

# Biomarkers in Population Aging Research

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Rapid progress in the field of biological assessment has expanded the possibilities for enhanced biological measurement in population research. Incorporating biomarkers in social sciences, public health, and behavioural research creates exciting opportunities that include better measurement of health and disease, validation of self-reported behaviours, and measurement of exposures to environmental agents. Biological Marker (Biomarker) is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biological measures collected in the population setting can include direct measures of physical or physiological characteristics (eg height, weight, BMI, waist-hip circumference or blood pressure), functional testing (eg cognitive function, balance, grip strength), or collection of specimens that require laboratory processing in order to generate analyzable data. Such data may also be generated via experiments embedded in population studies (eg neuropsychiatric, psychophysiological, or sensory testing). Biomeasures also include measures of the physical environment that influence human biology (eg radiation or noise).

The National Research Council recommends that biomarkers be incorporated in a social survey to a) capture health data from a portion of the population that otherwise would not have this type of data recorded, b) investigate molecular determinants of common health outcomes, and c) study interactions between biomarkers and social conditions that may subsequently lead to declines in health outcomes.<sup>1</sup>

The inclusion of biomarkers is particularly important for less-developed countries like India, where access to health care tends to be limited due to low income and the lack of insurance. According to the World Bank, the 2005 gross national income per capita in India was \$720, and less than 10% of the Indian population had health insurance (either public or private).<sup>2</sup> India's aging population is particularly at risk for undiagnosed diseases, furthermore a significant level of self-reporting

bias exists. Education is also known to be an important determinant for identifying health problems, but literacy rate in India was just 61% in 2004.<sup>3</sup> Therefore, the importance of biomarkers is critical to gauge the health conditions of the Indian population, particularly the older adults.

There are people who reach the age of 85 in a very good physical and mental condition. There are others who have extensive cognitive difficulties and physical disorders already by the age of 60. A person's biological age is more indicative of their health than their chronological age. Understanding the mechanisms of aging and the relationship between aging and disease is essential to help us address the health needs of older population. However, the inability to quantify aging in individuals has limited the study of the biology of aging. Currently, aging is indirectly measured as a function of the increasing rate of mortality within populations. While aging contributes to the progressive increase in mortality, it is only indirectly related to life span. Life span and chronological age gives little indication of the dynamic changes that occur within an individual and the functional capabilities of that individual. Currently there is no way to relate the population-level phenomenon of increasing mortality to the age-related biological declines within individuals. As well, the field of aging is left without a standardized measure for measuring aging in studies or monitoring potential interventions in the aging process. Evaluation of an anti-aging theory or program is feasible in the laboratory, using experimental animals, not so with humans. The proposed solution to this problem is to find a set of biomarkers to act as a meter of the aging process. A biomarker would be a physiological or genetic parameter that changes with age, and it would predict mortality and morbidity better than chronological age.<sup>4</sup> It should be able to predict mortality while the majority of the population was still alive, and it would be able to predict the outcome of other age-sensitive tests.<sup>5</sup>

It is generally believed that seven major health areas are affected by aging: cardiovascular health, glucose regulation, brain function, muscle and skeletal health, endocrine function, immune system and oxidative stress.

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Biomarkers of aging are physical properties in the human body which indicate that the body is aging. The best markers will be the ones which are not susceptible to influence from the outside environment and have a clear association with aging. Ideally a true biomarker must predict the rate of aging and be a better predictor of life span than chronological age. It must be able to be tested on a regular basis and must work both for humans and other species, such as laboratory animals. A set of biomarkers would allow researchers to assess an individual's biological age, and their expected individual life span, as opposed to their chronological age. It is difficult to quantify aging within and between individuals for two major reasons, which is primarily why biomarker research has thus far yielded no positive results. First, genotype alone does not explain the rate of aging. In human twins, as well as genetically identical organisms raised in the lab life span varies substantially. A second major problem in quantifying aging is variation within individuals. Different organ systems age at various rates within the body, so the existence of a single indicator of the rate of aging seems unlikely. Traits that most directly relate to the aging process would make the best biomarkers; that is, their effect would not be influenced by other variables. However, without an established theory of aging it is difficult to determine which traits or systems best reflect aging. The use of multiple biomarkers can predict mortality more accurately than chronological age.

Biomarkers of aging could be divided in three major categories; a) markers which determine the biological age, eg skin elasticity and visual accommodation, b) markers which predict the remaining life expectancy eg DHEA-S, hand grip strength, etc and c) markers which determine disease susceptibility eg systolic blood pressure and glucose tolerance tests. All of the biomarker tests can be classified either as laboratory tests (eg blood and urine tests) or as physical tests undertaken in a clinic. Frequently used and validated biomarkers are: 17-ketosteroid/ 17-hydroxycorticosteroid ratio (male), ascorbic acid, IL-6, APOE, norepinephrine, epinephrine - plasma (male), creatinine clearance, DHEA-S, PSA total (male), fibrinogen, testosterone free (male), zinc- serum, hemoglobin A1C, maximum oxygen uptake (male), basal metabolic rate, blood pressure-pulse, blood pressure- systolic, lung capacity- FEV1, lung capacity- FVC, handgrip strength, body mass index (female), near vision, caries index, periodontal index, skin elasticity, hair baldness (male), and hair grayness. In addition, there are also a number of other factors with insufficient experimental data like body

flexibility, blood urea nitrogen, LDL cholesterol, melatonin levels, static balance, serotonin levels and many others.

Common anthropometric and performance biomarkers used in population research are a) Anthropometric measures: height, weight, waist and hip circumferences b) Blood pressure and pulse systolic and diastolic blood pressure and pulse rate; c) Lung function: lung peak flow rate d) Walking speed; e) Grip strength f) Chair stands and g) Cognitive function by Mini-Mental State Examination (MMSE). Among blood based biomarkers, measures of inflammation, apolipoproteins, hemoglobin, and immune function have important prognostic values.

The inflammatory response is the body's integrated yet diverse reaction and defense against homeostatic disturbances, particularly infection and injury. However, chronic inflammation may nonetheless be harmful and can lead to atherosclerosis.<sup>6,7</sup> Peripheral blood markers of inflammation, such as CRP, have been identified as independent prognostic indicators for increased incidence of cardiovascular events and mortality, and functional impairment in older adults.<sup>8,9</sup>

Apolipoproteins are the protein components of low-density lipoprotein (LDL) and HDL cholesterol. The major apolipoprotein of LDL is apolipoprotein B100 (Apo B), while apolipoprotein A-I (Apo A-I) has been frequently used to estimate the HDL levels.<sup>10</sup> Although high LDL and low HDL cholesterol are classic cardiovascular risk factors, the available data from the recent, large, well-conducted, prospective epidemiologic studies support the conclusion that Apo B and Apo A-1 are better markers for the risk of atherosclerosis and cardiovascular events than LDL and HDL cholesterol, respectively.<sup>11</sup>

Anemia, decreased Hb concentration in the blood, has been shown to independently predict mortality, morbidity, and various measures of functional status, including lower muscle strength, mobility difficulty, difficulties with basic and instrumental activities of daily living, and worsening cognitive functioning.<sup>12,13</sup>

Primary EBV infection occurs during the first few months to years of life in developing countries. Adequate cell-mediated immune function is critical for maintaining the virus in a latent state over the lifetime of an individual. Therefore, impaired cell-mediated immune function would allow EBV to reactivate and release viral antigens into blood circulation, leading to EBV antibody production. Previous studies in developing countries have demonstrated a linkage between a

higher degree of psychosocial stress and lower levels of cell-mediated immune function, measured by increased EBV antibody levels.<sup>14</sup>

The benefit of using more than one biomarker to better predict health outcomes has been well demonstrated in health research.<sup>15</sup> For example, allostatic load has been proposed as a cumulative measure of dysregulation across multiple physiological systems, and has been postulated to impact health risks. In the allostatic load model, increased risk is hypothesized to result not only from large and clinically significant dysregulation in individual systems, but also from more modest dysregulation present in multiple systems. These biomarkers along with other measures (blood pressure, body mass index (BMI), waist-to-hip ratio (WHR), lung peak flow rate, HbA1c allow us to better characterize health status by assessing the cardiovascular (blood pressure, apolipoproteins), respiratory (lung peak flow), metabolic (BMI, WHR, HbA1c, apolipoproteins), inflammatory (CRP), immune (EBV antibody), and hematological (Hb) systems simultaneously.

The collection of biomarkers in a population study can add a significant cost to the project with a need to plan logistics. Dried blood spot (DBS) specimens, blood spots on filter paper made from capillary blood collected from a finger prick, have greatly simplified the process of collection of blood sample in non-clinical studies. The use of filter paper for the collection and analysis of human blood dates back to the early 1960s, when DBS specimens were used to measure phenylalanine in newborns for the detection of phenylketonuria.<sup>16</sup> For bioassays, the collection of capillary blood on filter paper has several advantages over venous puncture that make it ideal for field-based research. Finger-prick blood sampling eliminates the need for a trained phlebotomist to collect and process blood samples. Sample collection is relatively painless and noninvasive, with minimal inconvenience and burden imposed on participants. Samples collected do not have to be centrifuged, separated, or immediately frozen. Because the filter papers can be stacked and packaged in air-tight containers and kept at ambient temperatures without significant deterioration for a number of days, transportation to a centralized location for freezer storage is comparatively uncomplicated. In general, any analyte that can be measured from whole blood, serum, or plasma can in principle be measured from DBS specimens for epidemiological studies.<sup>17</sup> The Newborn Screening Quality Assurance Program at the Centers for Disease Control and Prevention in the United States has been providing external quality

assurance for the filter paper blood collection device, for newborn-screening laboratories and for epidemiological research using DBS specimens.

Some of the major datasets that have collected biomarker data include Coronary Artery Risk Development in Young Adults (CARDIA); Cardiovascular Health Study (CHS); The Atherosclerosis Risk in Communities Study (ARIC); Social Environment and Biomarkers of Aging Study (SEBAS) in Taiwan; English Longitudinal Study of Ageing (ELSA); MacArthur Study of Successful Aging; Dynamics of Health, Aging and Body Composition (HEALTH ABC); Hispanic Epidemiologic Studies of the Elderly (Hispanic EPESE) 1993-2004; The Swedish Adoption/Twin Study of Aging (SATSA); Individual differences among the oldest-old (OCTO-Twin); National Health and Nutrition Examination (NHANES III, IV) Whitehall Study; and WHO Study of Ageing and Adult Health (SAGE) .

There are several ethical issues related to research involving human subjects and the collection of biological specimens regarding confidentiality and disclosure of results, treatment arrangements, long-term storage and future use of specimens.

Although biomarker research faces many biological and technical obstacles, the discovery of valid biomarkers could have significant social impact. The ability to measure biological age could be an important clinical tool in assessing risk for medical procedures, or the likelihood of developing an early onset of age-related diseases. The results of biomarkers of aging could also be of great interest to insurance companies and employers for setting premiums and retirement age, respectively. Second, the discovery of biomarkers could accelerate the development of anti-aging interventions in humans. Despite some scientific pessimism, biomarker research should remain a fundamental part of gerontology in order to better study aging and hopefully improve the health of an aging population.

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