Using biomarkers as indicators of frailty to understand deviation from the Gompertz mortality curve at the oldest ages

PAA 2006 Extended Abstract

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Background:

Demographers have recognized for decades that mortality at the oldest ages does not continue to increase exponentially, but rather declines somewhat from the rates predicted by the Gompertz curve. This pattern is theorized to be the result of heterogeneity in mortality risk, but little research has examined this issue empirically. Most work by demographers has emphasized innate, perhaps genetic, heterogeneity (Vaupel et al. 1979, 1998; Yashin et al. 1999). This paper extends this work by hypothesizing that traditional clinical risk factors provide a good indicator of the heterogeneity of the population for mortality risk. Previous research suggests that a summary measure of clinical risk factors increases until approximately age 65 and begins to level off (Crimmins et al., 2003; Crimmins et al., forthcoming). This paper extends that research by relating a summary measure of physiological dysregulation to mortality.

Methods:

Data

The National Health and Nutrition Examination Surveys (NHANES) are nationally representative, cross-sectional surveys of the non-institutionalized U.S. population including interview, clinical examination, and laboratory test data. Briefly, NHANES III included a stratified multi-stage probability sample collected between 1988 and 1994 (N=16,697). Mortality follow-up data are available through 2000. All analyses were weighted to reflect the non-institutionalized population of older adults in the U.S.

Measures

A frailty index was constructed using 10 biomarkers of risk, including three indicators of cardiovascular health (systolic and diastolic blood pressure and pulse); four indicators of metabolic risk (total cholesterol, glycated hemoglobin, body mass index, and HDL cholesterol); and three indicators of inflammation (fibrinogen, albumin, and C-reactive protein). For each measurement, subjects were coded using clinical definitions of risk, with values outside the normal operating range defined as risk. A summary measure was created by summing the number of biomarkers at risk levels. Summary measures of biological risk are related to traditional health outcomes of old age including mortality, cardiovascular disease, and loss of physical and cognitive functioning (Seeman et al. 2001, 2004).

Analysis

Descriptive statistics are used to observe the mean level of biological risk by age and differences in biological risk among participants who died versus those who lived by age for persons over 40. Hazard models are used to estimate age-sex specific rates of mortality at varying levels of biological risk. Age-specific rates of onset of biomarkers above risk levels among survivors are used to provide population estimates of the risk of inset of frailty states. Projection models are used to describe the impact of mortality selection by biological risk on the surviving population.

Preliminary results:

Biological risk starts to increase in the population relatively early in adulthood. The increase in population-level biological risk is most rapid at younger ages, continuing to rise through ages in the 80s and then leveling off (Figure 1). Deaths among the NHANES III participants from the year of their interview though 2000 can be used to examine the differences in biological risk at the date of interview among those who die and those who survive through the period of NDI search (Table 1). The mean level of biological risk among those who have died in age groups from 40 through 90.is fairly similar across the ages. Thus, those who die at 40 and those who die at 80 are similar in these indicators of risk, while survivors are also fairly similar across the ages.

Conclusion

In the population, those with the highest risk are being eliminated at all adult ages, leaving the surviving population at the next age group healthier than it would have been without deaths. By the age of 80, those who have many risk factors are eliminated, explaining why mortality does not increase as expected. Persons particularly susceptible to these indicators of biological risk have earlier death. Biological risk appears to be a good indicator of the heterogeneity of frailty levels of the population, and provides an explanation for a previously unexpected relationship between very old age and mortality.

Figure 1: Mean Biological Risk by Age in NHANES III

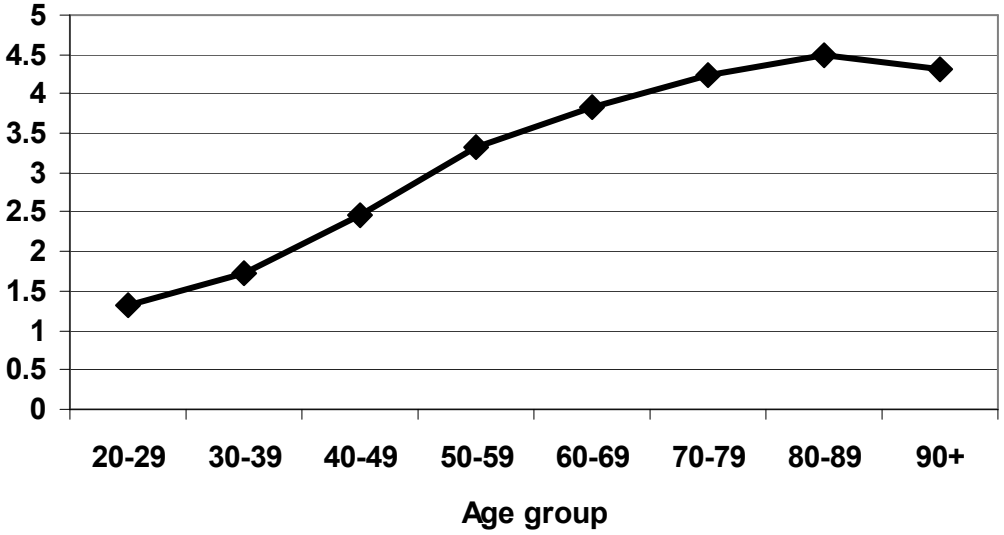

Table 1: Mean Biological Risk* for NHANES III (1988-1994) Participants by Age and 2000 Vital Status

Age	Mean Number of High Risk Biological Indicators		
	Dead	Not Dead	p for difference
40-49	1.89	1.22	<.0001
50-59	2.04	1.64	0.0006
60-69	2.09	1.77	<.0001
70-79	2.07	1.78	<.0001
80 and over	1.82	1.62	0.0079

N=16,697 (those who have data on at least 4 or more indicators out of 10)

* Biological risk measure based on Diastolic BP, Systolic BP, Pulse Rate, Total Cholesterol, Glycated Hemoglobin, BMI, HDL cholesterol, CRP, Albumin, Fibrinogen

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