# Inflammation genes and longevity and successful ageing in elderly Costa Ricans

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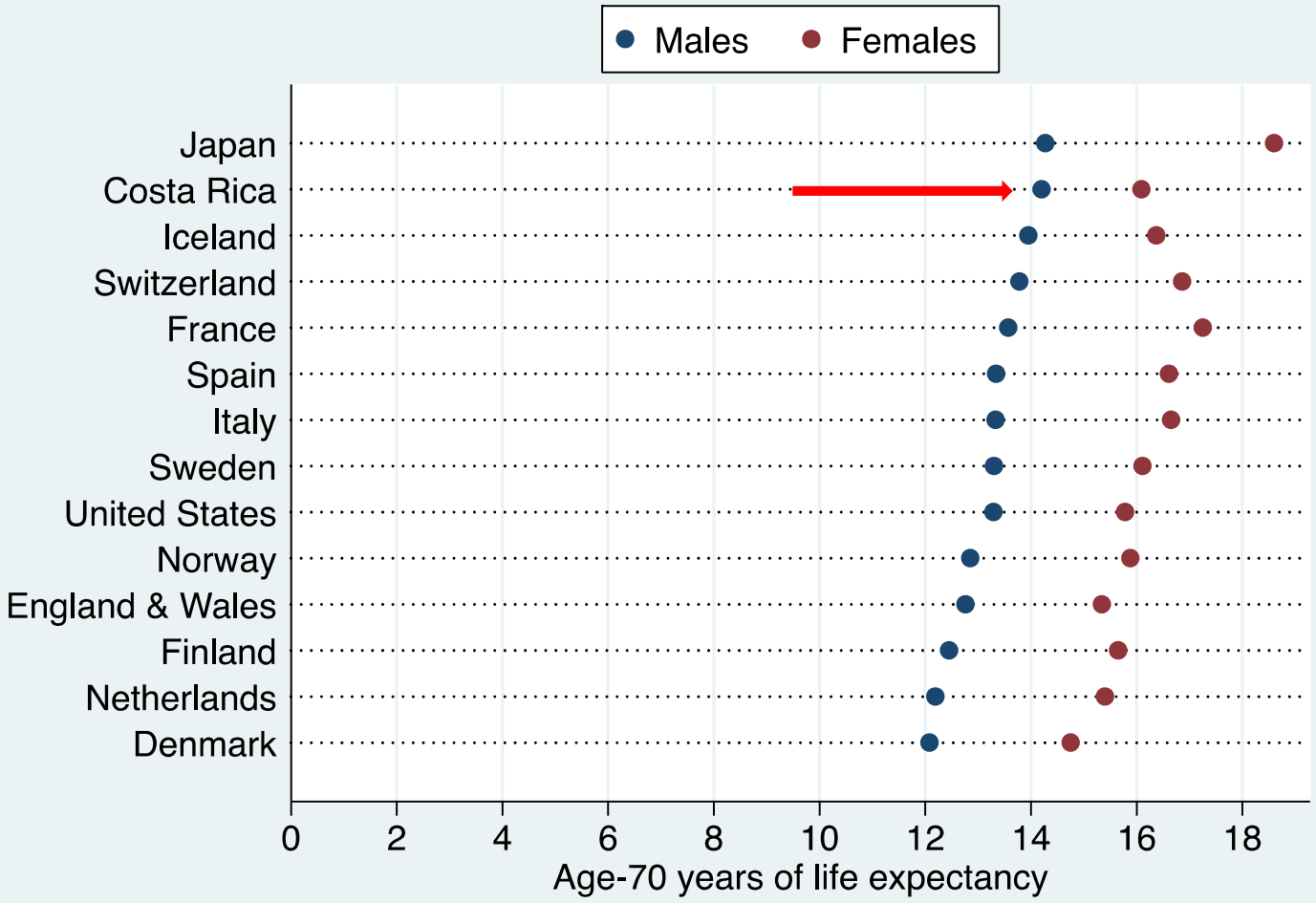
# Background

- Exceptional longevity of elderly Costa Ricans, particularly males.
- Longevity may be associated to low levels of systemic inflammation.
- Some genes modulate inflammation response

# The high life expectancy of elderly males in CR




Sources: Human Mortality Data Base (HMD); CCP: http://ccp.ucr.ac.cr/observa/CRindicadores/

Explore if good genes are part of the explanation of Costa Rican longevity

Focus on two inflammation genes (IL-1B3954 and IL-1RN)

# Inflammation: a double-edged sword

- Response of host immune system to trauma or infection:
  - Healing effect in acute phase (fever, somnolence, high leukocyte, CRP, IL…)
  - Low-level, chronic → accumulates damage age-related diseases (AD, atherosclerosis, diabetes, sarcopenia, cancer)
- Several genes modulate pro- and anti-inflammatory response

# IL-1 genes and longevity

- IL-1B(3954) pro-inflammatory: C→T polymorphism higher IL
- IL-1RN inflammation antagonist: allele L→2 polymorphism higher IL
- Higher IL  people could be better healers
- Low-level systemic IL → More chronic diseases, less longevous.
- CC studies in Italy (134/997) and Finland (250/400) fail to find assoc.

# Data and methods

- CRELES = Costa Rican Longitudinal Study of Healthy Aging.
- Panel of ~3.000 adults 60+ with oldest old oversampled
- DNA from blood cells in 2,700,  250 quasi-centenarians
- Genotyping done with PCR
- 5 year survival follow up (2005-11):  750 deaths, survival-time database
- About 20 biomarkers—hard data on health

# Analysis strategy

- Allele frequency in the two IL genes:
  - By sex
  - Quasi-centenarians vs. younger
  - Death  vs. survivors
- Survival curves and  hazard regression by allele polymorphisms → conventional metrics
- Effects on 18 biomarkers, using OLS regressions.

# Minor Allele Frequencies--MAF

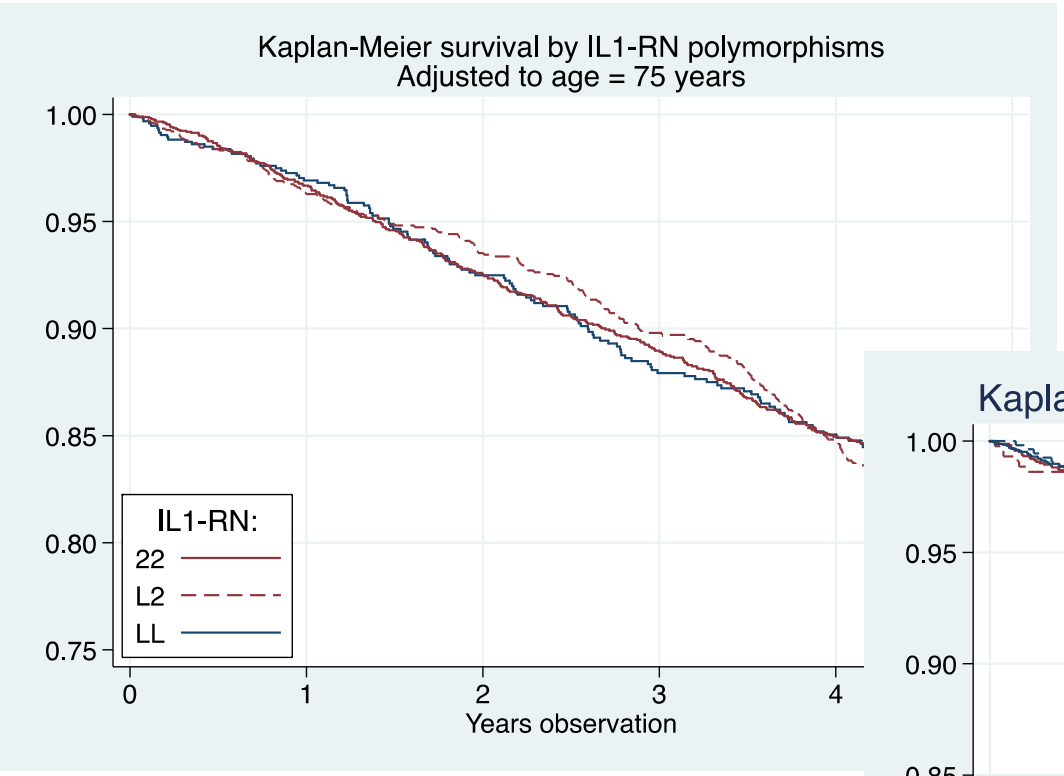
| IL-1B(3954) | | | IL-1RN | | |
|---|---|---|---|---|---|
| Genotype | N | MAF | Genotype | N | MAF |
| CC | 2158 | | LL | 1346 | |
| CT | 572 | | L2 | 798 | |
| TT | 18 | | 22 | 558 | |
| total | 2748 | | total | 2702 | |
| Allele | | | Allele | | |
| C | 4888 | | L | 3490 | |
| T | 608 | 0.111 | 2 | 1914 | 0.354 |

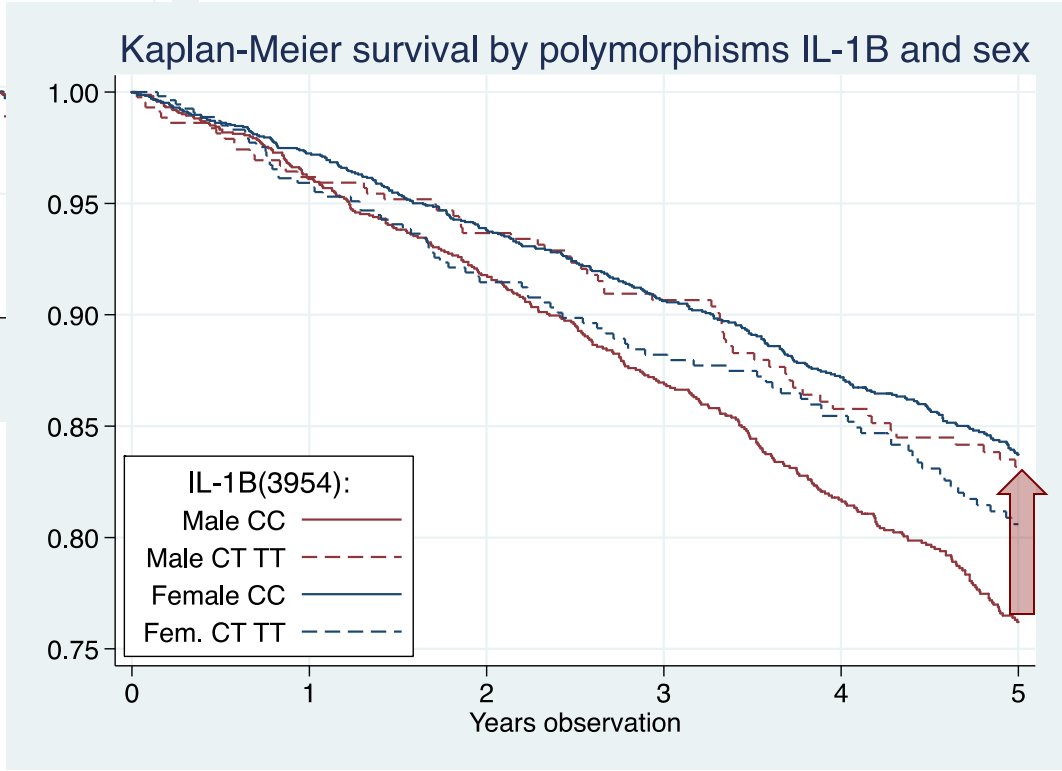
| | | |
|---|---|---|
| Caucasic | .10 - .20 | > .35 |
| Asian pops. | <.05 | < .10 |

# MAF by sex, longevity and survival

| Age and survival | IL-1B = T | | IL-RN = 2 | | (N. Observations) | |
|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | Males | Females |
| Total | 0.113 | 0.109 | 0.353 | 0.355 | (1256) | (1492) |
| *Quasi-centenarian* | | | | | | |
| Age 95+ | 0.077 | 0.093 | 0.325 | 0.349 | (117) | (129) |
| 60-94 | 0.116 | 0.110 | 0.356 | 0.356 | (1139) | (1363) |
| *Fisher P* | *(0.082)* | *(0.464)* | *(0.383)* | *(0.891)* | | |
| *5 year survival* | | | | | | |
| Death | 0.088 | 0.115 | 0.352 | 0.333 | (364) | (373) |
| Survived | 0.123 | 0.107 | 0.353 | 0.363 | (892) | (1119) |
| *Fisher P* | *(0.012)* | *(0.541)* | *(1.000)* | *(0.155)* | | |

# K-M survival by polymorphisms



# Gompertz hazard regression DRRs

| Genotype | Base model | | SES adjusted# | |
|---|---|---|---|---|
| --Allele | Males | Females | Males | Females |
| IL-1B--T | 0.75 * | 1.13 | 0.70 * | 1.08 |
| IL-RN--2 | 1.12 | 0.97 | 1.10 | 0.95 |
| $\alpha$ (1,000s) | 10.5 ** | 8.7 ** | 22.8 ** | 17.3 ** |
| $\gamma$ (%) | 8.3 ** | 8.3 ** | 7.1 ** | 7.1 ** |

DRR = Death Rate Ratio or relative hazard of those polymorphism
Baseline Gompertz: $h(x) = \alpha \exp(\gamma x)$, where: $x$ = age - 60
# Controlled by: education, household wealth, 3 regions, urban/ rural, and a childhood deprivation scale
* sig. at P<.05, ** sig at P<.01

# Metrics of the IL-1B→T advantage

| IL-1B gene | Median life (years)* | | Centenarians (%)* | |
|---|---|---|---|---|
| Allele | Males | Females | Males | Females |
| C | 22.5 | 24.5 | 3.4 | 6.2 |
| T | 25.5 | 23.2 | 8.0 | 4.3 |

* For a cohort of 60-year olds

# 18 Biomarkers, 9 groups

1. *Metabolic indicators:* Fasting Glucose; HbA1c
2. *Cardio Vascular:* Diastolic BP; Systolic BP
3. *Lipids:* Triglycerides, Total-, HDL-Cholesterol
4. *Stress:* urine Cortisol; DHEAS; Telomere length
5. *Inflammation:* CRP
6. *Organ specific function reserve*: creatinine clearence (kidney); handgrip (sarcopenia)
7. *Nutrition:* Knee height; BMI; waist
8. *Functionality*: ADL disability scale
9. *Mental health*: cognitive MMS, geriatric depression test

# 18 OLS regressions

Normalized biomarker as Y variable

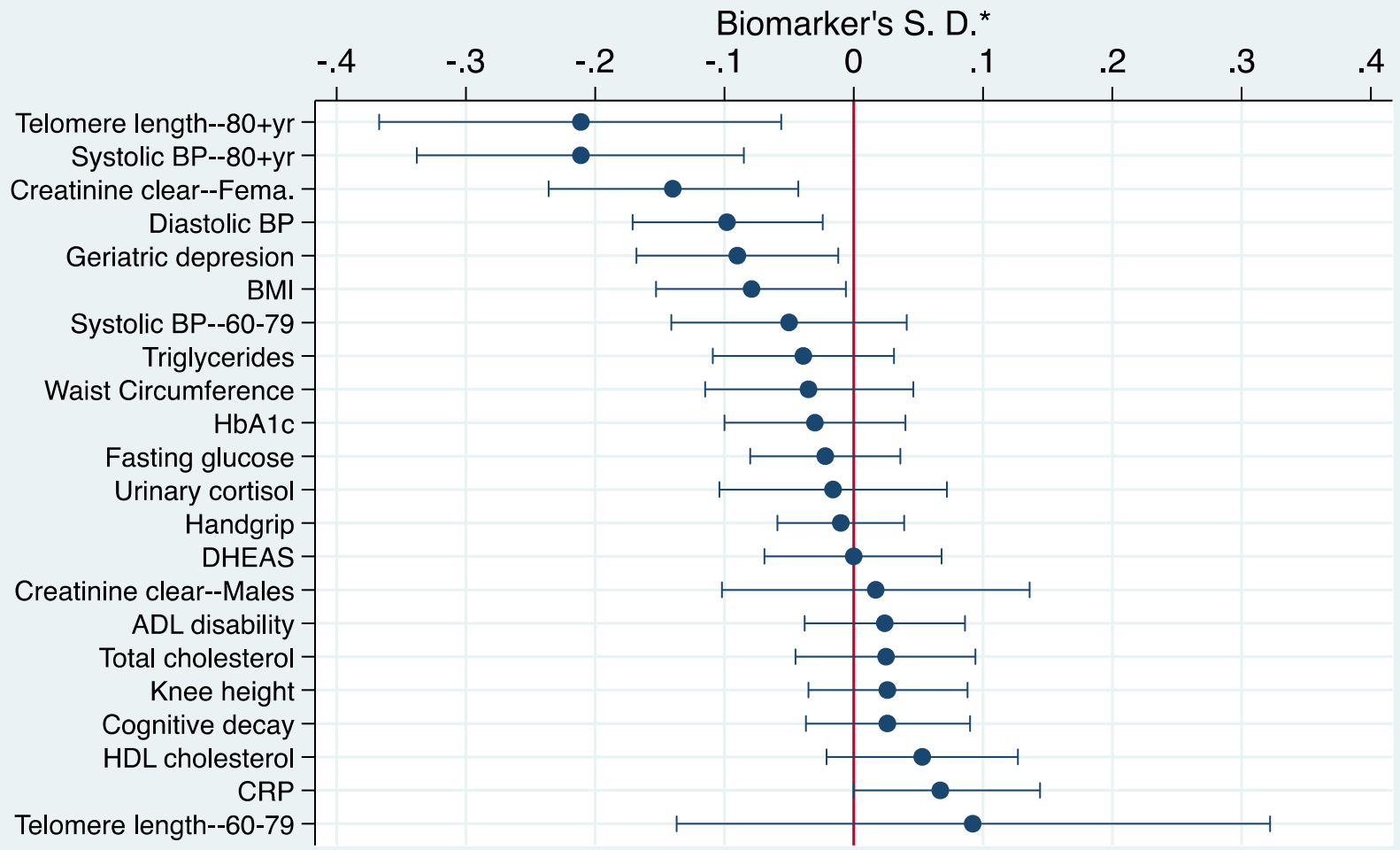
Effect of allele T polymorphism

Controls for

- Age-continuous
- Age-square
- Sex

Interactions of allele T with:
sex & 80+, kept only 3 significant

# IL-1B=T effects on biomarkers




*Effects of IL-1B=T estimated with OLS regression on each normalized-biomarker with controls for age and gender

# Conclusions

- Unexpectedly, elderly men with a pro-inflammation polymorphism gene have lower mortality → more longevous
- This does not mirror in the MAF of quasi-centenarians: fewer pro-IL gene
- Those with the pro-IL gene have some metabolic advantage: BP and BMI
- And, as expected, higher CRP
- Complex relationship, more research needed

Thank you!