Web appendix 1

Methods:

Derivation of models of mortality rates as a function of age

Model 1: This model assumes a linear relationship of mortality rates with age. Indeed, this model is implicit in the statement of the current hypothesis that "the increase in absolute heart disease mortality accelerates at menopause". Such a model would suggest the picture that the upward slope of absolute mortality versus age is approximately constant before menopause, and would change to a different slope about the time of menopause in women.

$$Mortality\ Rate = \beta_0 + \beta_1 * age + \beta_2 * (time\ since\ menopause) \qquad 1$$

If there is no change in slope at menopause, the estimate of β_2 will be zero.

Model 2: Survival of the organism results from an ongoing repair of tissue injury that is dependent on a pool of repair mechanisms (e.g., regenerative repair cells). Aging is hypothesized to be a result of loss of this pool. If the probability of removal of reparative cells due to cell division is constant over time, the reserve is lost at a constant proportion with age. Thus, we modeled the mechanism underlying aging as having a constant probability of loss of reparative reserve. In this model, fatal disease events are the result of faulty repair that is linearly related to the inverse of remaining reserve.

$$Surviving\ reparative\ reserve = A \times e^{-B \times age} \qquad 2a$$

which is a monotonically decreasing function where A and B are some positive constants. Thus

$$Mortality\ Rate = A' \times e^{B \times age} \qquad 2b$$

which is a monotonically increasing function where A' is some other constant. Thus

$$log(Mortality\ Rate) = log(A') + B \times age = \beta_0 + \beta_1 \times age \qquad 2c$$

Any changes occurring at menopause can be modeled similarly as in model 1:

$$log(Mortality\ Rate) = \beta_0 + \beta_1 * age + \beta_2 * (time\ since\ menopause) \qquad 2d$$

Thus modeling changes in proportional mortality in Model 2, rather than absolute mortality as in Model 1, can be interpreted as changes in reparative demands on an inexorably decreasing reserve of repair mechanisms (e.g., stem cells).

Spline models: The longitudinal death rates in the cohorts were evaluated using generalized mixed models. For comparability of model fit between the linear age dependence and the log-linear age dependence, the explained variance in the death rate data was calculated on the original scale (Gaussian residual errors). The cohort-mid-age variable was centered to facilitate computational convergence of the model.

$$Y_{ij} = \beta_0 + \beta_{age} \times (\text{mid-decadal age}) + \beta_{spline} \times (\text{age-spline}) + \gamma_j + \varepsilon_{ij}$$

$$\log(Y_{ij}) = \beta_0 + \beta_{age} \times (\text{mid-decadal age}) + \beta_{spline} \times (\text{age-spline}) + \gamma_j + \varepsilon_{ij}$$

where Y_{ij} is the *i*th observation of rate in the *j*th cohort; γ_j, ε_{ij} are the cohort-specific and observation-specific error terms; and β represent the fixed effect coefficients. For likelihood calculations to be comparable, the residuals from the models were specified in the same manner, i.e., on the absolute mortality rate scale. The variable "age-spline" was equal to 0 if mid-decadal age was<50 (i.e., younger than the 45-54 year-old cohort age, i.e., age<45), and equal to the mid-decadal age for older ages.

Sensitivity analysis included models with polynomial fit (i.e., quadratic and cubic fit). These models fit the data better than the linear models, but much worse than the log-linear and log-linear with spline models.

The cohort-mid-age variable was centered to facilitate computational convergence of the model. For most models computational convergence of models was achieved without centering the cohort-mid-age variable. The regression coefficient estimates were identical for centered and non-centered models.