Prevention, Early Warning and Causality in Metabolic Disease

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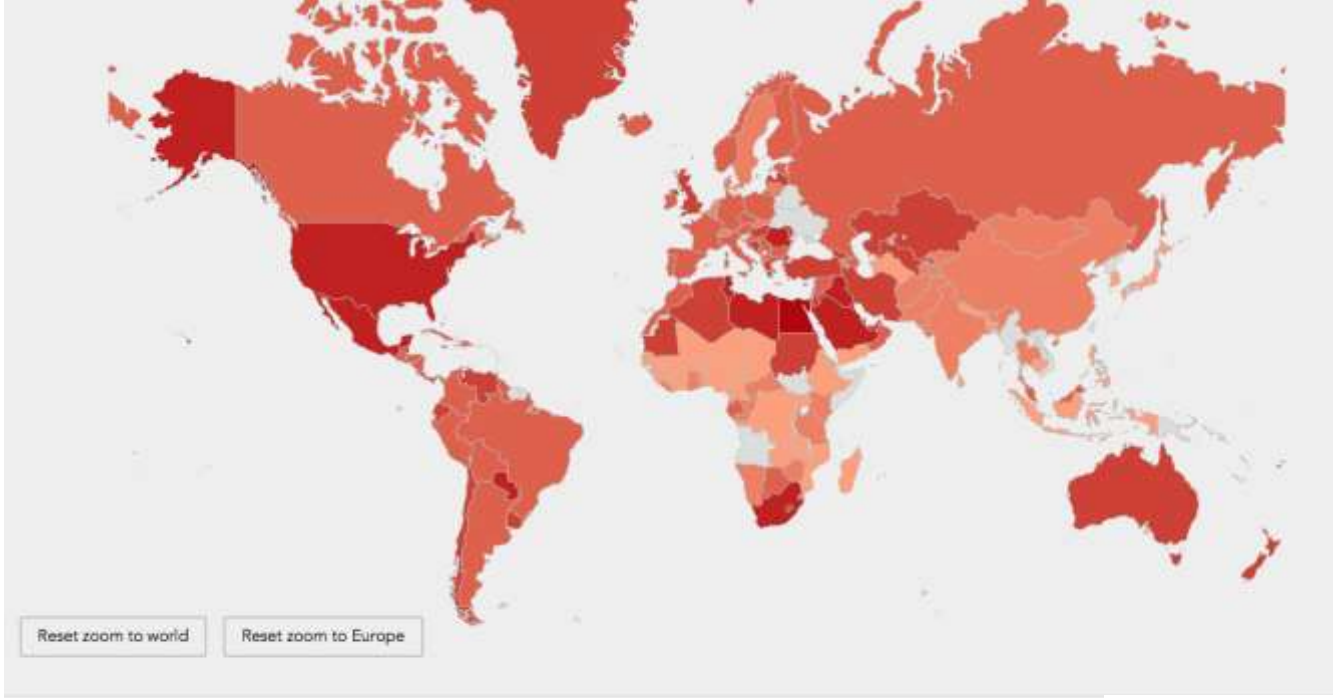
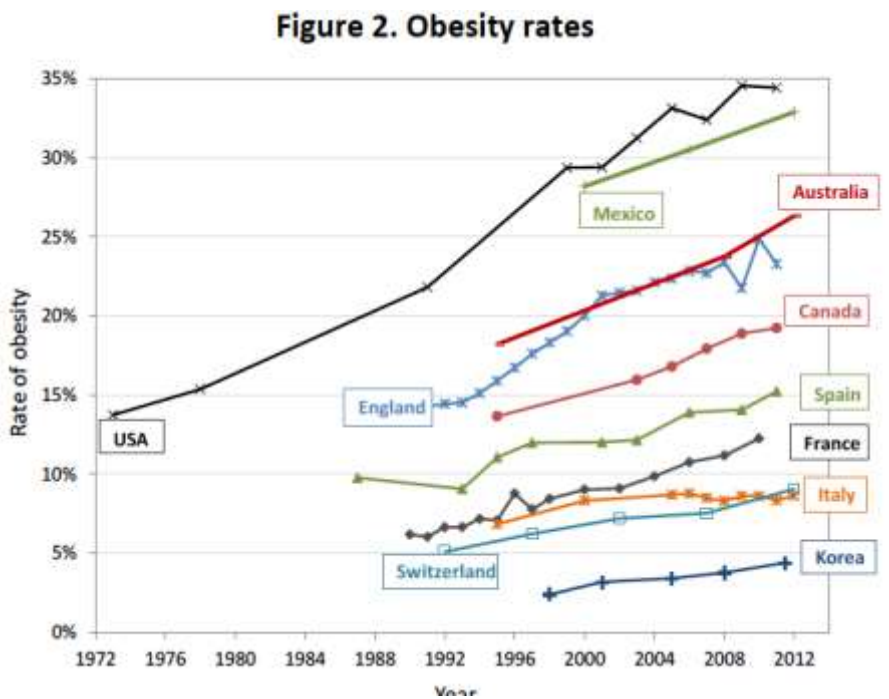
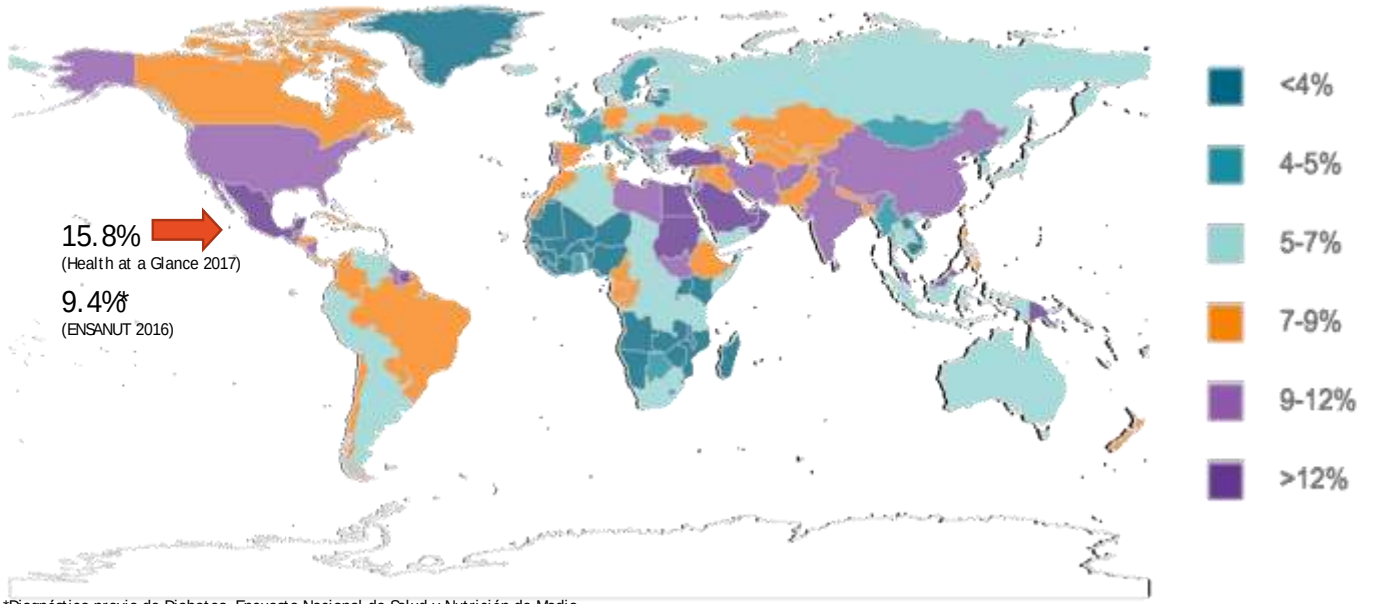
Why are they Important?





Because they're everywhere and getting worse



*Diagnóstico previo de Diabetes. Encuesta Nacional de Salud y Nutrición de Medio Camino 2016 (ENSANUT MC 2016) Informe final de resultados

OECD (2017), *Health at a Glance 2017: OECD Indicators*, OECD Publishing, Paris. *http://dx.doi.org/10.1787/health_glance-2017-en*

International Diabetes Federation. *IDF Diabetes Atlas, 8th edn.* Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org

And we're not doing a very good job at stopping them!

Estimates of Funding for Various Research, Condition, and Disease Categories NIH

Research/Disease Areas	FY 2016Actual (Dollars in millions)	2015 US Mortality	2015 US Prevalence (Standard deviation)
Cancer	5589.00	652,672	8.7% (0.20%)
Cardiovascular	2108.00	1,464,485	-
Chronic Obstructive Pulmonary Disease	97.00	292,471	6.2% (0.18%)
Diabetes 4/	1084.00	252,806	9.7% (0.22%)
Digestive Diseases	1745.00	-	-
Heart Disease	1289.00	1,202,319	11.7% (0.26%)
Heart Disease - Coronary Heart Disease	419.00	536,339	6.1% (0.17%)
Hypertension	224.00	427,631	27.0% (0.33%)
Inflammatory Bowel Disease	126.00	2,966	-
Obesity	965.00	39,590	30.0% (0.38%)
Stroke	308.00	234,867	-
	13,954	5,106,146	
% of total	17%	73%	
Physical Activity	392.00	-	-
Prevention	7566.00	-	-
Tobacco	299.00	-	-
Nutrition	1615.00	-	-
Basic Behavioral and Social Science	1804.00	-	-
Behavioral and Social Science	4137.00	-	-
	15,813		

Are there Early Warnings for Metabolic Diseases?

Of course there are!

Many

But first…

Just what is an “Early Warning”?

There are two principal components:

A Prediction

$P(C(t)|\mathbf{X}(t'))$

And a rule

IF(CONDITION) THEN (ACTION)

where the CONDITION will depend on the prediction

$P(C(t)|\mathbf{X}(t'))$ What do we need for this to be useful?

- An EW for what? C(t)

- What indicates the EW?
  - $\mathbf{X}(t') = (X_1(t), X_2(t), \ldots, X_N(t))$ one or more factors

- What's the reliability of the Early Warning?
  - The predictability of the classifier P(. | .)
    - e.g. If $P(C(t)|\mathbf{X}(t')) \sim P(C(t))$ then its not a very reliable EW
- Is the EW actionable?
  - i.e., if we observe it can we do something to prevent C from occurring or alleviate its impact? If this is the case then we're changing $P(C(t)|\mathbf{X}(t'))$!

- Just how “early” is the EW?
- Depends on t-t’ (t > t’ causality)
- For t ~ t’ its not very early
- If t’ << t it may be *too early*

Preventative vs. curative medicine
Are you already in the state or not?

Even in the case that t ~ t’ it can still be very useful. In fact, its just standard medical diagnostics…

P(**X**(t)|C(t)) - The likelihood that you see the symptoms **X**(t) given the disease state C.

IF(P(**X**(t)|C(t)) > P_c) THEN (diagnose C)

Usually the heuristic P(**X**(t)|C(t)) is an estimate from the doctor.
Maybe some factors $X_i(t)$ are easier to measure but not standardly used. E.g., the spectrum of fluctuations of a time series, such as an ECG.

Biorhythm Scales

- From intra-cellular signaling
- to inter-cellular signaling
- to organ/organ signaling
- to environment/organ interactions
  - behavior: foraging, eating, sleep, etc.
- to behavior change and
- Evolution

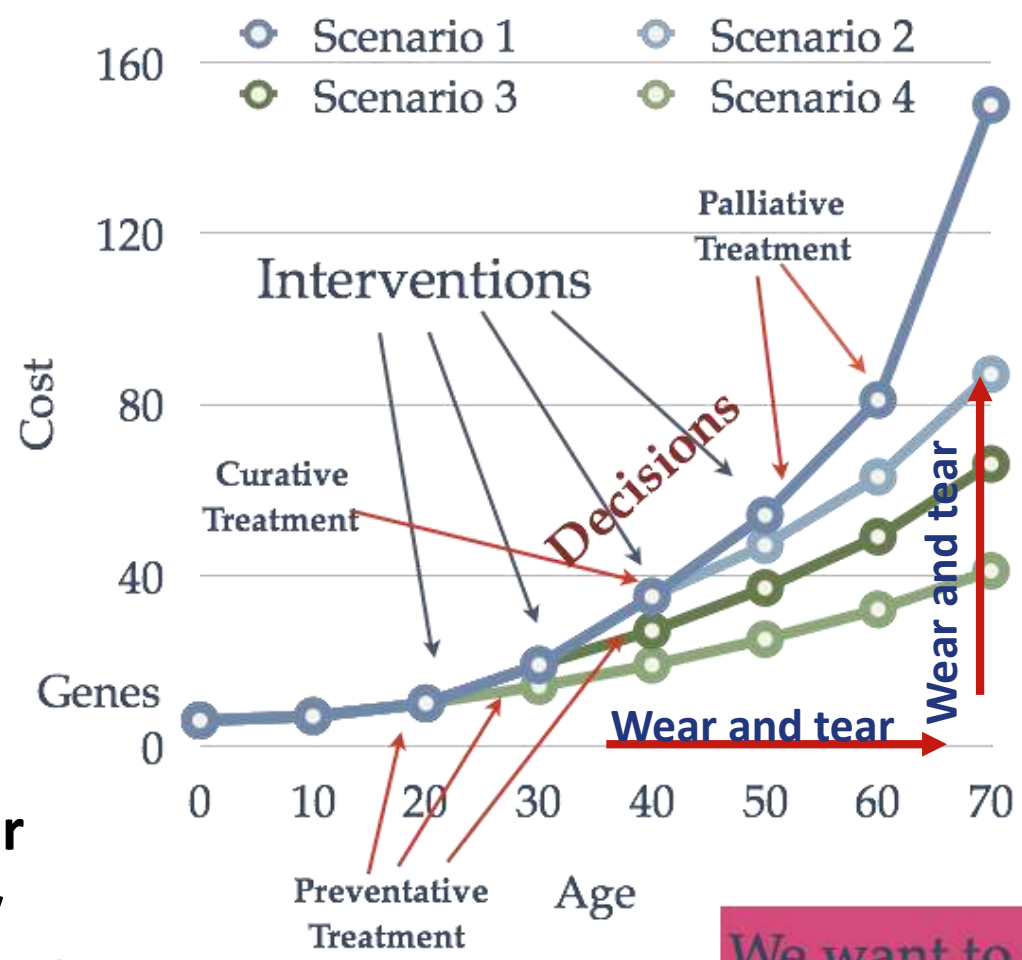
ms vs sec vs mins vs hours vs days vs weeks vs years vs…
“micro” versus “macro” homeostasis

What is the nature of the corresponding time series?
What is the natural variational scale?
What is the natural coarse graining scale?
When does the time series reflect adaptive versus ”deterministic” behavior?
Does it reflect homeostasis? (Over what time scale?)

Time series are adaptive

Associated with conduct and decision making

This can be a proxy for the behavior of many different time series



Scenario 1: Onset of obesity at 20
Continued obesity and onset of metabolic syndrome at 40
Onset of diabetes at 50
Onset of renal failure at 60
Death at 70

Scenario 2: Onset of obesity at 20
Continued obesity and onset of metabolic syndrome at 40
Onset of diabetes at 50
Adequate control and treatment of comorbilities at 60
Bad health and high cost at 70

Scenario 3: Overweight at 20
Obesity at 40
Onset metabolic syndrome at 50
Onset of diabetes at 60
Continued diabetes but no serious comorbilities at 60
Ill health and moderate cost at 70

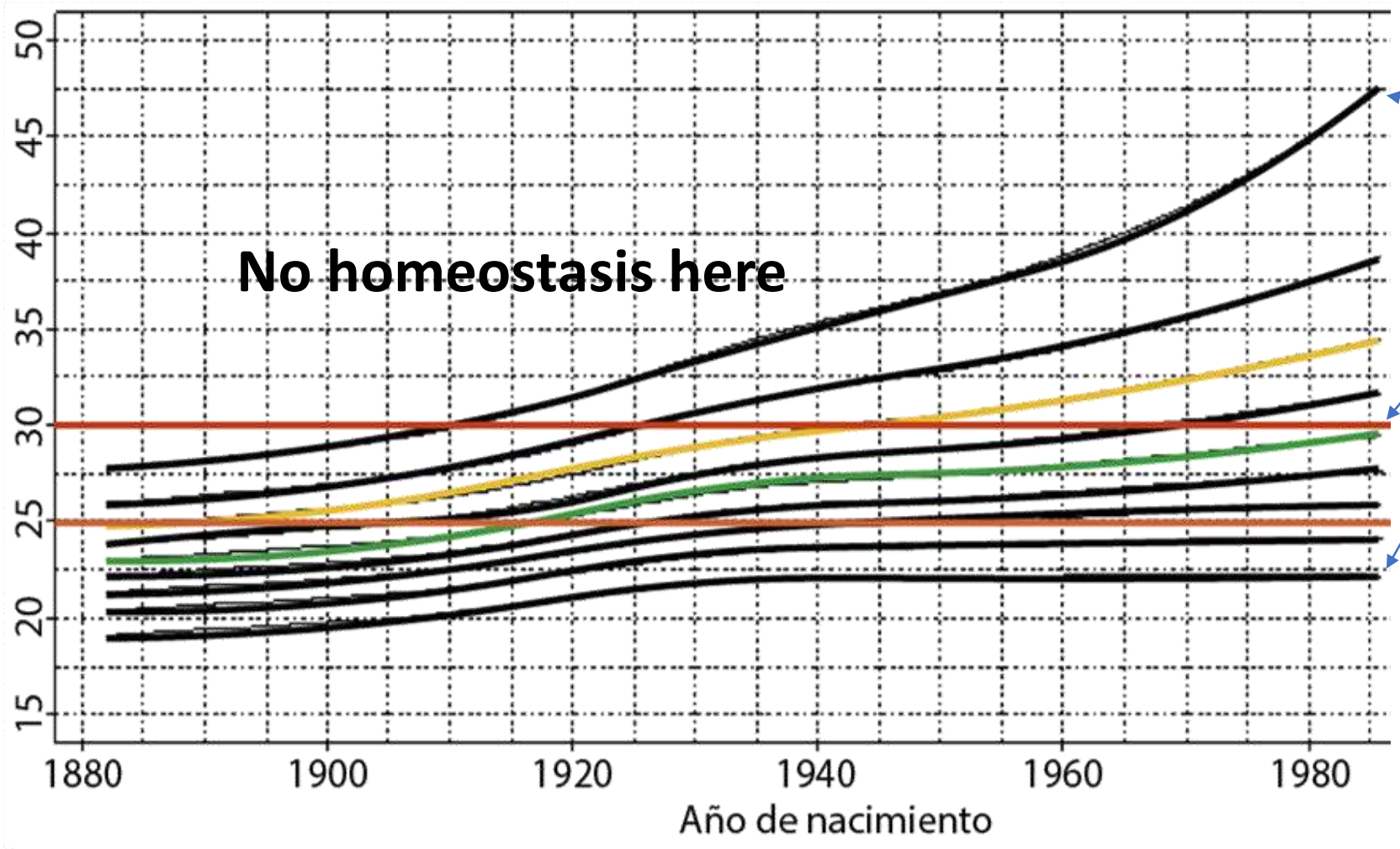
Scenario 4: Overweight at 30
Obesity at 50
Onset of metabolic syndrome at 60
Onset of diabetes at 70 but relative health

We want to predict and understand "histories"

There are EWs for passing from any one state to any other

Early warnings

Deciles trends in white US males by birth cohort



BMI Deciles

90th

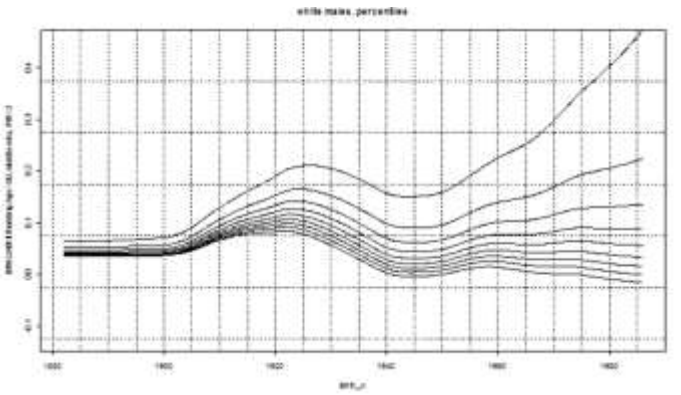
50th

10th

What factors (behaviours) are at the root of these differences?

Radical differences!

Rate of change of deciles trends

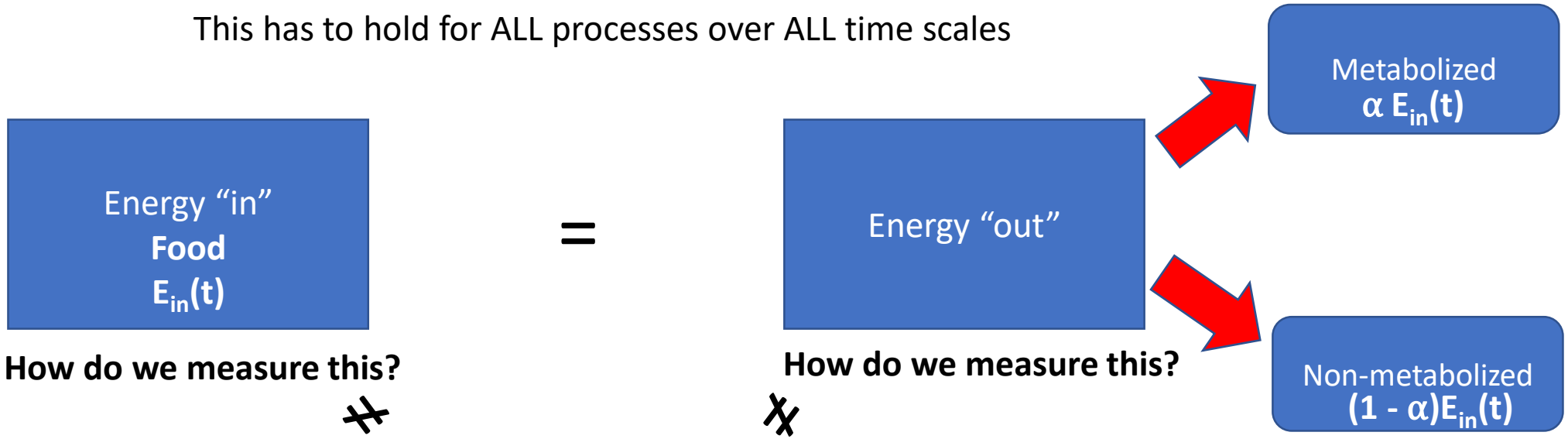


Remember: Evolution likes diversity

Komlos, J., & Brabec, M. (2010). The Trend of Mean BMI Values of US Adults, Birth Cohorts 1882-1986 Indicates that the Obesity Epidemic Began Earlier than Hitherto Thought. doi: 10.3386/w15862

Conservation of Energy

This has to hold for ALL processes over ALL time scales



How do we measure this?

How do we measure this?

Energy in > Energy needed is an EW for weight gain

Energy "needed"

How do we measure this?

And what does "Needed" mean anyway?

Energy “in”
Food

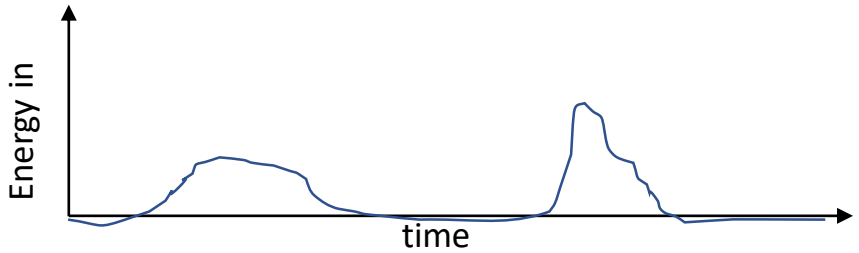
Behaviour in a given environment controls how much and what

Two principal dimensions: **Quantity** and “**Quality**”

How do we measure it?

The **gross energy** measured through bomb calorimetry is an upper limit on extractable energy

Standard calorie values try to account for digestibility



What happens to one unit of a given food?

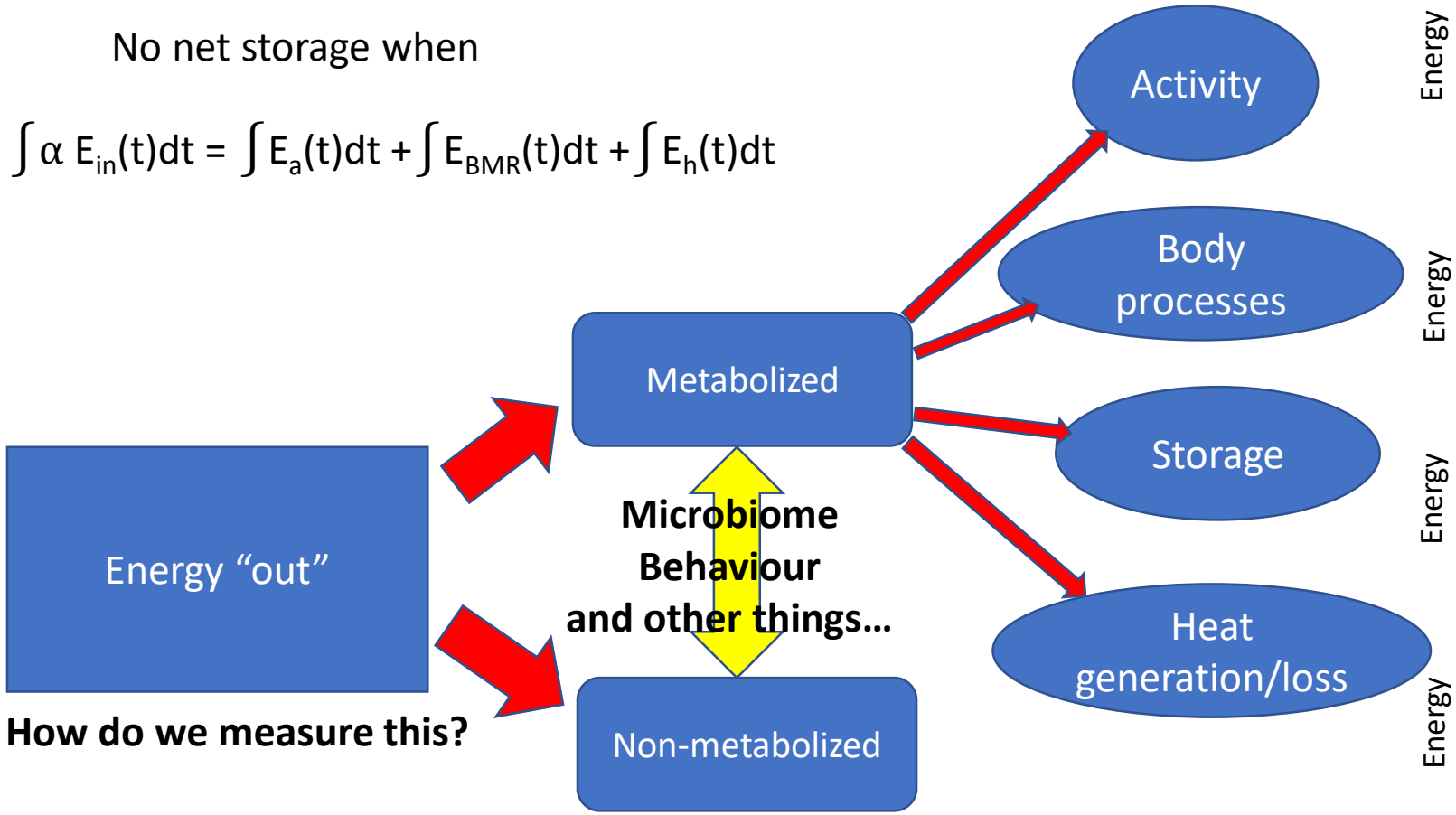
Extremely complex

Back to Energy Conservation

$$\int \alpha E_{in}(t)dt = \int E_a(t)dt + \int E_{BMR}(t)dt + \int E_f(t)dt + \int E_h(t)dt$$

No net storage when

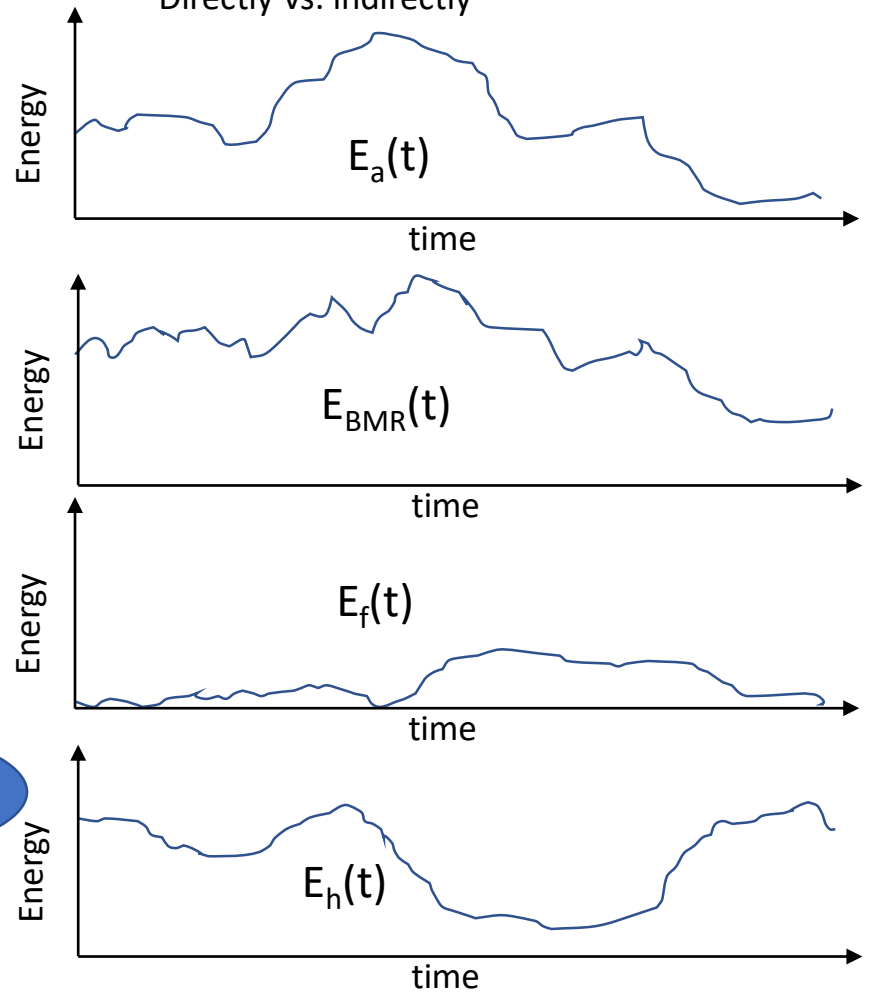
$$\int \alpha E_{in}(t)dt = \int E_a(t)dt + \int E_{BMR}(t)dt + \int E_h(t)dt$$



How do we measure this?

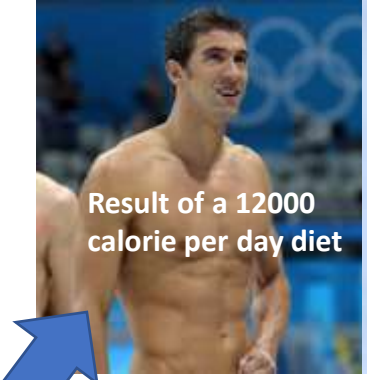
1) How do we measure these?

Directly vs. indirectly



2) How do they depend on behaviour?

3) How are they correlated in time?



Energy “needed”

Activity

Behaviour:
Direct and
Indirect

BMR

Behaviour:
Indirect

Heat generation

Behaviour:
Direct and
Indirect

Need versus Behaviour versus Environment

Needed for what?

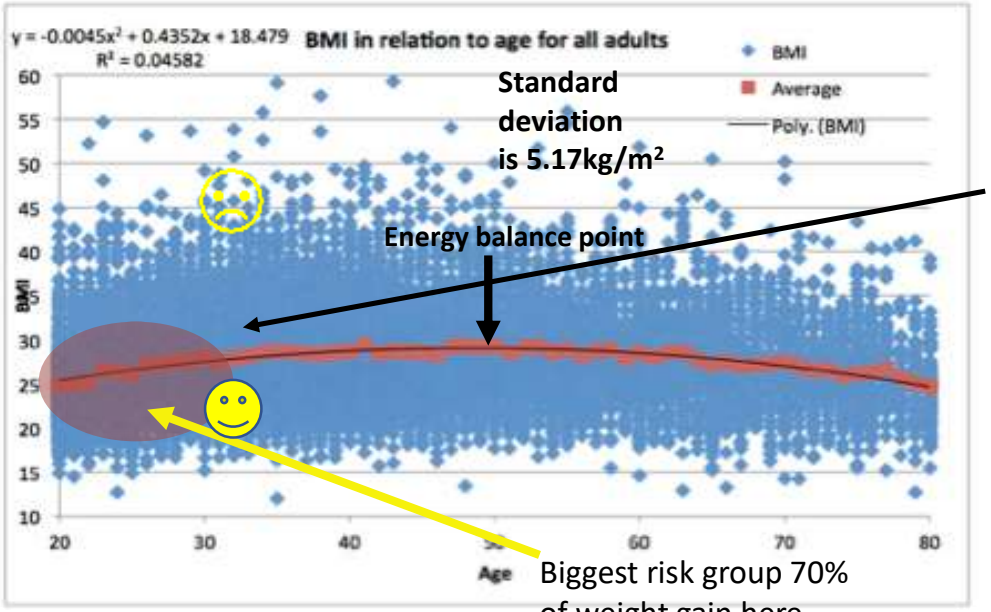
This is dependent on the environment both

now and in the future

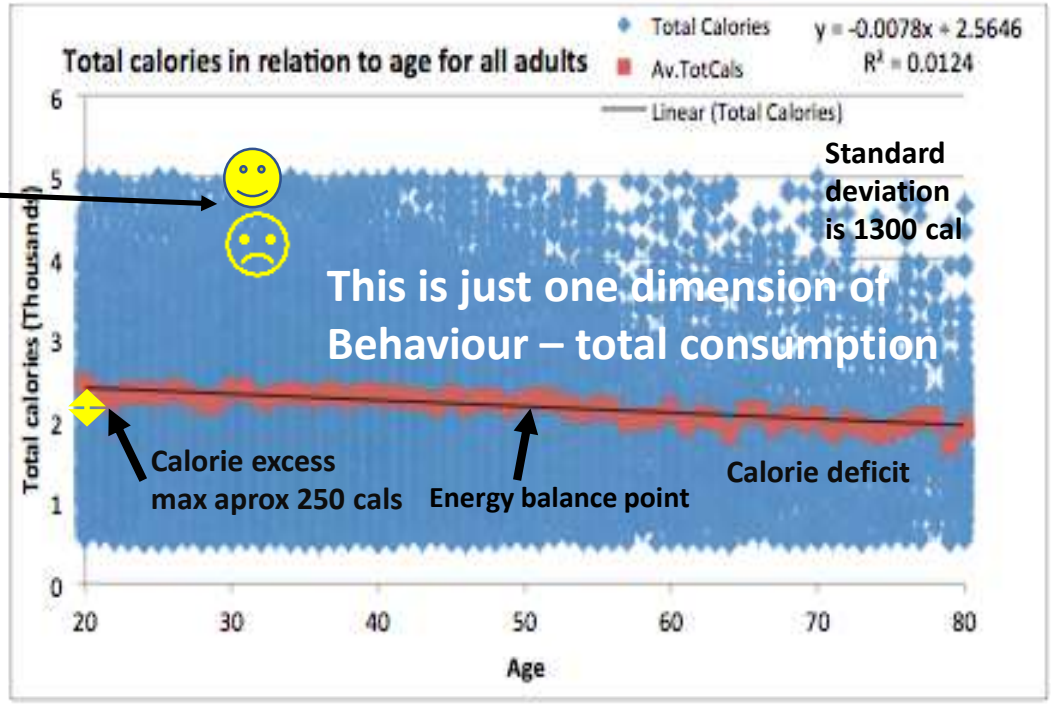
Are there Behavioural Early Warnings?

And no homeostasis here...

You aren´t what you eat you become what you eat



This isn't noise its multifactoriality



Epidemiological data from ENSANUT 2006

Regression of BMI change versus calorie excess

	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					29.236	0.343	0		
BMI Change	Constant	-1.954	0.362	-5.392			0	-2.68	-1.228
ALL	Total_Cals	0.904	0.167	5.407			0	0.569	1.239
	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					13.397	0.193	0.001		
BMI Change	Constant	-1.625	0.444	-3.656			0.001	-2.515	-0.734
Men	Total_Cals	0.724	0.198	3.66			0.001	0.328	1.121
	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					22.429	0.286	0		
BMI Change	Constant	-1.754	0.372	-4.711			0	-2.5	-1.008
Women	Total_Cals	0.833	0.176	4.736			0	0.481	1.185

This gradually decreasing calorie excess seems to be the motor for the population level increase in BMI.

Overeating as an Early Warning of obesity?

What are some other Early Warnings of Obesity?

What can someone's exercise pattern tell us?

Obesity % versus historical exercise behavior
A > recommended exercise, B < recommended, * don't care;
(30 years ago, 20y, 10y, 5y, 1y, now)

Exercise history	Obesity rate	Exercise history	Obesity rate
A*****	25.2%	AAA***	24.6%
B*****	24.0%	BBB***	25.1%
*A****	24.2%	AAB***	26.7%
*B****	25.1%	AAAA**	21.2%
****A*	17.0%	BBBB**	26.3%
****B*	29.8%	AAAB**	37.5%
AA****	24.9%	AAAAA*	13.0%
BB****	24.7%	BBBBB*	27.6%
AB****	27.5%	AAABB*	40.9%

Its worse to have had good habits and lost them than never to have had them

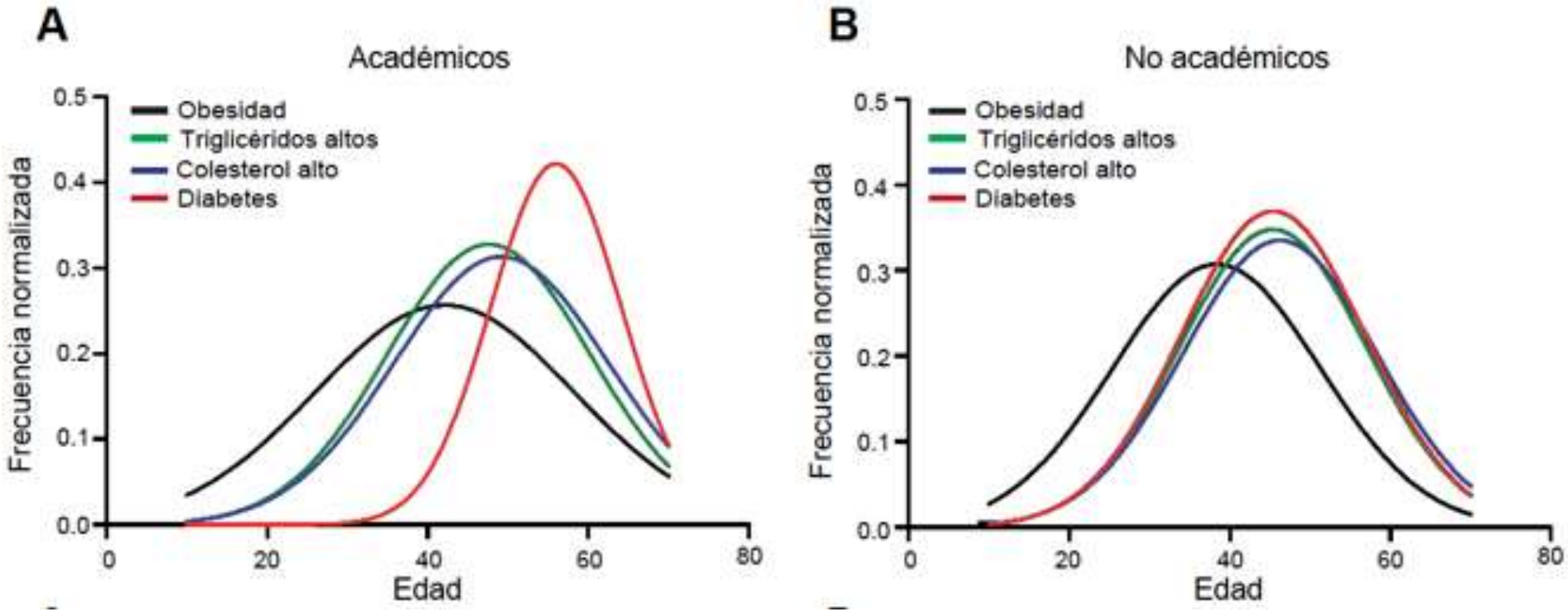
History	ϵ	N_x	N_{cx}	%	score
A*A*BB	3.56	94	38	40.43	0.73
AAA*B	3.55	91	37	40.66	0.74
AA**BB	3.53	113	44	38.94	0.67
AA**B*	3.40	131	49	37.40	0.60
A***BB	3.23	137	50	36.50	0.57
*A***A	-3.27	157	21	13.38	-0.75
**AAA	-3.27	157	21	13.38	-0.75
AA**AA	-3.51	103	10	9.71	-1.11
A**AA	-3.61	134	15	11.19	-0.95
***AA	-3.76	193	25	12.95	-0.79

What about other metabolic disorders? An Early Warning of what?

glucose stdev	glucose av	tbg stdev	tgb av	chol stdev	chol av	HOMA stdev	HOMA av
33.82	96.95	115.08	165.72	42.12	201.86	2.13	2.13
Variation factor	2.87	Variation factor	1.44	Variation factor	4.79	Variation factor	1.00
hdld stdev	hdld av	uric stdev	uric av	crs stdev	crs av		0.41
12.34	47.57	2.33	5.44	0.42	0.81		
Variation factor	3.86	Variation factor	2.34	Variation factor	1.95		
ldl stdev	ldl av	hba stdev	hba av	insulina stdev	insulina av		
56.58	122.47	1.29	5.35	6.41	8.44		
Variation factor	2.16	Variation factor	4.16	Variation factor	1.32		

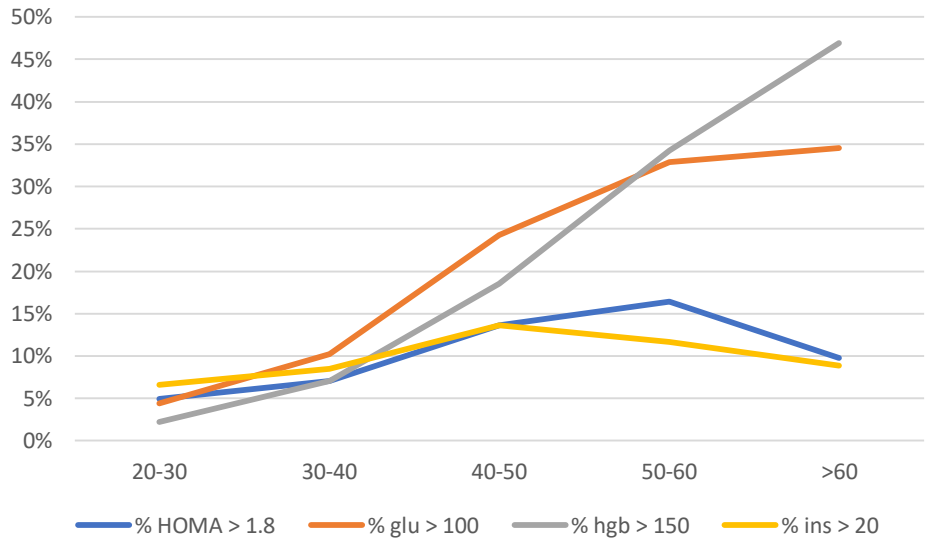
Homeostatic bounds are quite different for different metabolic biomarkers

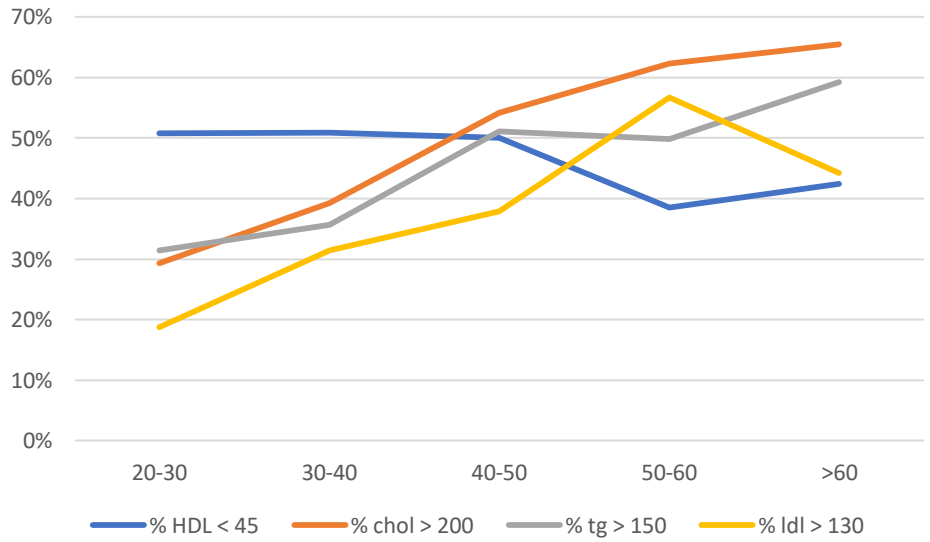
To get an Early Warning we need to be alert to it



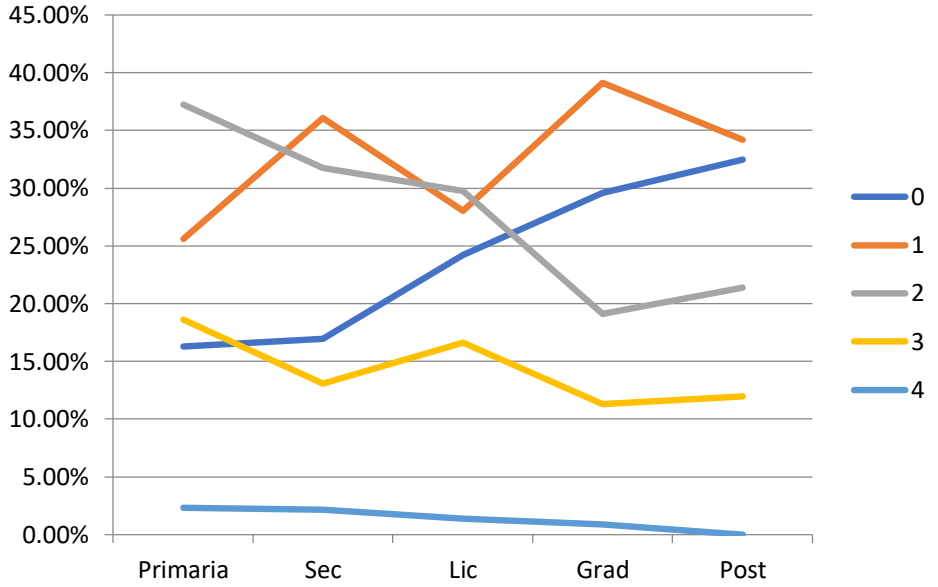
Heterogeneity of Aetiology of Metabolic Syndrome

Age and Education





What's Homeostasis?



Incidence of # of MS conditions additional to Waist circumference as a function education

# MS conditions	Primary	Sec	Lic	Grad	Post
0	16.28%	16.96%	24.22%	29.57%	32.48%
1	25.58%	36.09%	28.03%	39.13%	34.19%
2	37.21%	31.74%	29.76%	19.13%	21.37%
3	18.60%	13.04%	16.61%	11.30%	11.97%
4	2.33%	2.17%	1.38%	0.87%	0.00%

Metabolic wear and tear: BMI, age and educational level as “Early Warning” parameters

Table 3. Binomial logistic regressions of anthropometric, blood pressure, and fasting blood test variables taking as class variable the at risk population using the cutoffs of supplementary material Table S1, for the independent variables education (Edu), BMI, age and sex.

Variable	N	Edu		BMI		Age		Sex	
		exp(b)	p	exp(b)	p	exp(b)	p	exp(b)	p
BMI	1073	0.681	0.000 **			1.021	0.001 *	0.946	0.726
WC (women)	689	0.700	0.000 **			1.042	0.000 **		
WC (men)	384	0.912	0.384			1.047	0.000 **		
SBP	1073	0.760	0.022 *	1.190	0.000 **	1.065	0.000 **	0.393	0.000 **
DBP	1073	0.939	0.491	1.167	0.000 **	1.038	0.000 **	0.614	0.016 *
PP	1073	0.848	0.507	1.129	0.004 *	1.061	0.011 *	0.382	0.087
Glucose	1072	0.926	0.306	1.101	0.000 **	1.055	0.000 **	0.910	0.580
Hb A1c	1068	0.767	0.034 *	1.095	0.000 **	1.064	0.000 **	1.544	0.150
Insulin	1072	1.068	0.679	1.203	0.000 **	0.985	0.276	0.609	0.125
HOMA-IR	1071	0.846	0.011 *	1.240	0.000 **	1.013	0.022 *	1.075	0.624
Uric acid (women)	689	1.025	0.832	1.106	0.000 **	1.016	0.115		
Uric acid (men)	383	0.856	0.140	1.110	0.000 **	0.994	0.480		
Triglycerides	1072	0.859	0.014 *	1.091	0.000 **	1.025	0.000 **	0.469	0.000 **
Total cholesterol	1073	0.993	0.907	1.008	0.549	1.041	0.000 **	0.880	0.335
HDL (women)	689	0.770	0.001 *	1.116	0.000 **	0.983	0.012 *		
HDL (men)	384	0.737	0.002 *	1.065	0.007 *	1.002	0.797		
LDL	1070	0.986	0.813	1.009	0.489	1.037	0.000 **	0.805	0.109
Metabolic Syndrome	1073	0.827	0.005 *	1.202	0.000 **	1.036	0.000 **	0.960	0.789

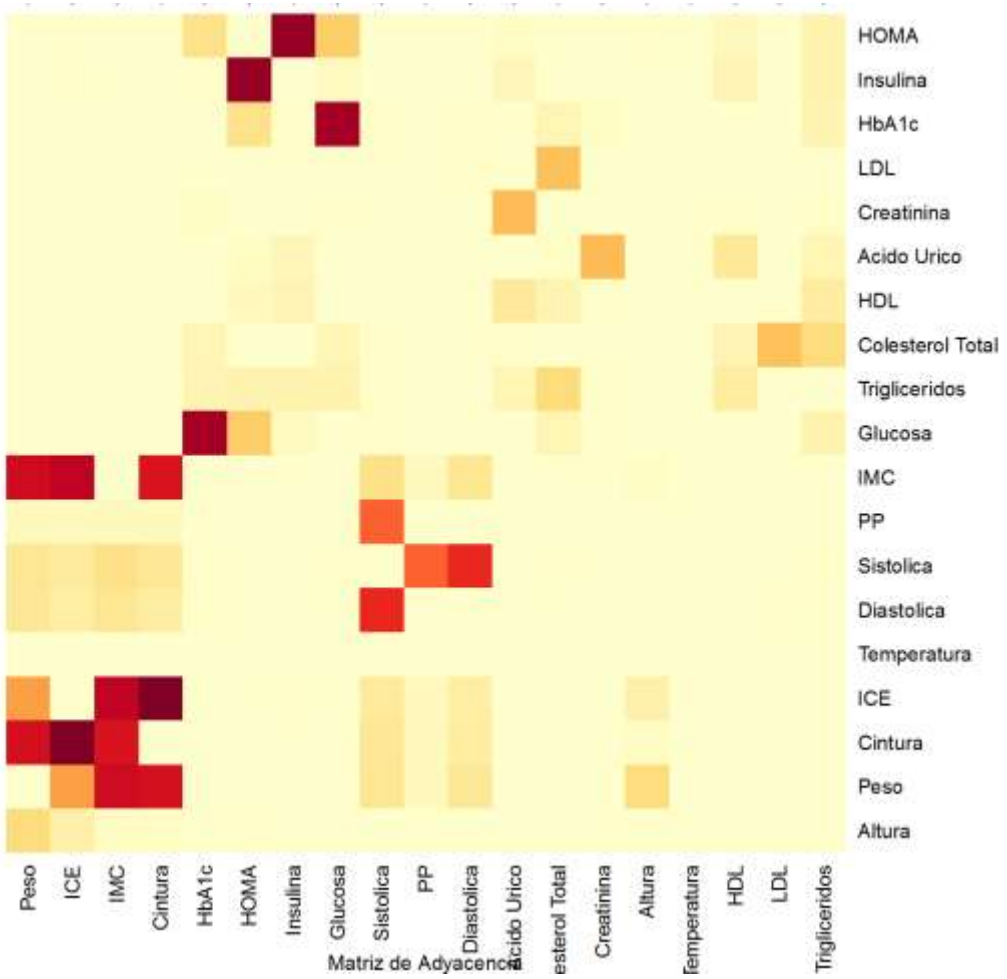
* indicates statistically significant at the $p < 0.05$ level.
** indicates statistically significant at the $p < 0.001$ level.

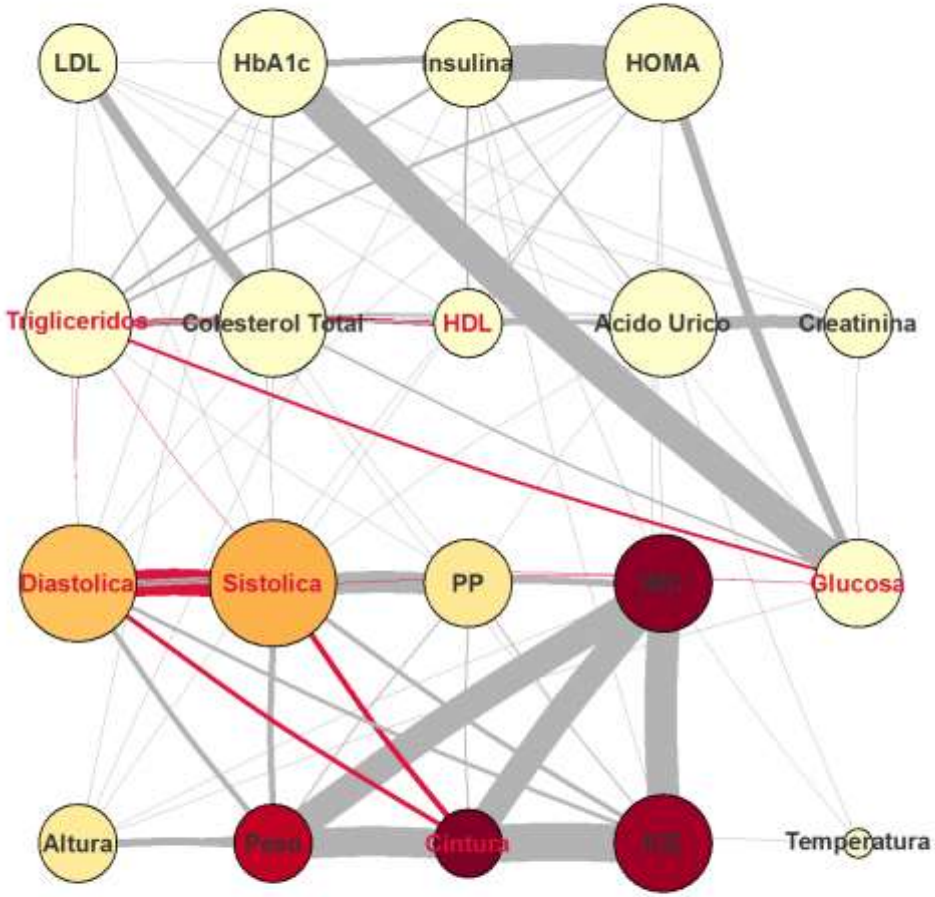
Dependent on Education

Independent of BMI and education

Need longitudinal data to really analyse EWs

The Physiolome over a Lifetime





The Physiolome over a Lifetime

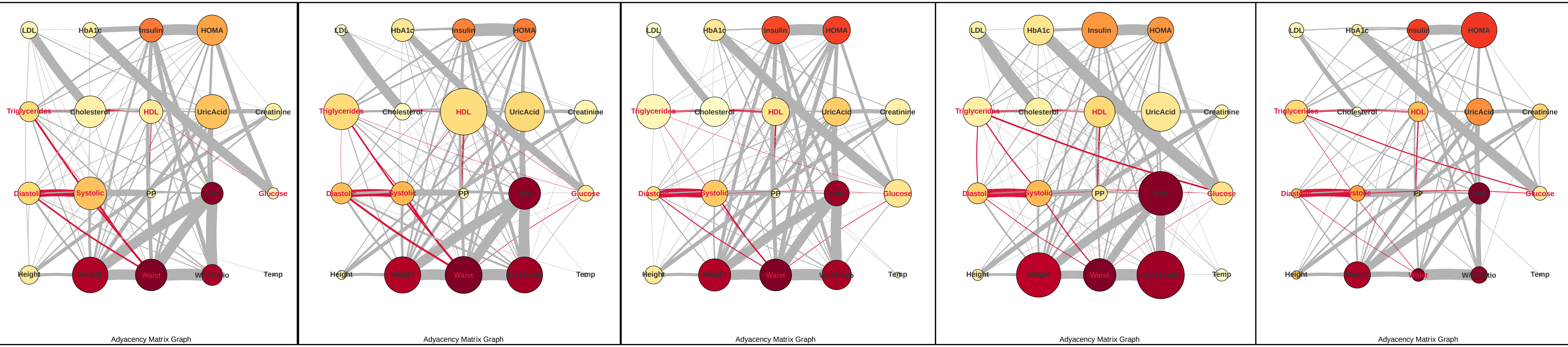
3ª a 7ª decades

The density of the graph increase

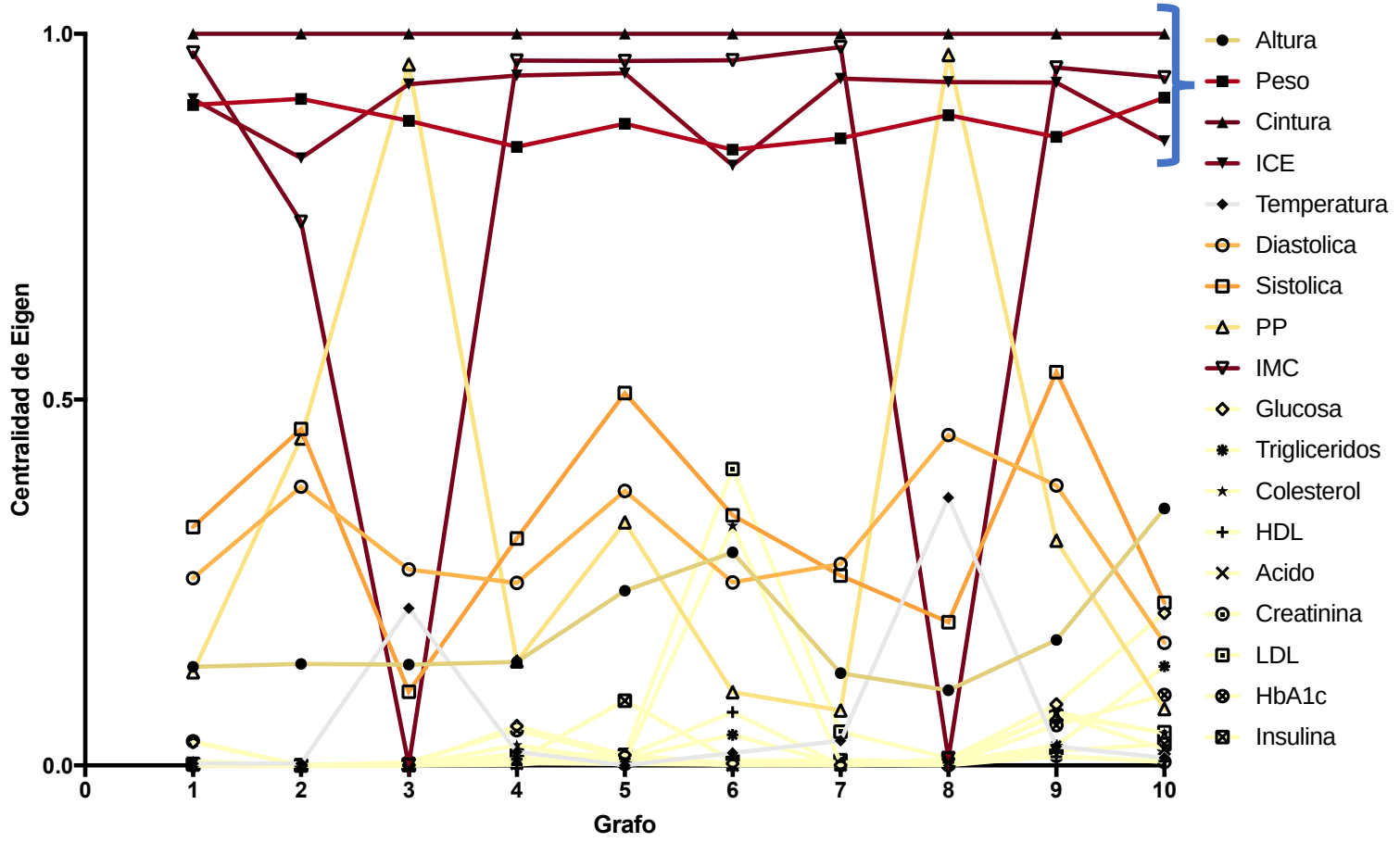
One sees the impact of BMI on insulin

And the effect of insuline on the metabolism of lipids and glucose.

Loss of glucose regulation and the impact on lipids



Centrality measure How important is a node?



1-5 life decades; 6-10 educational levels

Katz, L. (1953). “A New Status Index Derived from Sociometric Analysis.” Psychometrika, 18, 39-43.