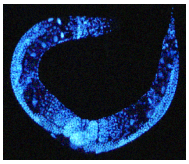
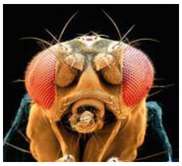
‘genetic predisposition for a healthy long life’

Rudi Westendorp, Leiden University Medical Center

it is 100% genetics

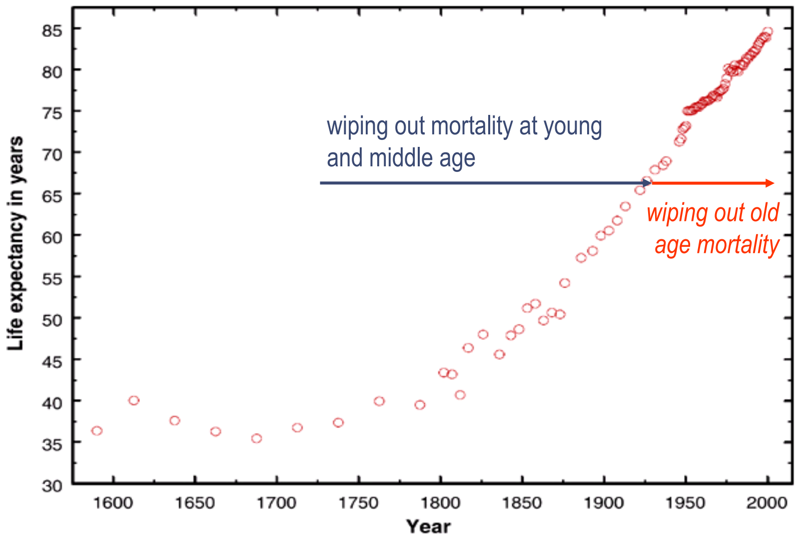




days weeks years decades

differences in longevity across species

it is 100% environment



Science 2002;296:1029

it is 200% both

genetic predisposition

X

environmental risk

=

disease or health

agenda…..

- old age disability and mortality can be postponed
- genetic cues are emerging
- variation in metabolism mark healthy longevity

compression of mortality

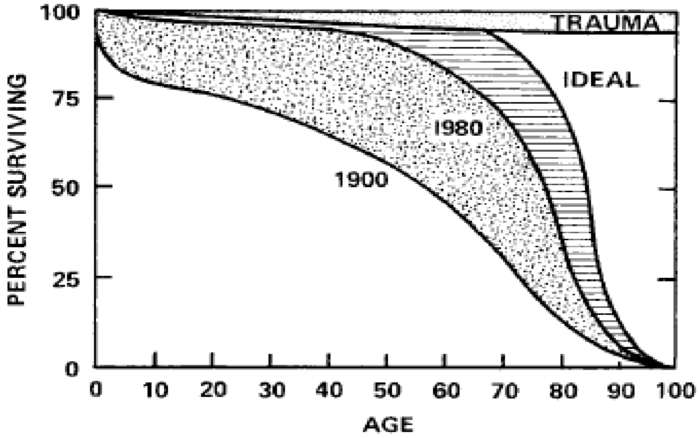


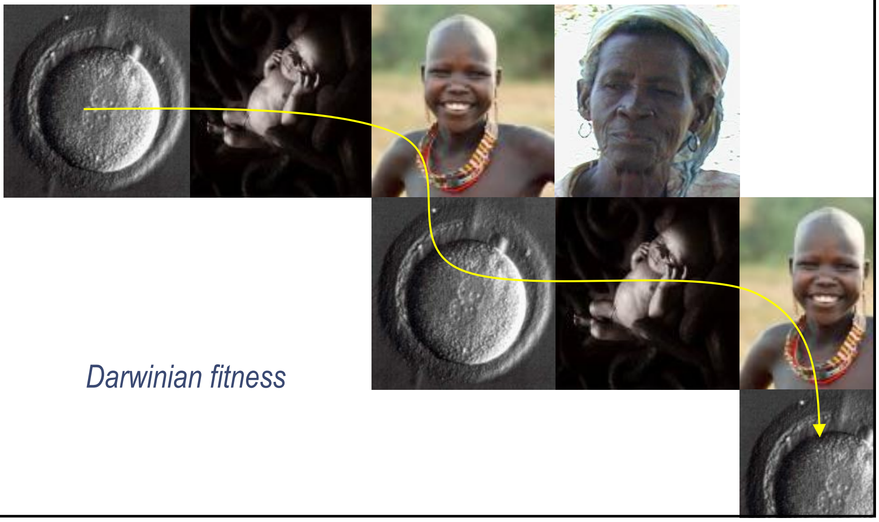
Figure 2. The Increasingly Rectangular Survival Curve.

Fries 1980

compression is falsified

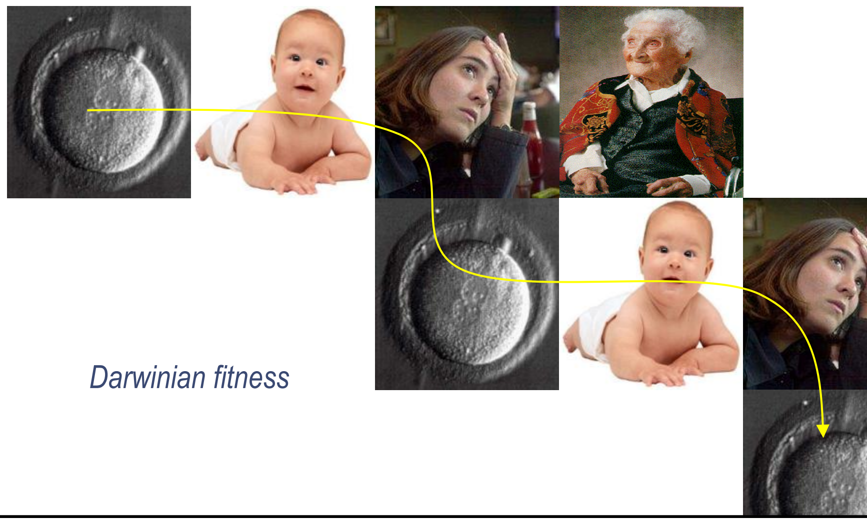
1. there is no program for death
2. mortality in old age decreases
3. maximum age at death increases
4. there is a right shift of mortality

program of fertility and survival



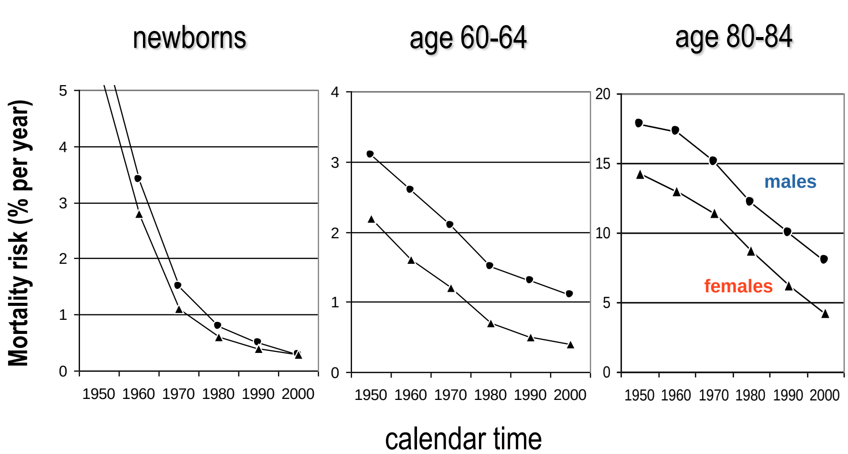
Darwinian fitness

life histories in France

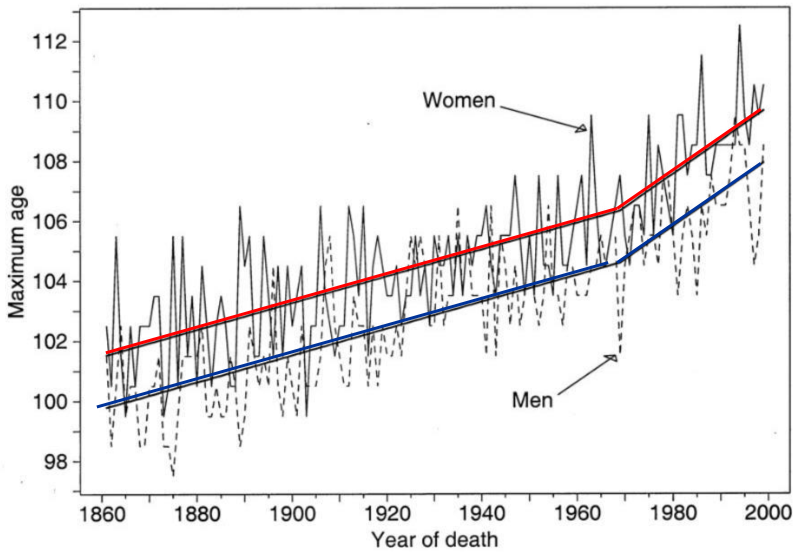


Darwinian fitness

mortality decrease in Japan

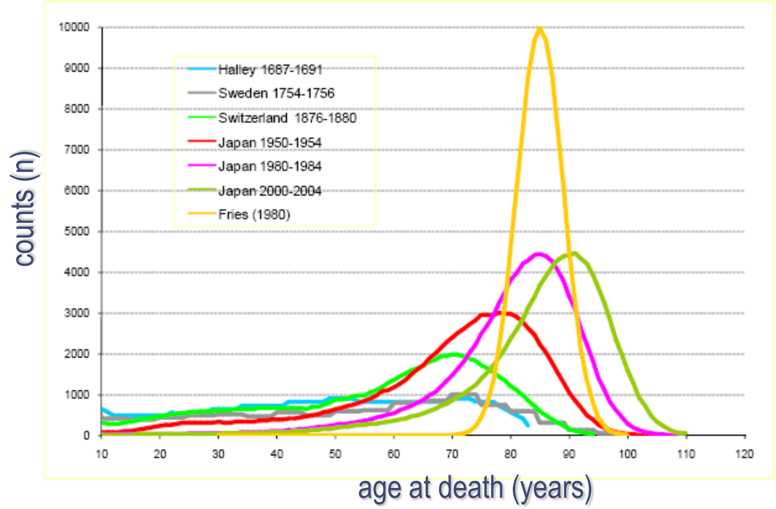


age at death (Sweden)



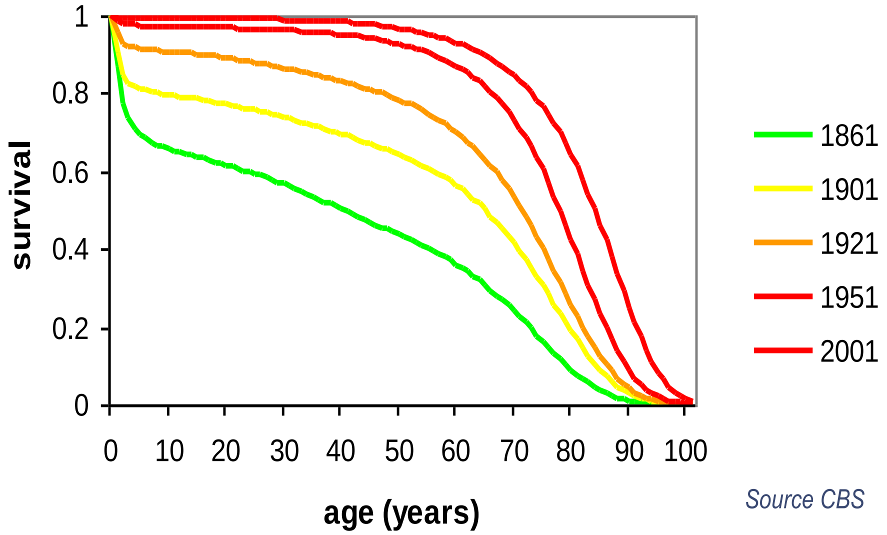
Science 2000;289:2366

outcomes of 100.000 births in various populations



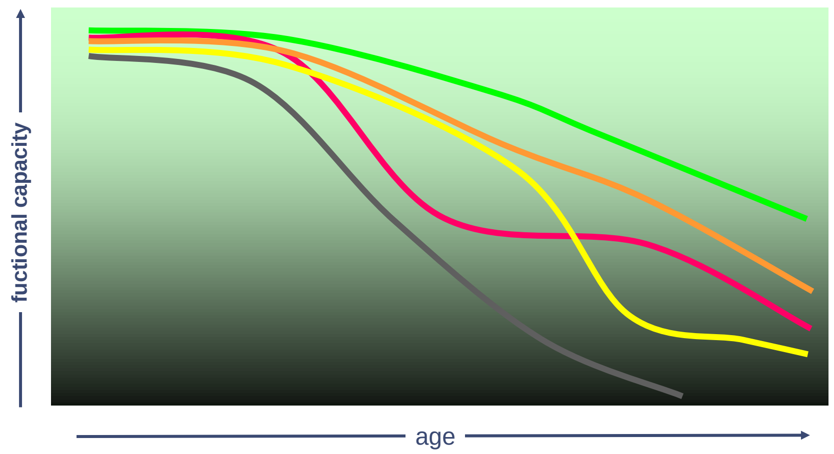
Robine et al 2008

right shift of mortality (Netherlands)

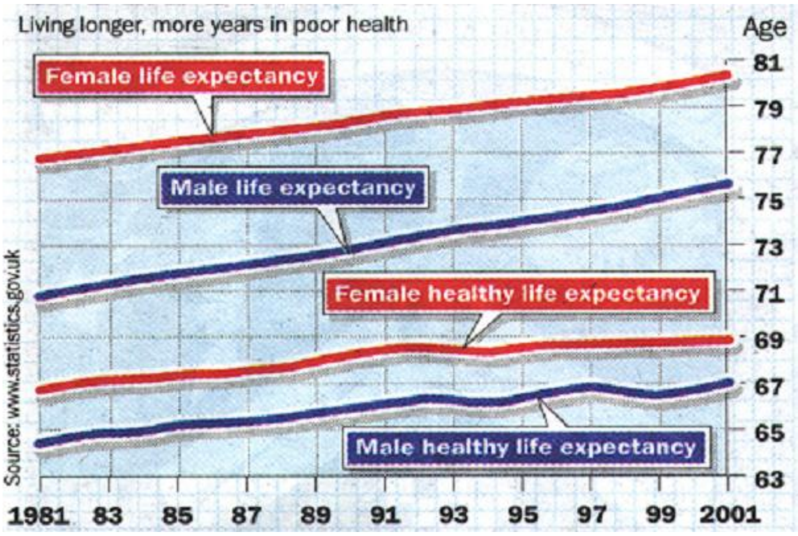


Source CBS

heterogeneity in frailty trajectories

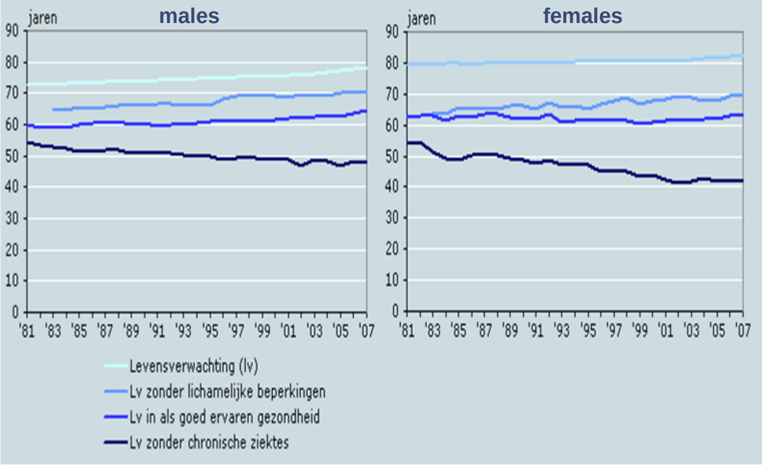


living longer, more years in poor health



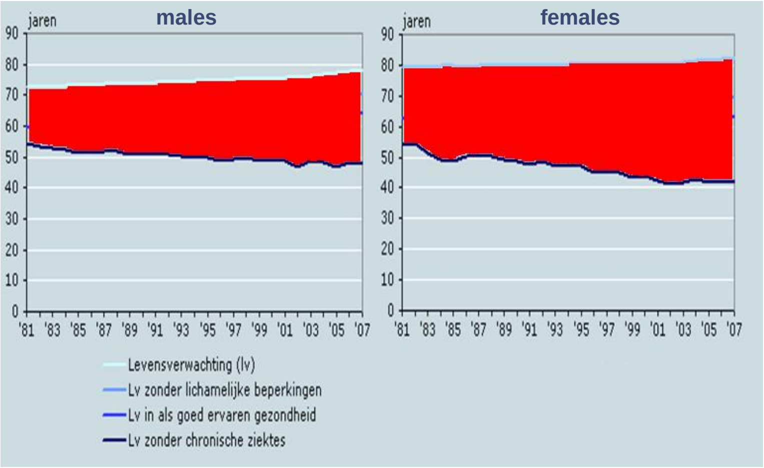
Times July 22, 2004

life expectancy in the Netherlands



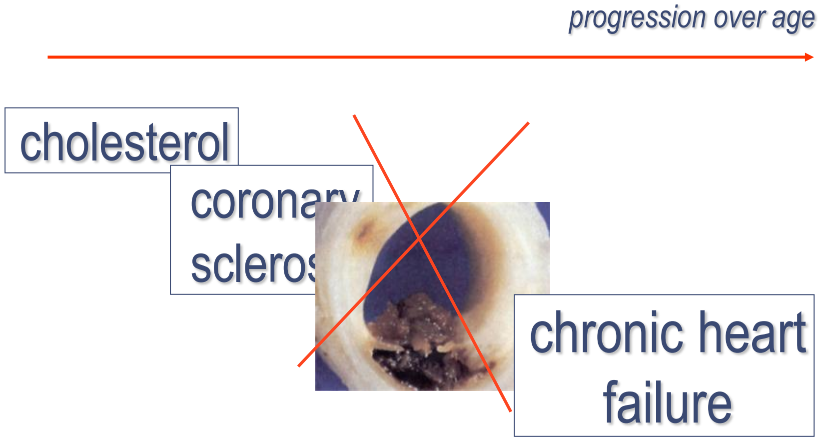
Source CBS

increasing years with multimorbidity



Source CBS

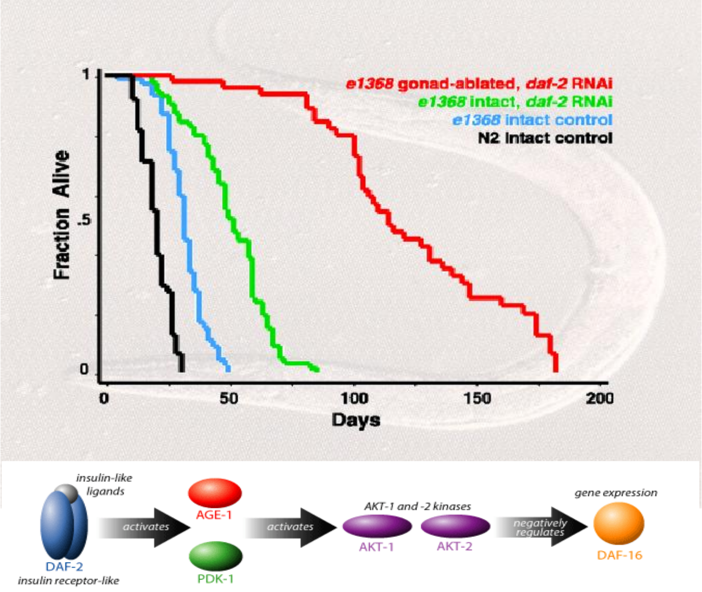
continous innovation



agenda…..

- old age disability and mortality can be postponed
- genetic cues are emerging
- variation in metabolism mark healthy longevity

the dauer pathway



longevity assurance across species

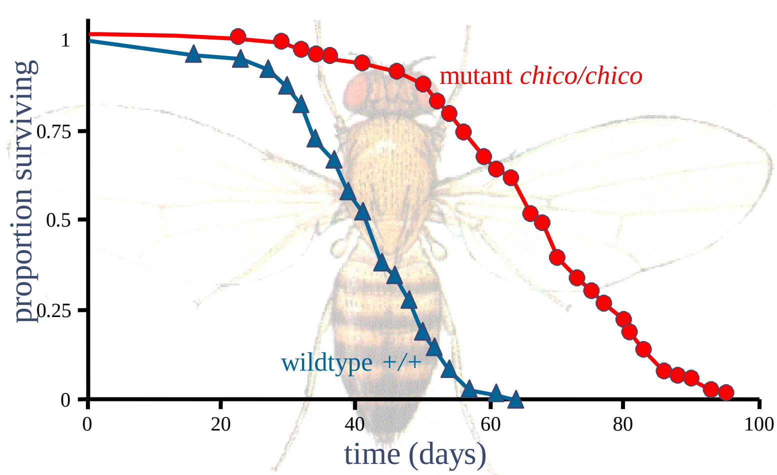
TH
GHR
GH-1
Ins/IGF1
Daf-2
Ins/IGF1
InRS
InsR/IG-1R
IGF-1
IRS-1

Daf-12
Liver XRα
Apo E,
ApoC3,B
Daf-16
FOXO-1, 3A

Stress resistance
Metabolic processes
Innate immunity
Toxin degradation

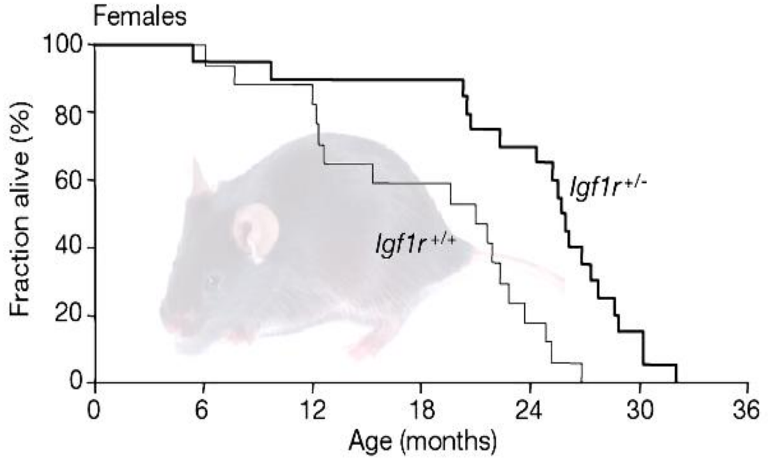
longevity
longevity
longevity
longevity

drosophila models



Clancy, et al.(2001), Tatar, et al (2001)

mice models



Holzenberger Nature 2003;421:182

mendelian randomisation

Leiden 85+ study

85 86 87 88 89 90 years

genetic variants and mortality risk

Leiden 85+ study

IGF-1/insulin signaling (score)	Females (n=704)			Males (n=325)		
	n	HR	95% CI	n	HR	95% CI
+1	6	1.5	0.59-3.8	1	13	1.7-102
0	57	1		27	1	
-1	186	0.89	0.63-1.3	84	1.26	0.77-2.1
-2	270	0.84	0.60-1.2	120	1.43	0.89-2.3
-3	155	0.78	0.54-1.1	76	1.28	0.78-2.1
-4	29	0.69	0.39-1.2	16	0.83	0.36-1.9
-5	1	-	-	1	-	-
p for trend		0.047			0.90	

GHRHR rs4988496, GH1 rs2665802, IGF1 CA repeat, INS VNTR, IRS1 rs1801278

Van Heemst et al. *Ageing cell* 2005;4:79-85

genetic variants and cognitive function

Leiden 85+ study

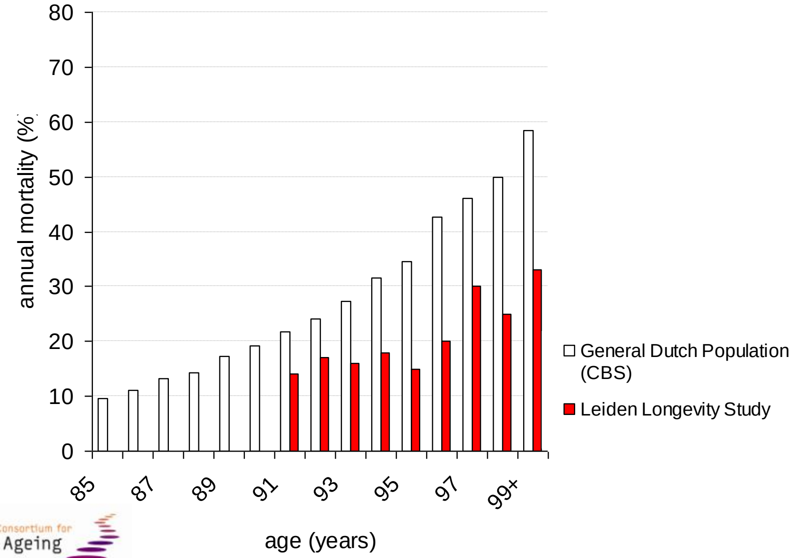
IGF-1/insulin signaling (score)	Females (n=684)			Males (n=296)		
	n	MMSE	SD	n	MMSE	SD
+1						
0	60	22.3	0.8	31	24.0	1.0
-1	193	22.5	0.5	89	25.7	0.6
-2	259	23.8	0.4	120	25.1	0.5
-3	139	24.0	0.6	73	24.3	0.6
-4	33	24.6	1.2	13	22.8	1.5
-5						
p for trend		0.010			0.21	

GHRHR rs4988496, GH1 rs2665802, IGF1 CA repeat, INS VNTR, IRS1 rs1801278

Euser et al. J Gerontol A Biol Sci 2008;63:907-10

five siblings aged 86 through 93 years

lower mortality risk



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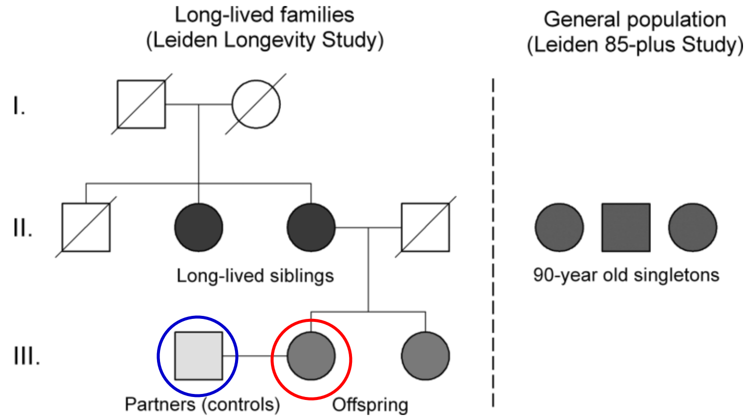
(inter-) generational comparisons



mortality risk in families

	obs (n)	exp (n)	relative risk
brothers and sisters	390	591	0.66 (0.60-0.73)
parents	198	261	0.76 (0.66-0.87)
children	82	117	0.65 (0.51-0.80)
partners	155	161	0.95 (0.82-1.12)

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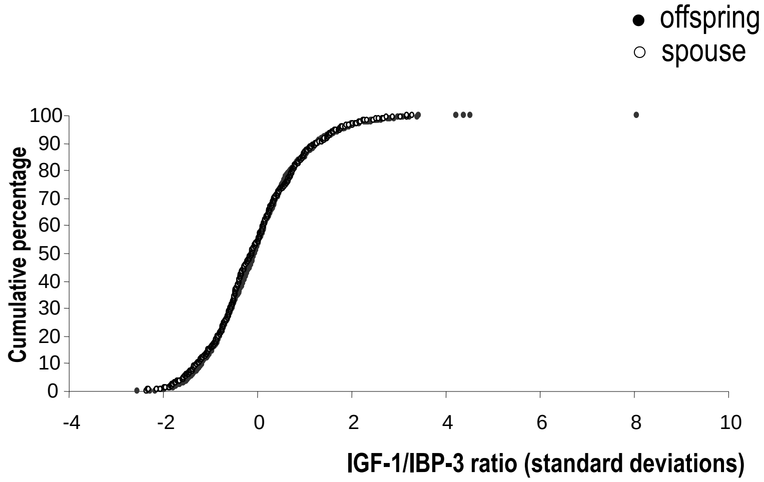
Schoenmaker et al. *Eur J Hum Gen* 2006

IGF-1 signaling in offspring



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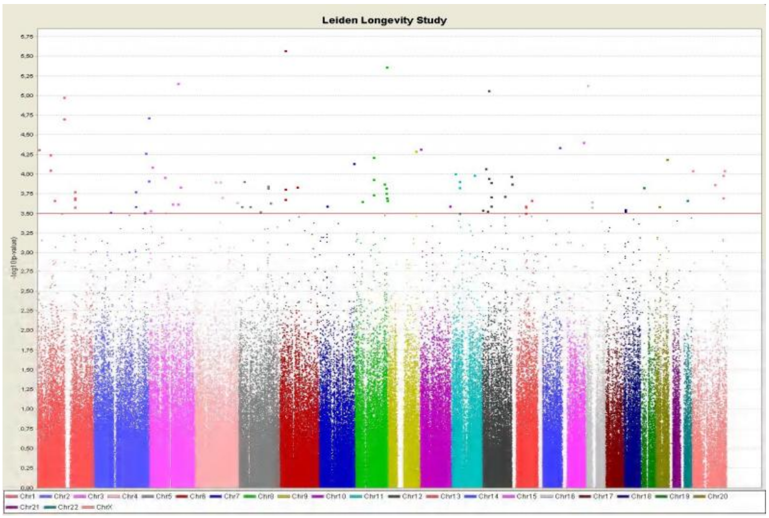
Rozing et al. J Ger Biol Science 2009

GWAS in Leiden Longevity Study



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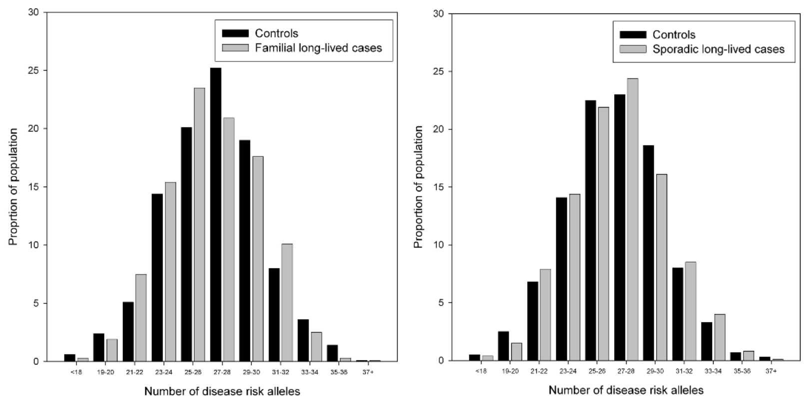
risk alleles in nonagenarians



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agenda.....

- old age disability and mortality can be postponed
- genetic cues are emerging
- variation in metabolism mark healthy longevity

studying offspring in middle age

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morbidities in offspring generation

	Offspring (*n* = 1423)	Partners (*n* = 632)	p-value
MI (%)	30 (2.1)	26 (4.1)	**0.011**
CVA (%)	50 (3.5)	18 (2.8)	0.559
HT (%)	311 (22.3)	168 (27.0)	**0.012**
DM (%)	54 (3.8)	44 (7.1)	**0.003**
Malignancies (%)	125 (8.8)	45 (7.2)	0.276
COPD (%)	52 (3.7)	24 (3.8)	0.745
RA (%)	21 (1.5)	5 (0.8)	0.154

Westendorp et al. JAGS 2009

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parameters in offspring generation

	Offspring (n = 1751)	Partners (n = 776)	p-value
Glucose (mmol/L)	5.78 (0.04)	6.11 (0.06)	**0.000**
ln insulin (mU/L)	2.77 (0.02)	2.87 (0.03)	**0.004**
Chol (mmol/L)	5.58 (0.04)	5.60 (0.04)	0.589
LDL (mmol/L)	3.33 (0.03)	3.33 (0.04)	0.992
HDL (mmol/L)	1.45 (0.01)	1.41 (0.02)	0.064
ln TG (mmol/L)	0.42 (0.02)	0.49 (0.02)	**0.002**
ln HsCRP (mg/L)	0.34 (0.03)	0.37 (0.04)	0.559

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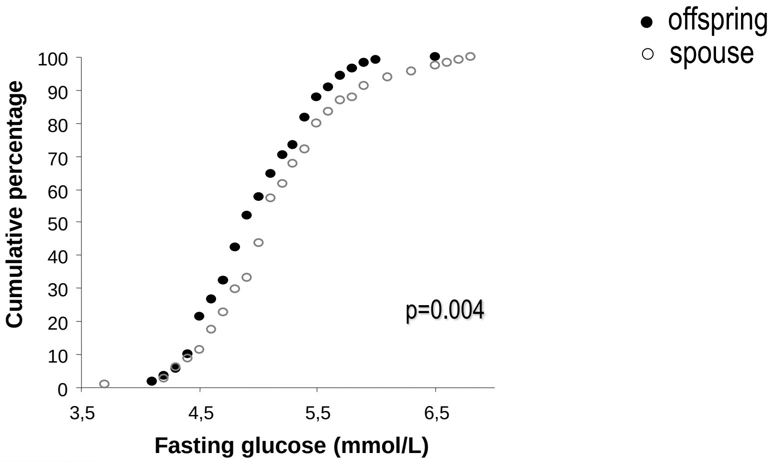
unpublished

fasting glucose in offspring

121 pairs; diabetics are excluded from the analyses



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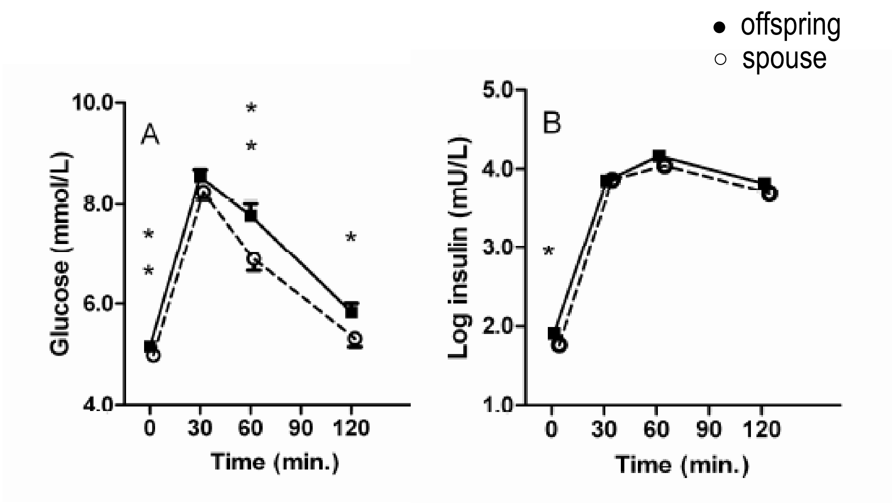
Rozing et al. JAGS 2009

OGTT in non diabetic offspring



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Rozing et al. JAGS 2009

biometrics in offspring generation

	Offspring (*n* = 121)	Partners (*n* = 114)	p-value
Weight (kg)	77.6 (1.1)	78.2 (1.2)	0.675
Length (m)	172 (0.5)	172 (0.6)	0.863
BMI (kg/m^2)	26.1 (0.4)	26.7 (0.7)	0.443
Waist circumference (cm.)	98 (0.9)	99 (0.9)	0.238
Hip circumference (cm.)	105 (0.8)	105 (0.7)	0.644
Waist-hip ratio	0.93 (0.01)	0.94 (0.01)	0.284
% body fat	28.7 (0.5)	28.1 (0.6)	0.368
Physical activity (sqrt)	57.7 (2.9)	59.4 (3.3)	0.666

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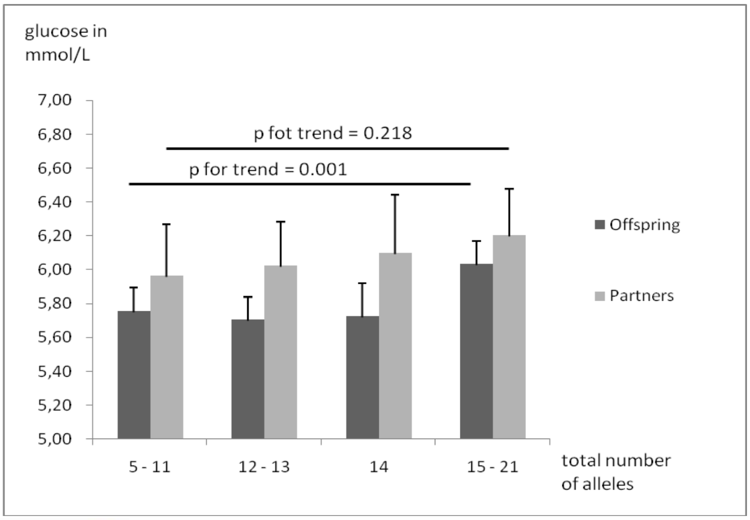
Rozing et al. JAGS 2009

thirteen genes associated with type 2 diabetes

SNP	Gene/locus	Location	Risk allele	Association
Rs10010131	WFS1 (Wolfram Syndrome 1)	4q16	Major	Beta cell function
Rs10811661	CDKN2A/2B	9q21	Major	Beta cell function
Rs1111875	HHEX (Hemato. exp. Homeobox)	10q23	Major	Beta cell function
Rs13266634	SLC30A8 (solute carries family 30)	8q24.11	Major	Beta cell function
Rs1495377	Unknown	12q15	Major	unknown
Rs1801282	PPARG (peroxisome prof.-act. Recep γ)	3p25	Major	Adipocyte differentiation
Rs4402960	IGF2BP2 (IGF-2binding protein 2)	3q27.2	Minor	Beta cell function
Rs5219	KCNJ11 (K inwardly-rectifying channel)	11p15.1	Minor	Beta cell function
Rs564398	CDKN2A/2B	9q21	Major	Beta cell function
Rs7754840	CDKAL1 (CDK5 reg. sub. Ass. protein 1)	6p22.3	Minor	Beta cell function
Rs7901695	TCF7L2 (Transcription factor 7 like 2)	10q25.3	Minor	Beta cell function
Rs7903146	TCF7L2 (Transcription factor 7 like 2)	10q25.3	Minor	Beta cell function
Rs8050136	FTO (fat mass and obesity associated)	16q12.2	Minor	Obesity

thirteen genes associated with type 2 diabetes



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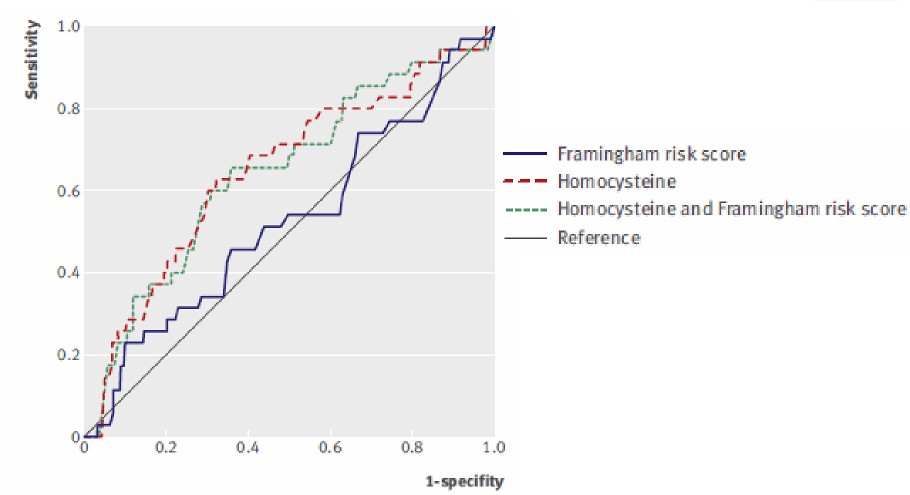
conclusions

- everything is genetic and environmental
- ‘familial longevity’ goes with a 30% decreased risk of morbidity and mortality at all ages
- the mechanisms are not yet clear
- prediction is difficult

prediction of CVD in older people

Leiden 85+ Study



de Ruijter et al. BMJ 2008;337:3083