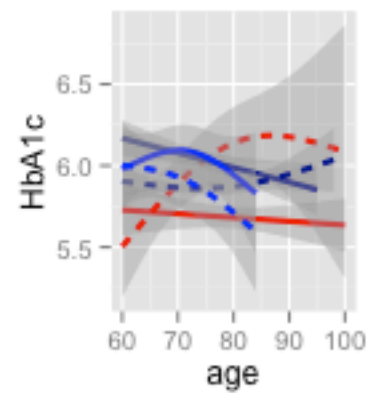
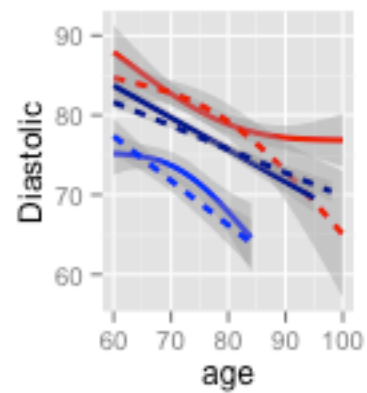
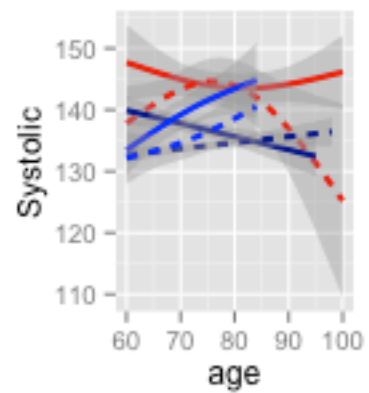












Caveat: age and cohort effects

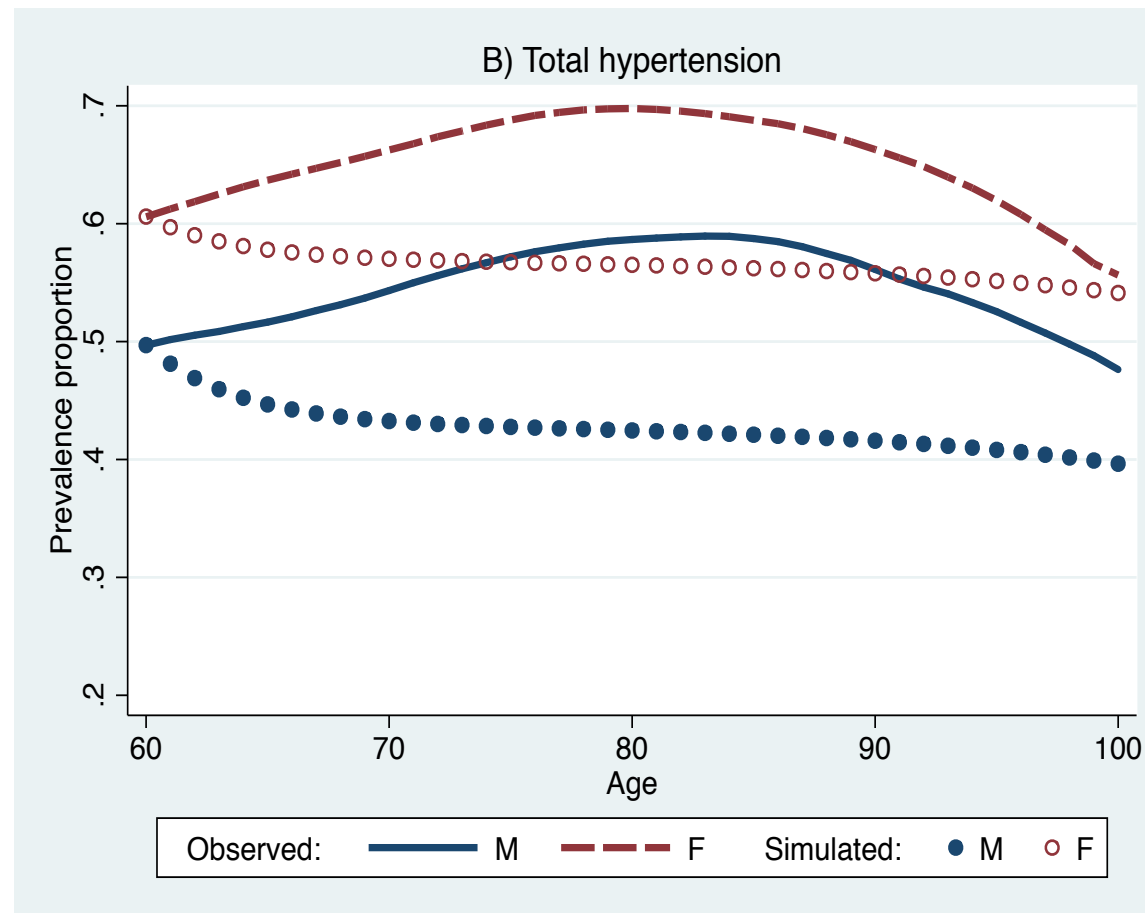
Our descriptive presentations have examined cross-sectional associations between age and biomarkers.

We use a STELLA based systems model to simulate population prevalence of biomarkers across ages *when age related change of biomarkers remains constant* despite changes in population composition.

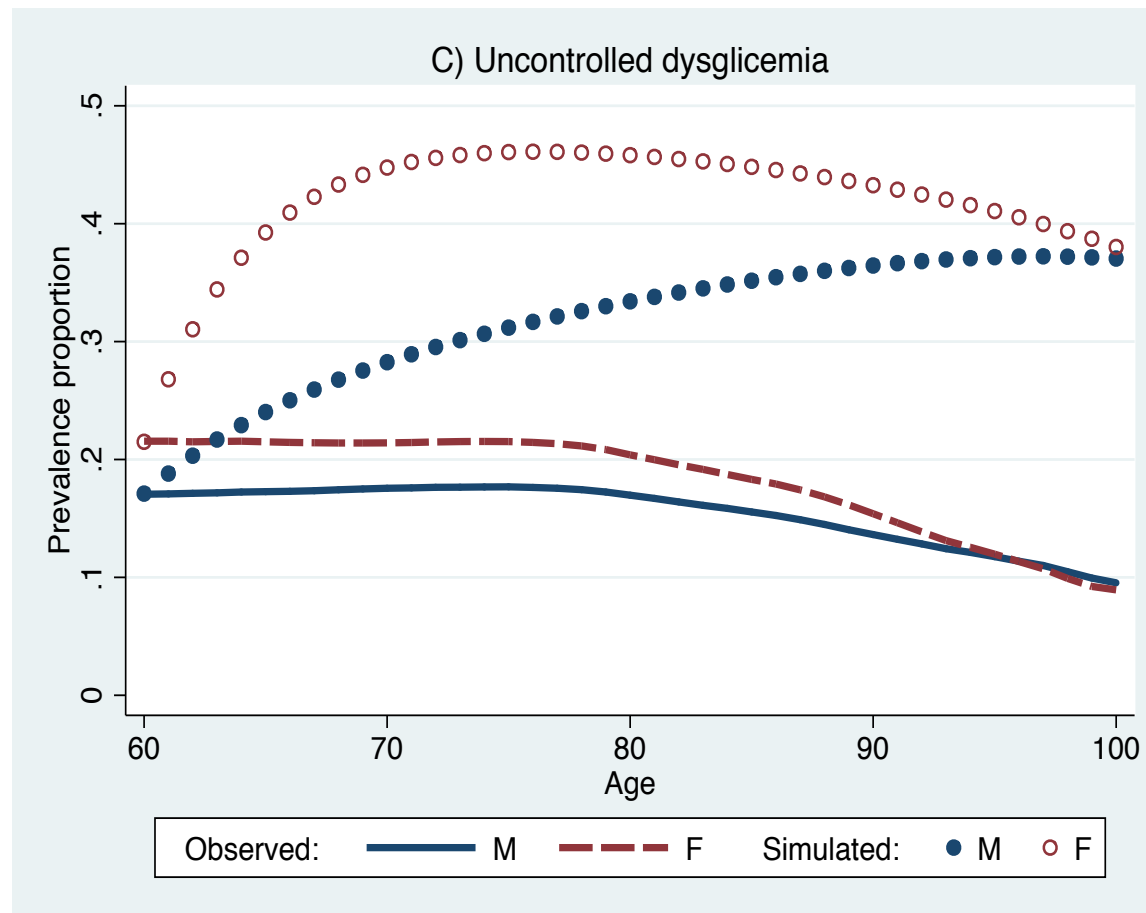
This enables the examination of potential contribution of individuals selecting out of the population to age specific biomarker means.

Conditions	Males		Females	
Uncontrolled hypertension				
Incidence rate (S.E.)	0.0638 (0.0033)	• 1.0112 ^x (0.0024)	same	
Remission rate (S.E.)	0.2873 (0.0134)		same	
Death rate ratio* (S.E.)	0.7493 (0.0769)		same	
Total hypertension				
Incidence rate (S.E.)	0.1098 (0.0076)		0.1514 (0.0088)	
Remission rate (S.E.)	0.1453 (0.0106)		0.1142 (0.0086)	
Death rate ratio* (S.E.)	1.1820 (0.0905)		same	
Uncontrolled dysglycemia				
Incidence rate (S.E.)	0.0440 (0.0082)	• 1.0205 ^x (0.0085)	0.1030 (0.0139)	• 0.9961 ^x (0.0069)
Remission rate (S.E.)	0.1065 (0.0146)		same	
Death rate ratio* (S.E.)	1.3859 (0.1614)		same	
BMI obesity				
Incidence rate (S.E.)	0.0393 (0.0058)	• 0.9737 ^x (0.0079)	same	
Remission rate (S.E.)	0.0753 (0.0132)	• 1.0397 ^x (0.0087)	0.0562 (0.0092)	• 1.0397 ^x (0.0087)
Death rate ratio*	1.0000		same	

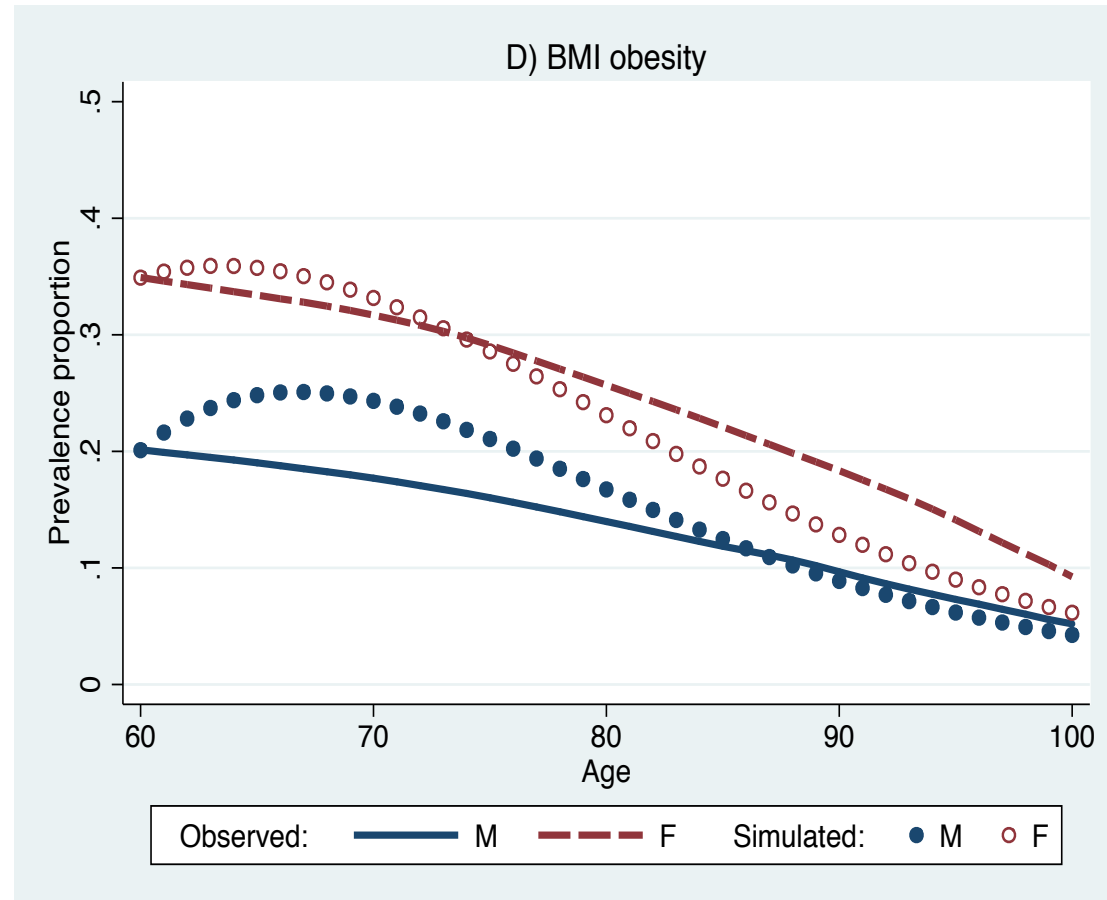
Hypertension: Observed and Simulated



Dysglycemia: Observed and Simulated



Obesity: Observed and Simulated

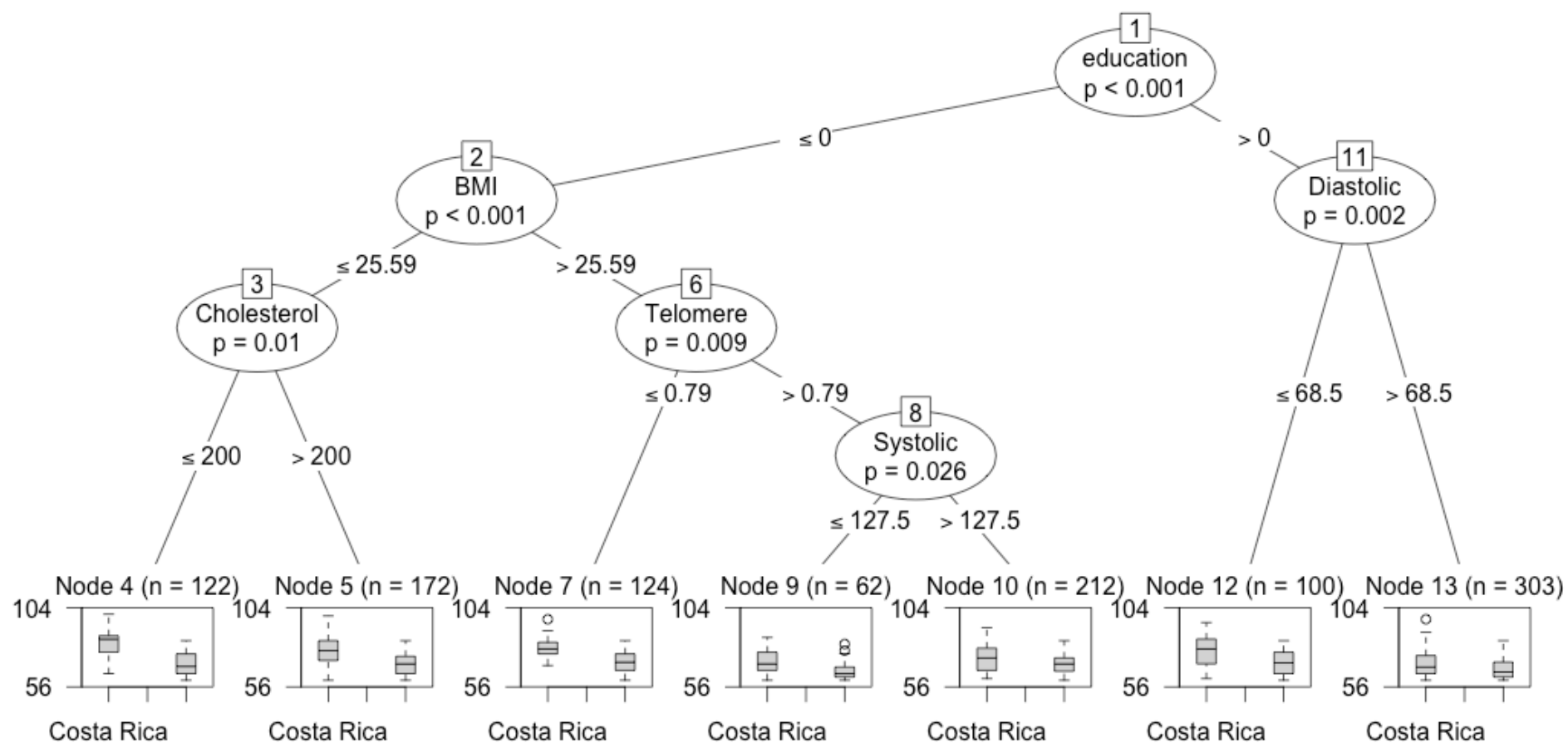


Subgroups and interactions between biomarkers

Use model based Recursive partitioning is an automated method for creating a regression tree (“party” package in R). Fixed part of model is **country**.

1. Splitting (partitioning)
2. When to stop (terminal nodes)
3. Pruning (optimized by 10 fold cross-validation)

Question: What subgroups of biomarkers best explain the differential relation between age and country?



Variance of age explained

	edf	Ref.df	F	p-value	
s (Systolic)	3.691	4.644	27.185	< 2e-16	***
s (CRP)	7.881	8.654	6.823	2.04e-09	***
s (HDL)	7.085	8.151	2.968	0.00241	**
s (Telomere)	6.931	8.059	6.739	7.20e-09	***

R-sq. (adj) = 0.0429 Deviance explained = 4.63%

Variance of age explained

	edf	Ref.df	F	p-value	
s (Diastolic)	6.427	7.434	32.823	< 2e-16	***
s (Systolic)	2.996	3.843	98.240	< 2e-16	***
s (Cholesterol)	2.249	2.893	52.480	< 2e-16	***
s (BMI)	4.205	5.283	106.087	< 2e-16	***
s (Telomere)	6.474	7.668	5.136	3.72e-06	***

R-sq. (adj) = 0.146 Deviance explained = 14.8%

Variance of age explained

	edf	Ref.df	F	p-value	
s (Diastolic)	1.000	1.000	57.145	8.38e-14	***
s (Systolic)	1.000	1.000	64.211	2.76e-15	***
s (Cholesterol)	1.571	1.974	3.179	0.04276	*
s (BMI)	2.592	3.370	10.081	6.27e-07	***
s (Telomere)	2.070	2.672	9.008	2.57e-05	***
s (HbA1c)	3.874	4.796	3.041	0.01126	*
s (Creatinine)	1.000	1.000	20.739	5.85e-06	***
s (CRP)	8.572	8.938	9.180	2.14e-13	***
s (Triglycerides)	1.000	1.000	8.297	0.00405	**
s (Glucose)	5.864	7.012	1.552	0.14571	
s (HDL)	1.000	1.000	1.604	0.20557	
s (Waist)	1.000	1.000	6.589	0.01039	*
R-sq. (adj) = 0.248 Deviance explained = 26.9%					

Summary 1: Descriptive analysis

In aggregate, there appears to be four biomarkers associated with aging: systolic blood pressure, CRP, HDL cholesterol and telomere length.

Less consistency once we look by education, gender and place.

Systolic associated with older age in U.S., but not in Costa Rica, and weakly among men.

CRP increasing among women, but among men only in Costa Rica.

Telomere length decreases with age across place, gender and education groups.

Summary 2: Caveats and Limitations

By using longitudinal measures of biomarkers with simulation modeling, we are able to consider plausible contributions of age and cohort effects.

Future work to examine the validity of biomarkers of aging should where possible consider selection out of populations.

Ongoing work should more explicitly include interactions.

Summary 2: Caveats and Limitations

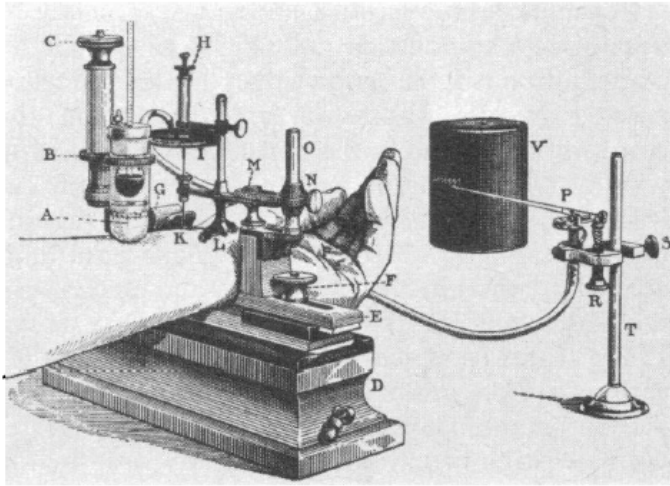


Fig 6 Von Basch's sphygmomanometer and stand, invented about 1881. Despite its unwieldy appearance this is a simple device. The india rubber cap, A, rests on the radial artery and the arm is clamped between E and G. K is a fine pad which also rests against the artery. H is a fine screw by which the tambour of the sphygmograph can be adjusted and P is one of Marey's tambours which communicates by a piece of elastic tubing with the tambour of the sphygmograph (by courtesy of the Wellcome Trustees)



Summary 2: Caveats and Limitations

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Metabolic Phenotyping in Health and Disease

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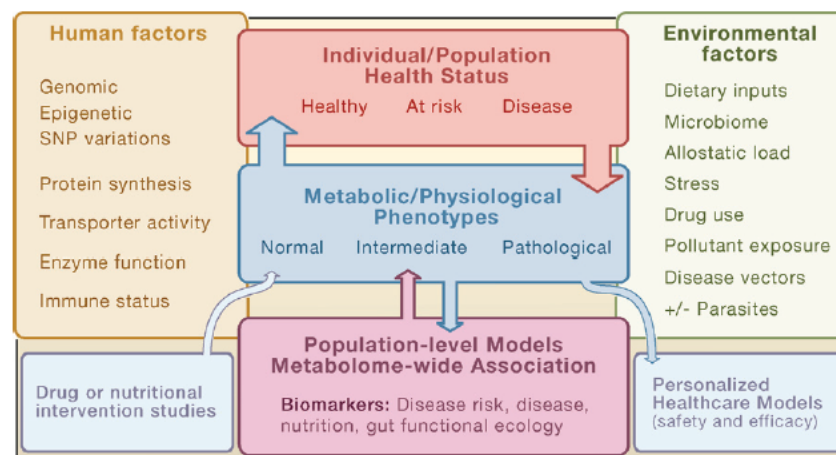


Figure 1. Interactions between Genes and the Environment and Their Effects on Health

Metabolic phenotypes (metabotypes) can be measured by profiling small molecules (<1 kDa) in biofluids (usually urine or blood) by spectroscopic techniques such as NMR. Metabolic phenotypes are influenced by intrinsic and environmental factors that determine health status and disease risk of an individual or group. Measuring and modeling the profile of all metabolites (metabolome) in an individual may provide insights into disease risk factors and etiology, information that could be used for personalized medicine.

Summary 3: Moving forward on biomarkers of aging.

2. The biomarker should reflect some basic biological process of aging and **certainly not the predisposition toward a disease state** or some inborn error in metabolism.
3. The biomarker should have **high reproducibility in cross-species comparisons** of functional or physiological age versus chronological age, particularly within the same classes and certainly within the same families of species.

Our analyses suggest that these requirements may be in opposition. That what is basic and conserved across species (3) is also not likely to be reflective of environmental influences but rather “predisposition” (2). By examining population subgroups, we show biomarkers of aging differ by context.

Thank you.



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