Integrating Biology into the Study of Health Disparities

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Socioeconomic status, ethnicity, and other salient social and demographic characteristics contribute to differences in health outcomes with age through multiple biological pathways. Investigators at the USC/UCLA Center on Biodemography and Population Health seek to clarify the multiple proximate biological mechanisms through which health differentials arise in mortality, cardiovascular disease, cancer, and physical and cognitive functioning. Founded in 1999, the center has developed multidisciplinary research teams and projects, incorporating biological, epidemiologic, and medical researchers along with more traditional demographic, behavioral, and psychosocial researchers to promote integrative research. Clarification of the effect of various biological risk factors on health outcomes as well as better understanding of their relationships to demographic, behavioral, psychological, and medical factors will provide more complete explanations of the sources of differentials in the health of populations and may improve our ability to develop effective interventions to reduce these differentials.

Population health disparities

A vast body of evidence documents that people who are poorer and who have less education are more likely to suffer from diseases, to experience loss of physical functioning, to be cognitively and physically impaired, and to experience high mortality rates (Adler et al. 1993; Hayward et al. 2000; Smith 1999; Williams 1990). Lower educational attainment has been linked to higher mortality from most causes (Rogers, Hummer, and Nam 2000; Steenland, Henley, and Thun 2002). Some chronic causes of mortality and morbidity are particularly associated with low education level; these include diabetes, hypertension, and heart disease. Disability, loss of functioning, and
cognitive impairment are also higher among those with lower levels of socioeconomic status (Crimmins, Hayward, and Seeman 2004; Jones and Gallo 2002; Seeman et al. 1994b; Albert et al. 1995).

The large health differentials by race and ethnicity in the United States are at least partially the result of differences in socioeconomic status. Blacks have significantly higher prevalence and incidence of many of the major chronic diseases, including hypertension, diabetes, and stroke, as well as greater levels of loss of functioning and disability (Hayward et al. 2000; Smith and Kington 1997). Hispanics are less clearly disadvantaged; most estimates of Hispanic life expectancy indicate that it is either similar to or longer than that of non-Hispanic whites and higher than that of black Americans (Hayward and Heron 1999; Rogers et al. 1996). Hispanics also appear to have lower mortality from cancer, cardiovascular disease, and chronic lung conditions (Markides et al. 1997; Sorlie et al. 1993). There are, however, some conditions from which Hispanics are more likely to die; the statistically most important is diabetes (Sorlie et al. 1993). Because the Hispanic population comprises a high proportion of immigrants, selectivity complicates the interpretation of these differentials (Crimmins et al. 2004; Palloni and Morenoff 2001).

Understanding health differentials

During the past four years, the Center on Biodemography and Population Health has contributed to clarifying the relative burden of mortality, disease, and disability among population groups, using demographic approaches to summarizing the life cycle effects of health differences. Center researchers have used the concepts of “years of life lost” and “healthy life expectancy” to clarify the relative life cycle effects of population health differentials. “Years of life lost” indicates how many years are not lived relative to the longest-lived group; “healthy life expectancy” divides years of life lived into healthy and unhealthy. Such methods can be linked to population composition to summarize effects of health differentials in actual populations; or they can eliminate population composition effects through the use of life table populations to compare the forces of mortality and morbidity across population subgroups (Robine et al. 2003; Crimmins and Cambois 2003). Multistate approaches to active life expectancy can be used to clarify the implications of changes in mortality and morbidity for population health (Crimmins, Hayward, and Saito 1994).

Crimmins and colleagues have estimated differences in healthy life expectancy for blacks and whites (Crimmins and Saito 2001; Crimmins, Hayward, and Saito 1996; Molla et al. 2003). Black Americans can expect to live more years than whites with a disabling health problem that has begun at an earlier age, and the differentials in healthy life are greater than differ-
entials in total life. Within both racial groups, differences in healthy life expectancy by education are large, and over time individuals with the highest levels of education among both blacks and whites have experienced the greatest increase in healthy life (Crimmins and Saito 2001). Coupling the years-of-life-lost approach with the years-of-healthy-life approach, we have documented that the most marked differentials manifest themselves in the far lower likelihood that black men with low education will reach old age (Crimmins and Saito 2001).

Using years of life lost, Wong and colleagues (2002) measured the impact of specific causes of death on differences in mortality by socioeconomic status and race. Before age 75, relatively few diseases account for most of the mortality disparities: cardiovascular disease accounts for about a third of both the educational and the black/white differences; lung cancer is another important contributor to the disparities by education.

We have also used the healthy-life-expectancy approach to estimate the length of time men and women spend living with specific diseases and impairments (Crimmins, Kim, and Hagedorn 2002). For instance, an average woman lives more years with heart disease than an average man even though men have higher incidence of and mortality from heart disease (Crimmins et al. submitted). This approach has also shown that on average women live longer with cognitive impairment than men because of lower female mortality (Suthers, Kim, and Crimmins 2003).

Much of the evidence that we have used in evaluating health differences points to an earlier onset of health problems among individuals with lower socioeconomic status and among blacks. This is analogous to an earlier “aging” of disadvantaged people. In an attempt to clarify this facet of population health differences, we have used data from the Health and Retirement Survey to estimate “equivalent ages,” or ages at which education subgroups of the population experience the same rates of prevalence or incidence of age-related health problems (Crimmins, Hayward, and Seeman 2004). Logistic and hazard equations relating age and education to prevalence and onset are the basis for estimates of age-specific rates of disease prevalence and onset for those with 8, 12, and 16 years of education (Figure 1). The base rate is that of the lowest education group at age 51 years, and equivalent ages are those at which individuals with 12 and 16 years of education experience the same rates. For those with 16 years of education, equivalent ages for onset and prevalence of disease are reached 5 to 15 years later than among those with less education.

Our use of demographic approaches to health differentials has clarified the importance of integrating life cycle effects into the study of health differences. While we focus on socioeconomic and race/ethnic differences, it is clear that age is an additional consideration in examining disparities across groups. Differentials tend to be greater before old age, and some dif-
FIGURE 1 Estimated equivalent ages of disease prevalence and onset for three educational groups: Health and Retirement Survey, persons aged 51 to 61 years at baseline


...differentials disappear (Crimmins, Hayward, and Seeman 2004). And while socioeconomic status and race are related to most health outcomes, differentials are larger for some outcomes than others. At older ages differentials in disability and loss of functioning are greater than differentials in the presence of major mortal diseases. All of these results point to a complex interaction of age-specific mortality and morbidity rates in producing health differentials in populations.

Seeman has pioneered research on the social and psychological pathways that are hypothesized to act as partial mediators of socioeconomic effects on health and mortality. She has documented the links between social and psychological factors and cardiovascular disease (Seeman and Syme 1987; Seeman 1991), as well as the links between such factors and patterns of cognitive and physical decline (Seeman et al. 1993, 1995, 1996, 1999, 2001; Unger et al. 1999) and mortality (Seeman et al. 1987, 1993). Most recently, she has elucidated the biological pathways through which social and psychological factors affect health and longevity, documenting links between social integration, support, and social conflict, and biological parameters known to affect health, including neuroendocrine function (Seeman...
Moving to a more integrative model

Integrative, multidimensional models linking social status and race/ethnicity to health outcomes through social, psychological, behavioral, and biological causal mechanisms have increasingly become a focus of research among demographers and health researchers. Center researchers have been in the forefront of efforts to integrate demographic and health approaches (Crimmins and Seeman 2001; Seeman and Crimmins 2001). Figure 2 provides a heuristic model of the multiple (and possibly interacting) pathways that are a focus of research sponsored by the USC/UCLA center. While the model appears static, this research recognizes that levels of biological risk and chronic health conditions grow out of social, psychological, economic, and medical conditions over the entire life cycle and are at the root of differences in healthy life and years of life lost (Link and Phelan 1995; Adler et al. 1993; Garber 1989).

While these mechanisms combine over the life cycle and contribute to differences in health in myriad ways, all the mechanisms must eventually work through biological factors to affect the "premature aging" or earlier

**FIGURE 2** Heuristic biopsychosocial model of health outcomes

- **Demographic factors**
  - Age
  - Sex
  - Ethnicity
  - Race
  - Nativity

- **Health behaviors**
  - Exercise
  - Drinking
  - Diet
  - Smoking

- **Social psychological**
  - Social support
  - Marital status
  - Depression

- **Health care**
  - Access to care
  - Insurance coverage
  - Use of medication

- **Socioeconomic status**
  - Education
  - Income
  - Wealth
  - Occupation

- **Biological risk**
  - Cardiovascular factors
  - Metabolic factors
  - Inflammation markers
  - Stress hormones
  - Vitamin/antioxidant status

- **Health outcomes**
  - Mortality (by cause)
  - Physical functioning
  - Cognitive functioning
  - Cardiovascular disease
onset of disease and disability among disadvantaged people. Indeed, many of these biological risk factors are at play decades before disease is clinically evident, and their early identification and treatment would be a promising approach to reducing mortality and morbidity at older ages. The cumulative lifetime levels of adversity and disadvantage experienced by persons of lower status are likely to result in higher levels of physiological deterioration at younger ages (Finch and Seeman 1999).

Understanding biological pathways

The USC/UCLA Biodemography Center has undertaken a number of projects to enhance our understanding of the biological processes through which population health differentials are generated. A particular approach has been to demonstrate the biological pathways through which traditional demographic variables (e.g., socioeconomic status, race/ethnicity, age, sex) affect health outcomes such as disease, disability, and mortality. The pathways we have considered include those that progress through multiple physiological systems including the cardiovascular, metabolic, endocrine, immune and inflammation, and sympathetic nervous systems. Genetic factors have also been a more recent focus of research.

Evidence links individual biological risk factors to education, other measures of socioeconomic status, race and ethnicity, and health outcomes. Biological variables frequently found in models explaining education/socioeconomic status, and race/ethnic differences in health in the United States include indicators of cardiovascular and metabolic processes such as blood pressure, lipid profiles, and relative weight (Winkleby at al. 1998, 1999; Kaplan and Keil 1993). More recently, markers of inflammation and coagulation processes have been recognized as potentially important predictors of vascular conditions (Finch et al. 2001; Wilson, Finch, and Cohen 2002). Inflammatory markers have been related to cardiovascular diseases and also have been shown to be distributed negatively by socioeconomic status, with lower educational status being associated with higher levels of such markers of inflammation (Danesh et al. 1998, 1999, 2000; Ishizaki et al. 2000; Wamala et al. 1999).

One focus of center researchers has been on the question of whether biological factors previously shown to be associated with health risks in general populations remain significant risk factors among older adults and how the importance of risk factors changes with age. Findings indicate that while some biological factors continue to be associated with increased health risks in older adults, others do not. For example, higher burdens of inflammation continue to be associated with increased risks for cognitive declines (Weaver et al. 2002) as well as with mortality in older adults (Hu et al. 2004). Higher homocysteine levels (generally the result of low dietary folate
intake) are associated with significantly increased risks for both physical and cognitive decline (Kado et al. 2002; Kado et al., in press). Elevations in other “stress” hormones (e.g., cortisol, epinephrine) are associated with increased risks for cognitive decline (Seeman et al. 1997a; Karlamangla et al., in press a) as well as risks for onset of new depression among older persons (Karlamangla, Chodosh, Seeman, in preparation). A recently completed project has provided intriguing evidence that lower reported happiness may be linked to increased risk for fracture in older adults through an association with higher cortisol exposures (Karlamangla, Singer, Greendale, Seeman, in preparation).

While the foregoing research has largely provided evidence of the continued impact of biological factors on risks for mortality and functional decline at older ages, center researchers have also recently documented potentially important age-related declines in the salience of several risk factors. Analyses have shown that, at older ages, not only is higher cholesterol not a risk factor for mortality but higher cholesterol levels are associated with less risk of mortality and lower risk for cognitive decline (Karlamangla et al. 2004). While surprising in light of the considerable evidence linking higher total cholesterol to increased risks for cardiovascular disease, these findings are consistent with a growing body of evidence indicating that total cholesterol is not associated with increased mortality among older adults (Anderson, Catelli, and Levy 1987; Corti et al. 1997; Volpato et al. 2001).

Center research has also examined the changing relationship with age between behavioral risk factors and mortality. The link between smoking and mortality is reduced in old age (Crimmins 2001), and the lack of a relationship between obesity and mortality in old age has been demonstrated in both the United States and Japan (Crimmins 2001). Research on variability of risk with age is providing a basis for developing life cycle models of health outcomes for which age-specific risk relationships are a crucial input. One aim of the research is to understand how risk varies over the life cycle and results in changes with age in the distribution of risk or heterogeneity of the population.

**Cumulative biological risk**

Center faculty have pioneered efforts to develop more comprehensive, cumulative models of biological risk and its impact on health and functioning over the life course. The search for summary scores that incorporate multiple biological risk factors is motivated by the observation that many individuals are exposed to several risk factors and small increases in multiple risk factors can lead to a substantial increase in overall risk, even if no single factor exceeds its clinically accepted threshold. Research on the metabolic syndrome (also known as Syndrome X, Insulin resistance syndrome, and cardiovascular
risk factor cluster), for example, has demonstrated the significantly increased risks for cardiovascular disease and mortality associated with the presence of a constellation of risk factors, including hyperinsulinemia, trunkal obesity, dyslipidemia, and hypertension (Trevisan et al. 1998; Lindblad et al. 2001; Lakka et al. 2002). Similarly, research from the Framingham Study has shown that a composite score created from multiple cardiovascular risk factors strongly predicts risk of coronary heart disease in the Framingham cohort as well as other population-based cohorts (Wilson et al. 1998; ATP III 2001).

The concept of allostatic load has been proposed as a more comprehensive, multisystem view of the cumulative physiological toll that may be exacted on the body through attempts to adapt to life’s demands (McEwen and Stellar 1993; McEwen 1998). Allostatic load is a measure of the cumulative impact of adaptive physiological responses that chronically exceed optimal operating ranges, resulting in wear and tear on the body’s regulatory systems. Such a multisystem approach may be useful in conceptualizing biological mediation of the effects of education/socioeconomic status and race/ethnicity on health and longevity.

The idea that allostatic load is a cumulative phenomenon derives from evidence in both animal and human studies that profiles of physiological dysregulation are frequently cumulative, with evidence of a narrowing of systems’ ranges of response and an overall reduction in the capacity to adapt with increasing age (Seeman and Robbins 1994; Young et al. 1980; Rowe and Troen 1980; Shock 1977; Lipsitz and Goldberger 1992). The cumulative burden of physiological wear and tear is, at least partially, a product of the individual’s interaction with the environment throughout life, with older individuals having more cumulative dysregulation but with substantial variability within any one age group.

A multisystem approach to biological risk similar to “allostatic load” provides a more comprehensive framework for conceptualizing the concurrent biological pathways through which education, other indicators of socioeconomic status, stressors, health behaviors, and other factors may affect health outcomes over the life course. Biological risk measurements also have the potential to provide some of the earliest evidence of pathophysiological processes that ultimately progress to clinical disease. A multisystem view of biological foundations of health risks seems well suited to investigating influences of broad sets of factors that are associated with differences in socioeconomic status. These biological systems are the pathways through which the individual’s interaction with his/her environment is translated into physiologically adaptive (or nonadaptive) responses.

The multisystem approach attempts to incorporate information about the multiplicity of potentially additive and/or synergistic biological processes that operate continually as we interact with our environment. A multisystem approach to investigation of biological “health risk” profiles seeks to
move us beyond traditional approaches that have identified individual "risk factors." The approach explicitly considers the simultaneous and potentially cumulative impacts of physiological effects from multiple regulatory systems—consistent with growing evidence of counter-regulatory links between various major physiological systems, with changes in one leading to alterations in the patterns of activity in others.

Initial efforts to test empirically the concept of allostatic load were undertaken by an interdisciplinary team, including Teresa Seeman, Bruce McEwen, Burton Singer, Ralph Horwitz, and Jack Rowe (Seeman et al. 1997a). The initial conceptualization of allostatic load was based on available data from the MacArthur Study of Successful Aging and included ten biological parameters: systolic blood pressure, diastolic blood pressure, waist-to-hip ratio, ratio of total/HDL cholesterol, HDL cholesterol, glycosylated hemoglobin, cortisol, norepinephrine, epinephrine, and DHEA-S. These represent physiological activity across the cardiovascular system, the metabolic system, the hypothalamic–pituitary axis, and the sympathetic nervous system. In subsequent analyses, additional indicators have included renal functioning, lung capacity, markers of inflammation and coagulation, and these have added to the explanatory power of the measure (Seeman et al. 2004).

The initial conceptualization of allostatic load in the MacArthur Study was based on a simple count of the number of markers (from a set of ten) for which the subject scored in the upper 25 percent of the distribution, a summary measure that has been shown to predict mortality as well as risk for decline in physical and cognitive functioning among a sample of initially healthy older persons (Seeman et al. 1997b; Seeman et al. 2001). Subsequent analyses have explored several alternative techniques whereby individual indicators can contribute differentially and through their entire range of values to risks for outcomes of interest (e.g., through use of factor analyses, canonical correlation, and recursive partitioning techniques; Seeman et al. 2004; Karlamangla et al. 2002; Singer, Ryff, and Seeman 2004). Use of these more refined approaches has clarified that the optimal weighting of the individual components of biological risk differs depending on the outcome of interest and suggests that levels of risk follow a continuous pattern (e.g., risks accrue not only from clear deviations from "normal/optimal" levels of functioning, but from more modest deviations as well)—providing support for the use of the full continuum of values for the various biological indicators. Despite the apparent gains in predictive ability with more complex operational definitions of biological risk, comparisons of the simple count index with the more refined measures do not indicate major differences in their ability to predict health outcomes, and the simple summed measure has the advantage of being easily defined and interpreted across populations.

While current conceptualizations of allostatic load include most of the components of the Framingham risk score and the metabolic syndrome
(i.e., traditional cardiovascular risk factors such as blood pressure, cholesterol, relative weight, and glucose dysregulation), analyses of the relative contributions to health risks of these traditional risk factors for cardiovascular disease versus the additional factors (e.g., stress hormones) have indicated that both sets of factors make significant independent contributions, so that the more inclusive allostatic load measure is a better predictor of health outcomes (Seeman et al. 2001; Seeman et al. 2004; Karlamangla et al. 2002).

Most recently, center researchers in collaboration with others have begun to examine differences in allostatic load by socioeconomic status. Analyses based on the MacArthur Successful Aging Study have demonstrated that a summary index of cumulative allostatic load is related to education, with lower education being associated with greater allostatic load (Seeman et al. 2004). These analyses also demonstrate that differential allostatic load mediates approximately 35 percent of the education-related differences in mortality among the study group of persons 70 to 79 years of age at the beginning of observation. Levels of social integration (known to be negatively related to mortality; Seeman 1996) are significantly and negatively associated with allostatic load in older men, with parallel though nonsignificant patterns seen among older women (Seeman et al. 2002). Similar findings have been reported for middle-aged adults (Singer and Ryff 1999).

Biological risk pathways at younger ages are being investigated, with particular attention to the trajectories of biological risk development at younger ages. Analyses of trajectories of developing cardiovascular risk based on data from the Coronary Artery Risk Development in Young Adults Study (CARDIA) have shown that socioeconomic status differences in risk profiles are evident in young adulthood (e.g., beginning when subjects were aged 18–30) and that these socioeconomic status–associated differences tend to become more accentuated over time. Those at highest risk initially show the steepest trajectories of increasing risk over the next ten years (Karlamangla et al., in press b). These associations hold true for childhood socioeconomic status as measured by parental educational attainment and participant’s own educational attainment. In each case, socioeconomic status was found to be negatively associated with a summary index of cardiovascular risk in whites. Although the trends were similar for blacks, the “gains” from college education in terms of lower cardiovascular disease risk scores were smaller and did not achieve statistical significance in men (Karlamangla et al., in press b).

Additional work based on the National Health and Nutrition Examination Survey (NHANES) is investigating socioeconomic status and ethnic differences in age-related patterns of cumulative biological dysregulation in a nationally representative sample of persons aged 20 years and older. Our initial analysis indicates that differences in biological risk by race/ethnicity
and socioeconomic status will provide significant explanations for the mechanisms producing observed health differences. Defining biological risk using clinical guidelines where available and definition of risk as used in the MacArthur data where not available, we examined the average number of risk indicators out of 13 markers by education and race/ethnicity for persons from ages 20 to 90 years (Wong and Crimmins 2002). Average age-specific numbers of biological risk markers by education level are shown in Figure 3a. Similar to results reported above for the CARDIA sample, educational differentials in biological risk appear as early as age 20 years; however, they are particularly marked in the age range 35 to 65 years. Those with more than 12 years of education have markedly lower biological risk up until the older ages; at ages over 70, biological risk appears to level off, perhaps because death removes those with high levels of biological risk from the population (Crimmins et al. 2003).

The National Health and Examination Study III data collected by the US National Center for Health Statistics also provides the opportunity to examine differences in biological risk among large samples of blacks and Hispanics (primarily of Mexican origin) (Wong and Crimmins 2002). While blacks and Hispanics have similar levels of biological risk, they have higher average age-specific levels of biological risk than non-Hispanic whites up until the older ages (Figure 3b). Evidence of the earlier aging of these minority groups is demonstrated: levels of biological risk for Hispanics and blacks at age 45 are characteristic of whites at age 55. Race/ethnic differentials are also greatest in the 35 to 65 age range. At the older ages, the three groups have similar levels of biological risk, again perhaps linked to the selection by mortality for low biological risk at older ages.

Genetic markers

Center research has begun to include genetic factors along with other biological risk markers. In the MacArthur sample, the presence of APOE4 alleles has been linked to cognitive decline (Bretsky et al. 2003; Ewbank, this volume). Most recently, research has examined possible gene–environment interactions. To date, this research has focused on possible interactions between the APOE genotype and potentially "protective" factors such as education or serum antioxidant levels in relation to risks for cognitive decline. Our general hypothesis has been that such protective factors might be more important in protecting against risks for decline among those with the e4 allele (i.e., the group at higher risk based on genotype). For education, we found no evidence for an interaction with APOE genotype (i.e., those with and without the e4 allele show parallel education differences in risks for cognitive decline) (Seeman et al., in press). By contrast, antioxidant levels appear to contribute significantly to reduction of risk for cognitive decline for those with
FIGURE 3  Mean number of biological risk factors by education and ethnicity

a. by education

Risk factors

<12 years
12 years
>12 years

Age (years)

b. by ethnicity

Risk factors

Black
Hispanic
White

Age (years)

the e4 allele, while differences in antioxidant levels do not affect risks for those without the e4 allele (Hu et al., submitted). Additional analyses are examining possible synergistic relationships between presence of the e4 allele and comorbidities associated with increased risk for cognitive decline (e.g., diabetes, hypertension, cardiovascular disease).

The center has also recently funded an innovative project to examine possible relationships between socioeconomic status and other indexes of psychosocial disadvantage and evidence of DNA damage (e.g., shorter telomere length, greater mitochondrial damage). Future work will include additional genetic markers and their relationships to more traditional biological risk factors as well as demographic and social characteristics.

Summary and future directions

During its first four years of funding, the USC/UCLA Center on Biodemography and Population Health has integrated biological and medical results with demographic measures of population health. Evidence has been amassed linking factors central to demographic models of population health (e.g., socioeconomic status, ethnicity, sex) to various health outcomes; specific attention has been given to evidence for mediating pathways through biological, behavioral, and psychosocial factors (Crimmins, Hayward, and Seeman 2004; Crimmins and Seeman 2001; Seeman and Crimmins 2001). Empirical work has examined the effect of socioeconomic status and race/ethnic differentials on years of healthy life and years of life lost to various major causes of death (Wong et al. 2002; Crimmins and Saito 2001). A series of papers have identified biological processes likely to mediate socioeconomic status differences in a variety of health outcomes (e.g., Seeman et al. 2004; Hu et al. 2004; Karlamangla et al., in press b). Multiple interactive processes account for observed variation in health, including processes relating to socioeconomic status and genotype, as well as biological systems. Integrative research, incorporating attention to biological, epidemiologic, and medical data, along with more traditional demographic, behavioral, and psychosocial factors, is necessary to understanding and projecting demographic trends and to designing interventions to reduce undesirable differences in population health.

Plans for coming years at the center focus on three major areas of interest: 1) better and more comprehensive assessment of biological factors as well as development of better operational measures of cumulative biological risks; 2) additional attention to the role of genetic factors, and in particular to possible gene–environment interactions in relation to health risks; and 3) expansion of modeling approaches that reflect lifecourse influences affecting population health as well as continued attention to the overarching (and possibly interactive) effects of socioeconomic status and race/ethnicity.
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