Today's Research on Aging

Program and Policy Implications

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# Use of Biomarkers in Predicting Health and Mortality

Biomarkers—biological indicators—are increasingly employed in empirical studies of human populations to understand physiological processes that change with age, diseases whose onset appears linked to age, and the aging process itself. The Behavioral and Social Research Program at the National Institute on Aging supports research investigating the link between biological risk factors and health or mortality in the older populations. This newsletter reviews research supported by NIA and other institutions.

## What Are Biomarkers?

Biomarkers are used to monitor and predict the health of a population, to identify individuals with particular resistance or susceptibility to health problems, and to evaluate therapeutic interventions. A wide range of biomarkers exists, each reflecting activity in at least one biological system—for example, in the immune, cardiovascular, or metabolic system. Eileen Crimmins and her colleagues (forthcoming) described the range of biomarkers used to study aging in living human populations; the table (page 2) gives a partial list of these biomarkers.

### In This Issue



This review summarizes research related to the objectives of the National Institute on Aging, with emphasis on work conducted at the NIA demography centers. Our objective is to provide decisionmakers in government, business, and nongovernmental organizations with up-to-date scientific evidence relevant to policy debates and program design. These newsletters can be accessed at www.prb.org/TodaysResearch.aspx.

Alone or in combination, biomarkers can provide an early warning system of risk for future adverse health outcomes. Many of these biomarkers are relatively easy to measure and are often part of routine medical examinations. Blood pressure, heart rate, and pulse are commonly measured indicators of cardiovascular functioning. Cholesterol and triglycerides provide information on metabolic processes and have been used increasingly to evaluate the risk of coronary heart disease. Body measurements such as weight, body mass index (BMI), and waist-to-hip ratio serve as indicators of obesity, chronic metabolic disorders, and fatty deposits. T-cell counts provide information about the status of the immune system; cortisol, a steroid hormone, is often produced in response to chronic stress. An electrocardiogram (EKG or ECG) tests the functioning of the heart by measuring electrical impulses and then graphically displaying them.

## Predictors of Illness, Disability, and Death

Biomarkers are much better predicators of disease (illness) and death than self-reported health status (Goldman 2007). Even when individuals have already provided information on their physical, mental, and cognitive health, biomarkers provide additional information that improves our ability to predict whether an individual is likely to live or die. Biomarkers collected in physical exams, such as markers of cardiovascular disease and diabetes, and those not usually part of routine physicals, such as immune markers, are useful predictors of health.

An individual biomarker, once it exceeds a certain threshold, is an indicator of risk for future illness or death due to problems in a particular biological system. By adding risk indicators together, an index may be created that captures higher health risks signaled by biological processes that occur simultaneously in an individual. However, such indices do not tell us about specific multiple paths that may produce high risk of adverse health outcomes. One study found that older males were more frequently at high risk for adverse health outcomes due to a combination of impairments in the functioning of the immune system and the neuroendocrine

**Some Biomarkers Are Collected in Routine Medical Exams.**

| Biomarkers | Description | Associated Health Outcomes |
|---|---|---|
| Systolic blood pressure (SBP) | Index of cardiovascular activity: maximum pressure in an artery when the heart is pumping blood throughout the body | Cardiovascular death (CVD), stroke, coronary heart disease (CHD), mortality |
| Diastolic blood pressure (DBP) | Index of cardiovascular activity: lowest pressure in an artery when the heart is resting | Cardiovascular death, stroke, CHD, mortality |
| Resting pulse rate | Indicator of heart functioning and measure of overall fitness | CHD, mortality |
| Total cholesterol | Aids in the synthesis of bile acids and steroid hormones | In middle-age: CHD and all-cause mortality. In older ages: U-shaped relation to death |
| Low-density lipoprotein (LDL) | Transports cholesterol from the liver to be incorporated into cell membrane tissues | CHD, atherosclerosis, stroke, peripheral vascular disease |
| High-density lipoprotein (HDL) cholesterol | Protective cholesterol | Lower atherosclerotic CVD |
| Triglycerides | Fat substance stored for energy use | Heart attack, CHD, coronary artery disease, pancreatitis |
| Fasting glucose | Measures amount of sugar in blood; indicator of diabetes | Diabetes, CHD, mortality, poor cognitive function |
| Body mass index (BMI) | Indicator of the balance between energy intake & energy expenditure | CVD, diabetes mellitus, stroke, mortality, some cancers, osteoarthritis |
| Waist-to-hip ratio | Indicator of abdominal obesity | Hypertension, CHD, noninsulin dependent diabetes and stroke |
| T-cells | White blood cells that protect against pathogens and tumors | Cancer, mortality, artherosclerosis, Alzheimer's disease |
| Cortisol | Steroid hormone that reflects body's response to physiological stress | CVD, poor cognitive functioning, fractures, functional disability, mortality |
| Electrocardiogram (EKG) | Measurement of electrical impulses in the heart | Cardiovascular risk, stroke, mortality |

**Source:** Crimmins et al. (forthcoming).

system—the interaction of the nervous system and the endocrine system (Gruenewald et al. 2006). In older females, high risks of adverse health outcomes usually stem from high systolic blood pressure in combination with impairments signaled by other biomarkers (see table, page 2).

## A Century of Change

Medical histories of acute and chronic diseases as well as biomarkers obtained from body measurements (anthropometric indicators such as height and weight) are available in medical and pension records of Union Army veterans. The Early Indicators Project created a longitudinal sample based on veterans' records combined from up to a dozen sources (Fogel 2004). The project has provided an accurate description of the burden of disease and disabilities among men ages 50 and older at the beginning of the 20th century, filling in gaps in health statistics that were unavailable until the National Health Interview Survey began in the 1960s.

The Early Indicators Project provides evidence of a decline in illness and disease that paralleled the mortality decline of the epidemiological transition, where chronic conditions replaced acute conditions as the major causes of deaths. Chronic disease began early in life and was more prevalent in the early 20th century than later. The average male age of onset of chronic conditions was delayed by over 10 years and male life expectancy increased by an average of 6.6 percent over the course of the 20th century.

Using a longitudinal sample of aging based on records for Union Army veterans combined with records from World War II veterans, researchers found that between the 1900s and the late 1980s, changes in frame size (as measured by waist-to-hip ratios) explain nearly 50 percent of the decline in death rates for those ages 65 and older. Also, changes in body size had significant implications for long-term decline in chronic conditions.

Evidence also suggests that height is determined by both environment and genetics and that as height increased among Americans in the last century, susceptibility to some diseases decreased. Diane Lauderdale and Paul Rathoutz (1999) found that unhealthy environmental conditions affect stature: Height differences between brothers from the counties where height was lower on average were likely to be greater than expected among brothers living in the same county. Soldiers with short stature were also more likely to contract certain diseases, including tuberculosis (studies discussed in Fogel 2004).

Over a period of 100 years, the height and weight of male recruits in the military increased, but their hip-to-waist ratios remained the same (Costa 2004). Among those with similar body mass index, abdominal fat as measured by hip-to-waist ratio was greater for Union soldiers who survived to 1900 than for soldiers in the 1950s and 1980s. Both low and high abdominal fat were related to increased death rates, but low abdominal fat increased the risk of death almost twice as much as high abdominal fat. These findings are similar to recent studies that in the elderly population, being underweight is a greater risk factor for death (Flegal et al. 2005; Grabowski and Ellis 2001).

## Health and Happiness

In a study that looked for a relationship between biological indicators and health, Steptoe and his colleagues (2005) found negative emotional states such as depression to be associated with increased risk of diabetes, coronary heart disease, disability, and early death. Happiness levels were higher on leisure than working days, and individual differences were consistent across days. People who were happy most of the workday were also happier during the leisure day.

The more often that middle-aged men and women experienced moments of happiness over a working day, the less elevated was their 24-hour cortisol output. This association held regardless of age, gender, socioeconomic position, body mass, and smoking behavior. Similar patterns were observed on a leisure day. The relationship between reduced cortisol and happiness is potentially relevant to health. Cortisol is related to a range of chronic diseases including obesity, Type 2 diabetes, hypertension, and autoimmune conditions. Elevated cortisol (found among those with the lowest levels of happiness) might contribute to health risk if it persists over months or years.

People who experienced more moments of happiness reported less psychological stress, but the effects of happiness were still found in individuals with different levels of psychological distress. This finding supports the notion that positive emotional states are directly related to biological processes rather than affecting health through the reduction of psychological stress. Positive emotional states may produce favorable patterns of functioning in several biological systems and so may be relevant to reducing the risk of physical illness.

## Allostatic Load

Allostatic load has been proposed as a conceptualization of the cumulative biological burden exacted on the body through attempts to adapt to life's demands (Seeman et al. 2001). Additive indices, whose values represent the number

of biological risk factors or some weighted combination of these factors, have been used to measure allostatic load. Using a measure of allostatic load that captured risk across multiple biological systems, Seeman and her colleagues found that higher scores on their index were associated with a greater risk of death in the next seven years and also with greater likelihood of a decline in cognitive and physical functioning. Omer Gersten (2008) tested the concept of cumulative biological burden with a measure of neuroendocrine allostatic load (NAL) among respondents in the Social Environment and Biomarkers of Aging Study (SEBAS), a nationally representative survey of Taiwan conducted in 2000. Findings from this study suggest that the neuroendocrine biomarkers may reflect a transient state at the time of the study rather than an accumulation over a stressful life. However, Seeman and her colleagues (2004) found individual neuroendocrine biomarkers to be significantly predictive of mortality nine years later, suggesting that with respect to the ultimate health outcome—death—the effects of stress on the neuroendocrine system are not transient.

Consistent with findings that show more moments of happiness to be associated with lower stress, researchers have also found that better social relationships are associated with lower allostatic loads, as is higher educational attainment (Seeman et al. 2002 and 2004).

## Weathering Race and Poverty

In the United States, blacks are more likely than whites of a similar age to experience stressful situations. For example, blacks more consistently encounter interpersonal discrimination, discrimination in housing and employment, material hardship, and multiple unpaid caregiving roles. Researcher Arline Geronimus (1996, 2001, 2006, 2007) proposed a "weathering hypothesis" in which exposure to such experiences and persistent high-effort coping have a cumulative biological impact. Geronimus posits that the early health deterioration observed among African Americans relative to Euro-Americans is a consequence of their repeated experiences with social and economic adversity.

Using National Health and Nutrition Examination Survey data, Geronimus and fellow researchers (2006) examined the allostatic load scores for adults ages 18 to 64 and estimated the probability of a high score by age, race, gender, and poverty status. As the weathering hypothesis would predict, they found that blacks had higher scores than did whites at all ages, but particularly between ages 35 and 64. Racial differences were not explained by poverty alone. Poor black women had the greatest probability of high allostatic load, followed by nonpoor black women. Cohort effects did not explain the racial or gender disparities.

Unlike more common theories explaining racial disparities in health, the weathering hypothesis does not emphasize youthful indiscretion, individual behavior, or material deprivation, alone (Geronimus 2007). Instead, it allows for the possibility that premature health deterioration may be a result of working hard and fulfilling responsibilities. Geronimus argues that individuals with a strong belief in controlling their destiny may experience adverse health outcomes because they are constantly struggling to break through obstacles they encounter. The weathering hypothesis also allows for more-rapid health deterioration as these experiences accumulate in early adulthood when people take on more competing obligations. This hypothesis may explain the divergence of black and white morbidity and mortality after age 20.

The mechanisms through which weathering may work include exposure to poverty, physical environmental hazards, and social stressors in residential and work environments. In addition, the early development of chronic conditions, themselves an outcome of weathering, can add to an individual's stress, further increasing weathering effects. The impact of these conditions can be exacerbated by being medically underserved. Other possible mechanisms for weathering include the internalized effects of stigma, or frustration and anger at racial injustice. The weathering hypothesis also predicts the racial differences in age trajectories of hypertension prevalence found in the United States. Differences between blacks and whites start out small, but then increase with age.

A recent analysis (Epel et al. 2007) of cellular aging suggests one mechanism through which persistent stress increases the risk of disease. Researchers examined several indicators of aging at the cellular level to test the hypothesis that stress affects health by changing the rate of cellular aging. Epel and her colleagues found that both perceived stress and persistent stress are significantly associated with signs of aging at the cellular level—higher oxidative stress, lower telomerase activity, and shorter telomere length—in peripheral blood mononuclear cells from healthy premenopausal women. Based on differences in telomere length, on average, cells in women with the highest levels of perceived stress were the equivalent of 10 years older than cells in low-stress women. These findings suggest that at the cellular level persistent stress may promote earlier onset of age-related diseases by promoting deterioration of some protective attributes of cells.

## Ongoing Issues

Aging increases risk of disability and chronic disease, with many older adults experiencing multiple chronic conditions in old age (Singer, Ryff, and Seeman 2004). Some evidence exists to support theories that increased health risks in old age are the result of psychological and environmental stressors that accumulate over time. These stressors potentially can disrupt the regulation of biological systems. However, not all individuals or population groups seem to be equally susceptible to the effects of stress. Questions remain as to which factors mediate biological responses to stress—genetic predisposition, lifestyle choices, or socioeconomic factors.

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POPULATION REFERENCE BUREAU

1875 Connecticut Ave., NW, Suite 520, Washington, DC 20009 USA
Tel.: 202-483-1100 | Fax: 202-328-3937
E-mail: popref@prb.org | Website: www.prb.org

## The NIA Demography Centers

The National Institute on Aging supports 13 research centers on the demography and economics of aging, based at the University of California at Berkeley, the University of Chicago, Harvard University, the University of Michigan, the National Bureau of Economic Research, the University of North Carolina, the University of Pennsylvania, Pennsylvania State University, Princeton University, RAND Corporation, Stanford University, the University of Southern California/University of California at Los Angeles, and the University of Wisconsin.

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## For More Information

**Biomarkers of Aging and Diseases of Aging, October 2007**
www.afar.org/biomarkersconference.html

**Chicago Workshop on Biomarkers in Population-Based Health and Aging Research, June 2007**
http://biomarkers.uchicago.edu/2007%20Chicago%20Biomarker%20Workshop%20Proceedings.pdf

**NIA Workshop on Allostatic Load, November 2007**
www.nia.nih.gov/NR/rdonlyres/AF0997F6-0C16-4A76-96C0-D3780F00E6D4/8839/AllostaticLoadBackgroundMaterials.doc

**Stacy Tessler Lindau and Thomas W. McDade**
"Minimally Invasive and Innovative Methods for Biomeasure Collection in Population-Based Research," in *Biosocial Surveys*, ed. Maxine Weinstein, James Vaupel, and Kenneth Wachter (Washington, DC: National Academies Press, 2007).

**Older Americans: 28 Key Indicators of Well-Being**
http://agingstats.gov/Agingstatsdotnet/Main_Site/Default.aspx

**Older Americans—Historical Perspective of Three Cohorts of Older Americans**
http://agingstats.gov/agingstatsdotnet/Main_Site/Data/2008_Documents/timeline.pdf