

HEALTH DECLINE, AGING AND MORTALITY: HOW ARE THEY RELATED?

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**THE MOST IMPORTANT FINDING OF THE LAST CENTURY
IN THE AREA OF EXPERIMENTAL STUDIES OF AGING
SUGGESTS:**

- ***senescence can be modulated***



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IN THE AREA OF EXPERIMENTAL STUDIES OF AGING
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- *senescence can be modulated*

- *longevity can be increased*

- *ages at onset of chronic disorders can be postponed*

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How can connection between senescence, health and longevity be studied in humans?

**How senescence manifests itself
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Hypotheses:

Senescence affects:

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Senescence affects:

- *Age related changes of physiological indices*

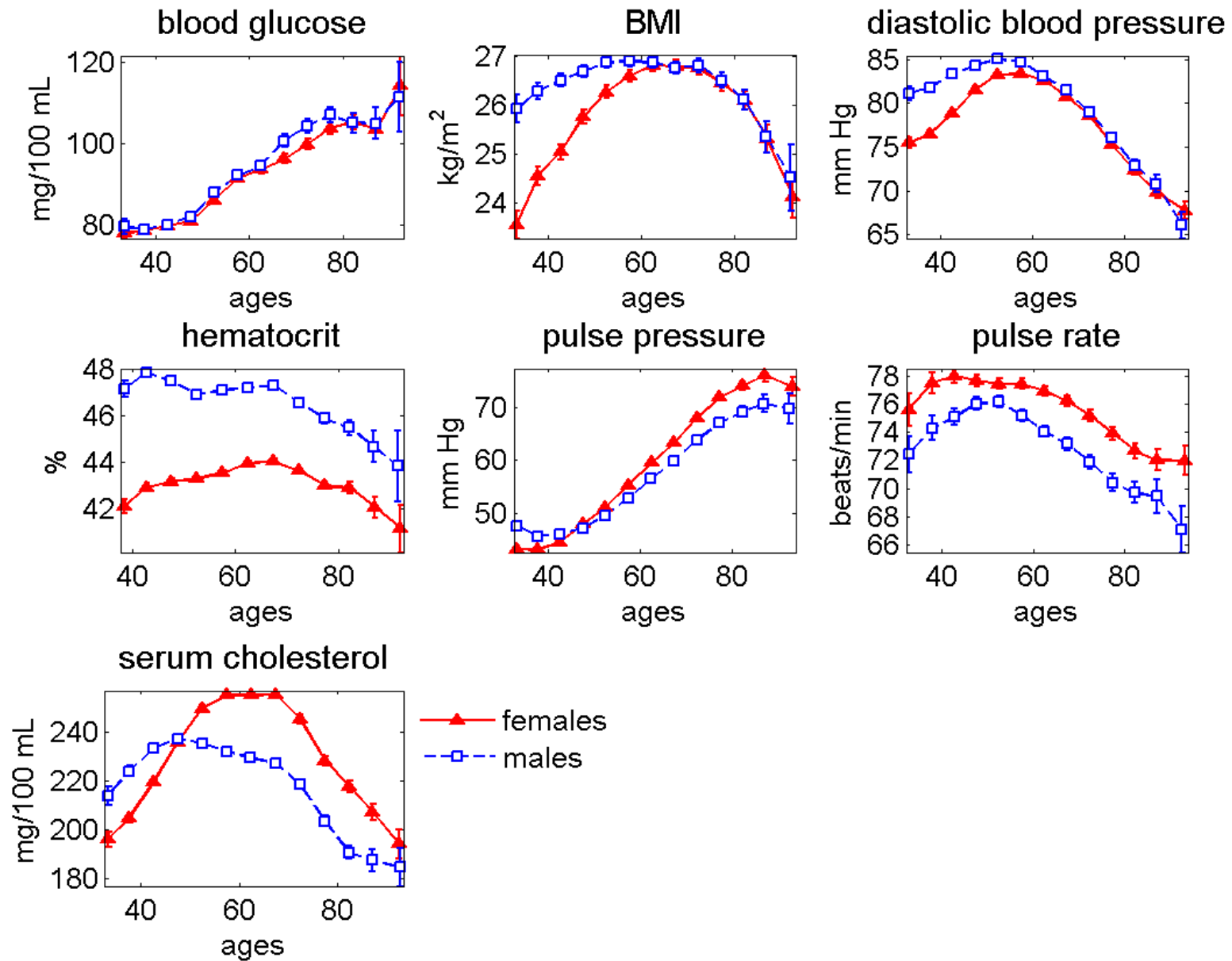
How senescence manifests itself in longitudinal data?

Hypotheses:

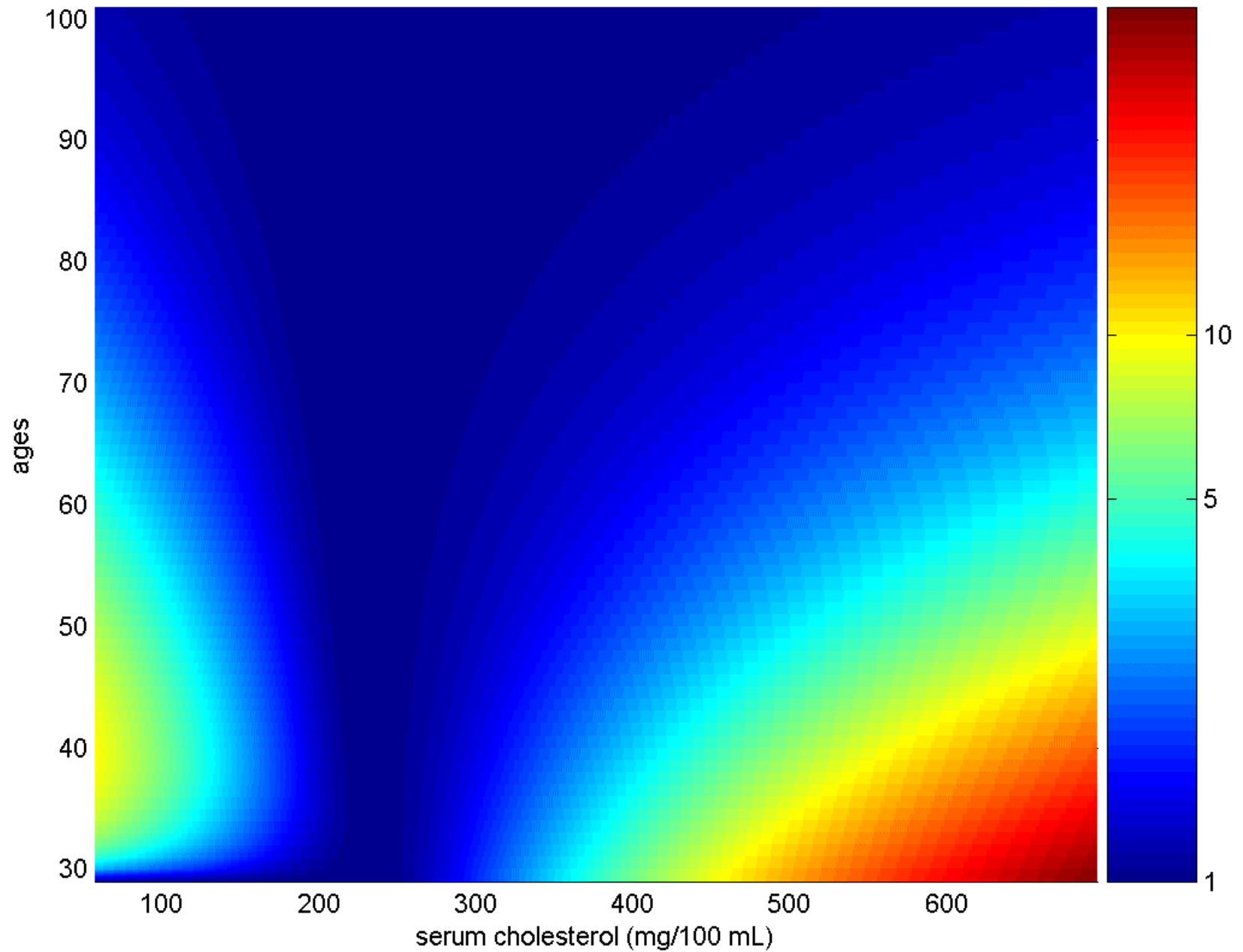
Senescence affects:

- *Age related changes of physiological indices*
- *Age related changes in the shape of risk functions*

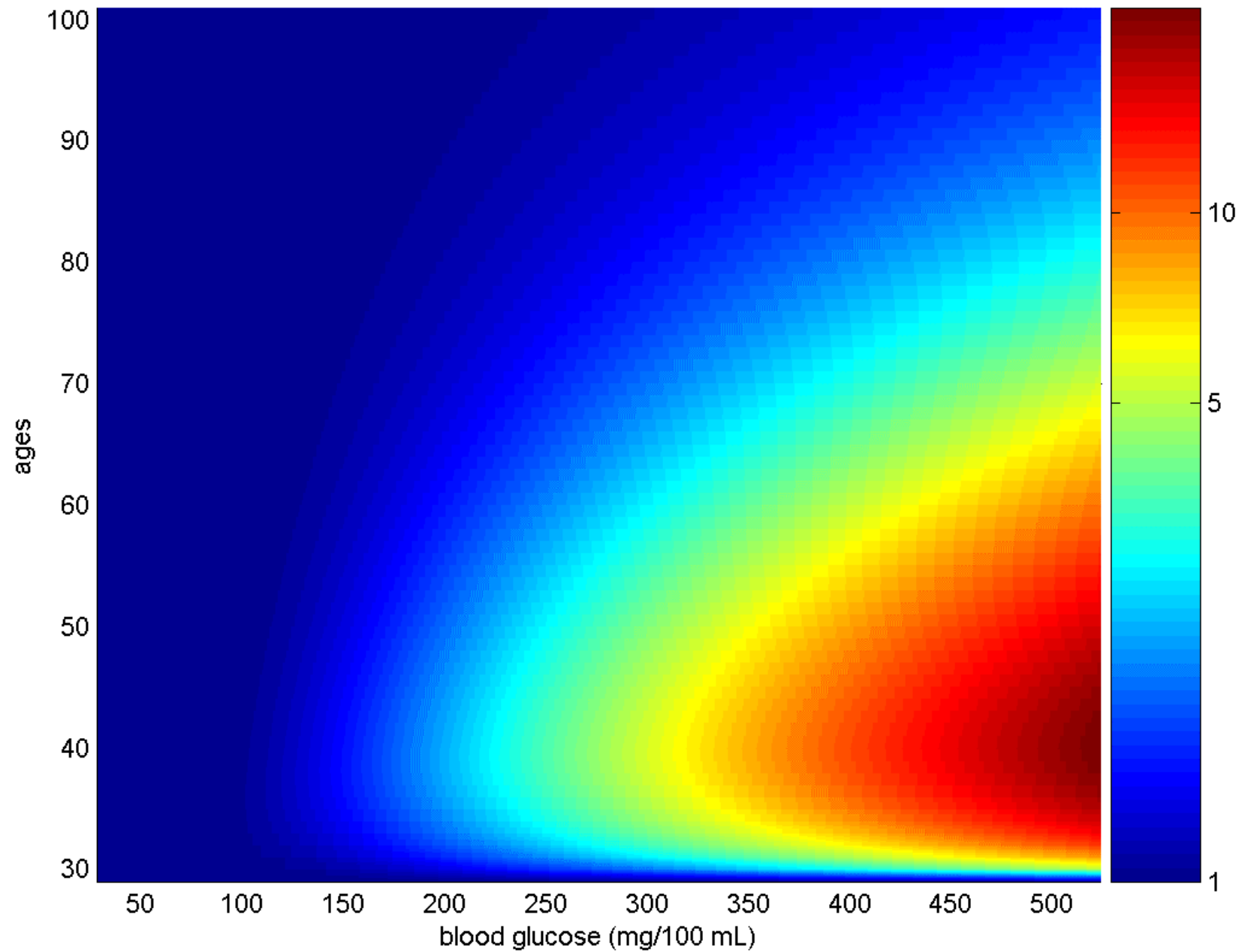
Manifestation of senescence in age trajectories of physiological indices



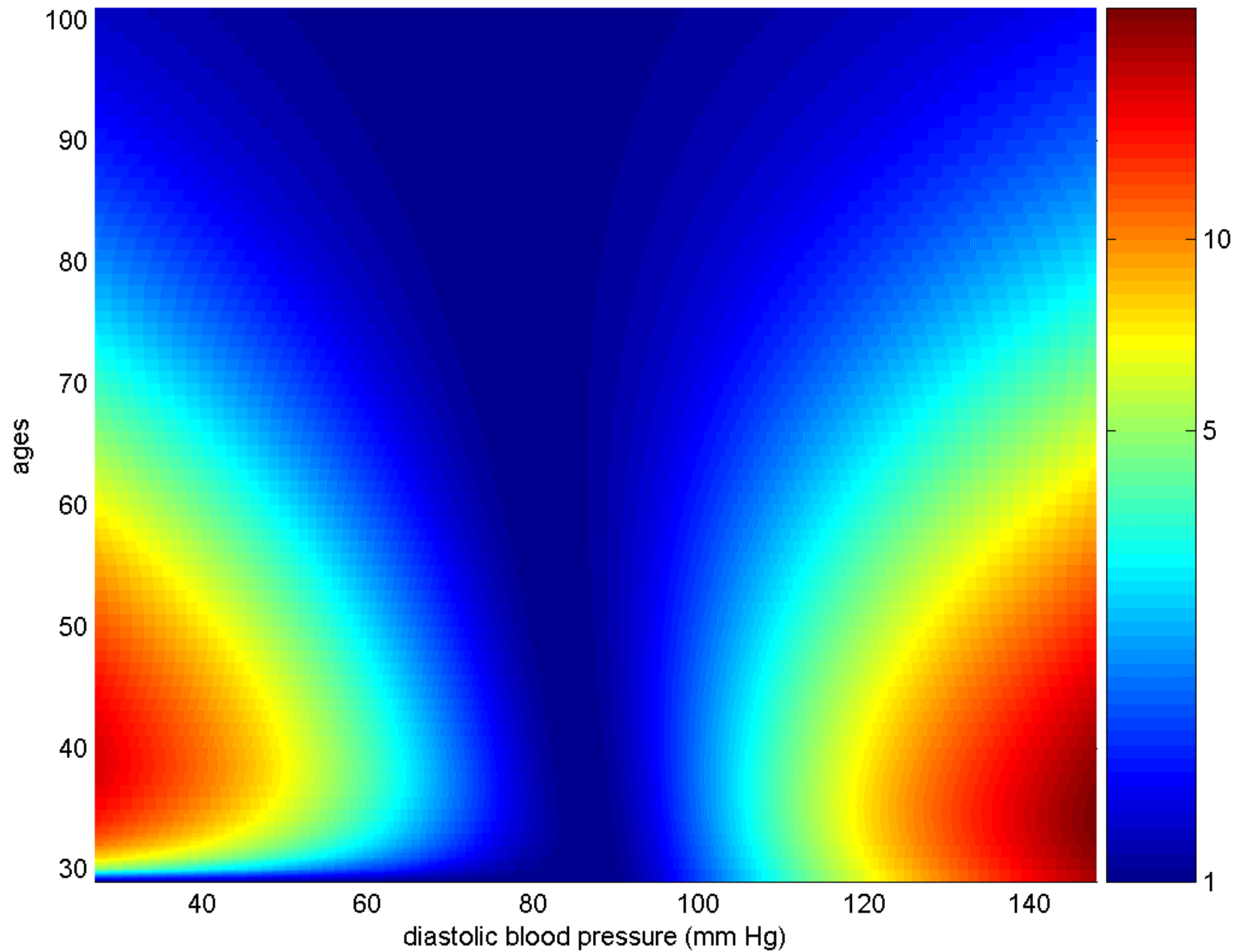
Relative risk of death w.r.t. "optimal" serum cholesterol (log. scale)
males, Framingham data



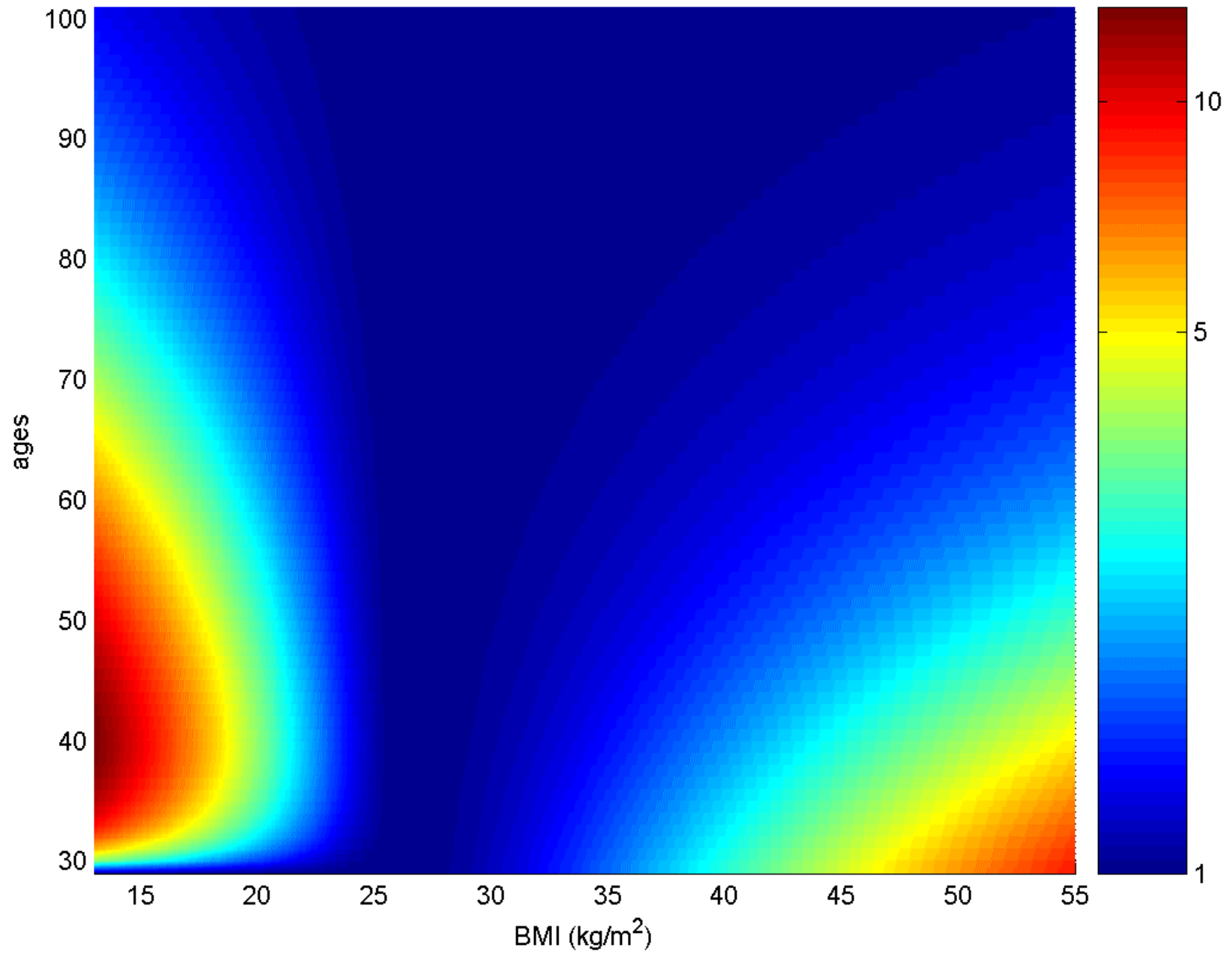
Relative risk of death w.r.t. "optimal" blood glucose (log. scale)
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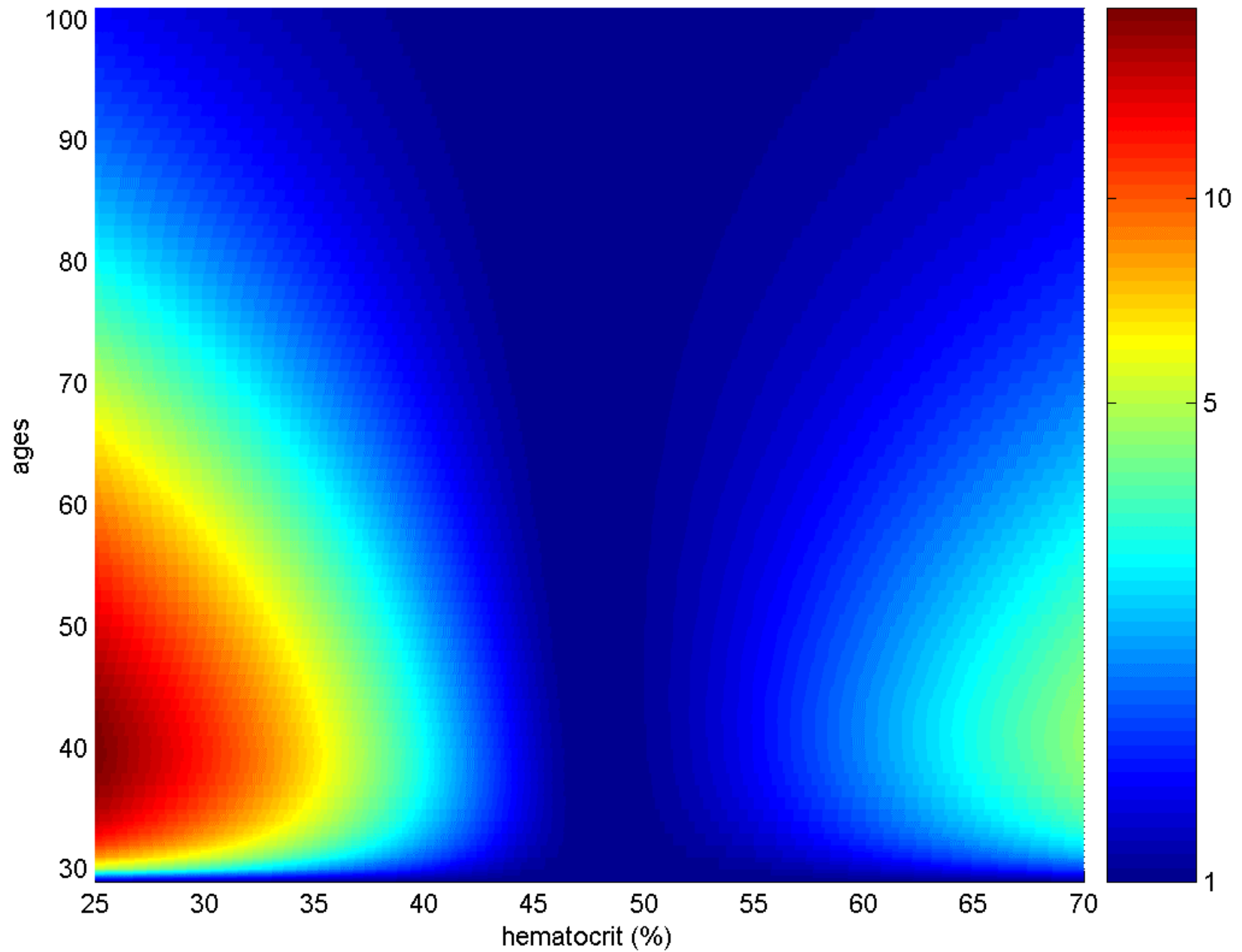
Relative risk of death w.r.t. "optimal" diastolic blood pressure (log. scale)
males, Framingham data



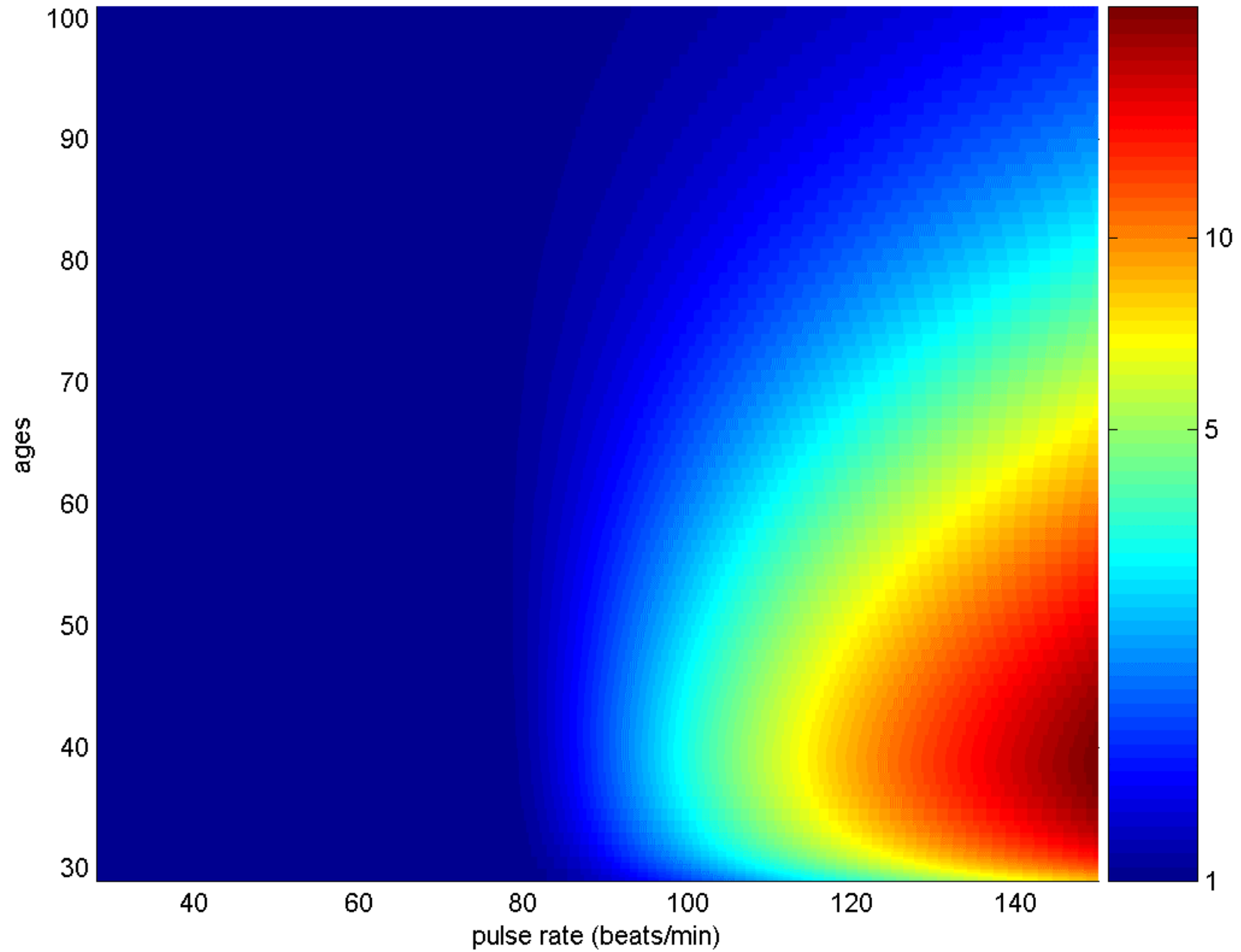
Relative risk of death w.r.t. "optimal" BMI (log. scale)
males, Framingham data



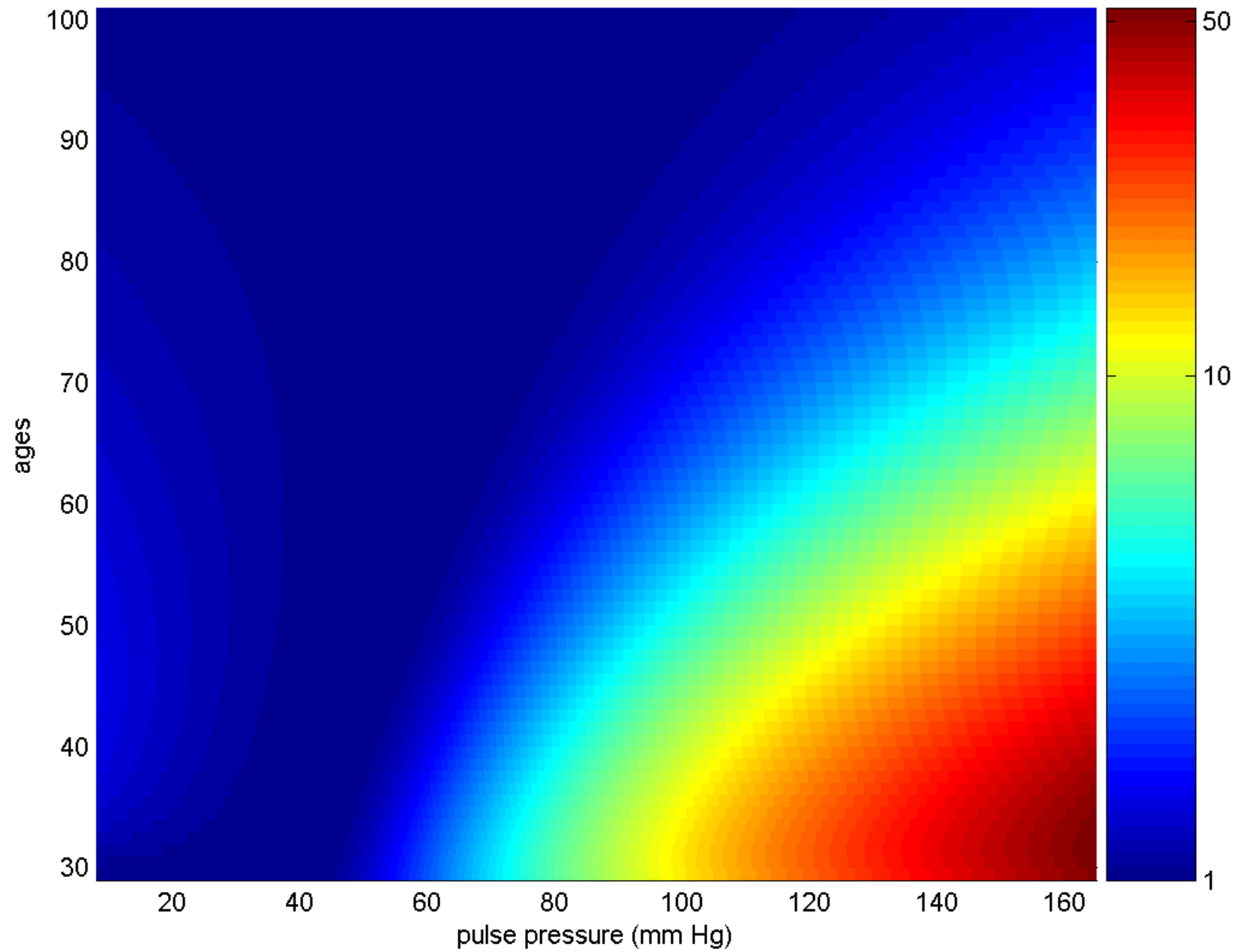
Relative risk of death w.r.t. "optimal" hematocrit (log. scale)
males, Framingham data



Relative risk of death w.r.t. "optimal" pulse rate (log. scale)
males, Framingham data



Relative risk of death w.r.t. "optimal" pulse pressure (log. scale)
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MODIFIED QUADRATIC HAZARD MODEL OF AGING AND MORTALITY

$$Y_{t_{k+1}} = Y_{t_k} + a_{t_k} \left(f_{t_k}^1 - Y_{t_k} \right) (t_{k+1} - t_k) + \sigma_1 \sqrt{t_{k+1} - t_k} \varepsilon_{t_k}, \quad k > 1, \quad Y_{t_1},$$

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Application to the Index of Cumulative Deficit (ICD)

The deterioration of human health with age is manifested in changes of thousands of physiological and biological variables. The contribution of some of such changes to mortality risk may be small and cannot be reliably detected by existing statistical methods. A cumulative index of health/well-being disorders, which counts changes in observed variables on the way of losing health, may be an appropriate way to take the effects of such variables into account. In this paper we investigate regularities of the aging-related changes in human health/well-being/survival status described by such an index using the new version of the quadratic hazard model of human aging and mortality. We found that the shape and the location of the mortality risk, considered as a function of the introduced health-related index, changes with age reflecting the decline in stress resistance and the age-dependence of the “optimal” health/well-being status. Comparison of these results with findings from early studies using the Cox’s-like model of risk function indicates that the result are likely to describe regularities of deterioration in human health during the aging process

Data. The Index of Cumulative Deficit (ICD)

The ICD is constructed from answers to 32 questions from the NLTCS detailed questionnaires including: *difficulty with eating, dressing, walk around, getting in/out bed, getting bath, toileting, using telephone, going out, shopping, cooking, light house work, taking medicine, managing money, arthritis, Parkinson's disease, glaucoma, diabetes, stomach problem, history of heart attack, hypertension, history of stroke, flu, broken hip, broken bones, trouble with bladder/bowels, dementia, self-rated health, as well as problems with vision, hearing, ear, teeth, and feet.*

All of these deficits are assessed in five waves of the NLTCS. We define the ICD as an unweighted count of the number of such deficits divided by the total number of all potential deficits considered for a given person. For instance, if an individual has been administered 32 questions and responded positively (there is a deficit) to 6 and negatively (no deficit) to 24 of them, then the ICD for this person will be 0.2. In this way, we avoid the problem of missing answers counting only those questions explicitly answered in a survey.

EXTENDED COX'S REGRESSION MODEL FOR EVALUATION OF NON-SYMMETRIC U-SHAPED HAZARD

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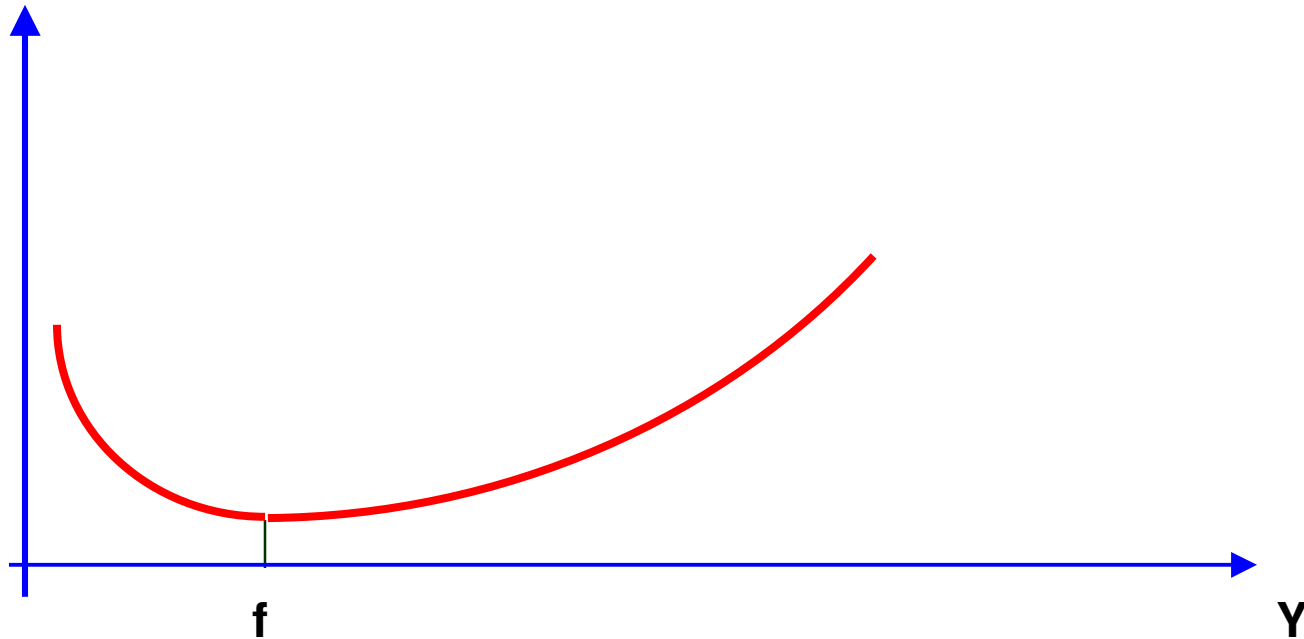
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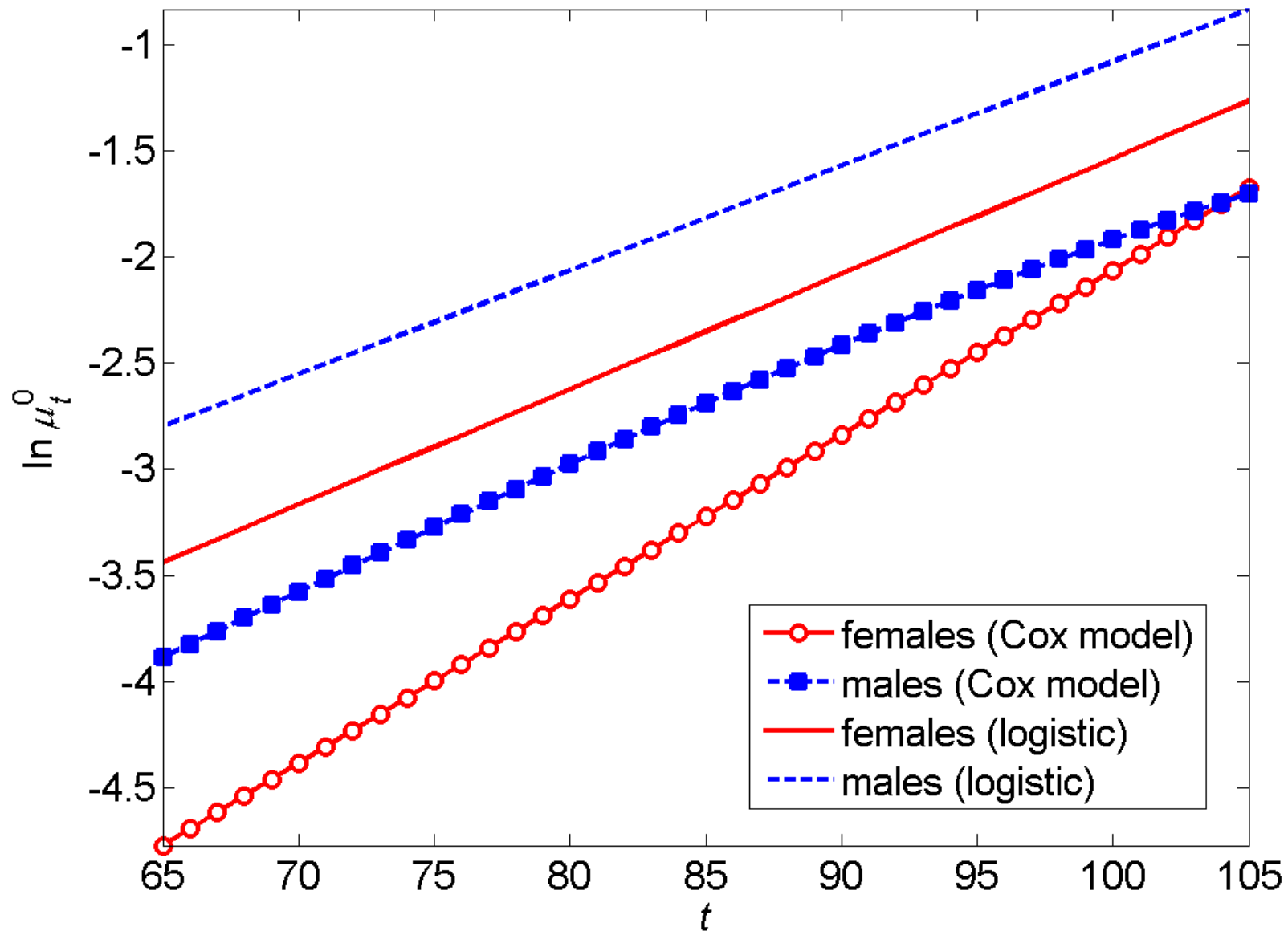
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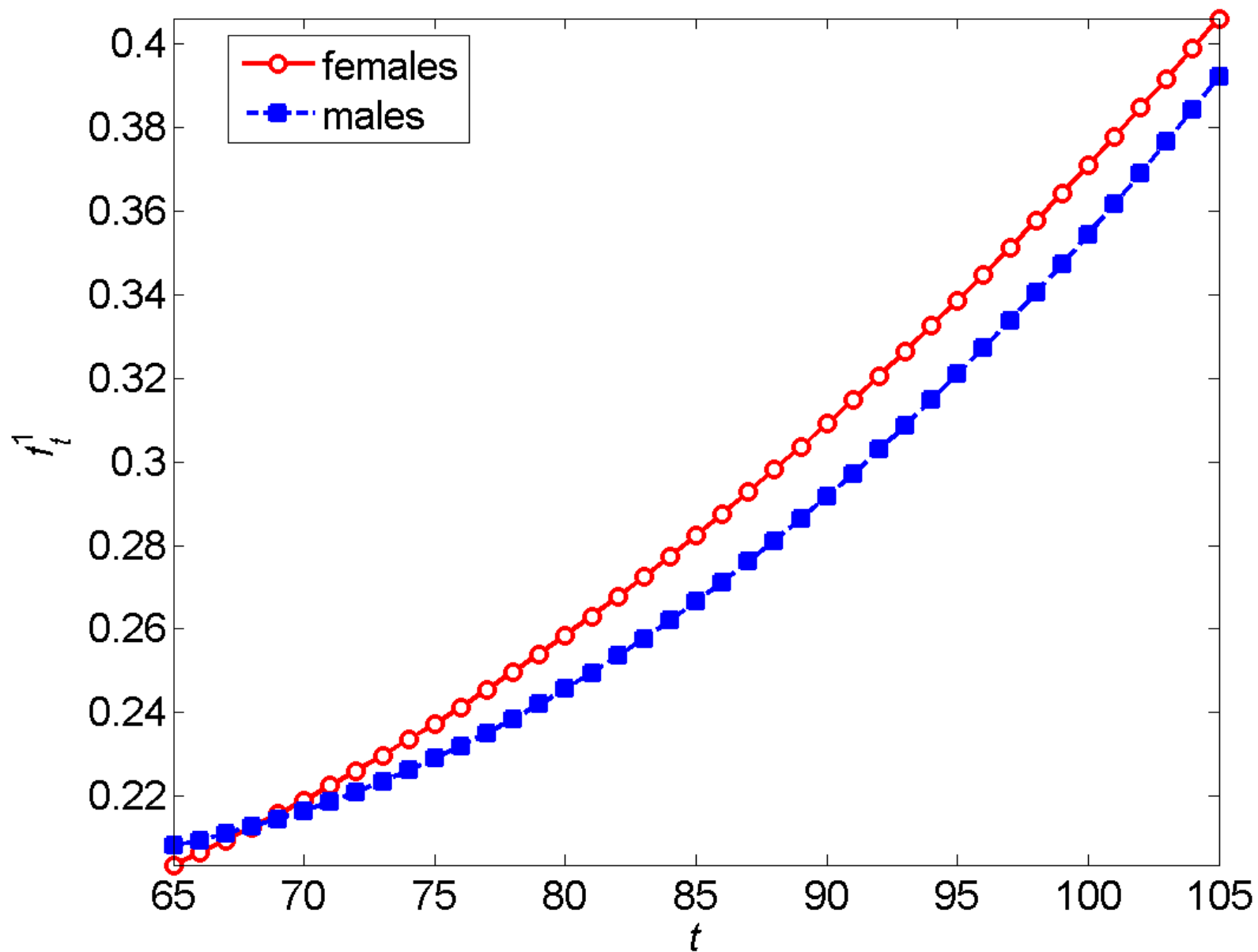
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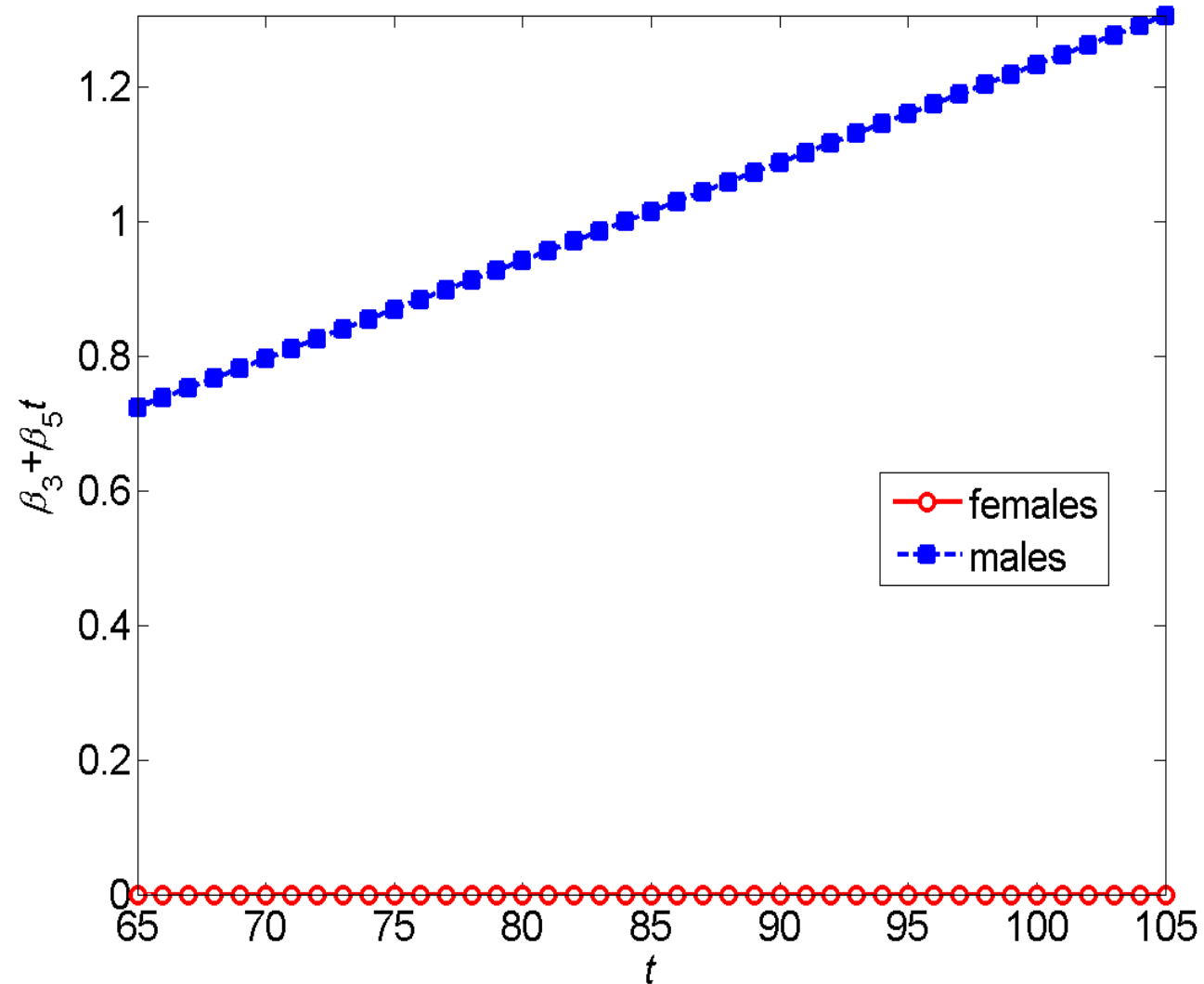
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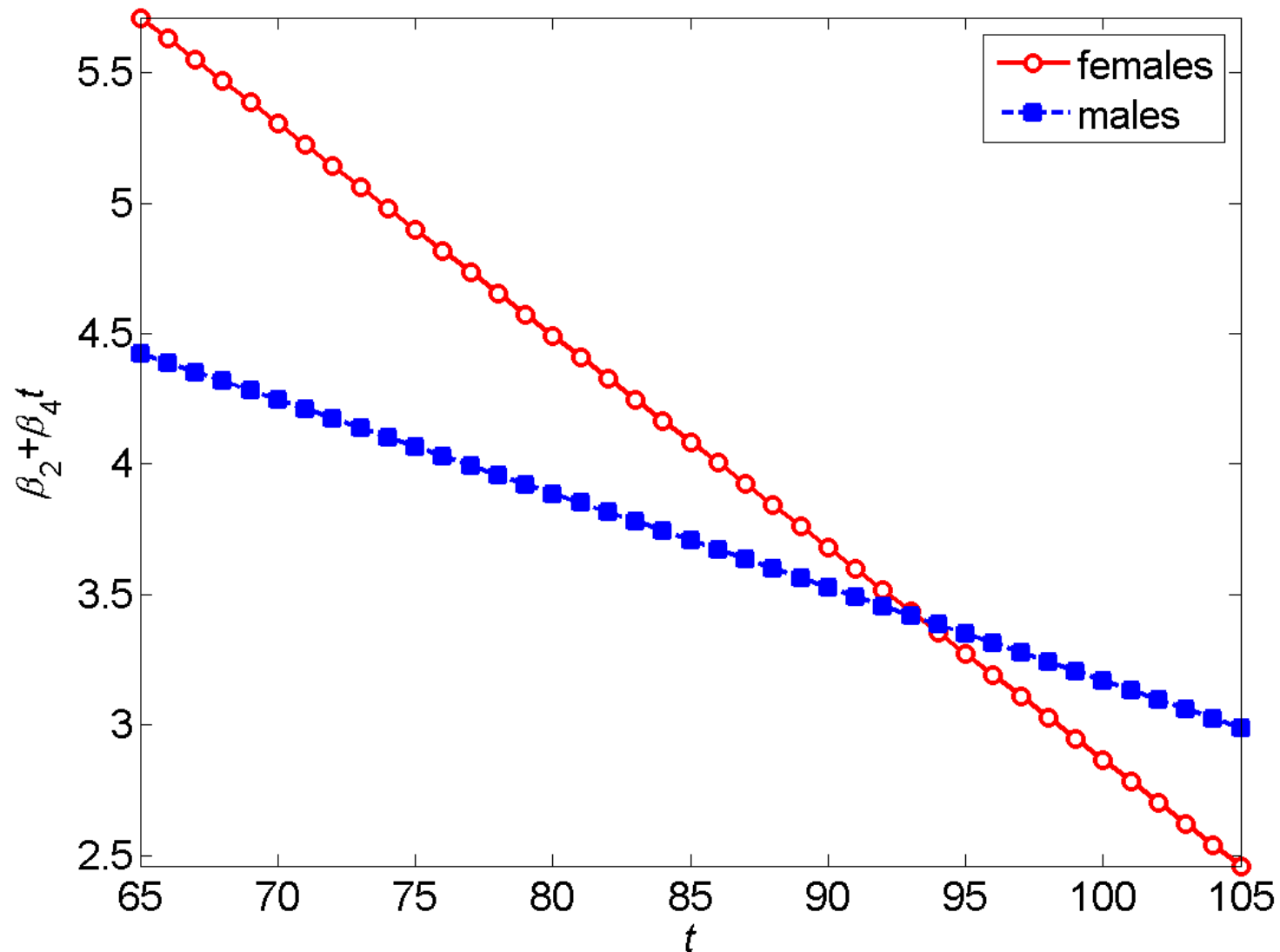
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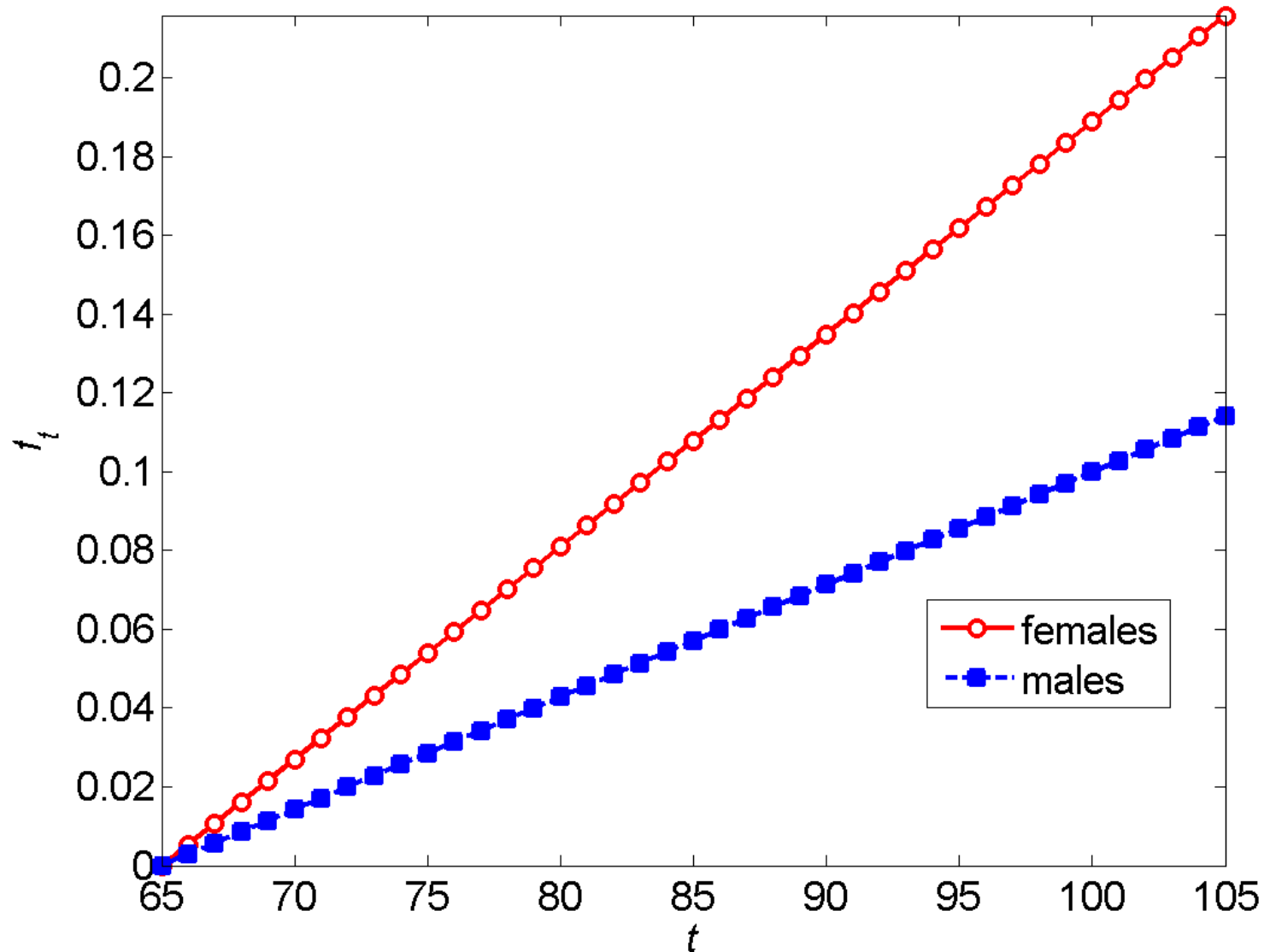
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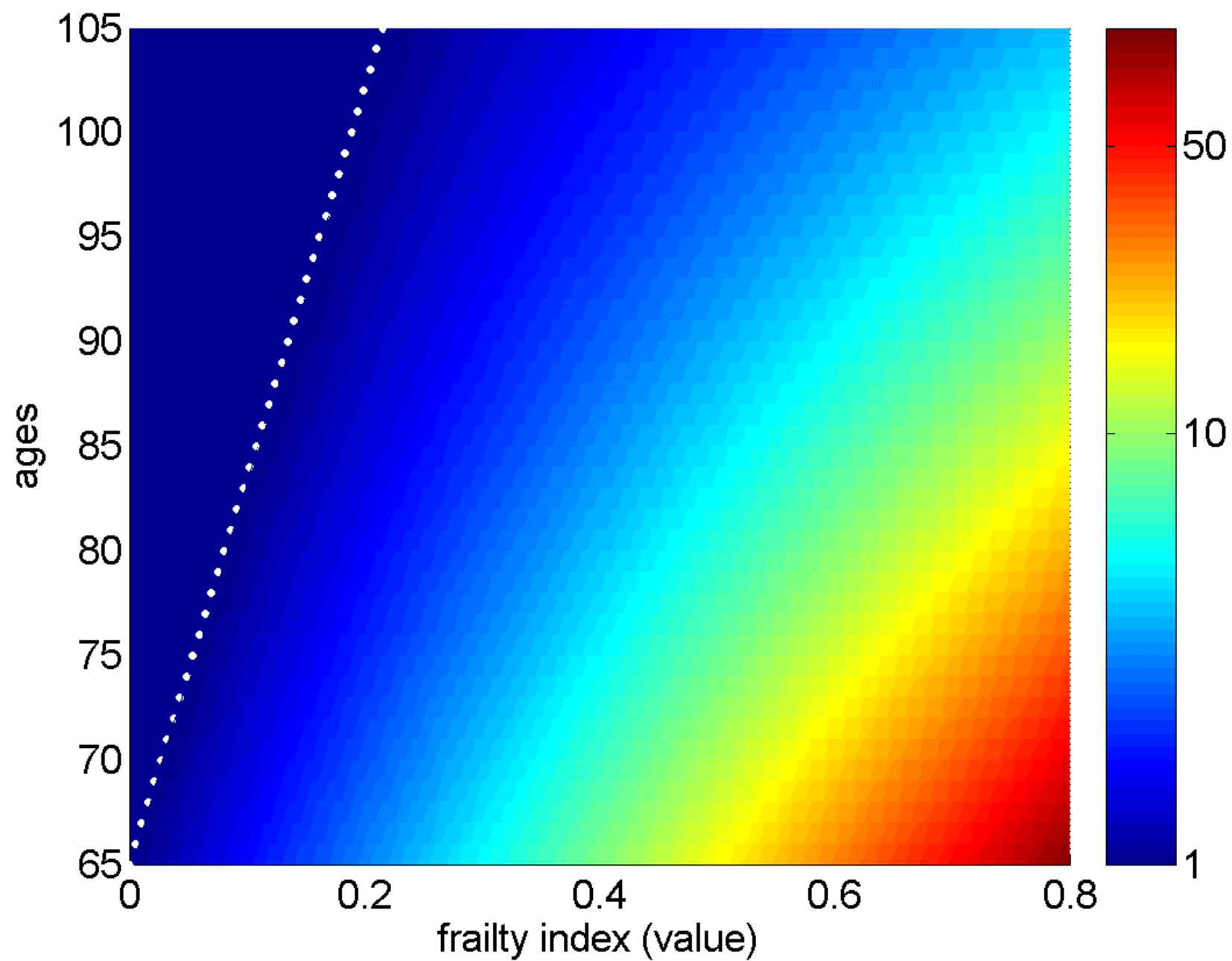
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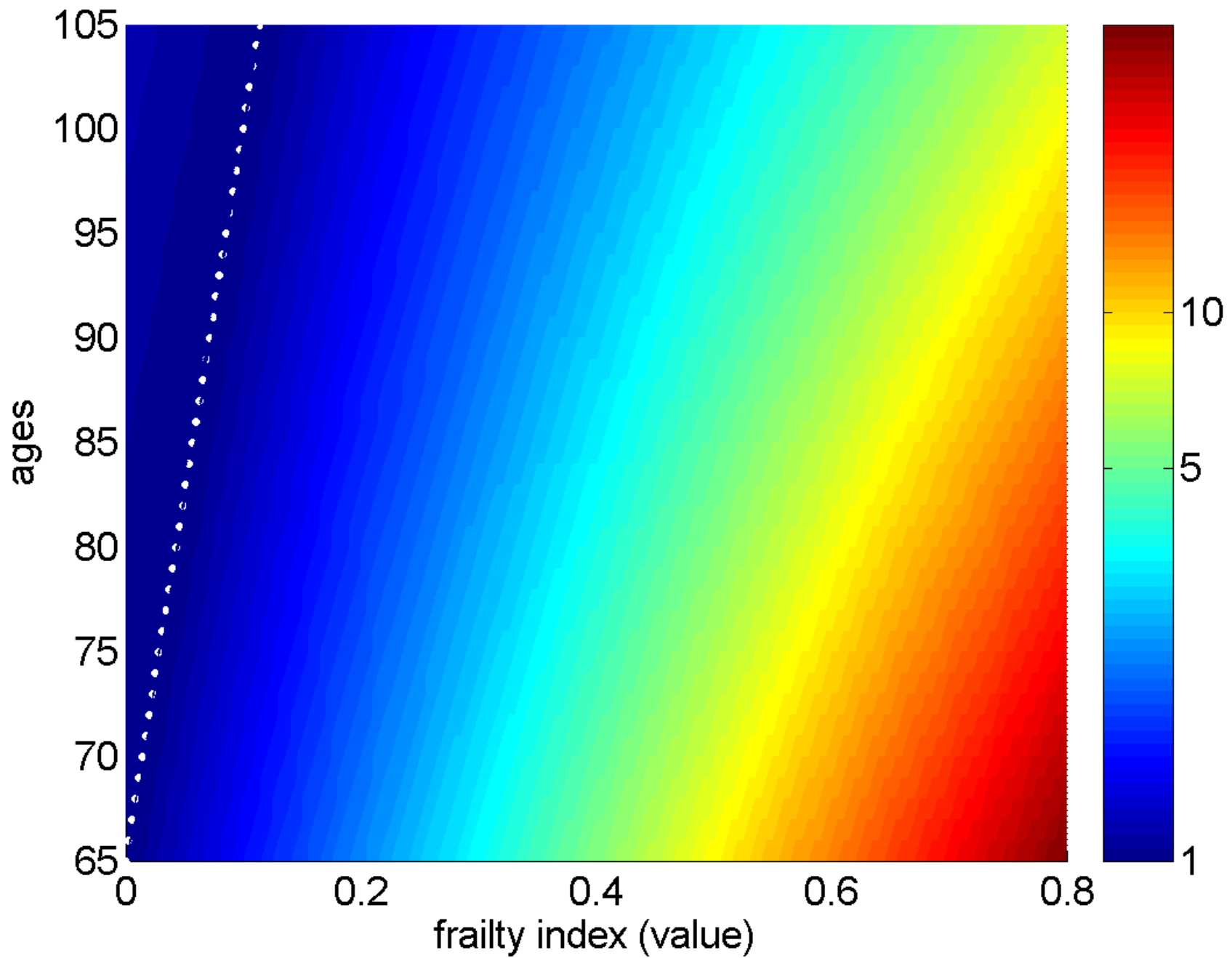
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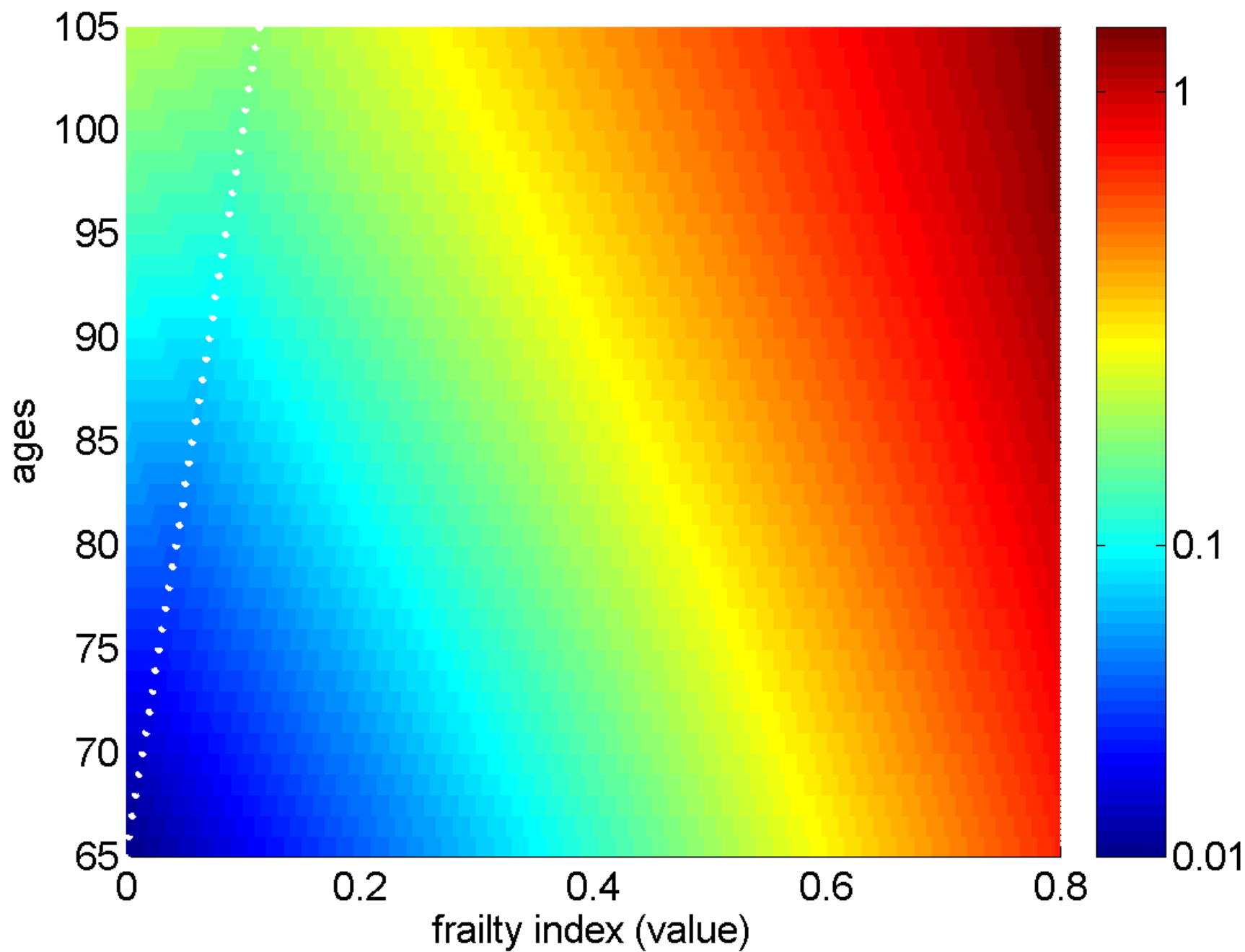
RR(t, Y_t) (log. scale): females, model Cox103



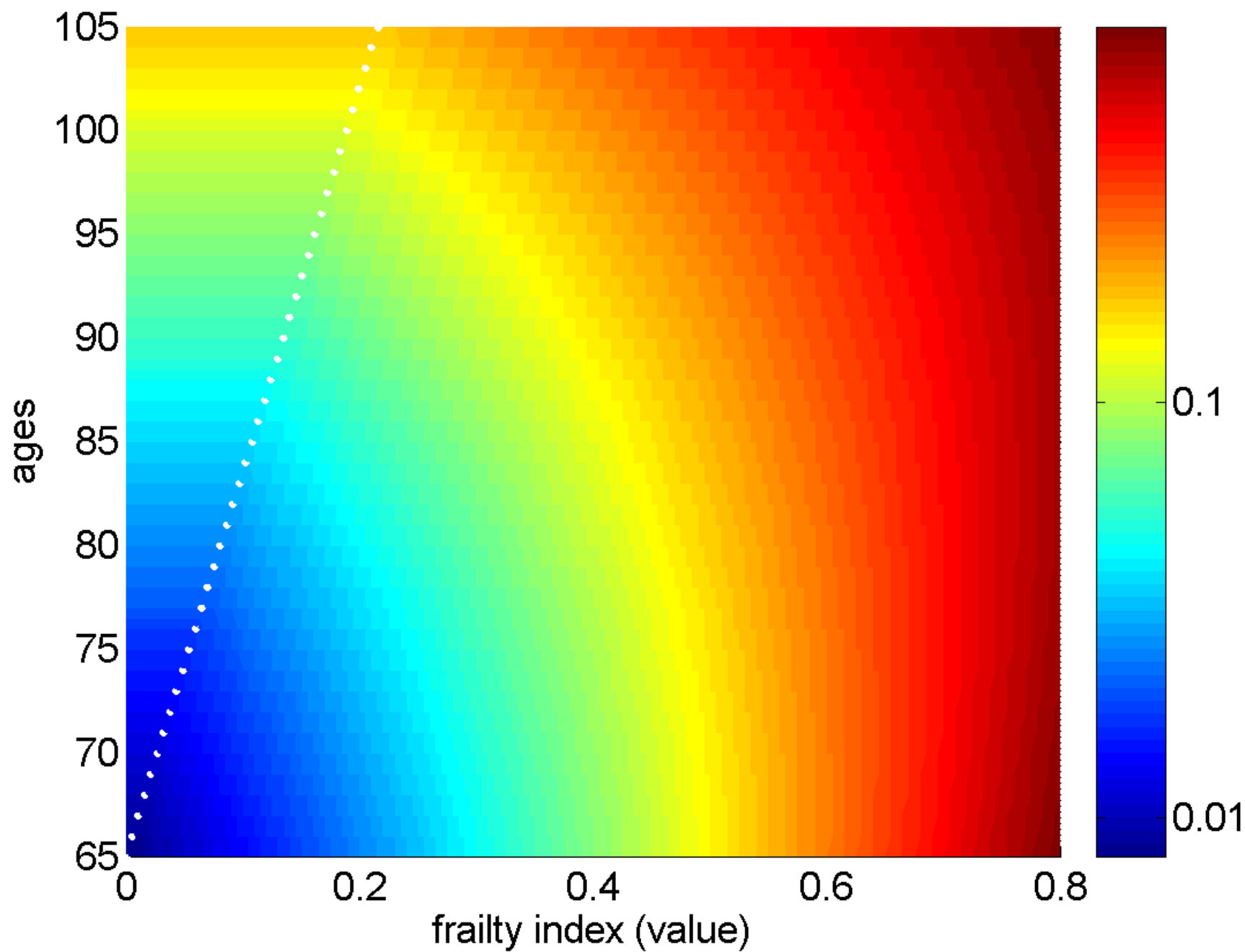
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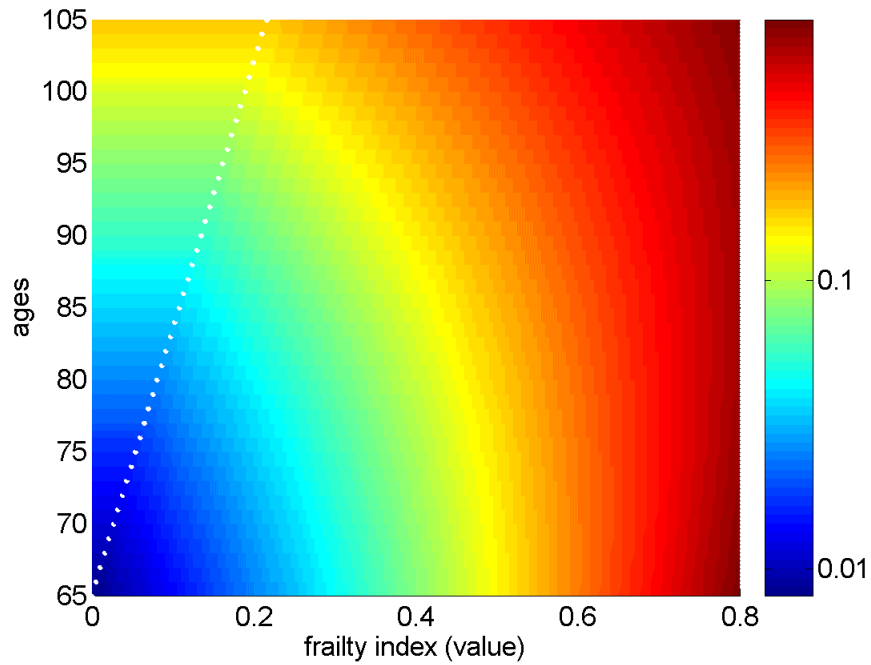
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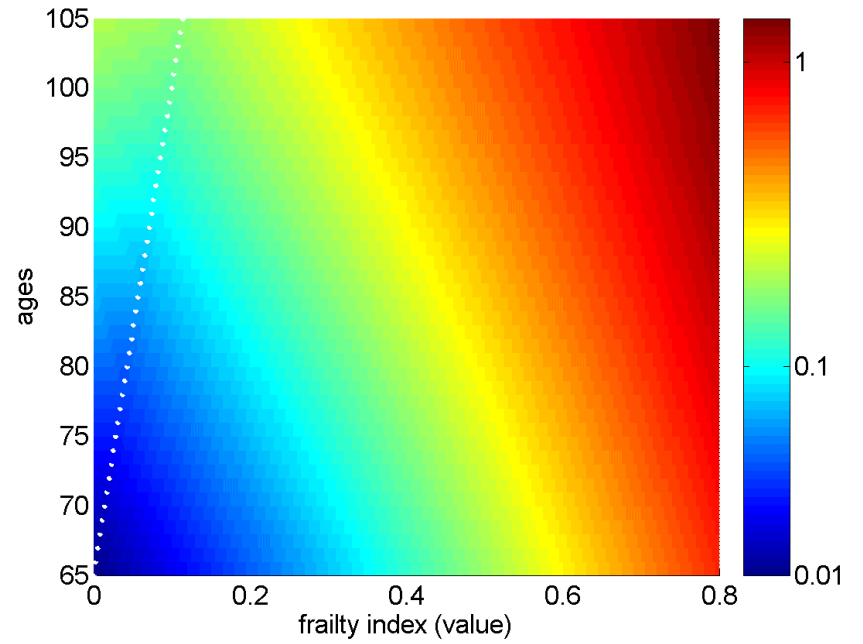
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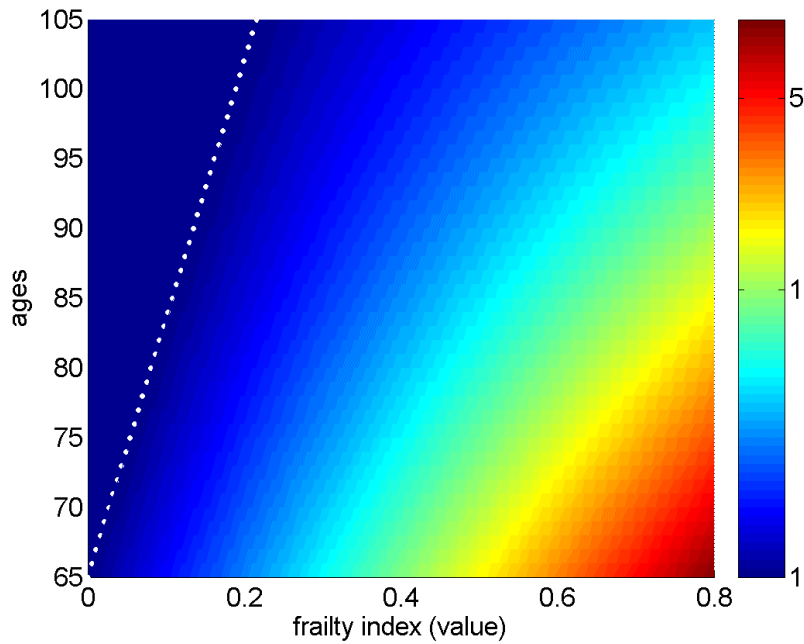
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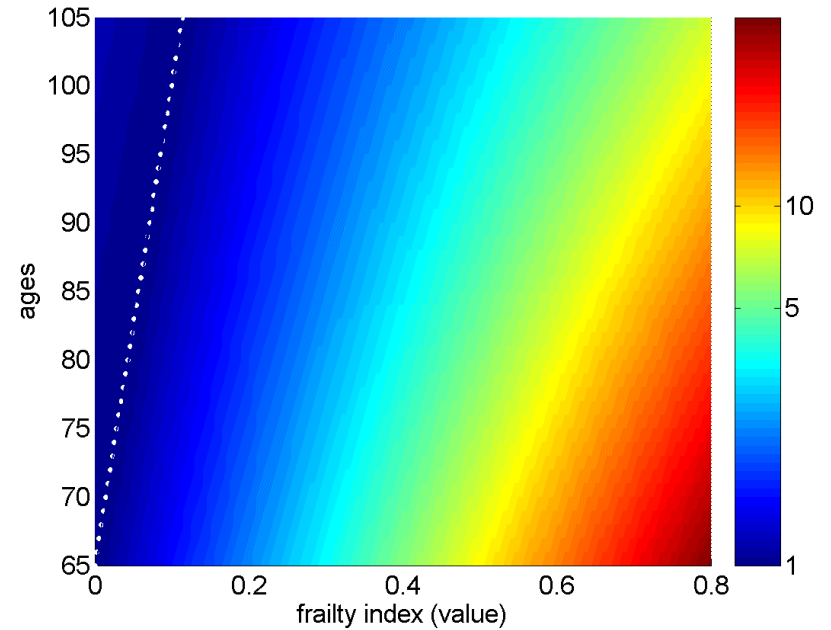
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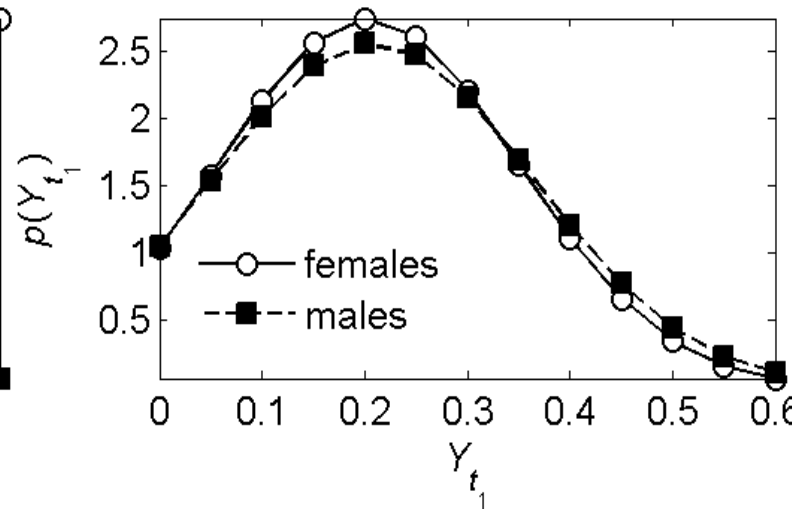
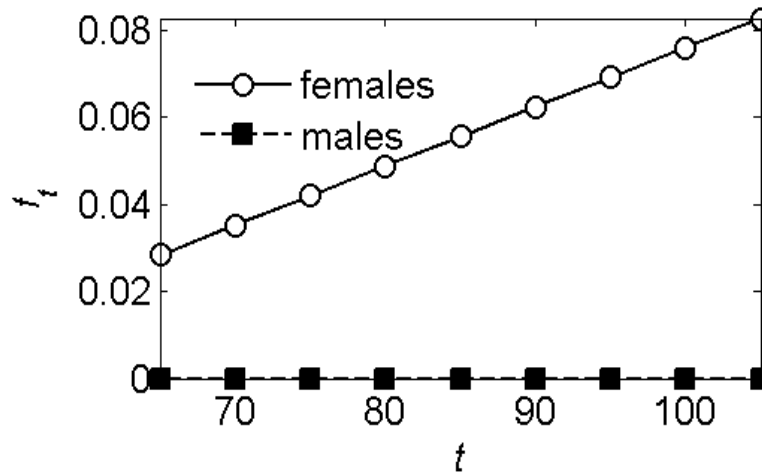
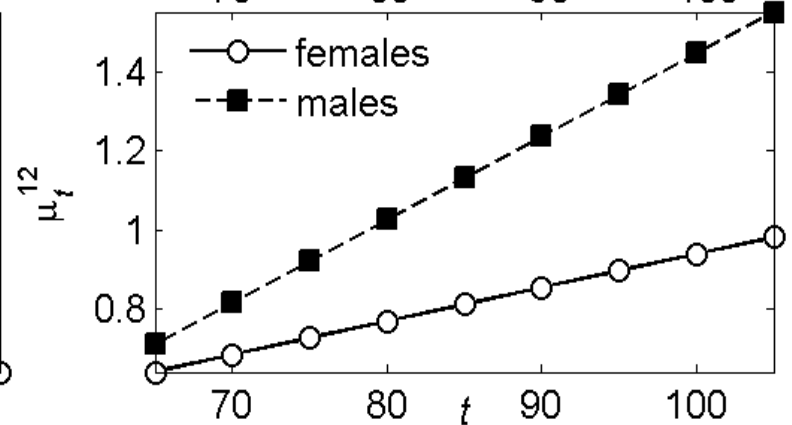
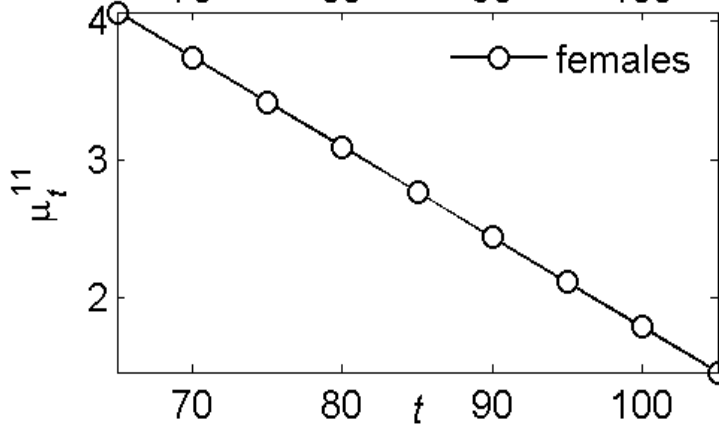
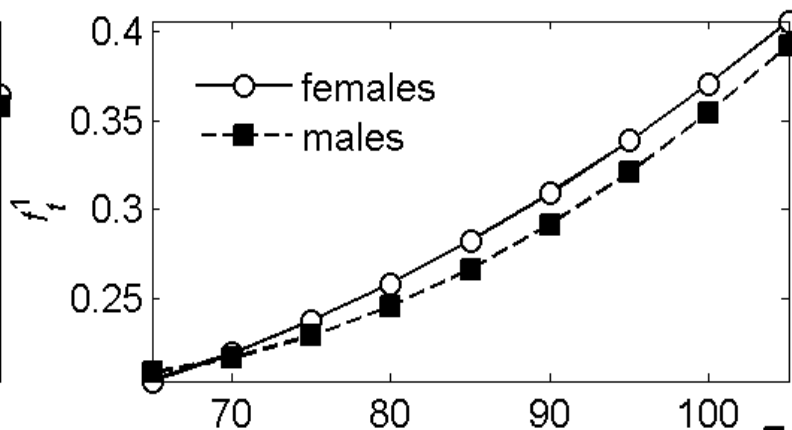
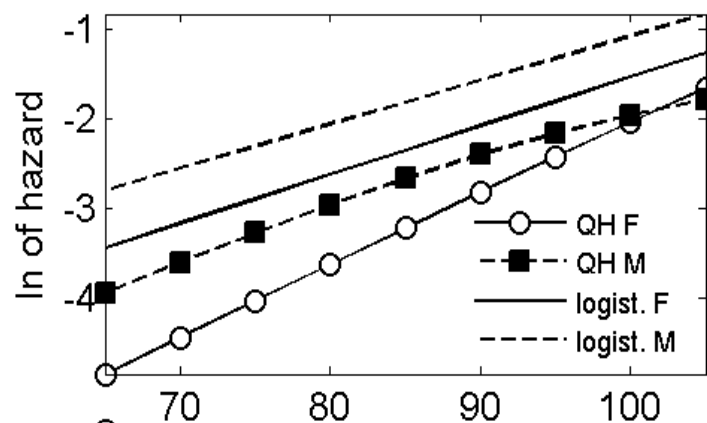
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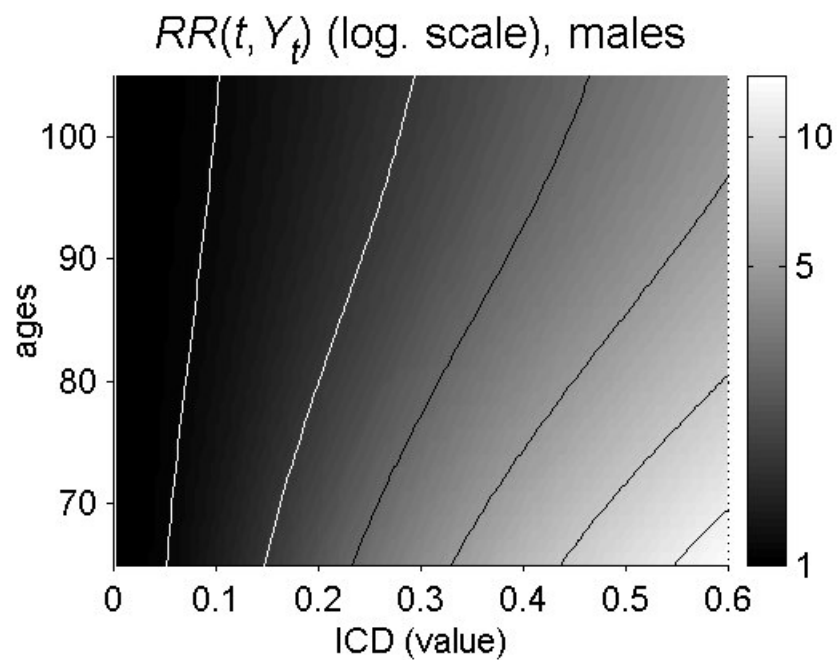
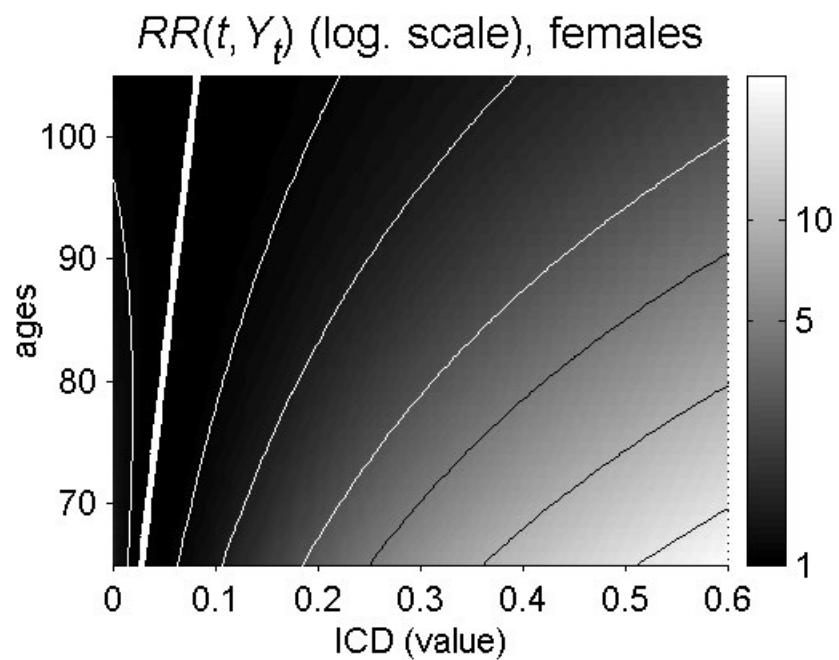
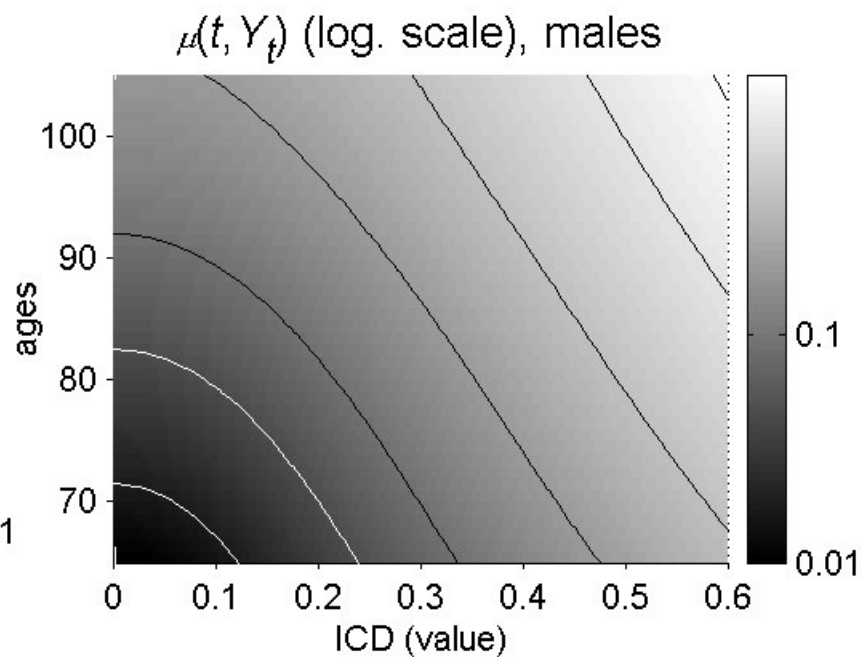
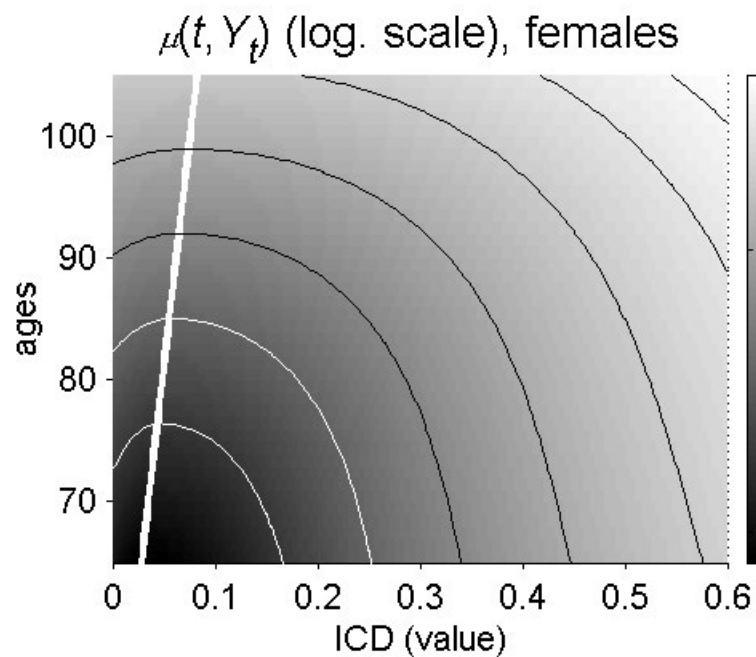
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CONCLUSIONS

- The index of cumulative deficit is a convenient indicator of age related changes in health/well-being status;
- The absolute and relative risks of death considered as functions of index of cumulative deficit show opposite patterns of age-related changes;
- *These changes suggest that:*
 - a) Resistance to stress declines with age
 - b) The relative contribution of senescence to mortality risk increases with age
 - c) The characteristics of the latter processes can be evaluated from longitudinal data

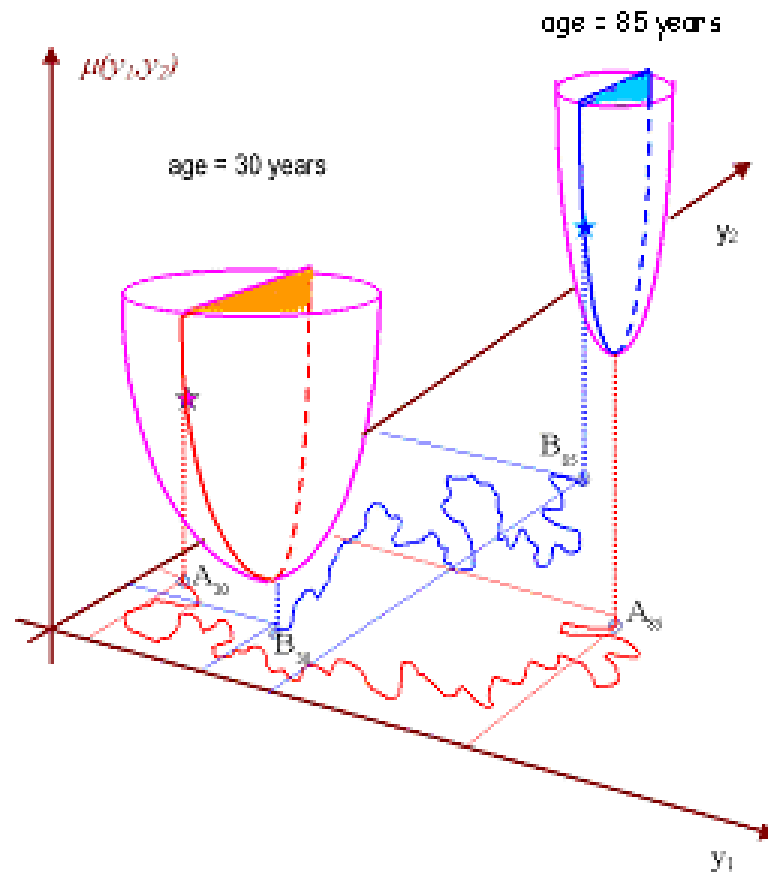


Fig. Risk of death or disease as a quadratic function of hypothetical risk factors (physiological indices) at ages 30 and 85 years. Individual “B” has a minimal risk at age 30 years. However at age 85 years its risk is higher than minimal. The risk of individual “A” at age 30 is higher than minimal. However, its risk at age 85 has minimal value.

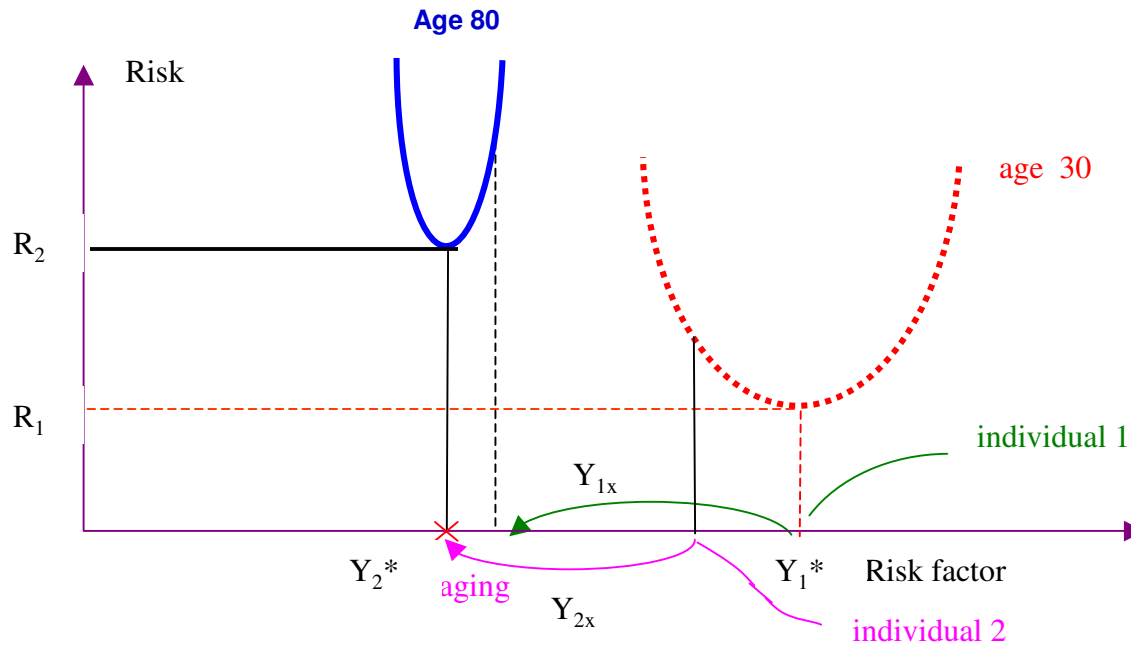
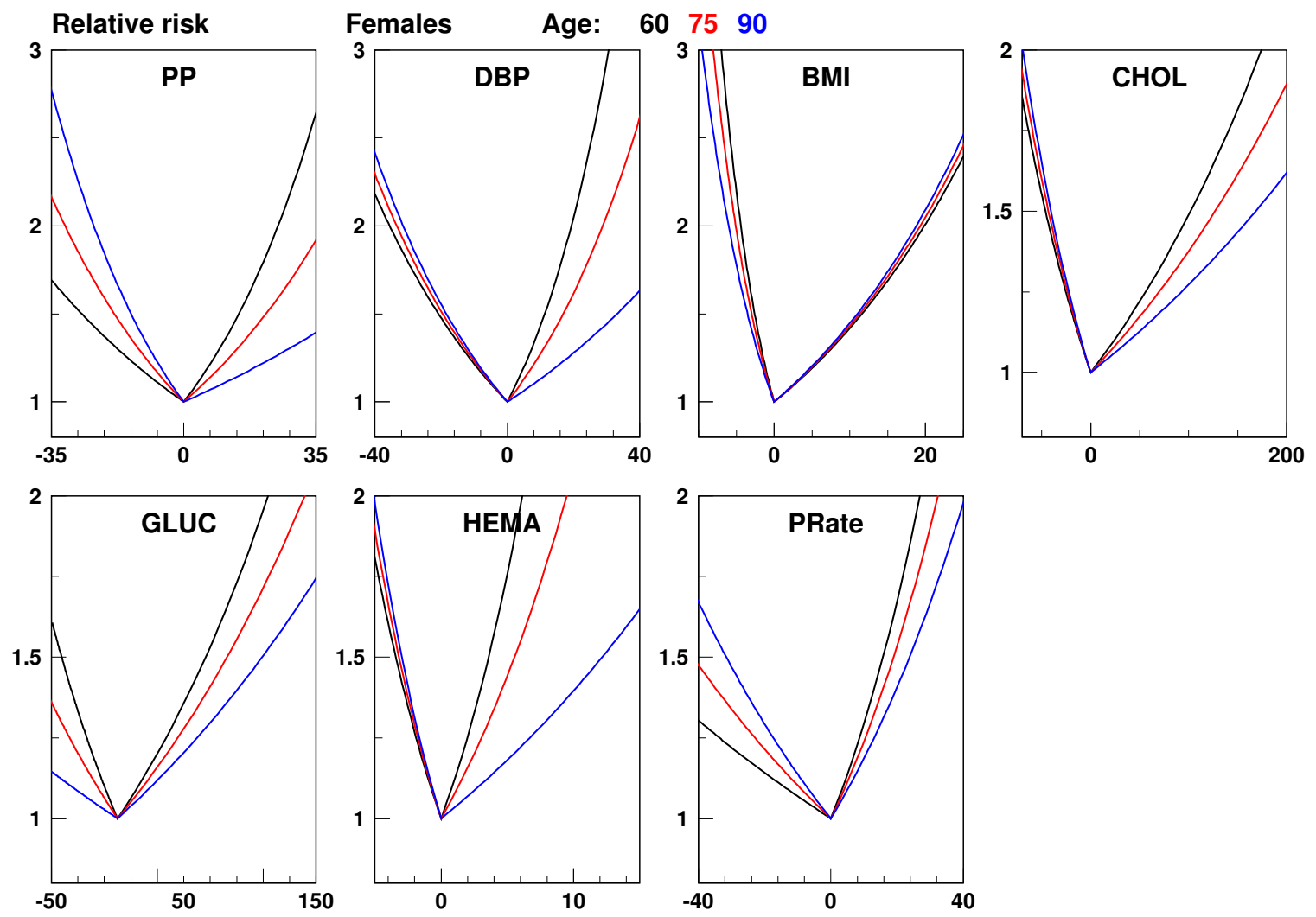


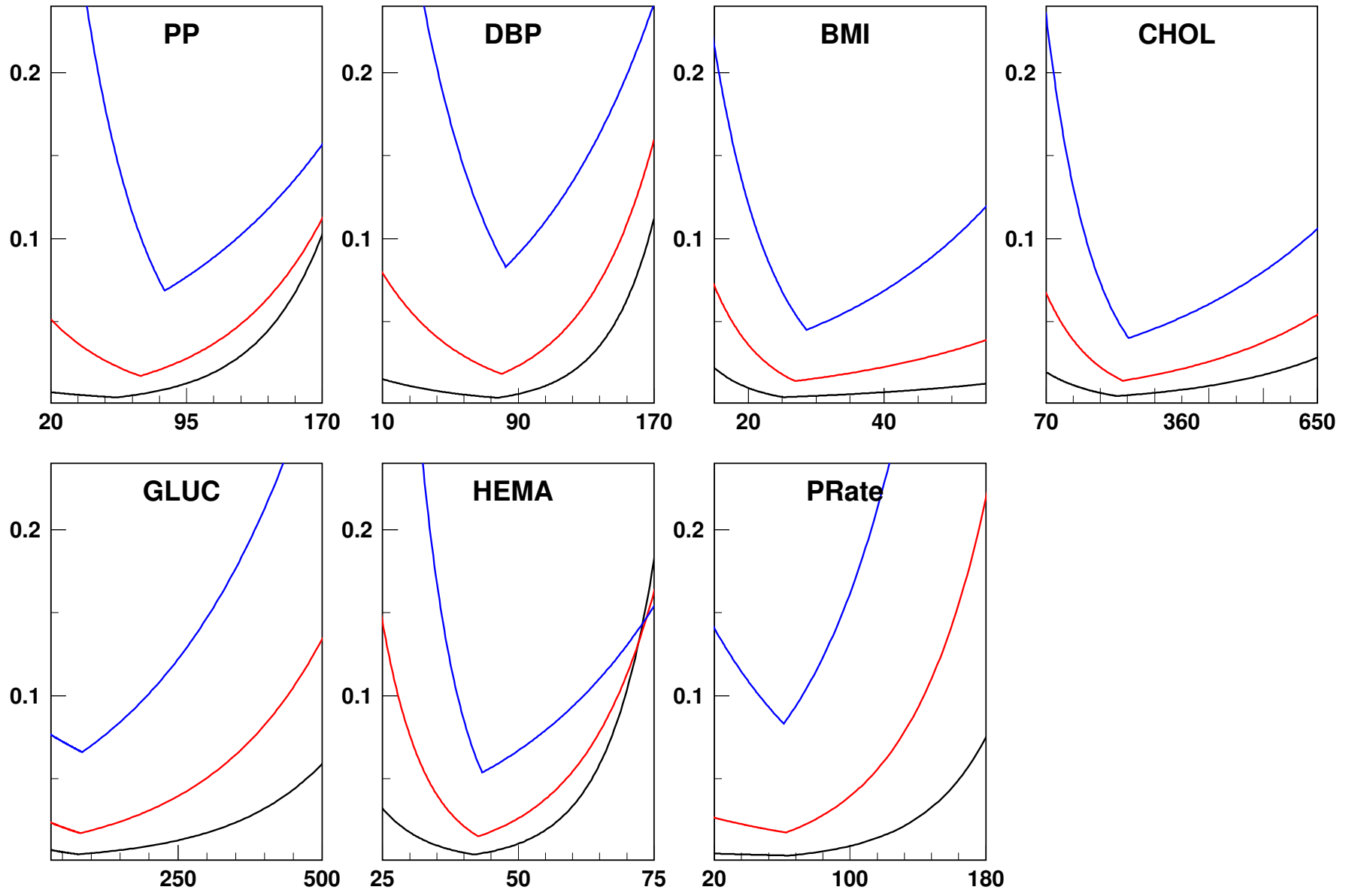
Fig. Values of risk factors (Y_1 for individual 1, and Y_2 for individual 2), optimal risk values (R_1 for age 30 and R_2 for age 80) as well as the optimal value of risk factors (Y_1 for individual 1, and Y_2 for individual 2) may change with age. The hypothetical quadratic hazard functions at age 30 (dotted line) and at age 80 (solid line). Individual 1 has minimal possible value of risk at age 30 and non-optimal risk at age 80. Individual 2 has non-optimal value of risk at age 30 and minimal possible risk at age 80.



Absolute risk

Females

Age: 60 75 90



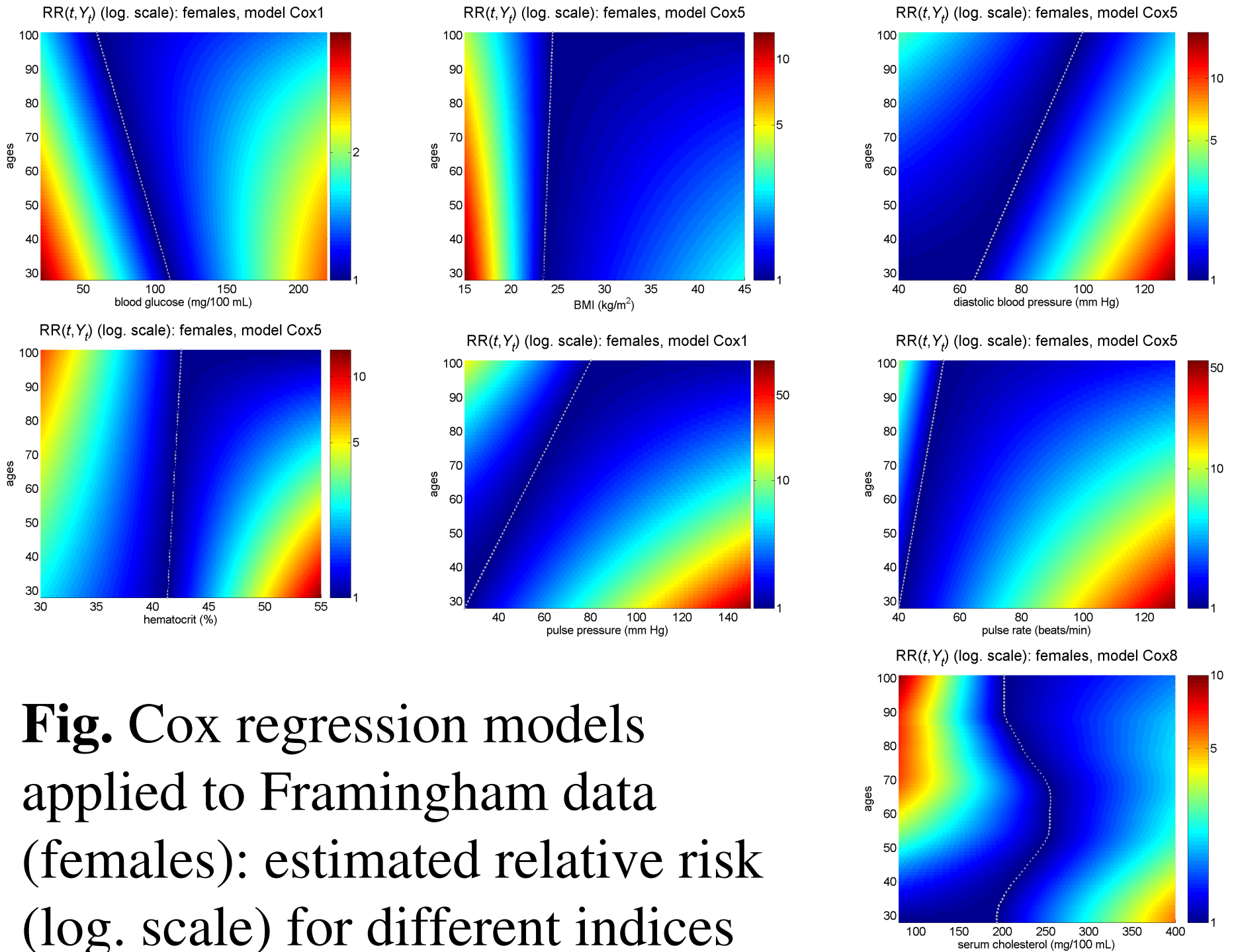


Fig. Cox regression models applied to Framingham data (females): estimated relative risk (log. scale) for different indices

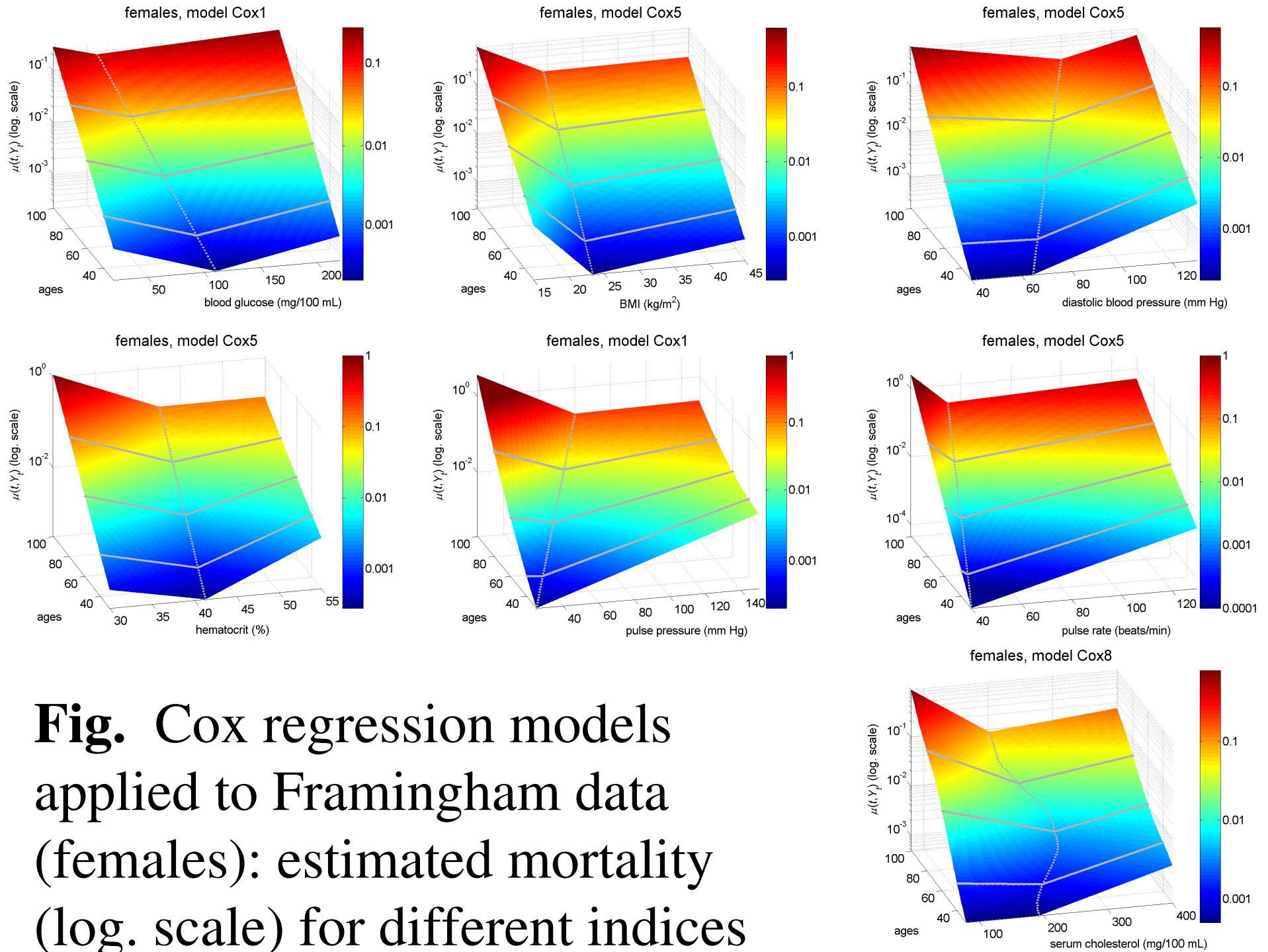


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Conclusions

Age trajectories of physiological indices may be used as predictors of life spans

The narrowing in the U-shape of risk functions with age is in agreement with the concept of declining stress resistance with age

The decline in relative risks with age indicates an increase in contribution of senescence related factors to the risk of death when individuals get older

More studies are needed to investigate effects of hidden heterogeneity in the rate of decline in stress resistance with age

