Coevolution of sociality and human life-history in humans

Influence of culture and behaviours on the evolution of senescence: selection of susceptibility alleles to late-onset diseases

Are old ages useless with respect to selection? A reconsideration of the common variants/common diseases hypothesis

Pavard, Coste et al. *In prep.*

Introduction

Nineties – "*genetic map of old age diseases* "

On the HapMap web site two years ago

> "*to a common disease (such as diabetes, cancer, stroke, heart disease, depression, and asthma) is associated common genetic variants*"

Genetic diseases after menopause ► No selection ► Only genetic drift ► Lower number of genetic variants but at higher frequency (Common variants) ► high prevalence of the disease (Common disease)

ABCA4	MACULAR DEGENERATION,,,
ABCC9	CARDIOMYOPATHY, DILATED, 1O
APOB	HYPERCHOLESTEROLEMIA,,,
APP	OCCIPITAL CALCIFICATIONS,,,
APP	CEREBRAL HEMORRHAGE,,,
C1QTNF5	RETINAL DEGENERATION
CFH	MACULAR DEGENERATION
CHMP2B	FRONTOTEMPORAL DEMENTIA
COL8A2	CORNEAL DYSTROPHY
ENO3	ENOLASE 3 DEFICIENCY
FGA	FIBRINOGEN
FLNC	FILAMINOPATHY
GBE1	POLYGLUCOSAN BODY DISEASE
GRN	FRONTOTEMPORAL DEMENTIA
HTRA2	PARKINSON DISEASE 13
ITM2B	DEMENTIA, FAMILIAL BRITISH
LRRK2	PARKINSON DISEASE 8
MAPT	FRONTOTEMPORAL DEMENTIA
MAPT	SUPRANUCLEAR PALSY,,,
MLH1	MUIR-TORRE SYNDROME
MPZ	CHARCOT-MARIE-TOOTH ,,,
PLEKHG4	SPINOCEREBELLAR ATAXIA
PMP22	GUILLAIN-BARRE SYNDROME,,,
PRNP	DEMENTIA, LEWY BODY
PSEN2	ALZHEIMER DISEASE, FAMILIAL,,,
RDS	VITELLIFORM MACULAR DYSTROPHY,,,
RNASEL	PROSTATE CANCER, HEREDITARY, 1
SNCA	DEMENTIA, LEWY BODY
SNCA	PARKINSON DISEASE, FAMILIAL,,,
SNCA	PARKINSON DISEASE 4,,,
SNCB	DEMENTIA, LEWY BODY
TGFBI	CORNEAL DYSTROPHY,,,
TGFBR2	COLORECTAL CANCER,,,,
TNFRSF11A	PAGET DISEASE OF BONE
TNNI3	TROPONIN I, CARDIAC,,,
TTID	MYOTILINOPATHY
VMD2	VITELLIFORM MACULAR DYSTROPHY,,,
ACTC	CARDIOMYOPATHY, DILATED, 1R
ACTC	CARDIOMYOPATHY, DILATED, 1A
ALPL	HYPOPHOSPHATASIA, ADULT TYPE
ALS4	AMYOTROPHIC SCLEROSIS 4,,,
ANKH	CHONDROCALCINOSIS 2
APC	ADENOMATOUS POLYPOSIS, COLON
APOA1	AMYLOIDOSIS, FAMILIAL VISCERAL
APOB	APOLIPOPROTEIN B
APOE	SEA-BLUE HISTIOCYTE DISEASE
ARHGEF10	SLOWED NERVE CONDUCTION,,,
ATP2A1	BRODY MYOPATHY
ATP2C1	BENIGN CHRONIC PEMPHIGUS
BMPR2	PULMONARY HYPERTENSION,,,
BRCA2	BREAST CANCER, FAMILIAL
BRIP1	BREAST CANCER, FAMILIAL
CDC73	PARATHYROID CARCINOMA
CDKN2A	MELANOMA-PANCREATIC CANCER
CFTR	PANCREATITIS, HEREDITARY
CHEK2	LI-FRAUMENI SYNDROME 2
CLCN2	EPILEPSY WITH GRAND MAL SEIZURES
COCH	MENIERE DISEASE
COCH	DEAFNESS
COL2A1	AVASCULAR NECROSIS
CPT2	CARNITINE PALMITOYLTRANSFERASE,,,
CRYAB	ALPHA-B CRYSTALLINOPATHY
CSRP3	CARDIOMYOPATHY, DILATED, 1M
CST3	AMYLOIDOSIS VI
CYP11B2	IgA NEPHROPATHY
DCTN1	LOWER MOTOR NEURON DISEASE,,,
DMD	CARDIOMYOPATHY, DILATED,,,
TYROBP	PRESENILE DEMENTIA ,,,
DSP	DESMOPLAKIN
DSP	ARRHYTHMOGENIC DYSPLASIA,,,
DSPP	DENTINOGENESIS IMPERFECTA,,,
DSPP	DEAFNESS,,,
DYSF	MIYOSHI MYOPATHY
DYSF	MYOPATHY,,,
EFEMP1	RETINAL DYSTROPHY,,,
ELN	CUTIS LAXA
ERCC4	XERODERMA PIGMENTOSUM,,,
EYA4	CARDIOMYOPATHY, DILATED, 1J
FBLN5	CUTIS LAXA
FGA	AMYLOIDOSIS,,,
FLCN	BIRT-HOGG-DUBE SYNDROME
FOXL2	PREMATURE OVARIAN FAILURE 3
FSHR	OVARIAN HYPERSTIMULATION
FTL	BASAL GANGLIA DISEASEpRE-40
GFI1	NEUTROPENIA, NONIMMUNE,,,
GLB1	GANGLIOSIDOSIS, GENERALIZED,,,
GNE	INCLUSION BODY MYOPATHY 2,,,
GNE	NONAKA MYOPATHY
GUCA1A	CONE DYSTROPHY 3
HCRT	NARCOLEPSY 1
HMBS	PORPHYRIA, ACUTE INTERMITTENT
HRG	HISTIDINE-RICH GLYCOPROTEIN
HRPT2	HYPERPARATHYROIDISM 1
HRPT2	HYPERPARATHYROIDISM 2
HSPB1	CHARCOT-MARIE-TOOTH DISEASE,,,
HSPB1	NEUROPATHY, DISTAL HEREDITARY,,,
HSPB8	CHARCOT-MARIE-TOOTH DISEASE,,,
ITM2B	DEMENTIA, FAMILIAL DANISH
KCNE2	ATRIAL FIBRILLATION, FAMILIAL, 1
KCNQ1	ATRIAL FIBRILLATION, FAMILIAL, 1
KRT17	STEATOCYSTOMA MULTIPLEX
KRT5	DOWLING-DEGOS DISEASE
LCAT	FISH-EYE DISEASE
LCAT	LECITHIN DEFICIENCY
LMNA	CARDIOMYOPATHY, DILATED, 1A
LMNA	MUSCULAR DYSTROPHY,,,
LMNA	EMERY-DREIFUSS MUSCULAR DYSTROPH
LMNA	CHARCOT-MARIE-TOOTH DISEASE,,,
LMNA	CARDIOMYOPATHY, DILATED,,,
LMNA	LIPOATROPHY WITH DIABETES,,,
MAPT	PICK DISEASE OF BRAIN
MAPT	PARKINSON-DEMENTIA SYNDROME
MEN1	MULTIPLE ENDOCRINE NEOPLASIA,,,
MEN1	HYPERPARATHYROIDISM 1
MFN2	CHARCOT-MARIE-TOOTH DISEASE,,,
MLH1	COLORECTAL CANCER,,,,
MPZ	CHARCOT-MARIE-TOOTH DISEASE,,,
MPZ	CHARCOT-MARIE-TOOTH DISEASE,,,
MSH2	COLORECTAL CANCER,,,,
MSH2	MUIR-TORRE SYNDROME
MYH9	SEBASTIAN SYNDROME
NAGA	KANZAKI DISEASE
NEUROD1	MATURITY-ONSET DIABETES ,,,
NF1	NEUROFIBROMATOSIS,,,,
NOTCH3	CEREBRAL ARTERIOPATHY,,,
NR3C1	GLUCOCORTICOID RECEPTOR
PARK7	PARKINSON DISEASE,,,,
PAX2	PAPILLORENAL SYNDROME
PEX7	REFSUM DISEASE
PFKM	GLYCOGEN STORAGE DISEASE VII
PGAM2	PHOSPHOGLYCERATE MUTASE,,,
PHKA1	MUSCLE GLYCOGENOSIS
PHYH	REFSUM DISEASE
PINK1	PARKINSON DISEASE 6,,,
PLAT	PLASMINOGEN ACTIVATOR,,,
PLG	PLASMINOGEN,,,
PLN	CARDIOMYOPATHY, DILATED, 1P
POLG	PROGRESSIVE OPHTHALMOPLEGIA,,,
POLG	PROGRESSIVE OPHTHALMOPLEGIA,,,
POLG	ENCEPHALOPATHY SYNDROME,,,
POLG	ATAXIC NEUROPATHY,,,
POLH	XERODERMA PIGMENTOSUM ,,,
PPARG	LIPODYSTROPHY,,,
PRKAG2	WOLFF-PARKINSON-,,,
PRNP	CREUTZFELDT-JAKOB DISEASE
PRNP	GERSTMANN-STRAUSSLER DISEASE
PRNP	FATAL FAMILIAL INSOMNIA
PRNP	HUNTINGTON DISEASE-LIKE 1
PRNP	SPONGIFORM ENCEPHALOPATHY,,,
PRSS1	PANCREATITIS, HEREDITARY
PSEN1	PICK DISEASE OF BRAIN
PSEN1	ALZHEIMER DISEASE,,,
PTEN	COWDEN DISEASE
PTEN	MENINGIOMA, FAMILIAL
PYGM	GLYCOGEN STORAGE DISEASE V
RAB7	CHARCOT-MARIE-TOOTH DISEASE,,,
RLBP1	FUNDUS ALBIPUNCTATUS
RS1	RETINOSCHISIS 1, X-LINKED, JUVENILE
SCN5A	BRUGADA SYNDROME
SCNN1B	LIDDLE SYNDROME
SCNN1G	LIDDLE SYNDROME
SERPINA1	PROTEASE INHIBITOR 1
SERPIND1	HEPARIN COFACTOR II
SERPINF2	PLASMIN INHIBITOR DEFICIENCY
SERPING1	ANGIOEDEMA, HEREDITARY
SERPINI1	ENCEPHALOPATHY, FAMILIAL
SGCD	CARDIOMYOPATHY, DILATED, 1L
SLC16A1	ERYTHROCYTE LACTATE,,,
SLC25A4	PROGRESSIVE OPHTHALMOPLEGIA,,,
SMN1	SPINAL MUSCULAR ATROPHY, TYPE IV
SPAST	SPASTIC PARAPLEGIA
SPG7	SPASTIC PARAPLEGIA 7,,,
SPINK1	PANCREATITIS, HEREDITARY
SPTLC1	NEUROPATHY,,,
TCF1	HEPATIC ADENOMAS, FAMILIAL
TCF2	MATURITY-ONSET DIABETES,,,
TGFBI	CORNEAL DYSTROPHY,,,
TGFBR2	MARFAN SYNDROME, TYPE II
TNNT2	CARDIOMYOPATHY,,,
TP53	BREAST CANCER, FAMILIAL
TP53	LI-FRAUMENI SYNDROME 1
TSC1	LYMPHANGIOLEIOMYOMATOSIS
TSC2	LYMPHANGIOLEIOMYOMATOSIS
TSHR	HYPOTHYROIDISM,,,
TSHR	HYPERTHYROIDISM,,,
TTID	MUSCULAR DYSTROPHY,,,
TTN	TIBIAL MUSCULAR DYSTROPHY
TTN	HEREDITARY MYOPTAHY,,,
TTN	MUSCURLAR DYSTROPHY,,,
TTR	AMYLOIDOSIS VII
TTR	TRANSTHYRETIN
VAPB	SPINAL MUSCULAR ATROPHY,,,
VAPB	AMYOTROPHIC LATERAL SCLEROSIS
VHL	VON HIPPEL-LINDAU SYNDROME
VPS13A	CHOREOACANTHOCYTOSIS
VSX1	CORNEAL DYSTROPHY,,,
WFS1	DEAFNESS,,,
BRCA1	BREAST CANCER, FAMILIAL
GSN	AMYLOIDOSIS V
HGD	ALKAPTONURIA
LYZ	AMYLOIDOSIS, FAMILIAL VISCERAL
MUTYH	COLORECTAL POLYPOSIS,,,
OPTN	GLAUCOMA,,,
SOD1	AMYOTROPHIC,,,
TNNI3	CARDIOMYOPATHY,,,

20 years later

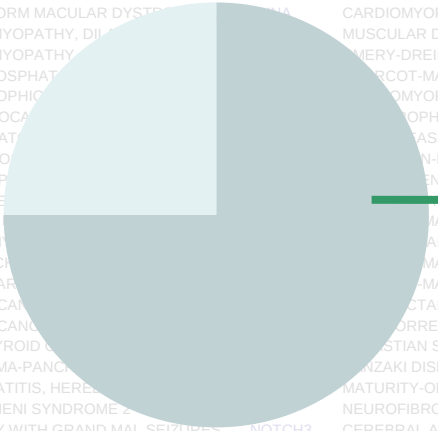
Blekhman (2008) – 205 couple gene - late onset diseases from OMIM

1 gene ►different diseases

1 diseases ►different genes

« most alleles involved in genetic diseases including familial forms of cancer, coronary artery diseases and Alzheimer dementia, are recent and rare. » *Wright A et al. (2003)*

Ex. **BRCA1** - Breast Cancer Information Core (BIC): More that 1000 alleles recorded



¾ of mutations at very low frequency (often in only one family)

Introduction

SCIENTIST AT WORK | DAVID B. GOLDSTEIN

A Dissenting Voice as the Genome Is Sifted to Fight Disease

By NICHOLAS WADE
Published: September 15, 2008

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The principal rationale for the $3 billion spent to decode the human genome was that it would enable the discovery of the variant genes that predispose people to common diseases like cancer and Alzheimer's. A major expectation was that these variants had not been eliminated by natural selection because they harm people only later in life after their reproductive years are over, and hence that they would be common.

Enlarge This Image

Ken Cedeno for The New York Times
GENE THINKER David Goldstein has not shied from unpopular positions.

This idea, called the common disease/common variant hypothesis, drove major developments in biology over the last five years. Washington financed the HapMap, a catalog of common genetic variation in the human population. Companies like Affymetrix and Illumina developed powerful gene chips for scanning the human genome. Medical statisticians designed the genomewide association study, a robust methodology for discovering true disease genes and sidestepping the many false positives that have plagued the field.

But David B. Goldstein of Duke University, a leading young population geneticist known partly for his research into the genetic roots of Jewish ancestry, says the effort to nail down the genetics of most common diseases is not working. "There is absolutely no question," he said, "that for the whole hope of personalized medicine, the news has been just about as bleak as it could be."

« The common disease/common variant idea is largely wrong […] natural selection has been far more efficient than many researchers expected »

J. Goldstein, Septembre 16, 2008

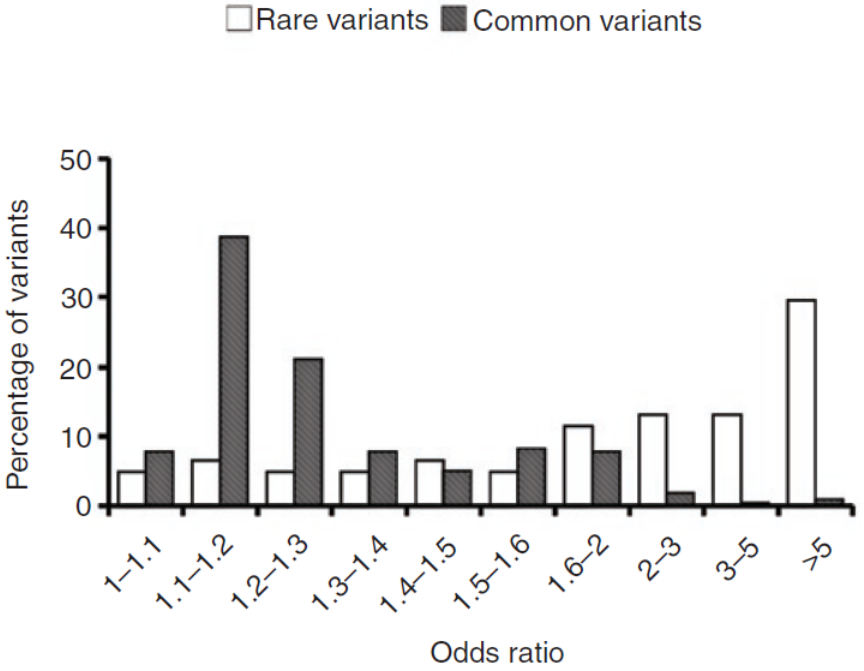


Figure 2 Distribution of odds ratios for common and rare variants. Odds ratios were obtained from the literature (**Supplementary Note**). We included 61 rare variants and 217 common variants in this analysis.

Bodmer and Bonilla (*Nature genetics*, 2008)

Introduction

Problem for population geneticists:

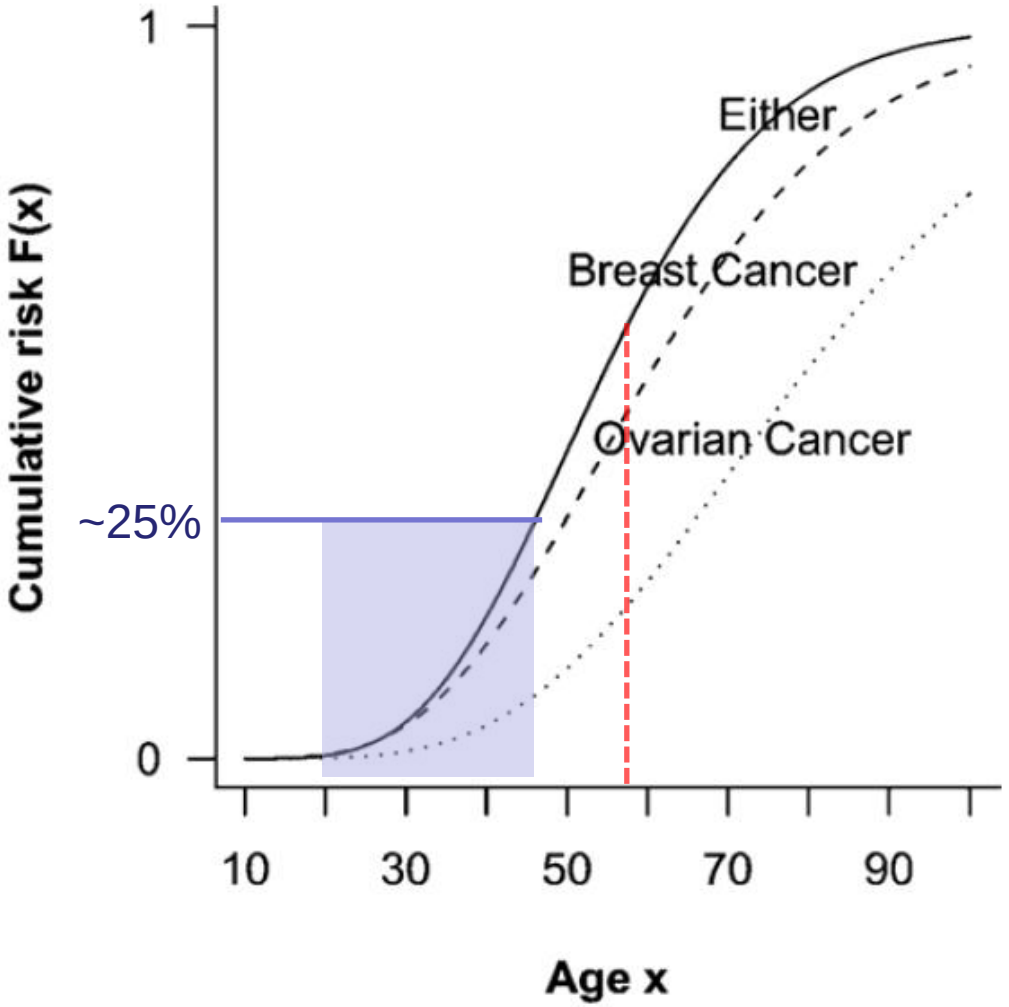
Multigenic diseases + Complex molecular pathway + Weak selection

► Selection tests from genetic data failed

What can then predict demographers?

Introduction

1. Variance in disease onset



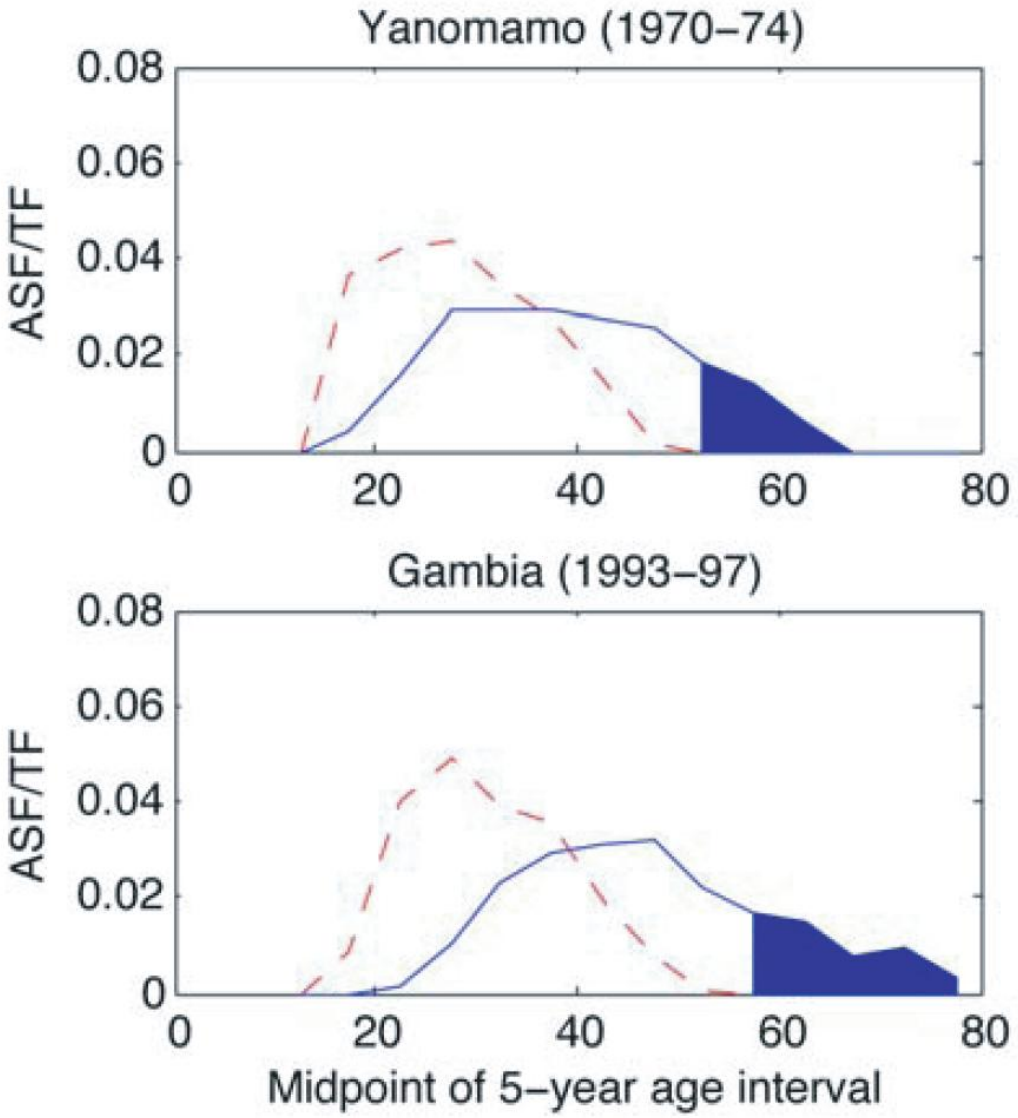
Diseases may occur *before* menopause even when the mean age at onset is *after* menopause

Ex. BRCA1

Pavard and Metcalf (2007)

Introduction

2. Males reproduction until old ages



Men (in blue) reproduce until old ages with younger women (in red).

Because of later age at marriage, remarriage and polygamy,

Tuljapurkar et al. (2007)

Introduction

3. Parental and grandparental care

This woman's age is 41…

Mothers, Fathers and

Grandmothers may care for

their immature children

long after menopause

Introduction

3. Parental and grandparental care

Who keeps children alive?
Sear and Mace (2008)

Motherless children have a

higher risk of death than children

whose mother are alive

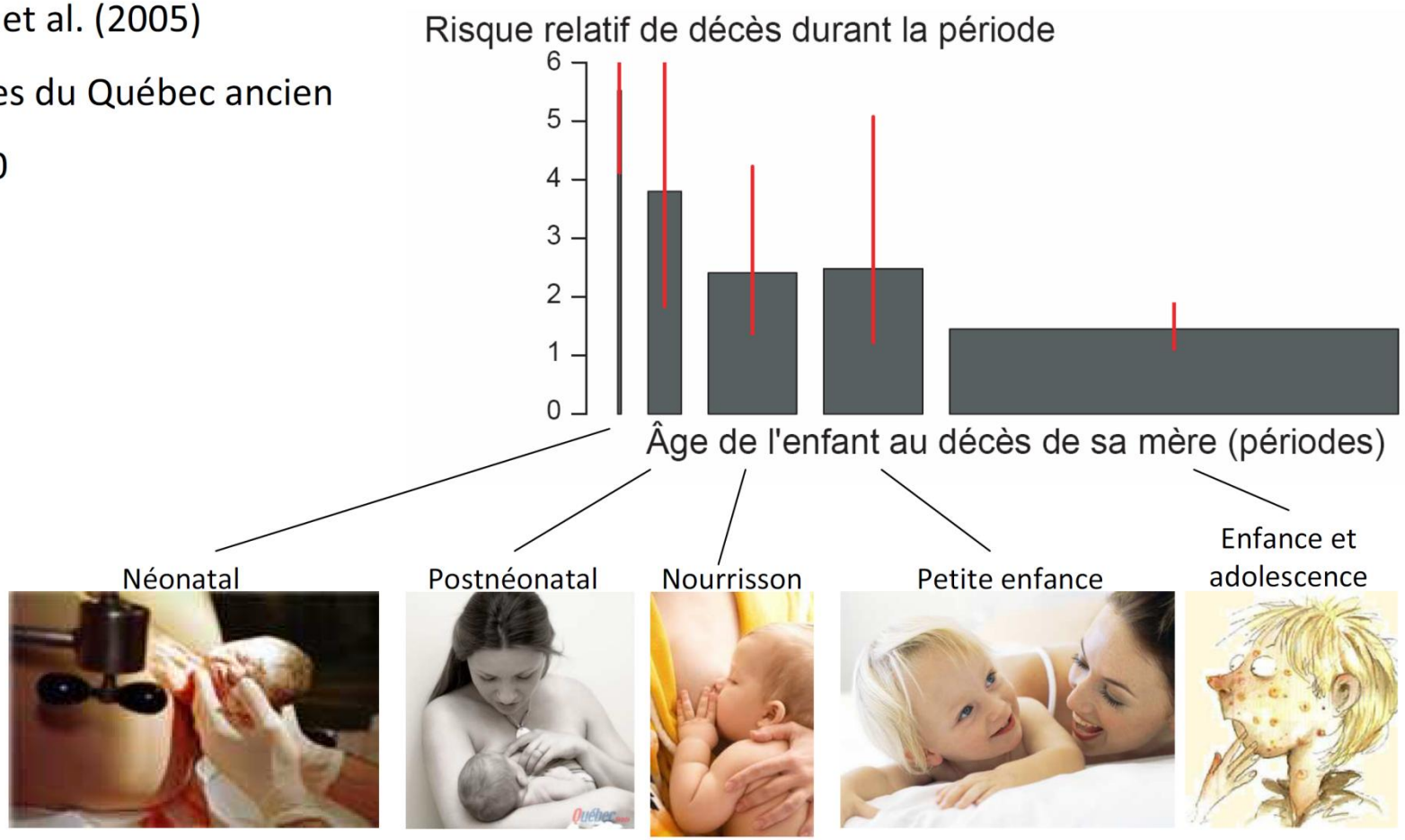
Population	Authors	Effect of mothers	Age of children studied
Nepal (Sarlahi) 1994–97	Katz et al. (2003)	+	0–24 weeks
Caribbean (St. Barthélemy) 1878–1976	Brittain (1992)	+	0–1 yr
Gambia (four villages) 1950–74	Sear et al. (2000, 2002)	+	0–5 yrs
Kenya (Kipsigis) 1945–90	Borgerhoff Mulder, (2007)	+	0–5 yrs
Burkina Faso (Nouna) 1992–99	Becher et al. (2004)	+	0–5 yrs
Sub-Saharan Africa [c] 1980s–2000	Zaba et al. (2005)	+	0–5 yrs
Canada (Quebec) 1680–1750	Beise (2005)	+	0–5 yrs
Poland (Bejsce) 1737–1968	Tymicki (2006)	+	0–5 yrs
Guinea–Bissau 1990–98	Masmas et al. (2004)	+	0–8 yrs
Paraguay (Ache) 1890–1971	Hill and Hurtado (1996)	+	0–9 yrs
Netherlands (Woerden) 1850–1930	Beekink et al. (1999, 2002)	+	0–12 yrs
Italy (Tuscany) 1819–59	Breschi and Manfredini (2002)	+	0–12 yrs
Canada (Quebec) 1625–1759	Pavard et al. (2005)	+	0–15 yrs
Sweden (Sundsvall) 1800–1895	Andersson et al. (1996)	+	0–15 yrs
Japan (Central) 1671–1871	Sorenson Jamison et al. (2002)	+	1–16 yrs
China (North East) 1774–1873	Campbell and Lee (1996, 2002)	+	~1–15 yrs

3. Parental and grandparental care

Pavard et al. (2005)

Données du Québec ancien

N=9840



Methods – *Presentation of the model*

Coefficient of selection of susceptibility allele:

For a large and realistic parameter space for disease onset (mean and variance)

In a two-sex model were men can reproduce at old ages

Where child survival depends on maternal, paternal and grandmaternal care

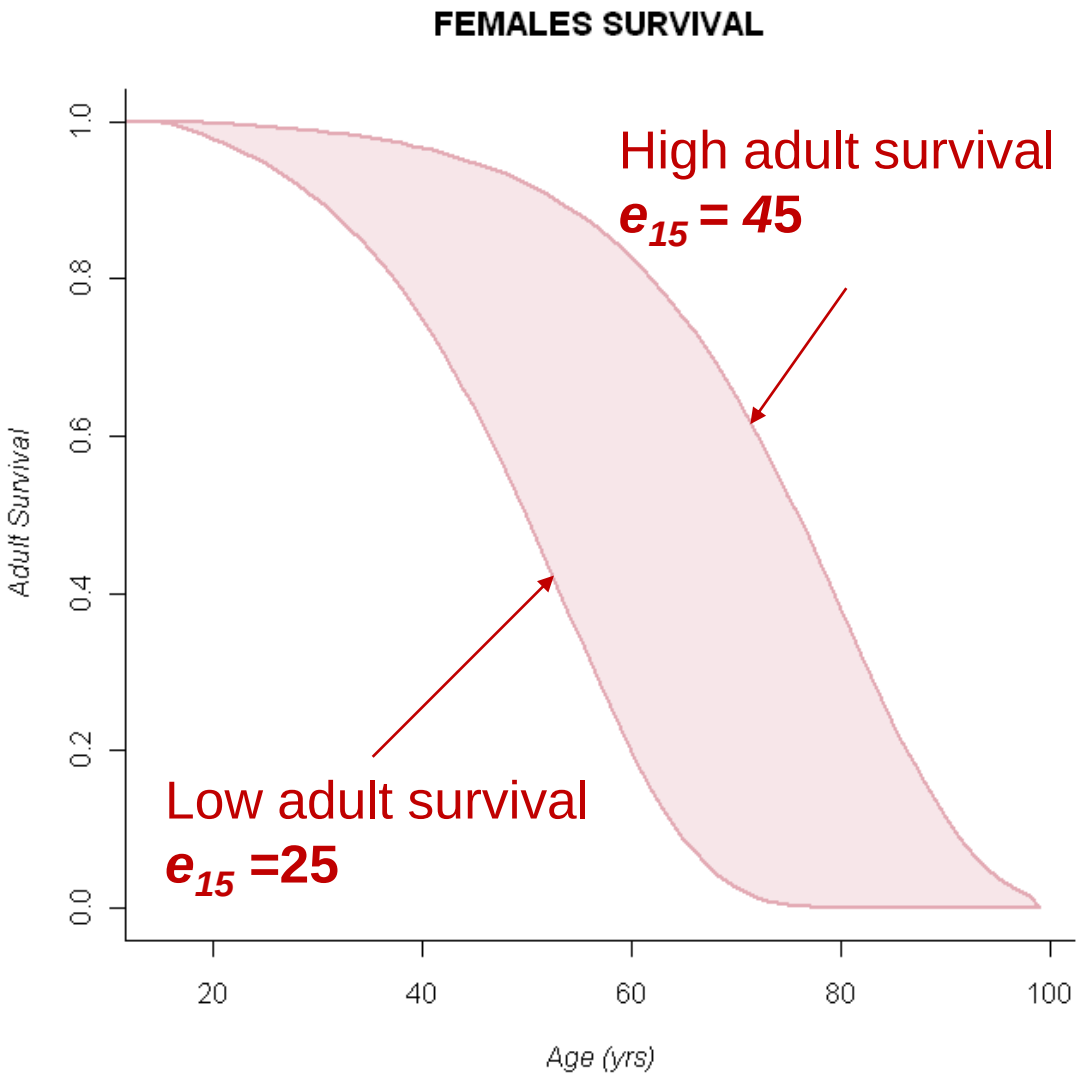
► Selective value of non-carriers (*population survival*) and carriers (*population survival * disease survival*)

Methods – *Survival of carriers and non-carriers*

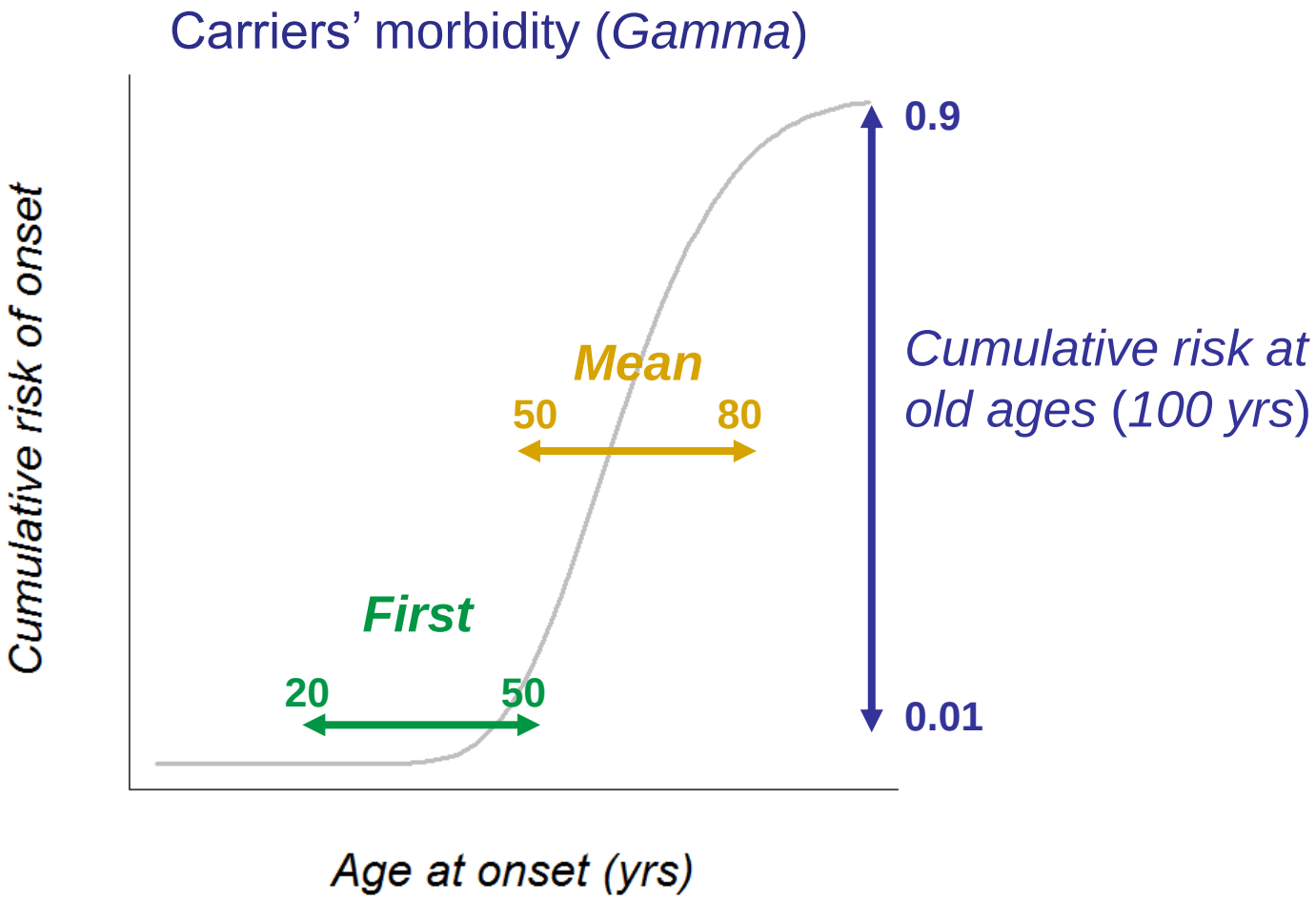
Non Carriers adult survival

Gompertz

$$L^f(x) = \exp\left[\frac{\rho a}{b}\left(e^{-b^{\dagger}x} - 1\right)\right]$$



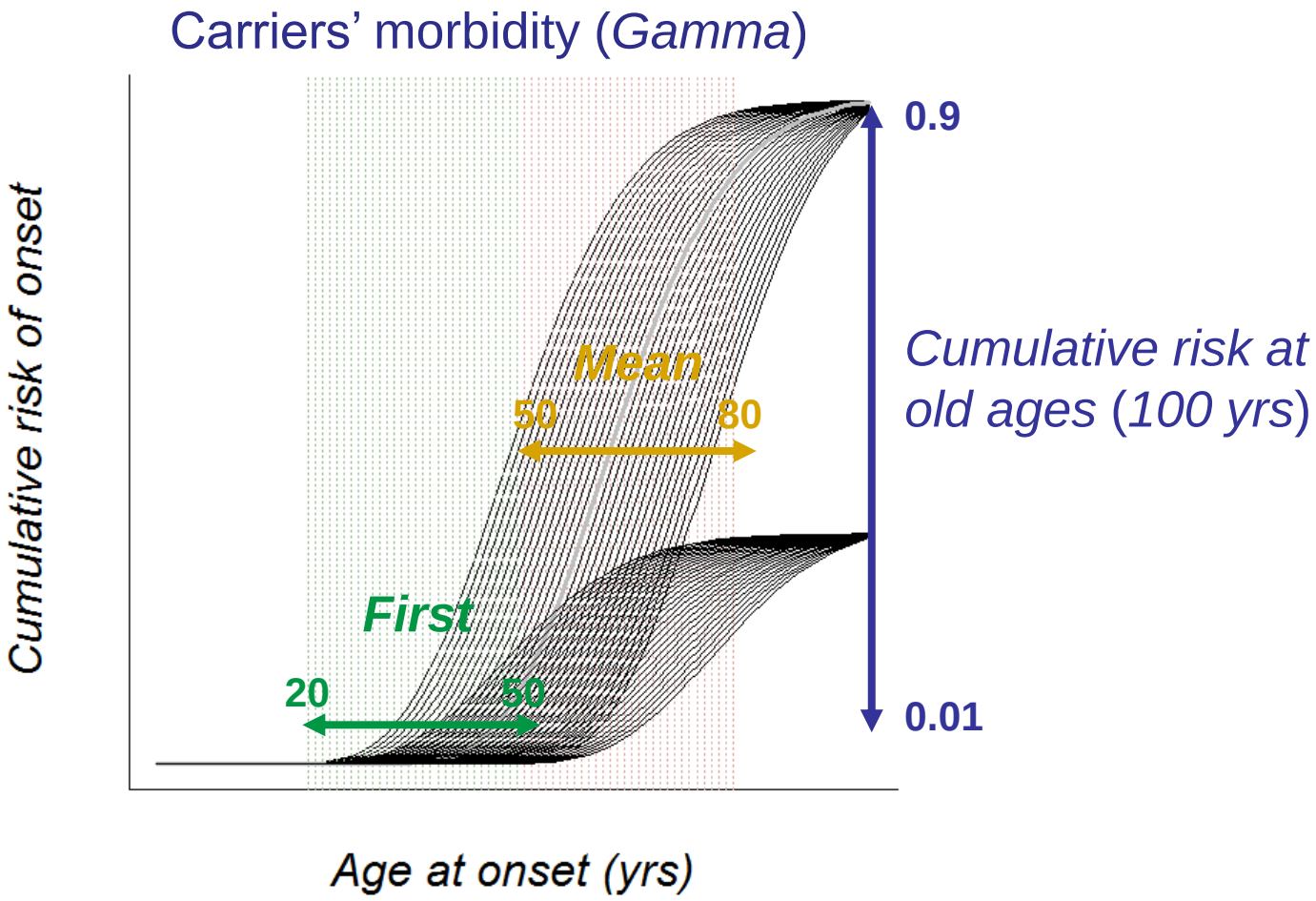
Methods – *Survival of carriers and non-carriers*



Except for BRCA1 and Huntington, distribution of age at onset is rare

For most diseases: familial cases study

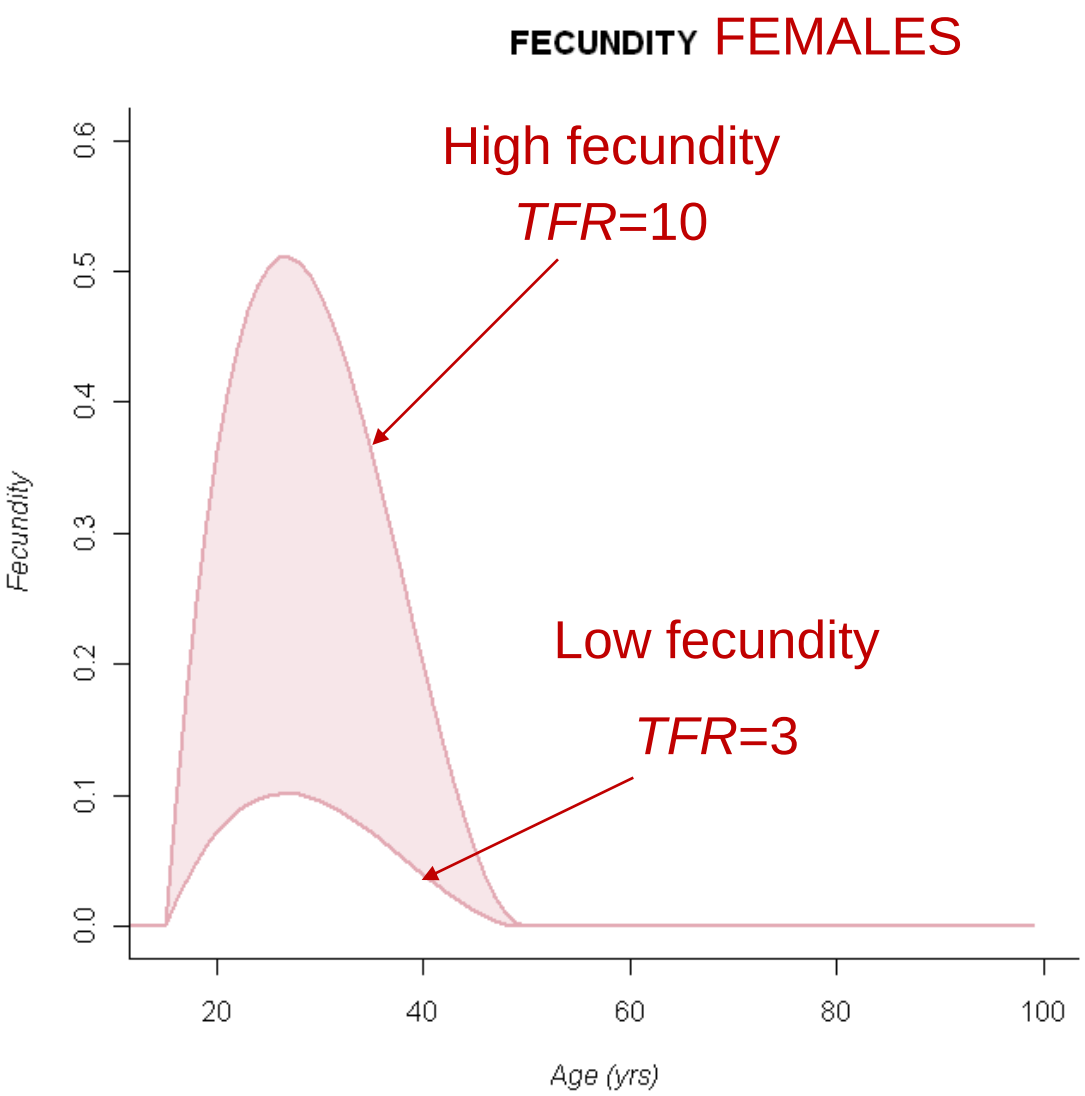
Methods – *Survival of carriers and non-carriers*



Except for BRCA1 and Huntington, distribution of age at onset is rare

For most diseases: familial cases study

Methods – *Fecundity (Brass Polynomial)*



Brass Polynomial

$$f^{f}(x) = c(x-\alpha)(\beta-x)^{2}$$

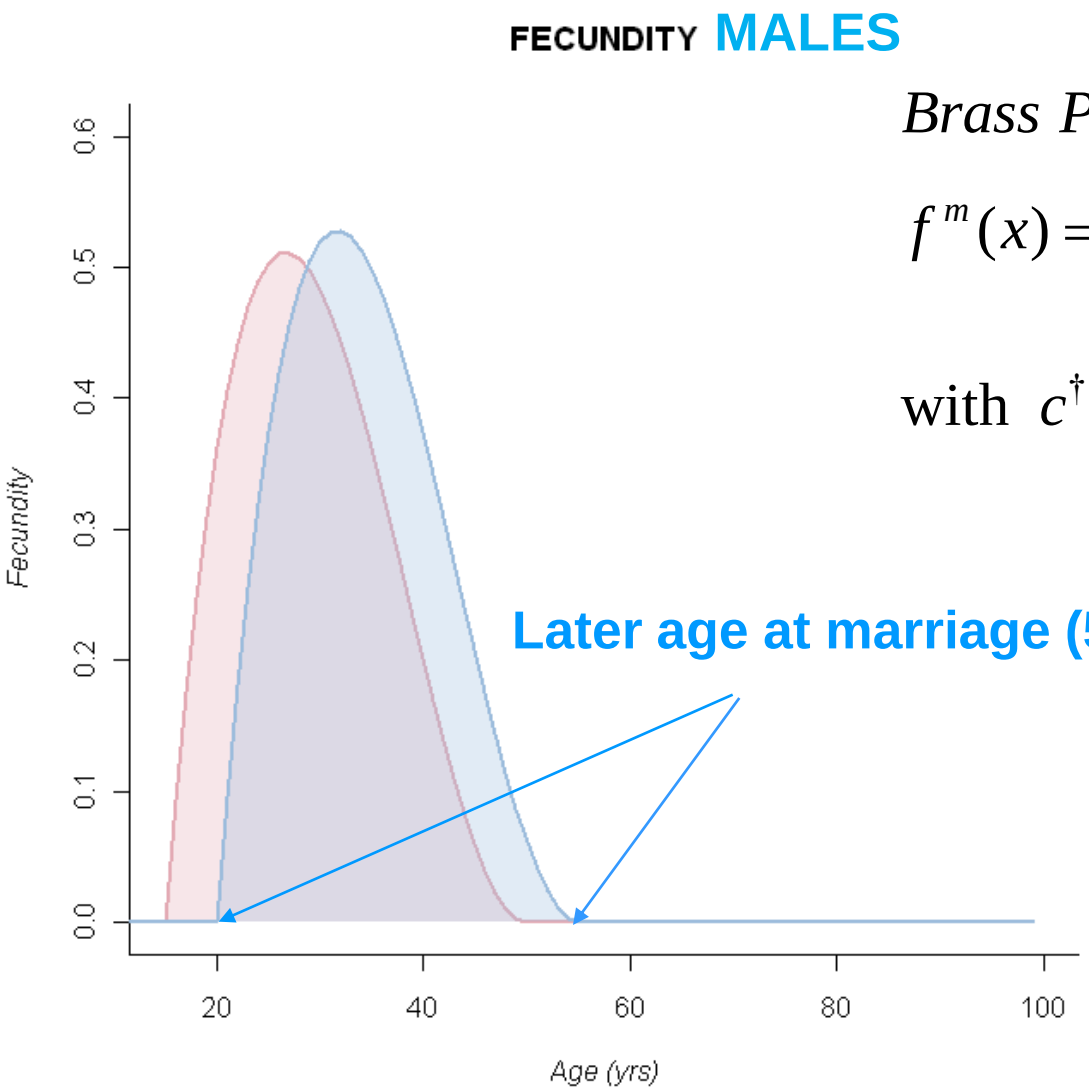
for $\alpha \le x \le \beta$

$\alpha = 15$

$\beta = 50$

c scales up and down

Methods – *Fecundity (Brass Polynomial)*

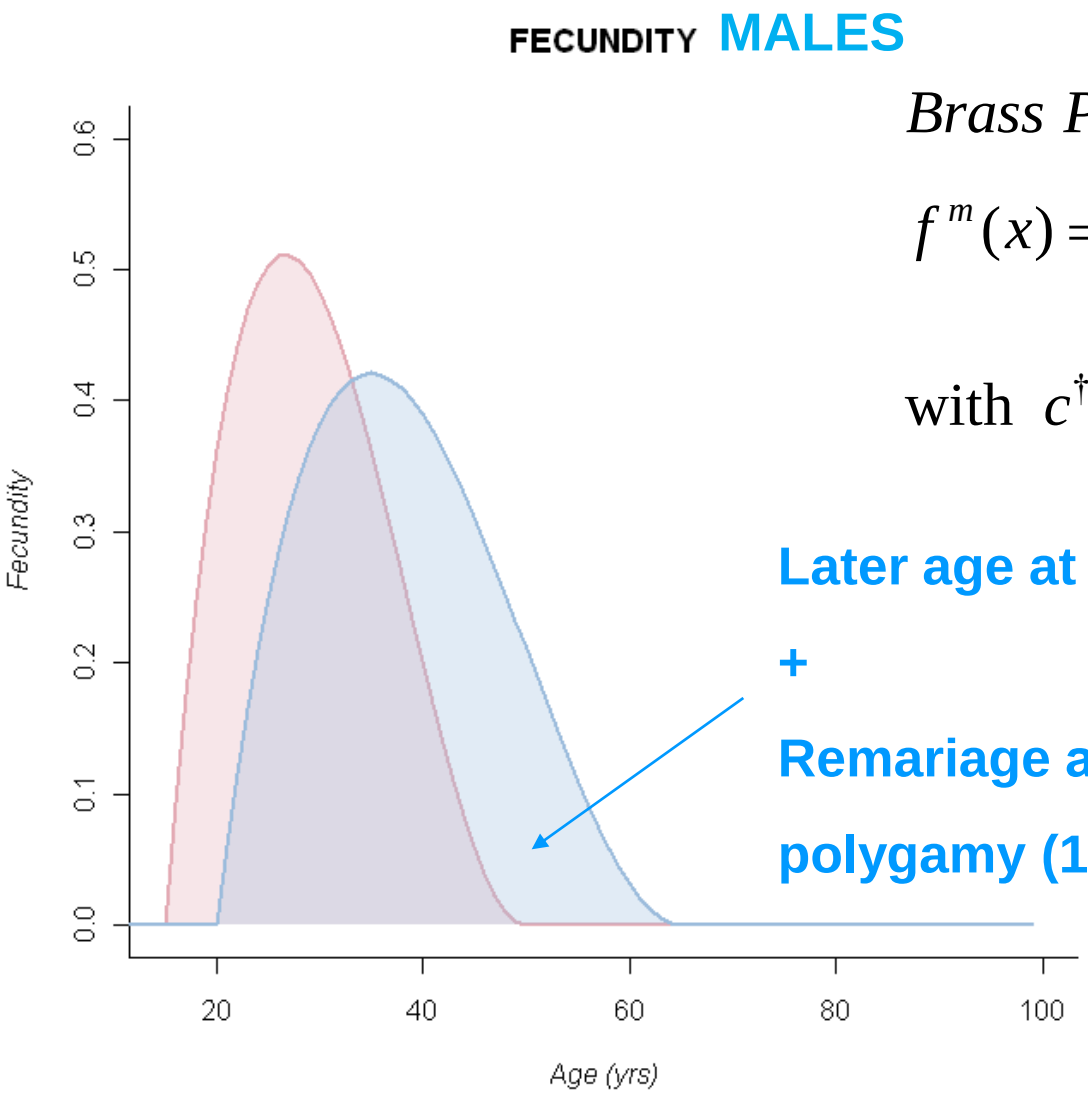


Brass Polynomial

$$f^m(x) = c^m\left(x-\alpha^m\right)\left(\beta^m - x\right)^2$$

$$\text{with } c^{\dagger} = \frac{\int_x L^f(x)\, f^f(x)dx}{\int_x L^m(x)\left(x-\alpha^m\right)\left(\beta^m - x\right)^2 dx}$$

Methods – *Fecundity (Brass Polynomial)*



Brass Polynomial

$$f^m(x) = c^m\left(x-\alpha^m\right)\left(\beta^m-x\right)^2$$

$$\text{with } c^{\dagger} = \frac{\int_x L^f(x)\, f^f(x)dx}{\int_x L^m(x)\left(x-\alpha^m\right)\left(\beta^m-x\right)^2 dx}$$

Later age at mariage (5 yrs)

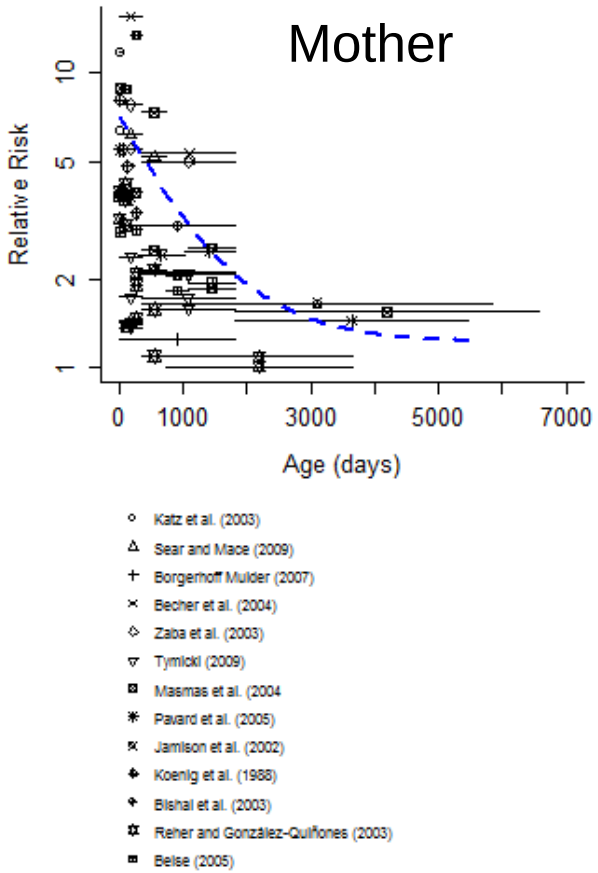
+

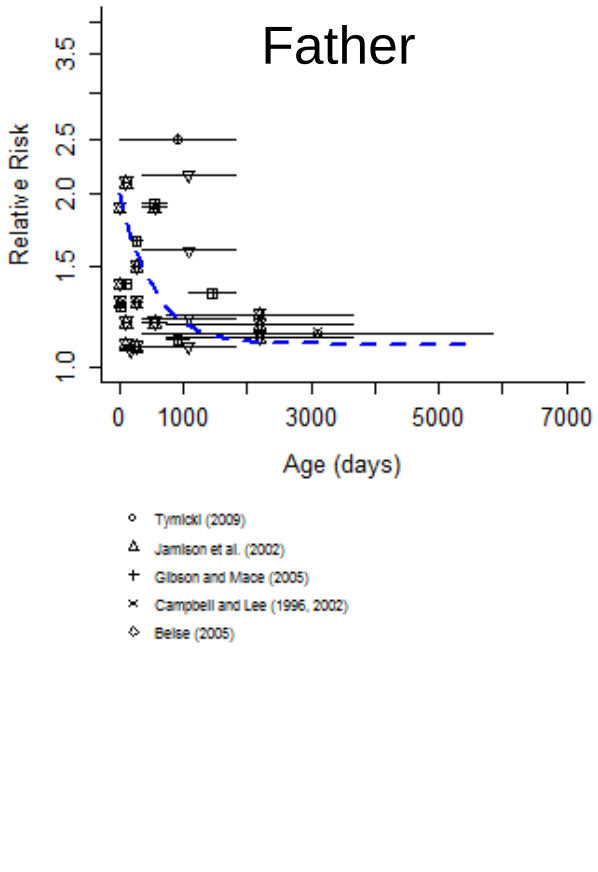
Remariage after divorce or wife's death ;

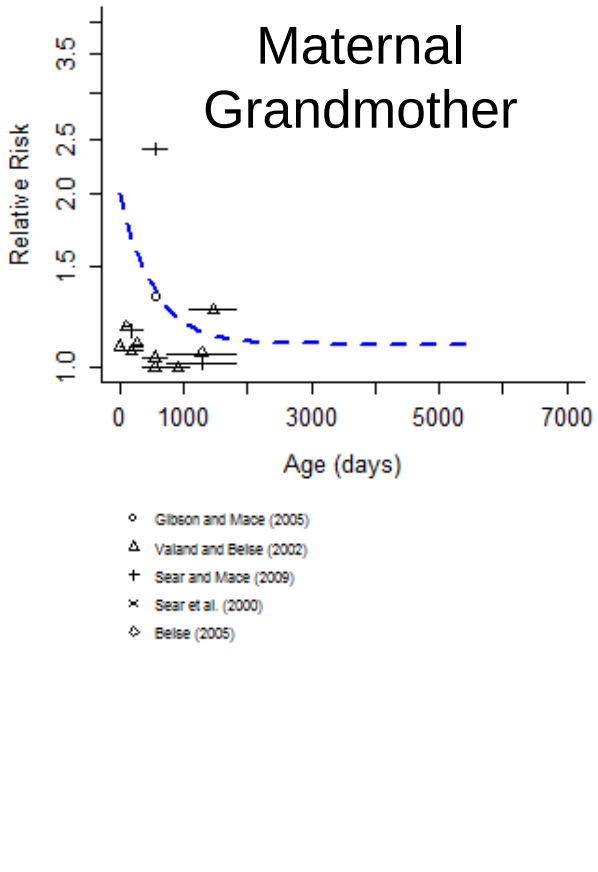
polygamy (10 yrs)

Methods – *Maternal, Paternal and Grandmaternal care*

Relative Risk of death of Orphans (from mother, father and maternal grandmother) compared to non-orphans

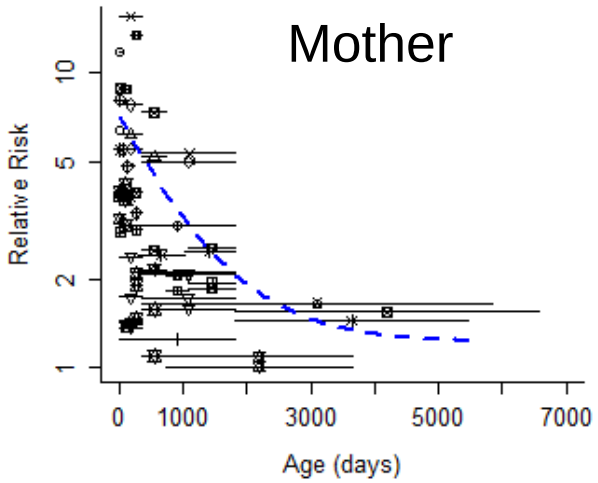


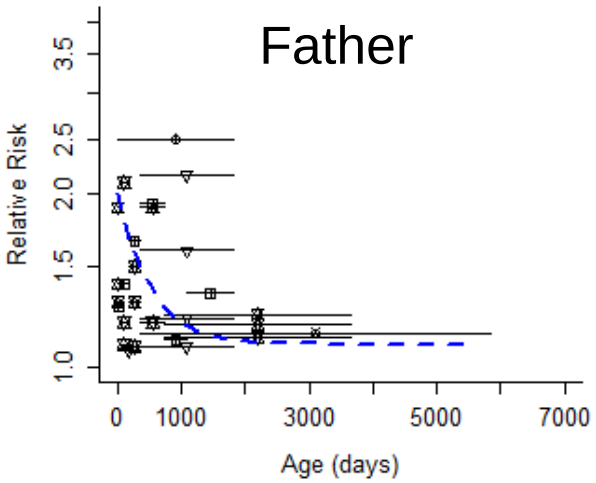


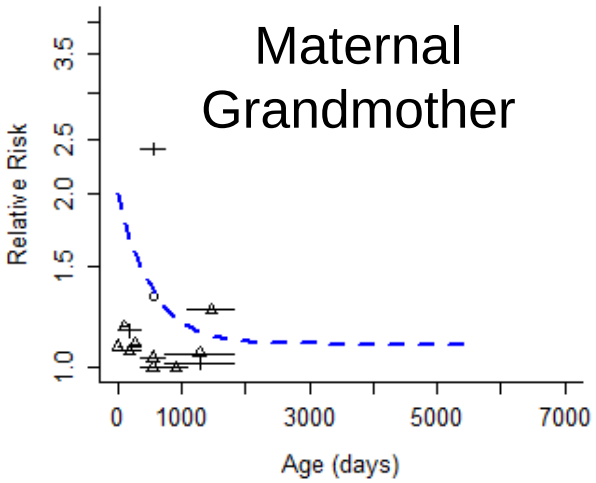


Methods – *Maternal, Paternal and Grandmaternal care*

Relative Risk of death of Orphans (from mother, father and maternal grandmother) compared to non-orphans







$S^{\alpha}(y_1)$

y_1 age at mother's death

$S^{\alpha}(y_3)$

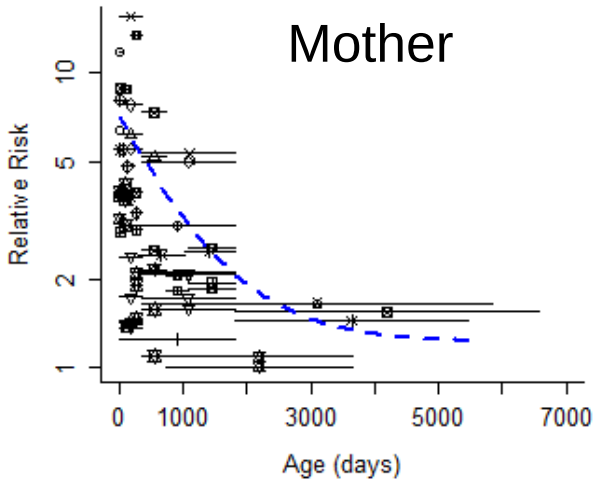
y_3 age at father's death

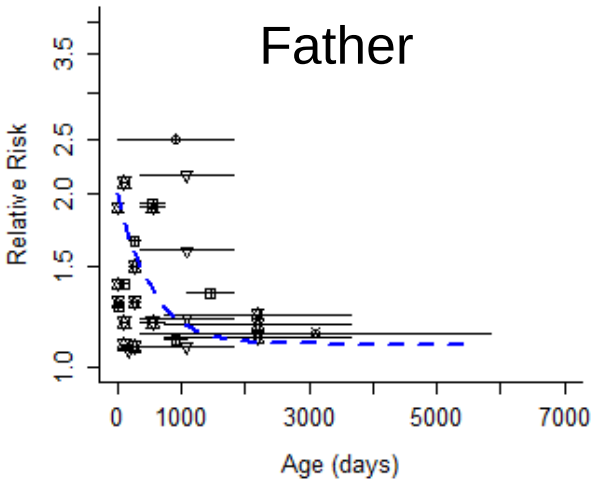
$S^{\alpha}(y_2)$

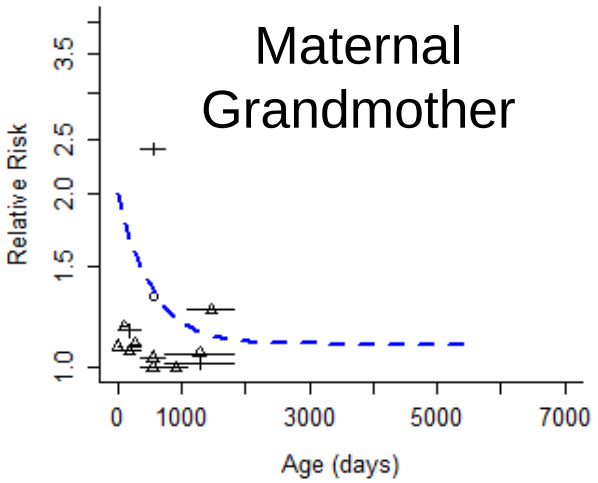
y_2 age at GM's death

Methods – *Maternal, Paternal and Grandmaternal care*

Relative Risk of death of Orphans (from mother, father and maternal grandmother) compared to non-orphans







$S^{\alpha}(y_1)$ $S^{\alpha}(y_3)$ $S^{\alpha}(y_2)$

y_1 age at mother's death y_3 age at father's death y_2 age at GM's death

$$S^{\alpha}(y_1, y_2, y_3)$$

Methods – *Calculation of the reproductive value*

The Euler-Lotka equation is:

$$1 = \int_0^{\omega} \left(\lambda^f\right)^{-x_1} l^f\left(x_1\right) f^f\left(x_1\right) dx_1$$

Replacing $L^f\left(x_1\right) = l^f\left(x_1\right) / \overline{S_\alpha}$

$$1 = \overline{S^\alpha} \int_\alpha^{\omega} \left(\lambda^f\right)^{-x_1} L^f\left(x_1\right) f^f\left(x_1\right) dx_1$$

Pavard (2007) showed that this is equivalent to:

$$1 = \int_\alpha^{\omega} \left(\lambda^f\right)^{-x_1} L^f\left(x_1\right) f^f\left(x_1\right) S^\alpha\left(x_1\right) dx_1$$

With $S^\alpha\left(x_1\right)$ being the child survival until maturity as a function of the mother's age at its birth

Methods – *Calculation of the reproductive value*

What we want is expressing $S^{\alpha}\left(x_1\right)$ as a function of $S^{\alpha}\left(y_1, y_2, y_3\right)$

To do this, we are looking for the probabilities for a child born to a mother at age x_1 to loose its mother, its maternal grandmother and its father at ages y_1, y_2 and y_3 respectively.

$$S^{\alpha}\left(x_1\right) = \iiint p\left(y_1 \mid x_1\right) p\left(y_2 \mid x_1\right) p\left(y_3 \mid x_1\right) S^{\alpha}\left(y_1, y_2, y_3\right) dy_1 dy_2 dy_3$$

Methods – *Calculation of the reproductive value*

Probability for a child to loose its mother at age y_1

$$p(y_1 \mid x_1) = \frac{L^f(x_1 + y_1)}{L^f(x_1)} h(x_1 + y_1)$$

Over all possible age y_1

$$\int_{y_1} p(y_1 \mid x_1) dy_1 = \int_0^{\varpi - x_1} \left(L^f(x_1 + y_1) / L^f(x_1) \right) h(x_1 + y_1) dy_1$$

Methods – *Calculation of the reproductive value*

Probability for a child to loose its maternal grandmother at age y_2

$$p(y_2 \mid x_1) = \int_{\alpha^f}^{\beta^f} p(x_2 \mid x_1)\, p(y_2 \mid x_1, x_2) dx_2$$

With

$$p(x_2 \mid x_1) = p(x_2) = \left(\lambda^f\right)^{-x_2} L^f(x_2)\, f^f(x_2) \overline{S^\alpha}$$

And

$$p(y_2 \mid x_1, x_2) = \frac{L^f\left(x_2 + x_1 + y_1\right)}{L^f\left(x_2\right)} h\left(x_2 + x_1 + y_1\right)$$

Over all possible age y_2

$$\int_{y_2} p(y_2 \mid x_1) dy_2 = \int_{-x_1}^{\varpi - x_1} \int_{\alpha^f}^{\beta^f} p(x_2) p(y_2 \mid x_1, x_2)\, dx_2 dy_2$$

Methods – *Calculation of the reproductive value*

Probability for a child to loose its father at age y_3

Assuming that fathers are always of the same age or older than the mother without further matrimonial structuring (structuring matrimony would indeed imply extending the model for incorporating widowing and divorced probability, remarriage probability and polygamy).

$$p(y_3 \mid x_1) = \int_{x_1}^{\beta^m} p(x_3 \mid x_1)\, p(y_3 \mid x_3) dx_3$$

With

$$p(x_3 \mid x_1) = \frac{\left(\lambda^m\right)^{-x_3} L^m(x_3)\, f^m(x_3)}{\int_{x_1}^{\beta^m} \left(\lambda^m\right)^{-x_3} L^m(x_3)\, f^m(x_3) dx_3}$$

Methods – *Calculation of the reproductive value*

Probability for a child to loose its father at age y_3

And $$p(y_3 \mid x_3) = \frac{L(x_3 + y_3)}{L(x_3)} h(x_3 + y_3)$$

Over all possible age y_3

$$\int_{y_3} p(y_3 \mid x_1) dy_3 = \int_0^{\varpi - x_1} \int_{x_1}^{\beta^m} p(x_3 \mid x_1)\, p(y_3 \mid x_3) dx_3 dy_3$$

Methods – *Calculation of the reproductive value*

- Input parameters are

$$L^f, L^m, F^f, F^m, S^\alpha\left(y_1, y_2, y_3\right)$$

- Euler-Lotka has 2 unknown parameters λ^f, λ^m

- But $\log\lambda \approx \frac{\log R_0}{T}$ is true at the third decimal in humans when the age unit is the year, therefore: $\log\left(\lambda^m\right) = \log\left(\lambda^f\right)\left(T^f / T^m\right)$

- We can then solve

$$1 = \int_\alpha^\omega \left(\lambda^f\right)^{-x_1} L^f\left(x_1\right) f^f\left(x_1\right) S^\alpha\left(x_1\right) dx_1$$

- And find the coresponding distribution $S^\alpha\left(x_1\right)$

Methods – *Calculation of the reproductive value*

Reproductive value of non carriers females

$$W^{NC} = \int_0^{\omega} L^f(x_1)\, f^f(x_1)\, S^{\alpha}(x_1)\, dx_1$$

(We can demonstrate that this holds when derivation are done for males)

W^C: similar equation + Morbidity

- Genetic compartment (Autosome, X-Chr, Y-Chr, Mt-Chr)
- Segregation coefficient (kin selection)
- Dominance
- Sex-specific pathology (male, female, both sex)

Methods – *Calculation of the reproductive value*

Here: Autosomal, Dominant mutation, disease in both sex

$$W^{C} = \frac{1}{2} W\left[\text{men}^{C}, \text{wife}^{NC}, \text{wife's mother}^{NC}\right] +$$

$$\frac{1}{2}\frac{1}{2} W\left[\text{women}^{C}, \text{husband}^{NC}, \text{mother}^{NC}\right] +$$

$$\frac{1}{2}\frac{1}{2} W\left[\text{women}^{C}, \text{husband}^{NC}, \text{mother}^{C}\right]$$

► First population genetics model incorporating maternal, grandmaternal and paternal care

► First compact model over only one generation

Methods – *Estimation of selection*

Assuming …

- An allele of susceptibility at very low frequency
- The disease is lethal (not benign as corneal dystrophy leading to night blindness)
- Death occurs at age at onset (not slowly degenerative disease)
- Independence between risk of onset and other causes of death within the population
- No pleiotropic effect of the alleles (eg. Smith et al. 2011 for BRCA1)
- Epidemiology of the disease was identical in the past (which is likely not the case in the cases of cancers, see Eaton et al. 1994)

Methods – *Estimation of selection*

Selection Coefficient

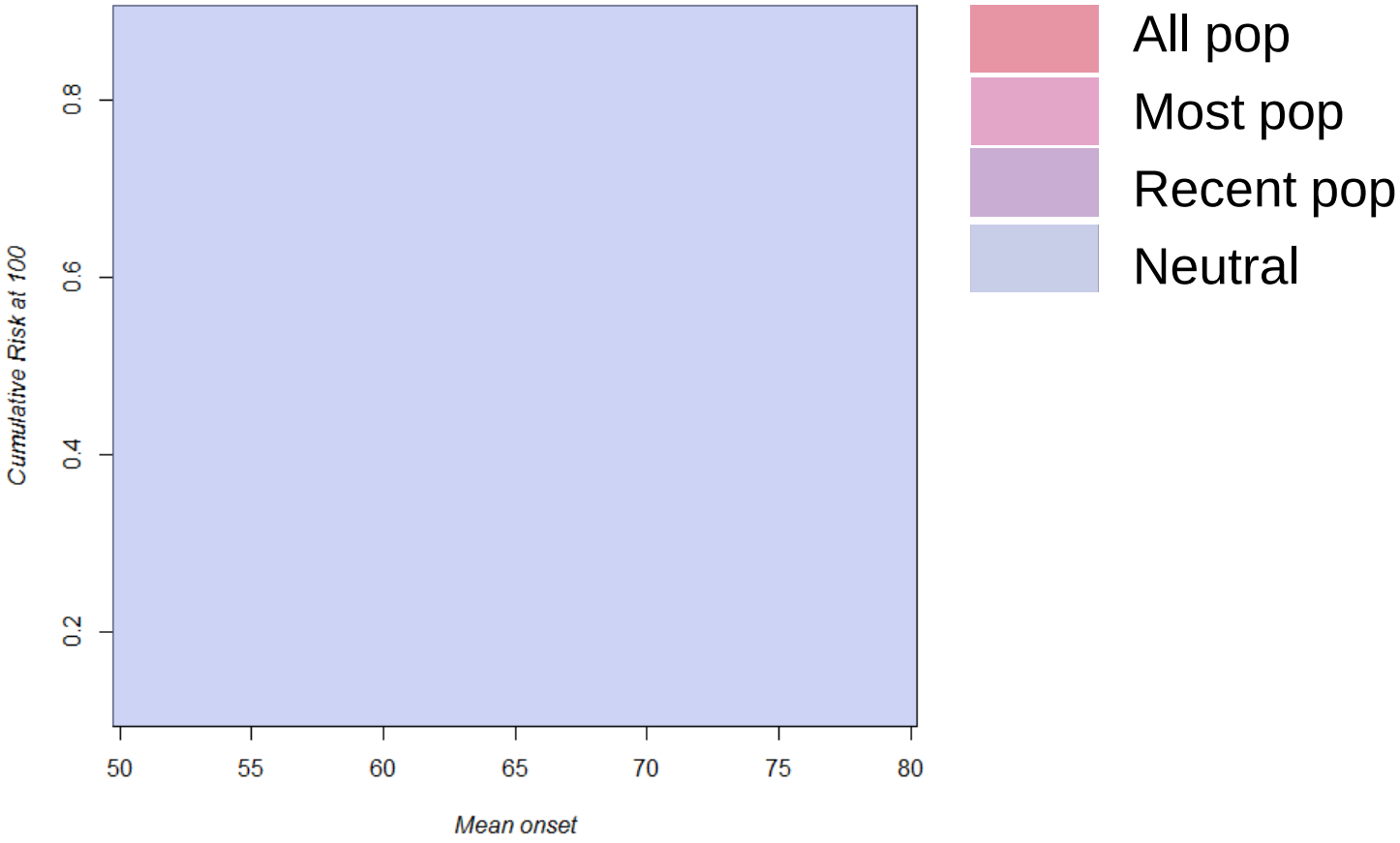
$$s = 1 - \frac{W^C}{W^{NC}}$$

Minimum effective size for which selection overcomes genetic drift

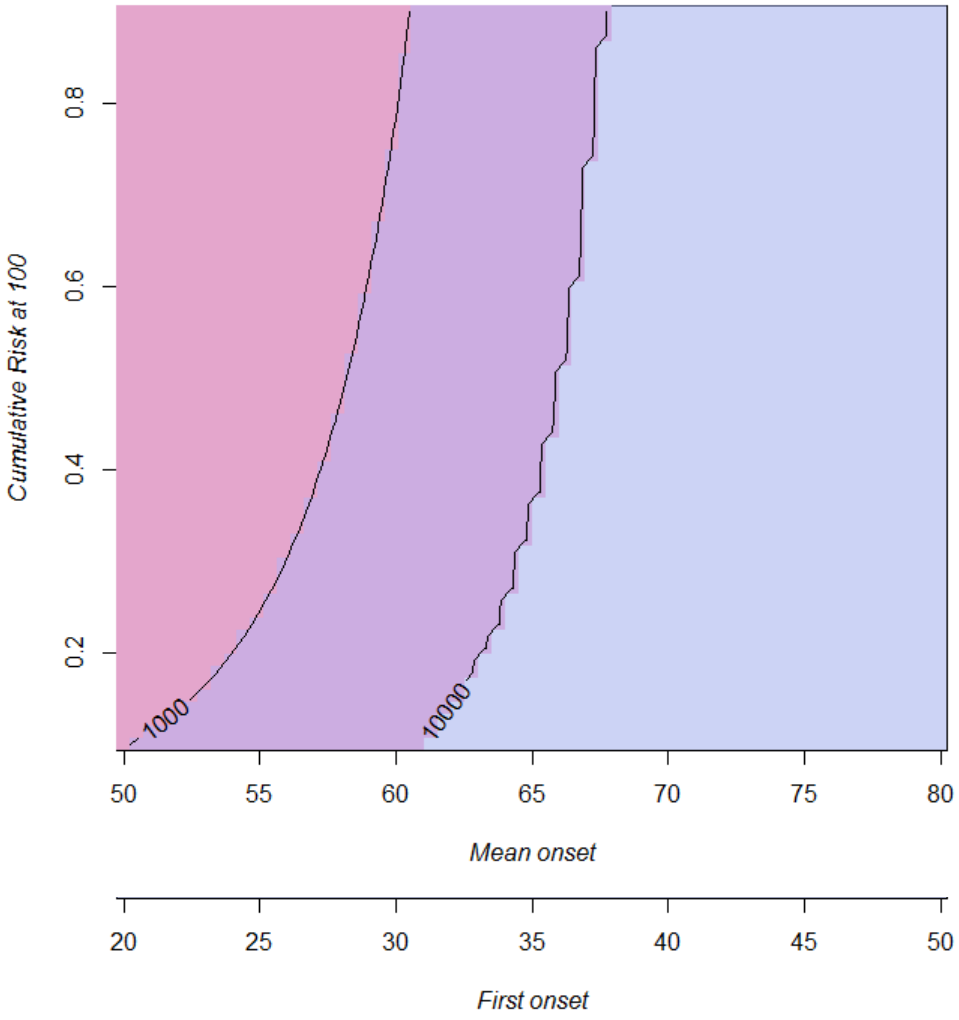
$$Ne_{\min} = \frac{10}{2s}$$ Kimura (1973)

$Ne_{min} < 100$	Negative selection all human pop
$100 < Ne_{min} < 1000$	Negative selection most human pop
$1000 < Ne_{min} < 10\ 000$	Negative selection only in recent human pop
$Ne_{min} > 10\ 000$	Neutral

Results


Cumulative Risk at 100
0.2
0.4
0.6
0.8
50
55
60
65
70
75
80
Mean onset
All pop
Most pop
Recent pop
Neutral

Results



All pop

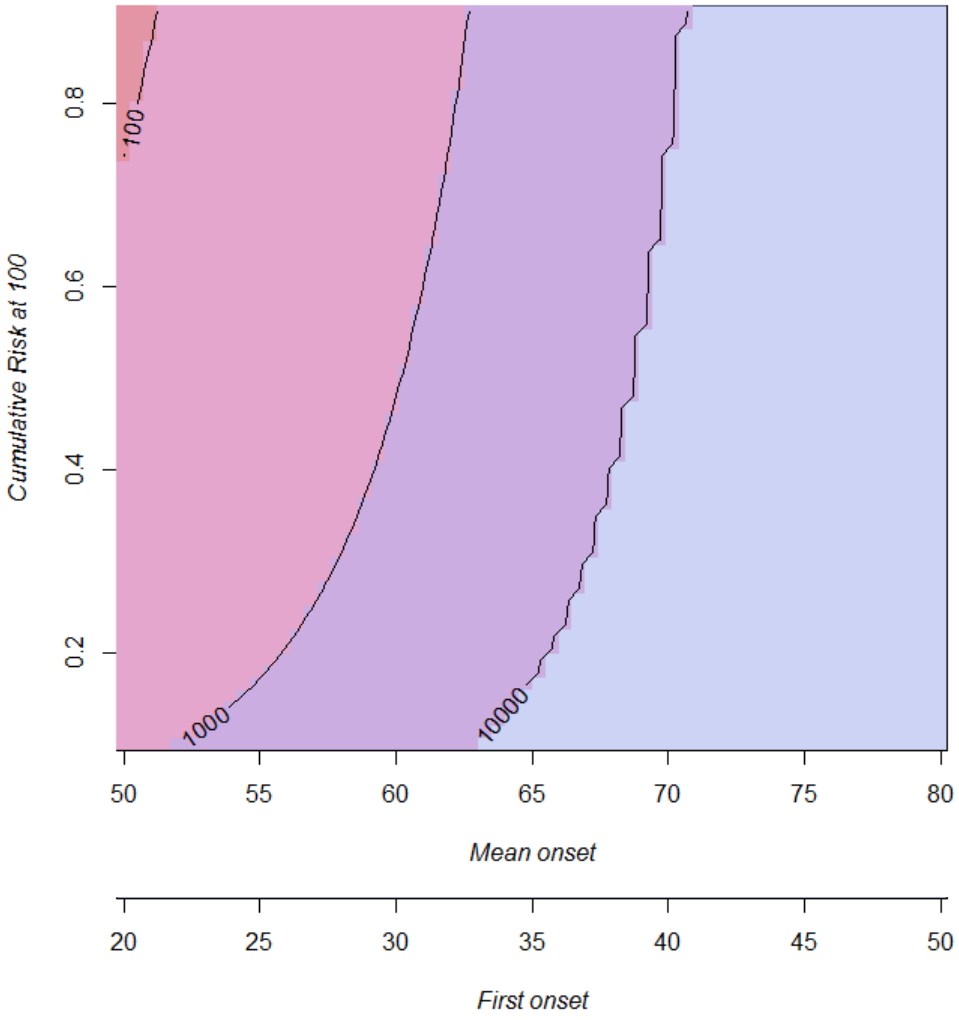
Most pop

Recent pop

Neutral

Variance in age at onset

Results



All pop

Most pop

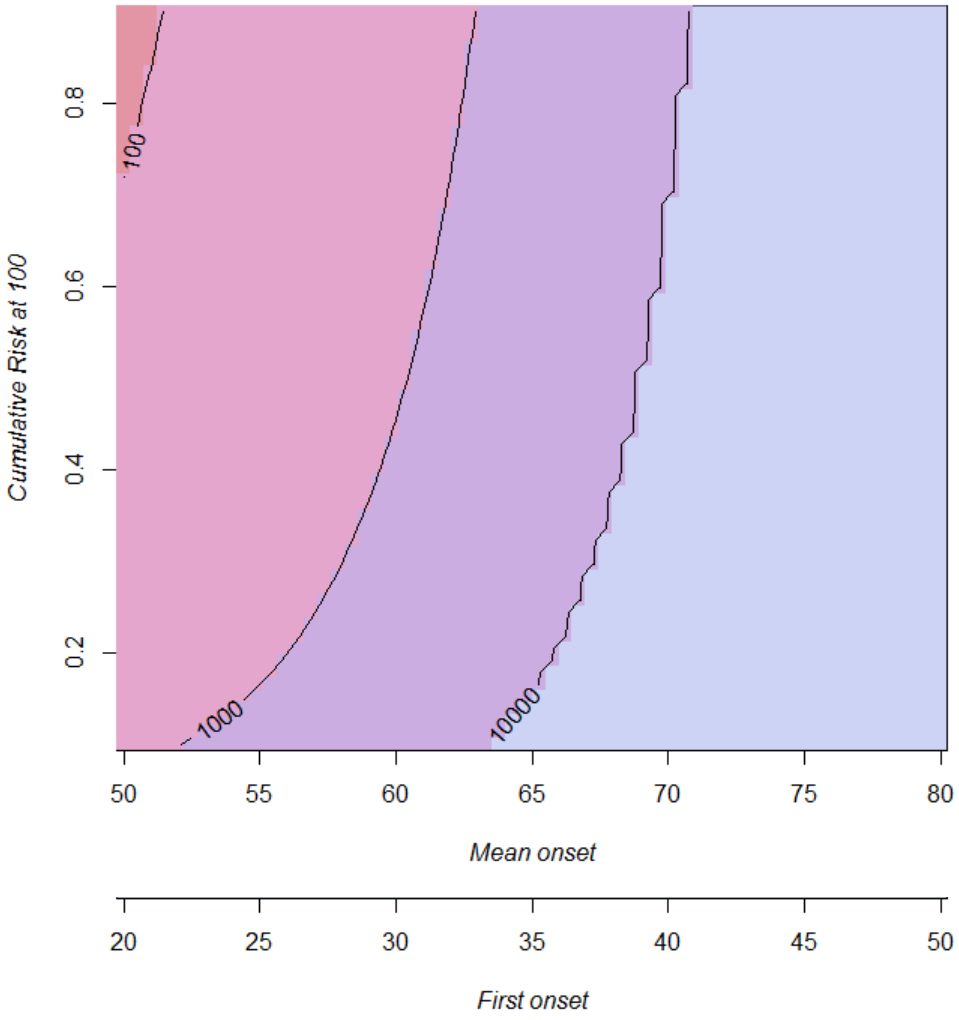
Recent pop

Neutral

Variance in age at onset

Maternal care

Results



All pop

Most pop

Recent pop

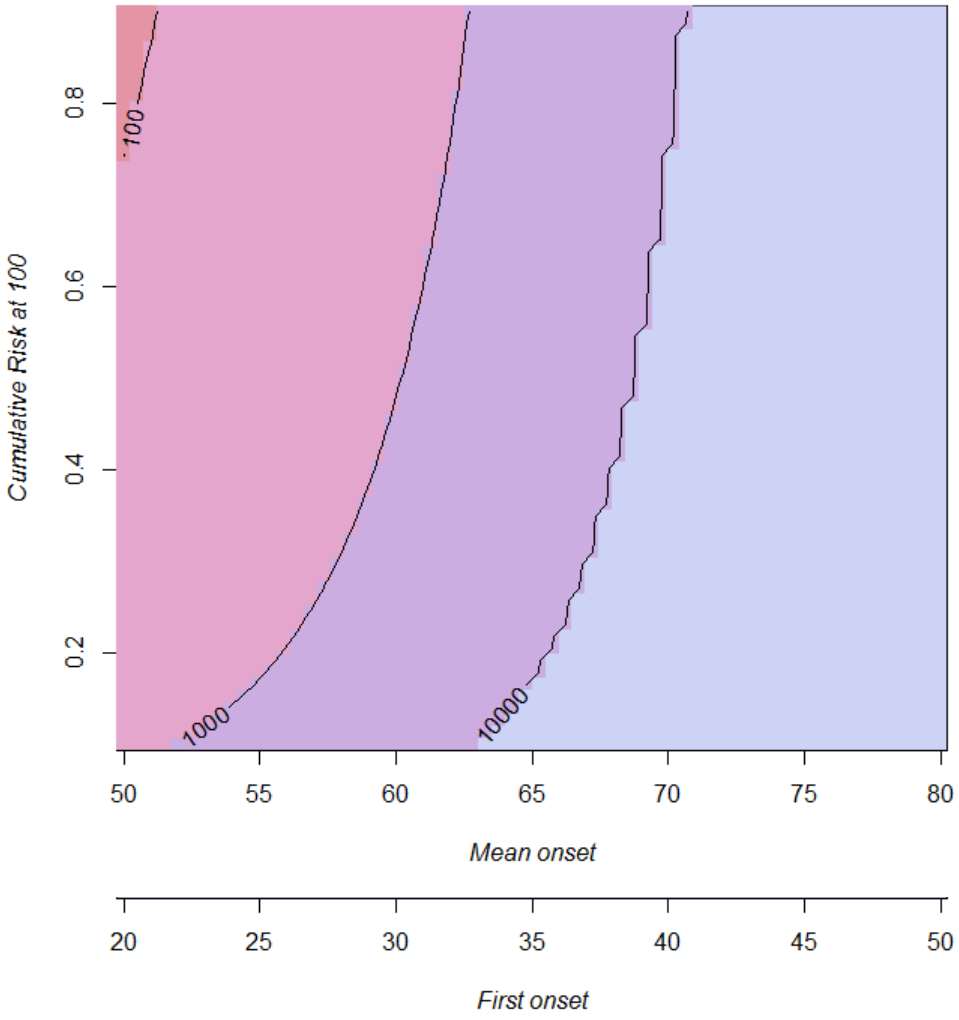
Neutral

Variance in age at onset

Maternal care

Paternal care

Results



All pop

Most pop

Recent pop

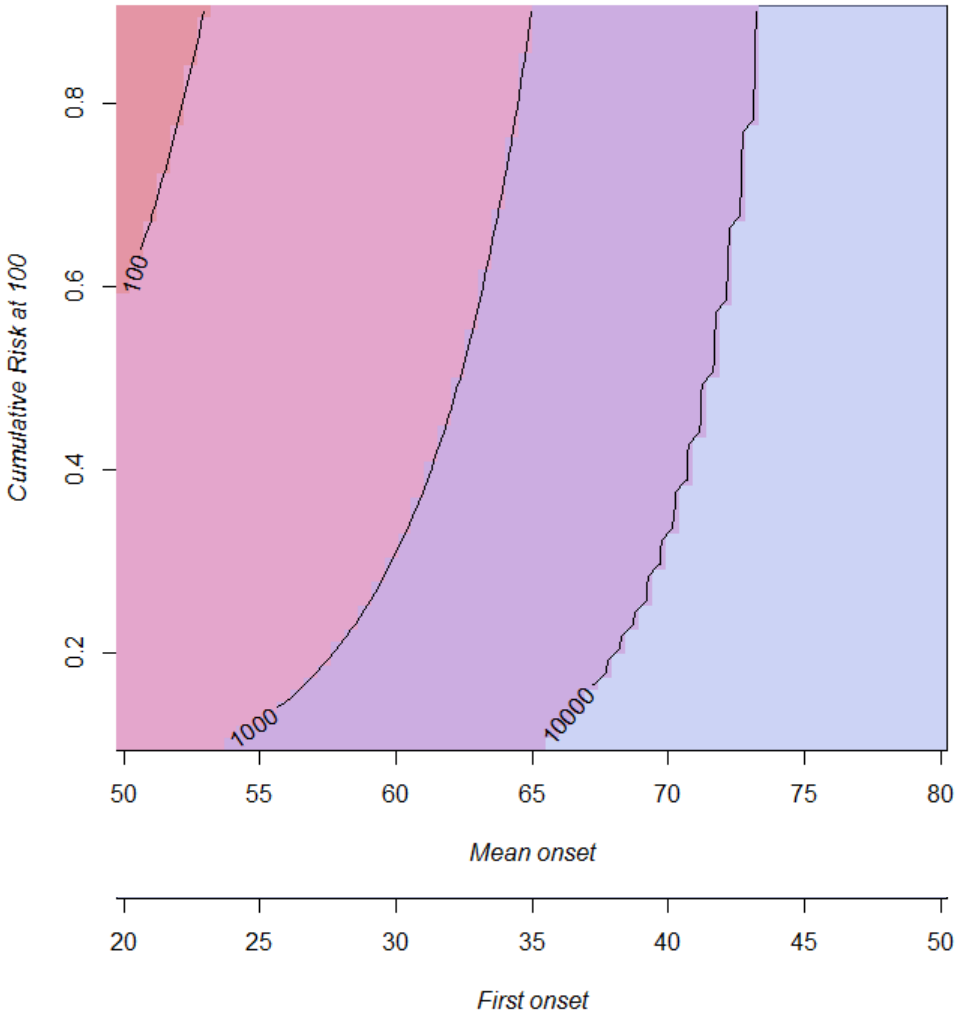
Neutral

Variance in age at onset

Maternal care

~~Paternal care~~

Results



All pop

Most pop

Recent pop

Neutral

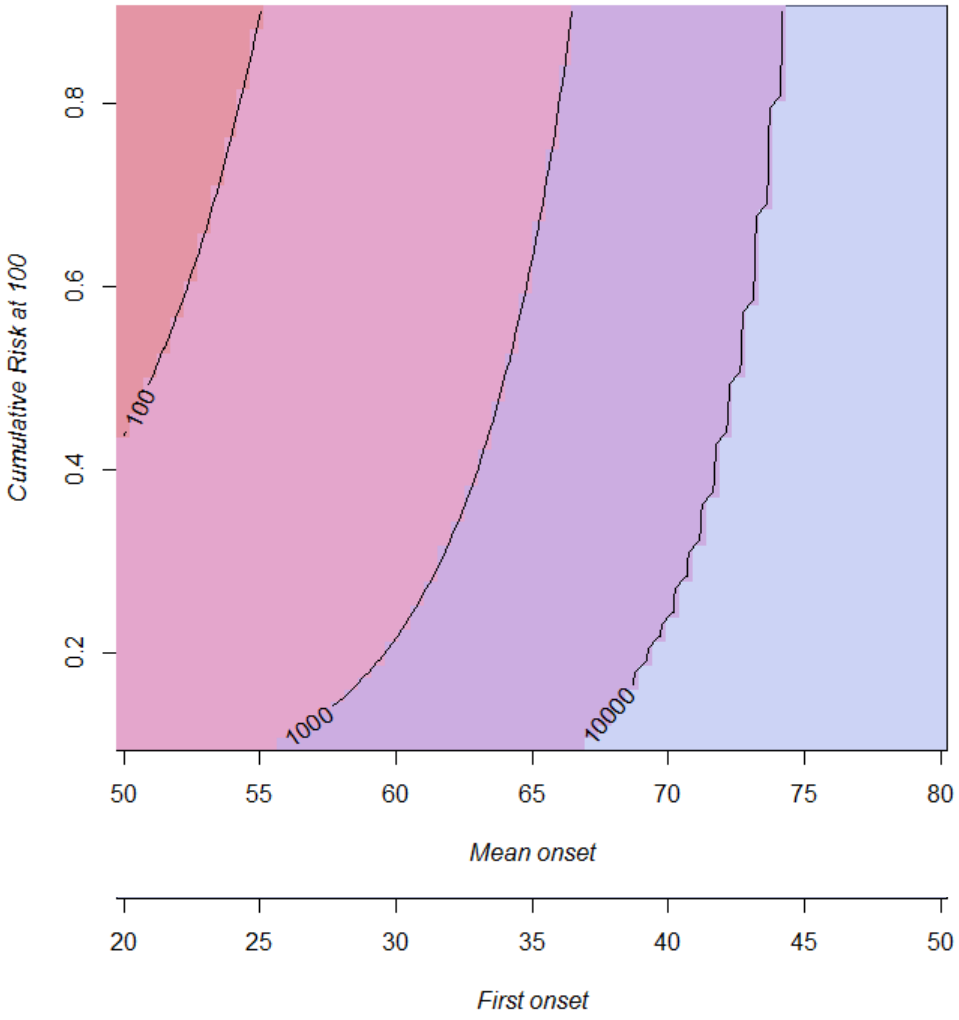
Variance in age at onset

Maternal care

~~Paternal care~~

Grandmaternal care

Results



All pop

Most pop

Recent pop

Neutral

Variance in age at onset

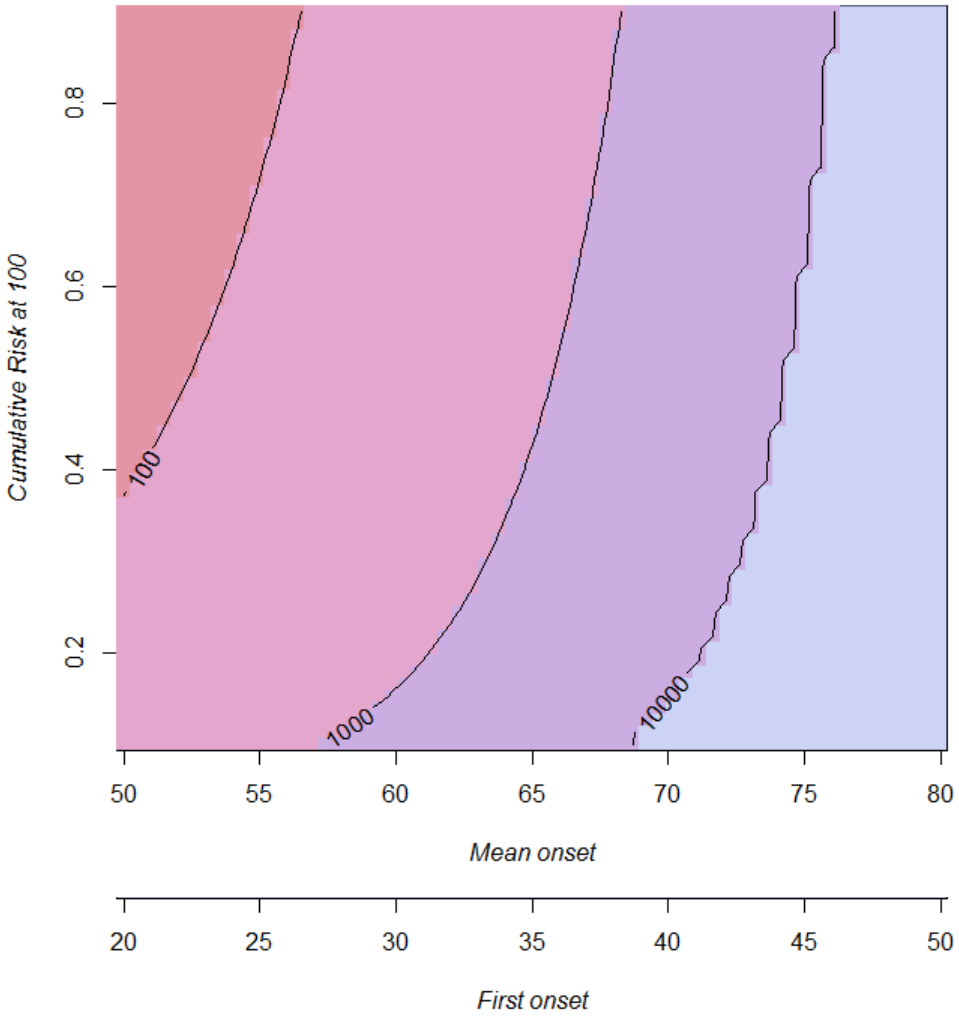
Maternal care

~~Paternal care~~

Grandmaternal care

Later age at first birth of men

Results



All pop

Most pop

Recent pop

Neutral

Variance in age at onset

Maternal care

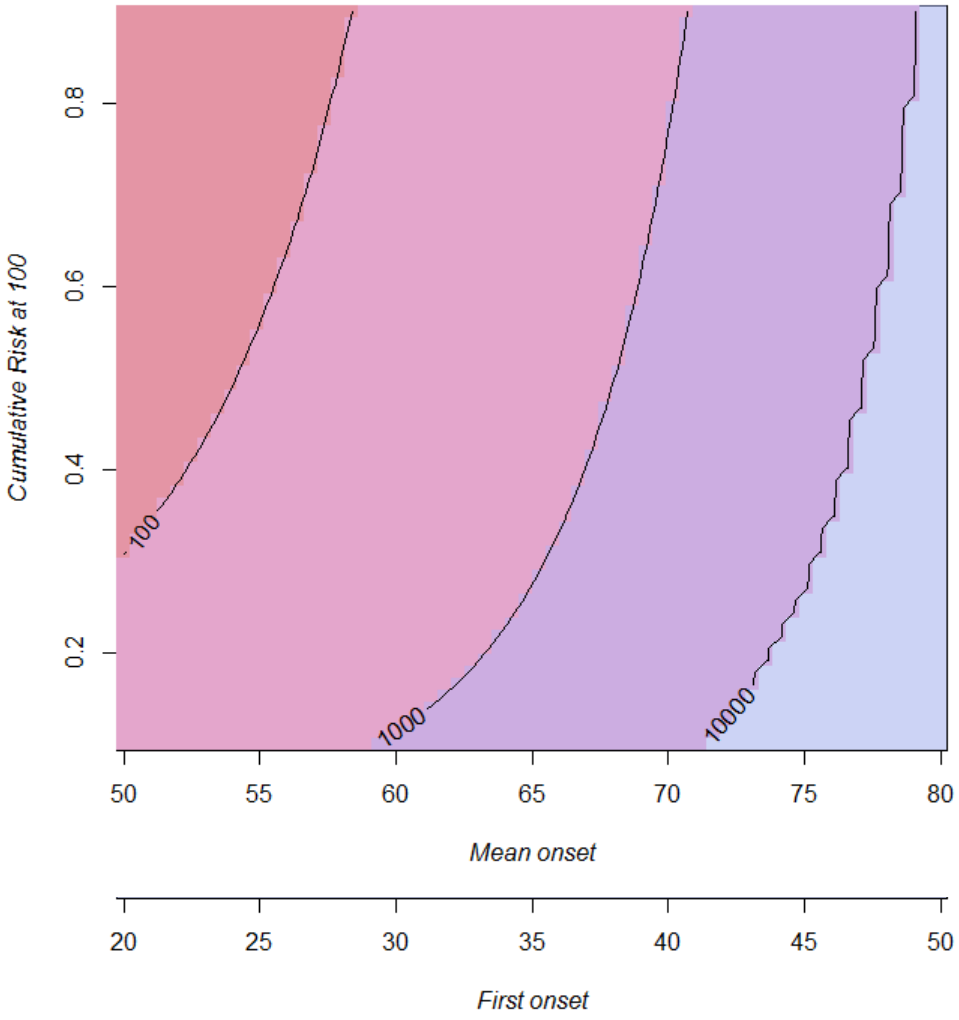
~~Paternal care~~

Grandmaternal care

Later age at first birth of men

Remariage/polygamy

Results



All pop

Most pop

Recent pop

Neutral

Variance in age at onset

Maternal care

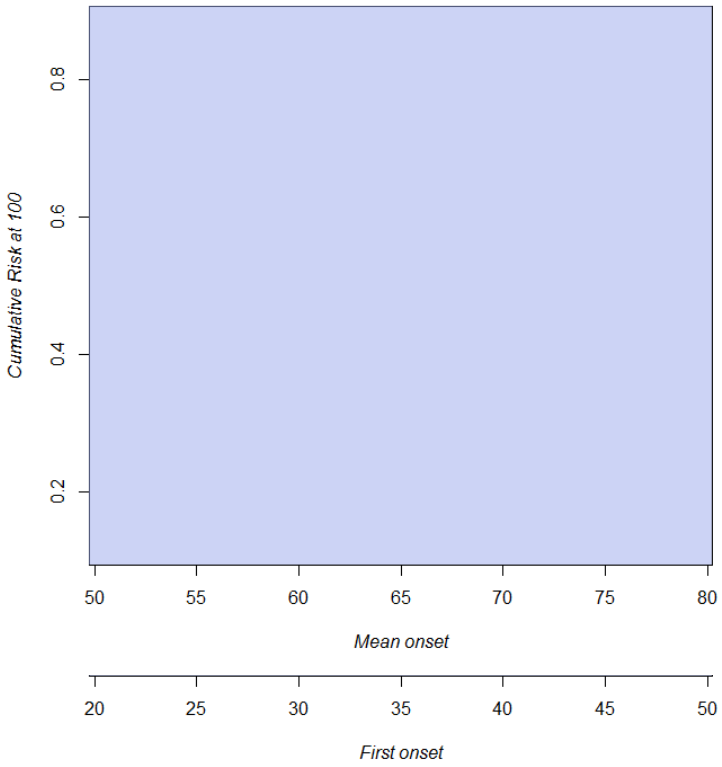
Paternal care

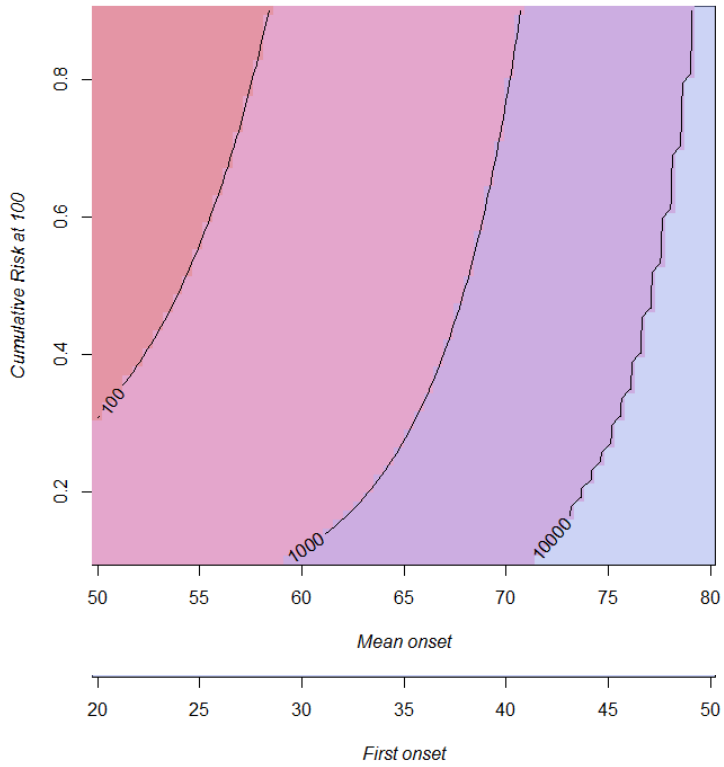
Grandmaternal care

Later age at first birth of men

Remariage/polygamy

Conclusion

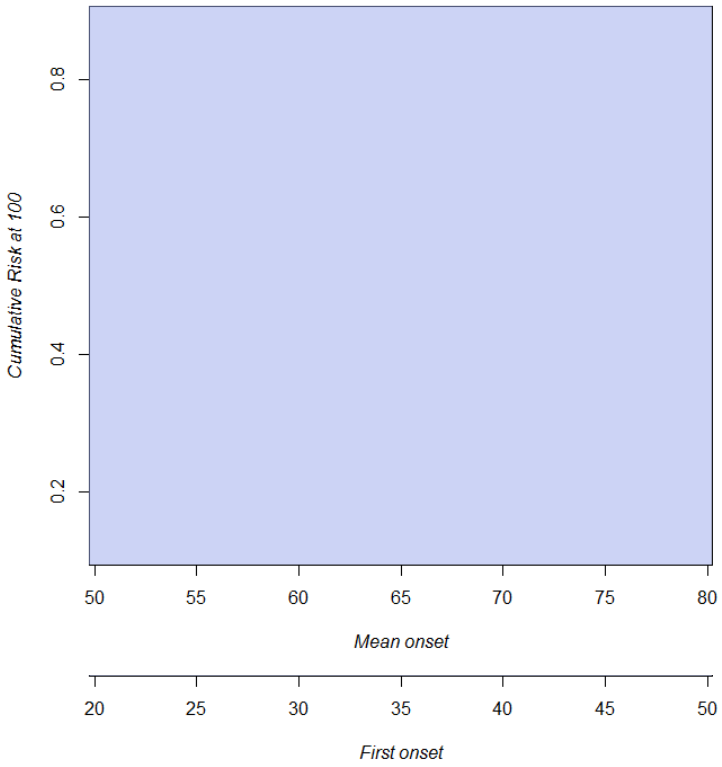


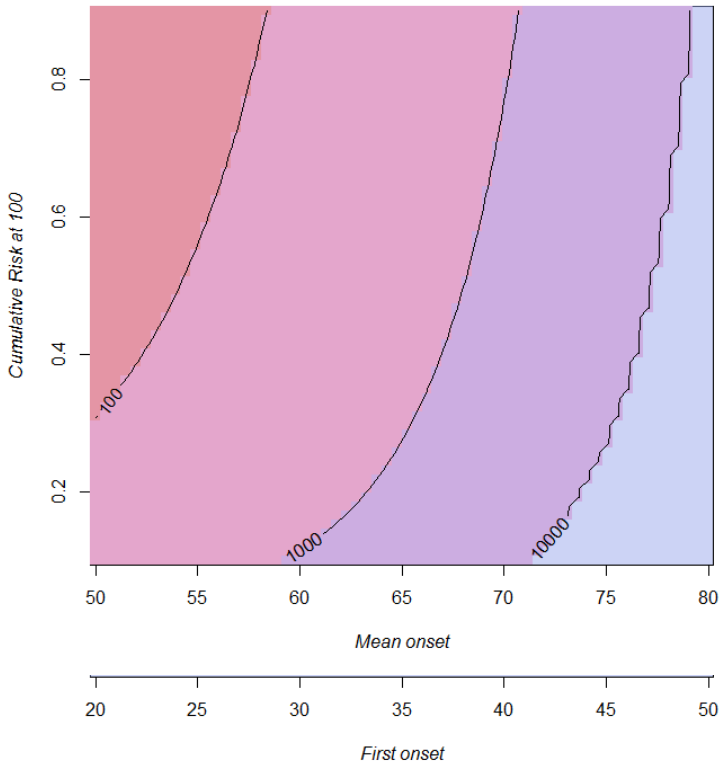


Negative selection at old ages is possible

- Physiopathology ► Epidemiologie
- Social - behavioural (care, matrimonial system) ► Demography

Conclusion



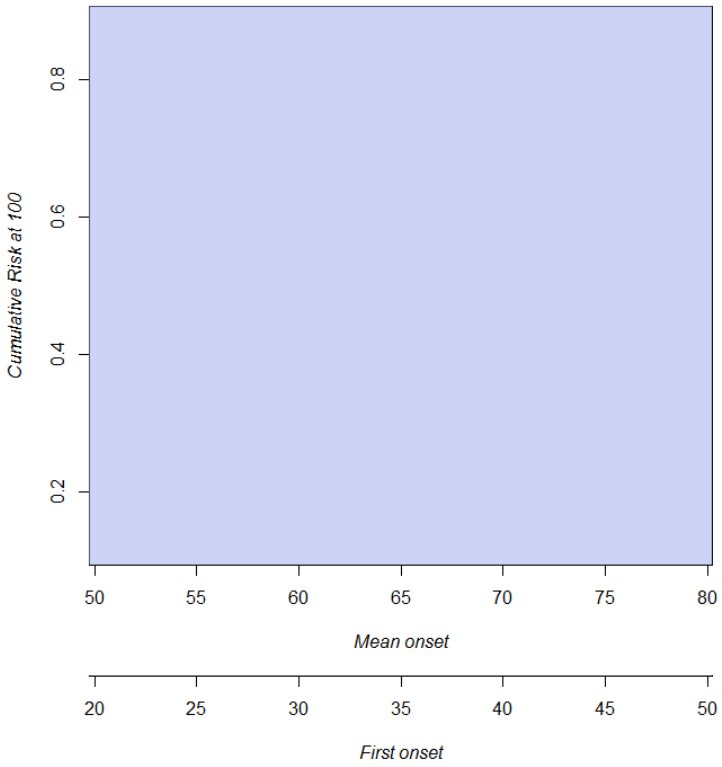


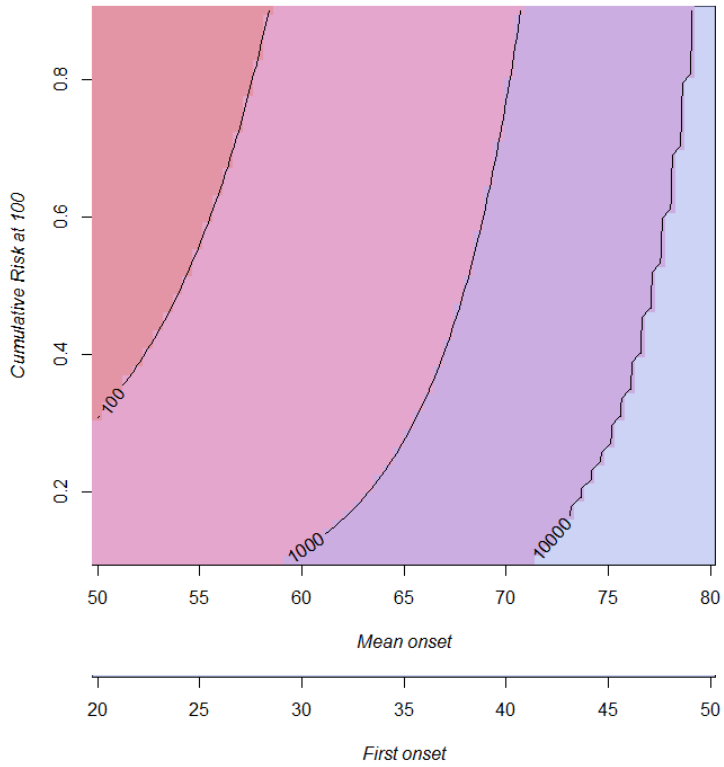
Negative selection at old ages is possible

- Physiopathology ► Epidemiologie
- Social - behavioural (care, matrimonial system) ► Demography

These factors are not independent: age at onset and care, matrimony and paternal care

Conclusion



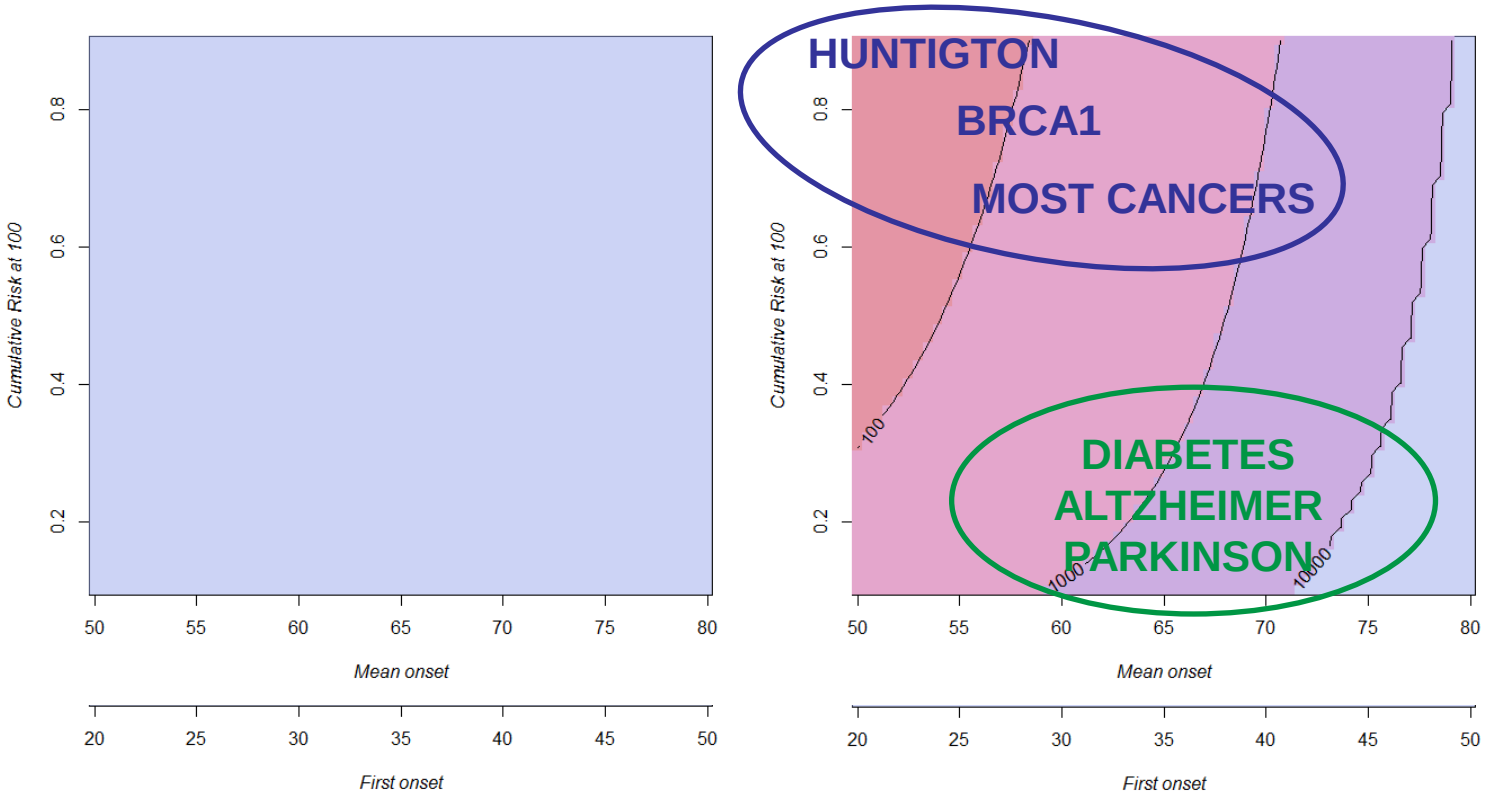


Negative selection at old ages is possible

- Physiopathology ► Epidemiologie
- Social - behavioural (care, matrimonial system) ► Demography

Purge of deleterious mutations even at old ages (eg 40-70 yrs old)

Conclusion

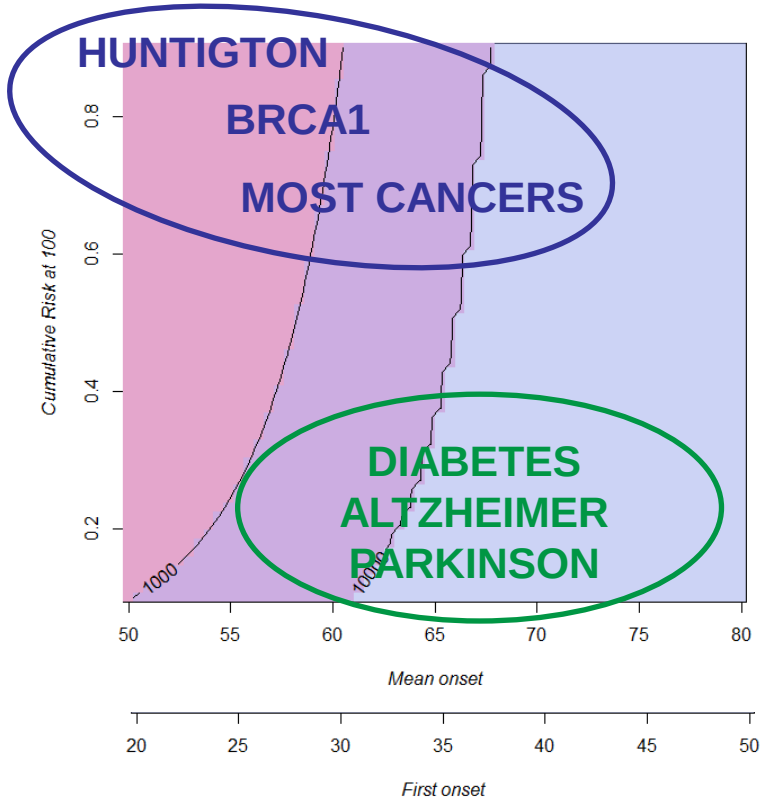


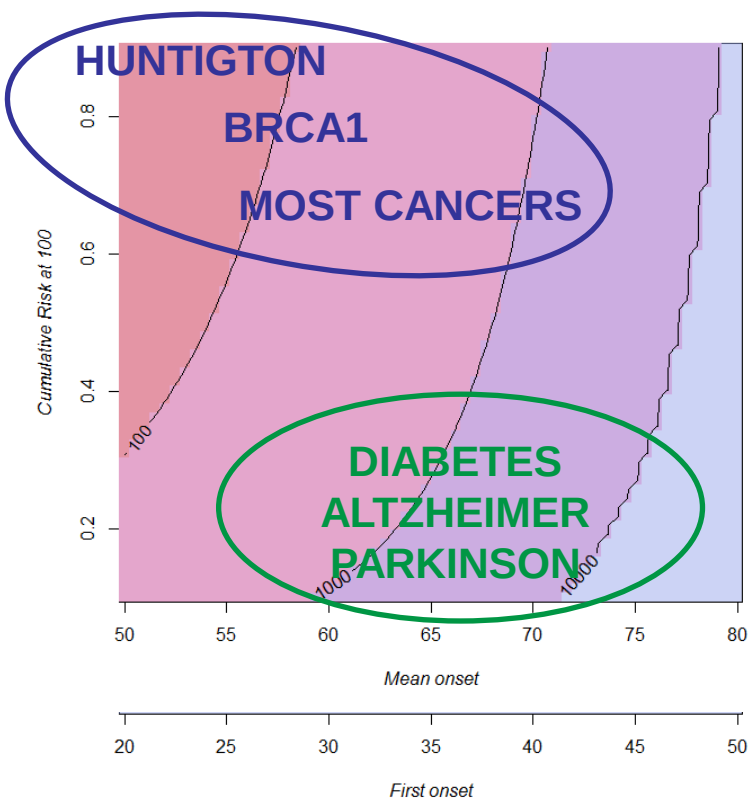
Negative selection at old ages is possible

- Physiopathology ► Epidemiologie
- Social - behavioural (care, matrimonial system) ► Demography

Possible predictions for couples gene-disease

Conclusion



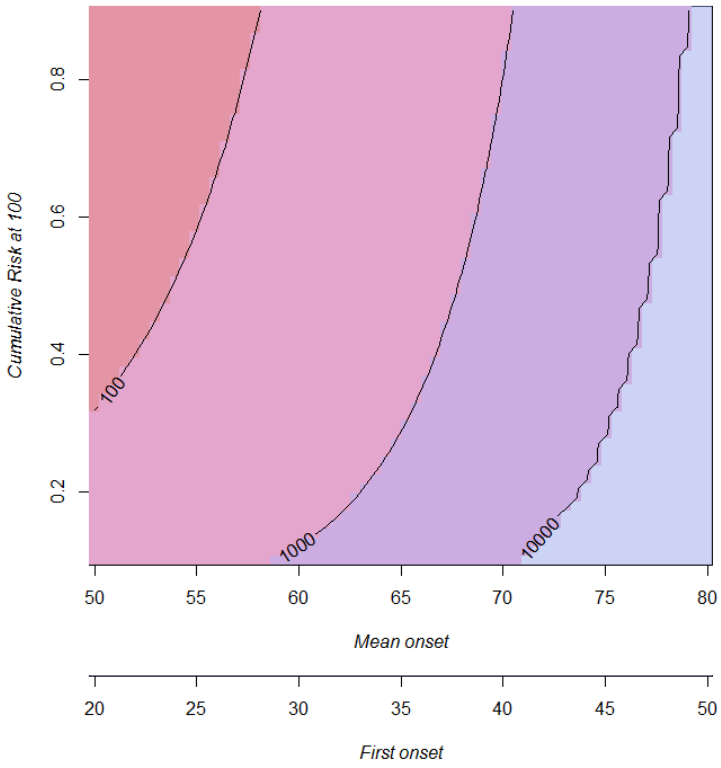


Negative selection at old ages is possible

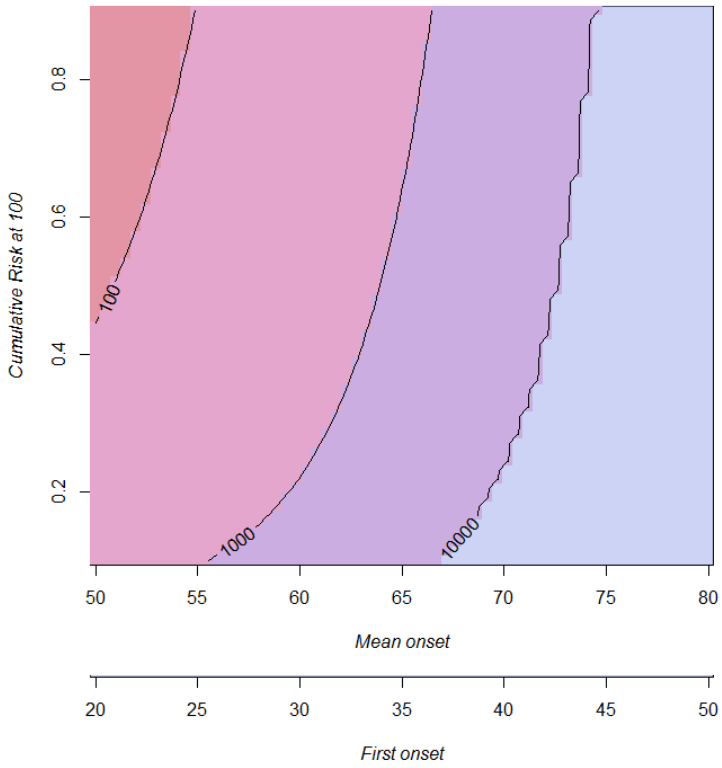
- Physiopathology ► Epidemiologie
- Social - behavioural (care, matrimonial system) ► Demography

Differences are expected between population due to culture

Conclusion



High survival, High fertility



Low survival, Low fertility

But no large influence of demographic regimes

► a change in 20 yrs in e_{15} is pushing back the selection gradient of only ~3 yrs in mean onset

Conclusion

Effect of care on child survival but…

- Effect of paternal and maternal care of adult children survival and repro
- Effect of sibling care and/or competition

Population dynamics is the key. Going beyond stable environment:

$$\mathbf{n}_{t+1} = \mathbf{A}\mathbf{n}_t$$

$$\mathbf{n}_{t+1} = \mathbf{A}\left(t\right)\mathbf{n}_t$$

$$\mathbf{n}_{t+1} = \mathbf{A}\left(\mathbf{n}(t)\right)\mathbf{n}_t$$

$$\mathbf{n}_{t+1} = \mathbf{A}\left(k\right)\mathbf{n}_t$$

$$\mathbf{n}_{t+1} = \mathbf{A}\left(\mathbf{w},\mathbf{K}\right)\mathbf{n}_t$$

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