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Cumulative biological risk and socio-economic differences in mortality: MacArthur Studies of Successful Aging

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Abstract

Previous research has suggested that socio-economic status (SES) differences in mortality are only partially explained by differences in life-style, psychological and social factors. Seven year mortality data (1988–1995) from the MacArthur Study of Successful Aging, a longitudinal study of adults, aged 70–79, from New Haven, CT; East Boston, MA; and Durham, NC; were used to test the hypothesis that a cumulative measure of biological dysregulation (“allostatic load”), reflecting multiple regulatory systems, would serve as a further mediator of SES differences in mortality. Logistic regression analyses revealed that a cumulative index of biological risk explained 35.4% of the difference in mortality risk between those with higher versus lower SES (as measured by less than high school education versus high school or greater educational attainment). Importantly, the cumulative index provided independent explanatory power, over and above a measure of doctor-diagnosed disease, though the latter also contributed to education-related variation in mortality risks. The summary measure of biological risk also accounted for more variance than individual biological parameters, suggesting the potential value of a multi-systems view of biological pathways through which SES ultimately affects morbidity and mortality.

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Introduction

An individual's socio-economic status (SES) represents one of the most enduring of all risk factors. Extensive evidence documents not only the higher morbidity and mortality associated with lower SES (Adler et al., 1994; Pincus & Callahan, 1995; Macintyre, 1997) but also the persistence of these SES gradients into older age (House, Kessler, & Herzog, 1990; Crimmins, Hayward, & Saito, 1996; Rogers, 1992). Indeed, recent

evidence suggests that SES-related mortality differentials at older ages are growing (Manton, Stallard, & Corder, 1997; Crimmins & Saito, 2001; Preston & Elo, 1995).

Though a variety of possible explanations for these social inequalities in health have been offered, differential exposure to chronic and acute stressors are hypothesized to contribute importantly. Evidence for SES-related differentials in exposure to stressors, particularly chronic ones, is abundant, with lower SES individuals consistently reporting more of various types of stressors—e.g., physical, economic and/or social (Dohrenwend, 1973; Kessler & Cleary, 1980; House et al., 1992; Turner, Wheaton, & Lloyd, 1995). More

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recently, there has been growing interest in elucidating the biological pathways that mediate between such SES-related exposures and increased disease/mortality (Marmot, Bobak, & Davey Smith, 1995; Seeman & Crimmins, 2001).

Gradients in biological risk factors by SES, with higher risk profiles being seen more commonly at lower levels of SES, have been shown for a number of traditional cardiovascular risk factors such as blood pressure (BP), cholesterol, relative weight, glucose and fibrinogen in many though not all studies (Bobak, Hertzman, Skodova, & Marmot, 1999; Brunner et al., 1997; Ishizaki, Martikainen, Nakagawa, & Marmot, 2000; Dyer et al., 1999; Marmot, et al., 1998; Feldman, Makuc, Kleinman, & Cornoni-Huntley, 1989; Karlamangla et al., submitted; Rose & Marmot, 1981; Bartley, Fitzpatrick, Firth, & Marmot, 2000; Kristenson, Kucinskiene, Bergdahl, & Orth-Gomer, 2001; Rosengren, Orth-Gomer, & Wilhelmsen, 1998). However, these gradients in cardiovascular risk factors appear to explain only a portion of SES differentials in mortality (Marmot et al., 1991; Marmot, Shipley, & Rose, 1984; Lynch, Kaplan, Cohen, Tuomilehto, & Salonen, 1996; Luoto, Pekkanen, Uutela, & Tuomilehto, 1994). Prior research, however, has generally focused on traditional cardiovascular risk factors and has largely examined the role of individual biological parameters and/or sets of these cardiovascular risk factors.

The potential value of considering biological mediation of the SES-health relationships from a broader multi-systems viewpoint is suggested by several facets of the SES-health relationship. First, SES gradients are observed with respect to a wide range of different pathophysiological disease processes and with respect to most major causes of death (Adler et al., 1994). Second, most of these outcomes are known to have multifactorial etiologies, encompassing multiple sources of biological dysregulation.

The concept of allostatic load has been proposed as a multi-systems view of the cumulative physiological toll that may be exacted on the body through attempts at adaptation to life's demands (McEwen & Stellar, 1993; McEwen, 1998). As such, allostatic load may represent a useful approach to conceptualizing biological mediation of SES effects on health and longevity. The concept of allostatic load originates from the idea that healthy functioning requires on-going adjustments of the internal physiologic milieu, with physiologic systems exhibiting fluctuating levels of activity as they respond and adapt to environmental demands—a concept referred to as allostasis (Sterling & Eyer, 1988). Importantly, allostasis emphasizes that while healthy functioning requires on-going fluctuation in physiological systems, these fluctuations should remain within optimal operating ranges of the physiologic systems. The concept of *allostatic load* is proposed as a measure of the

cumulative impact of adaptive physiological responses that chronically exceed optimal operating ranges, resulting ultimately in wear and tear on the body's regulatory systems such that they are no longer able to maintain parameters within normal operating ranges. Allostatic load is reflected in the cumulative total of physiological dysregulations across multiple physiologic regulatory systems, a total that is postulated to impact significantly 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 over time (Seeman & Robbins, 1994; Young, Rowe, Pallotta, Sparrow, & Landsberg, 1980; Rowe & Troen, 1980; Shock 1977; Lipsitz & Goldberger, 1992). The cumulative burden of such physiological wear and tear is, at least partially, a product of person-environment interaction throughout life, with older individuals generally having more cumulative dysregulation. Within an age group, however, there will be a range of allostatic loads that reflect differences in life experiences and physiological reactions to them. One of the important social conditions contributing to these differences in life experience is SES.

Using available data from the MacArthur Study of Successful Aging, we have previously reported on an initial operational measure of allostatic load which reflects information regarding levels of physiologic activity across the hypothalamic-pituitary-adrenal axis (HPA), the sympathetic nervous system (SNS), cardiovascular systems, and metabolic processes—each of which has been linked to increased risks for pathology (Seeman & Robbins, 1994; Seeman, Singer, Rowe, Horowitz, & McEwan, 1997; Matthews et al., 1986; Munck & Guyre, 1991; Bjorntorp, 1987; Despres et al., 1990; Abboud, 1982). This summary index of allostatic load predicted mortality as well as risks for incident CVD and declines in physical and cognitive functioning over 2.5 and 7-year follow-ups (Seeman, Singer, Rowe, Horowitz, & McEwan, 2001). Here, we examine the extent to which a cumulative index of biological dysregulation can explain observed SES differences in mortality risk in a cohort of older adults.

Materials and methods

Data for these analyses come from the MacArthur Successful Aging Study, a longitudinal study of relatively high functioning men and women, aged 70–79. As described in greater detail elsewhere (Berkman et al., 1993), subjects were sub-sampled on the basis of age and both physical and cognitive functioning from three

community-based cohorts in Durham, NC, East Boston, MA, and New Haven, CT that were part of the Established Populations for Epidemiological Studies of the Elderly (EPESE). Because the goal of this study was to investigate the role of lifestyle and other psychosocial factors in more successful aging, age was restricted to 70–79 years so as to reduce the impact of age per se on subsequent outcomes. Age-eligible men and women ($N = 4030$) were then screened on the basis of four criteria of physical functioning and two criteria of cognitive functioning to identify those functioning in the top third of the age group. The goal was to identify an initial group of relatively high functioning older adults who could be followed longitudinally to identify factors associated with more vs. less successful trajectories of aging (as defined by maintenance of better health and functioning and lower mortality).

Of the 4030 age-eligible men and women, a cohort of 1313 subjects met all screening criteria; 1189 (90.6%) agreed to participate and provided informed consent. Baseline data collection was completed between May 1988 and December 1989 and included a 90 min, face-to-face interview covering detailed assessments of physical and cognitive performance, health status and other behavioral and psychosocial characteristics. Subjects were also asked to provide blood samples and 12 h, overnight urines; 80.3% agreed to provide blood samples and 85.8% consented to provide urine samples.

All-cause mortality

Mortality follow-up was available for the cohort through 1995 by which time 273 (23%) of the original sample had died. Deaths among cohort members were identified through contact with next of kin at the time of each of two successive follow-ups for the cohort (1991, 1995), on-going local monitoring of obituary notices and National Death Index searches. Attrition for other reasons was minimal: only 43 (4.7%) of the original group were not known to be dead but were unable to be contacted as of 1995.

Socio-economic status

Years of education completed was used as the primary measure of SES. Though information on annual household income was also available, this information was felt to be a weaker indicator of SES for this older cohort due to lack of data on non-income related wealth (e.g. homeownership and investments) which has been shown to be a larger fraction of household economic resources at older ages (Kohn & Schooler, 1983; Smith, 1999). Indeed, analyses using available income data revealed parallel but weaker, non-significant effects to those reported below for education. Analyses of an index combining information regarding both education

(<HS; HS+) and household income (<\$10,000; \$10,000+) also indicated that differences in education (but not income) were associated with mortality differentials (data available on request from first author). Therefore, analyses reported here focus on educational attainment data only. Educational attainment was examined in terms of two categorical classifications reflecting major educational thresholds generally associated with differential economic opportunities. One categorization indicated those who completed grades 0–8 (no high school [HS]), 9–11 (some HS), 12 (completed HS), and 13+ (at least some college education). The second classification dichotomized the cohort into those who completed HS or more versus those with less than HS education.

Allostatic load

As described in previous work (Seeman et al., 1997), our operationalization of the concept of allostatic load was designed to summarize levels of physiological activity across a range of regulatory systems pertinent to disease risks. Parameters included in previous analyses were: systolic and diastolic BP; waist–hip ratio (an index of chronic levels of metabolism and adipose tissue deposition, thought to be influenced by increased glucocorticoid activity) (Bjorntorp, 1987); ratio of total to HDL serum cholesterol; blood plasma levels of glycosylated hemoglobin (Hb_{A1c} ; an integrated measure of glucose metabolism over the previous 30–90 days; Dunn et al., 1979); serum dihydroepiandrosterone sulfate (DHEA-S; a functional HPA axis antagonist) (Svec & Lopez, 1989); 12-h urinary cortisol excretion (an integrated measure of 12-h HPA axis activity); 12-h urinary norepinephrine (NE) and epinephrine (EPI) excretion levels (integrated indices of 12-h SNS activity).

For the current analyses, new data were available on several additional parameters, providing a more comprehensive assessment of cumulative biological dysregulation. These include several markers of inflammation including fibrinogen, interleukin-6 (IL-6), C-reactive protein (CRP) and low albumin (Ridker, Stampfer, & Rifai, 2001; Koukkunen et al., 2001). Two markers of important organ system (dys)function were also included: creatinine clearance (a marker of renal function) and peak flow (a measure of lung function).

Resting, seated systolic and diastolic BP were measured based on the average of the second and third of three readings, following the Hypertension and Detection Follow-up Program protocol (HDFP, 1978). Waist/hip ratio was calculated based on waist circumference (at narrowest point between the ribs and iliac crest) and hip circumference (at the maximal buttocks) (Lohman, Roche, & Martorell, 1988). Blood samples for assays of HDL cholesterol, total cholesterol, Hb_{A1c} , fibrinogen, IL-6, CRP and DHEA-S were obtained by

phlebotomists who visited subjects' homes the morning after their home interview. Although subjects were not required to be fasted, most blood samples were taken early in the morning before subjects had eaten. HDL was measured by direct homogeneous method (Genzyme Diagnostics, Cambridge, MA), total cholesterol by colorimetric, enzymatic methods (Siedel, Hagele, Ziegenhorn, & Wahlefeld, 1983) and serum levels of albumin were measured by automated Sequential Multiple Analyzer. Hb_{A1c} was assayed by affinity chromatography methods (Little, England, Wiedmeyer, & Goldstein, 1983) and DHEA-S by a one-site chemiluminescence immunometric assay on the Nichols Advantage. Fibrinogen was measured by automated clot-rate assay (Geffken et al., 1994;) based on the original method of Clauss (Clauss, 1957) using the ST4 instrument (Diagnostica Stago). IL-6 and CRP were measured by ELISA (High Sensitivity Quantikine Kit, R&D Systems, Minneapolis, MN).

Subjects also completed a 12-h urine collection from 8 p.m. on the evening after the interview to 8am the next morning. The over-night collection protocol served to minimize the potential confounding effects of physical activity as subjects generally spent this time at home (and much of that time in bed). Individual differences in overnight excretion of cortisol (CORT) as well as NE and EPI can therefore be seen as a measure of differences in "basal" operating levels of the HPA axis and SNS (i.e., non-stimulated levels of activity). Assays for NE, EPI, and CORT were performed by Nichols Institute; determinations were made by high pressure liquid chromatography (Canalis, Reardon, & Caldarella, 1982; Krstulovic, 1982). Results for each of the three measures is reported as "micrograms (NE, EPI, or CORT) per gram creatinine" in order to adjust for body size.

An index of overall biological dysregulation (allostatic load) was created by summing the number of these parameters for which the individual had a value in the highest risk quartile—i.e., top quartile for all parameters except HDL cholesterol, albumin, DHEA-S and peak lung function, for which membership in the lowest quartile corresponds to highest risk (see Table 1). In scoring individuals, the question arises as to how to score those taking medications that might influence levels of one or another of the biological parameters (e.g., anti-hypertensives, cholesterol lowering drugs or drugs for diabetes). Because the theoretical underpinnings of the allostatic load concept focus on the negative impact of actual physiological dysregulation, we elected to code subjects in terms of the actual physiological values observed for the various components of allostatic load. Those on medications that actually succeed, for example, in lowering BP or cholesterol are thus coded in terms of the lower levels of BP, or cholesterol, with the idea that lowered levels of these parameters are associated with less "wear and tear" on regulatory systems (i.e., lower allostatic load). For each of the 16 parameters, quartile criteria were defined based on the distribution of scores in the cohort. Membership in the upper/lower quartile represents a quantitative way of classifying those exposed to more extreme levels of system activity relative to the rest of the population and thus potentially at greater risk of disease pathology. Other methods of summarizing the data, including averaging *z*-scores and use of other criterion cut-points (including sex-specific criterion cutpoints) were also examined in earlier analyses and yielded comparable results (Seeman et al., 1997).

The potential value of summarizing information on dysregulations across these various markers is suggested by the fact that only modest correlations are seen among

Table 1
Criterion cut-points for individual biological components of allostatic load index in the MacArthur Study of Successful Aging, 1988

Biological parameters	Criterion cut-point	Mean (SD)
High diastolic BP (mmHg)	83.30	76.70 (10.49)
High systolic BP (mmHg)	148.00	137.76 (19.21)
High glycosylated hemoglobin (Hb _{A1c}) (%)	7.10	6.81 (1.88)
Low HDL cholesterol (mg/dl)	37.00	47.89 (15.20)
High total/HDL cholesterol ratio	5.92	5.03 (1.80)
High waist-hip ratio	0.94	0.88 (0.08)
High urinary cortisol (CORT) (µg/g creatinine)	25.69	21.70 (16.60)
High urinary norepinephrine (NE) (µg/g creatinine)	48.00	40.44 (21.89)
High urinary epinephrine (EPI) (µg/g creatinine)	4.99	4.00 (2.30)
Low albumin (mg/dl)	3.90	4.11 (0.29)
High IL-6 (pg/ml)	4.64	4.56 (5.53)
High C-reactive protein (CRP) (µg/ml)	3.19	3.23 (5.32)
Low best peak (l/min)	300.00	383.14 (117.68)
Low DHEA-S (mg/dl)	35.00	69.27 (48.74)
High fibrinogen (mg/dl)	336.00	91.97 (85.89)
Low creatinine clearance (ml/min)	44.64	62.79 (27.97)

our indices of dysregulation (less than 0.35 in all cases except for systolic and diastolic BP [$r = 0.58$]). Three separate sub-scales were also created, reflecting the subset of “cardiovascular risk factors” (i.e., BP and cholesterol measures, Hb_{A1c}, and waist–hip ratio), inflammatory markers (i.e., IL-6, CRP, albumin and fibrinogen) and stress hormones (i.e., urinary cortisol, NE, EPI and DHEA-S). Both the global index as well as these sub-scales were examined in analyses assessing mediation of educational differences in mortality.

For comparability with previous analyses, in addition to the analyses based on the 16 item index of allostatic load outlined above, we also ran parallel analyses using our original index of allostatic load based on only 10 of the 16 components. Because these latter analyses yielded comparable, though somewhat weaker, findings in all cases, results are reported only in footnotes (details are available on request from first author).

Covariates

Multivariable analyses included consideration of other demographic factors known to be associated with both SES and mortality—age, sex, and race. Age (in years) was measured as of the baseline interview. Race was coded Black versus other. Other known SES-related risk factors for mortality such as health behaviors were not included in the analyses because they represent potential mediators of education/SES differences in allostatic load. A measure of baseline “doctor-diagnosed” morbidity (i.e., number of reported chronic conditions) was examined in a series of secondary analyses designed to evaluate the extent to which our index of allostatic load was simply an alternative measure of morbidity versus contributing independent information regarding biological pathways through which education impacts on mortality risks. The index of baseline morbidity was based respondents reports as to whether a doctor had ever told them that they had a myocardial infarction, stroke, diabetes, hypertension, cancer, broken hip or other bones.

Analyses

Logistic regression (rather than proportional hazards) models were used to test for associations between education and mortality as specific date of death information was not available. The extent to which allostatic load mediates educational differences in mortality was estimated in terms of the percent reduction in the odds ratio (OR) for education comparing models with and without the proposed mediator (i.e., % reduction = $[(OR_{wo/mediators} - OR_{w/mediator}) / (OR_{wo/mediators} - 1)] \times 100$) (Szklo & Nieto, 2000). Because results of analyses with the newer 16 item index of allostatic load yielded comparable (though somewhat

stronger) results to those based on the original 10 item index, we present detailed results for the more comprehensive 16 item index, commenting in the text on results for the original 10 item index. Complete data on all 16 biological parameters and covariates were available for 657 of the original 1189 cohort members. Those excluded from the analyses were largely excluded on the basis of incomplete biological data (generally due to refusal to provide blood and/or urine samples); only 7 individuals were excluded due to other missing data. As shown in Table 2, those with complete data (i.e., those included in the analyses) did not differ from those excluded from the analyses in terms of their overall mortality, age, ethnicity, or reported number of chronic conditions. Those included in the analyses were more likely to be male; they also reported slightly higher household income and more education in terms of “average number of years completed”, though they did not differ in the percentages who did and did not complete high school or more (the measure of education used the final analyses). For the current analyses, 108 individuals included in earlier analyses of allostatic load could not be included due to missing data for newer biological components considered here; comparisons of those included in the current analyses ($N = 657$) with those examined in earlier analyses of allostatic load ($N = 765$) reveal no differences (data available on request from first author).

The possibility of non-linear risk relationships for allostatic load was examined by including a series of dummy variables reflecting increasing levels of allostatic load. Those with scores of zero or one served as the reference group (other risk categories = 2, 3, 4, 5, 6, and 7+). SAS version 8.00 was used for all analyses (SAS Institute, 1999).

Results

Descriptive statistics for the 657 cohort members included in the analyses are presented in column 2 (“Complete Data”) of Table 2. The sample was approximately 50% male, 18% non-White, and showed considerable socio-economic diversity. Educational attainment varied from less than 8th grade (15.8%), to high school (HS) (25.6%), and some college or more (21.8%). Participants reported slightly more than one chronic condition on average; the most commonly reported conditions were hypertension (45%), history of cancer (20%) and CVD (12%). Over the 7.5 year follow-up, there were 141 deaths (21.5%).

The relationship of educational attainment to mortality was examined initially in terms of four major categories (<8th grade, some HS, completed HS, went beyond HS). As shown in Fig. 1, the two groups who completed less than HS experienced similar and greater

Table 2

Descriptive statistics for allostatic load, socio-demographic, health status and health behaviors in MacArthur Successful Aging cohort in 1988

Variables	Included in analyses Complete data (<i>n</i> = 657) Mean(std.dev) or <i>N</i> (%)	Excluded from analyses Missing data (<i>n</i> = 532) Mean(std.dev) or <i>N</i> (%)	<i>p</i> -value for group difference
Mortality (% dead by 1995)	141 (21.5%)	132 (24.8%)	0.17
Allostatic load (mean)	3.9 (2.1)		
Education (years)	10.9 (3.3)	10.4 (3.3)	0.04
0–8	104 (15.8%)	99 (18.6%)	
9–11	242 (36.8%)	192 (36.2%)	
12 (completed high school)	168 (25.6%)	149 (28.1%)	
13+	143 (21.8%)	91 (17.1%)	0.15
% < HS	52.7	54.8	0.46
Income (annual household)	\$16,739.9 (\$12,791.1)	\$13,639.3 (\$11,475.6)	<0.0001
Covariates			
Age in 1988 (yrs)	74.2 (2.7)	74.3 (2.7)	0.35
Gender (%female)	50.4	61.7	0.0001
Ethnicity (% non-white)	17.8	20.2	0.31
Chronic conditions (#0–5)	1.2 (1.0)	1.2 (0.9)	0.79

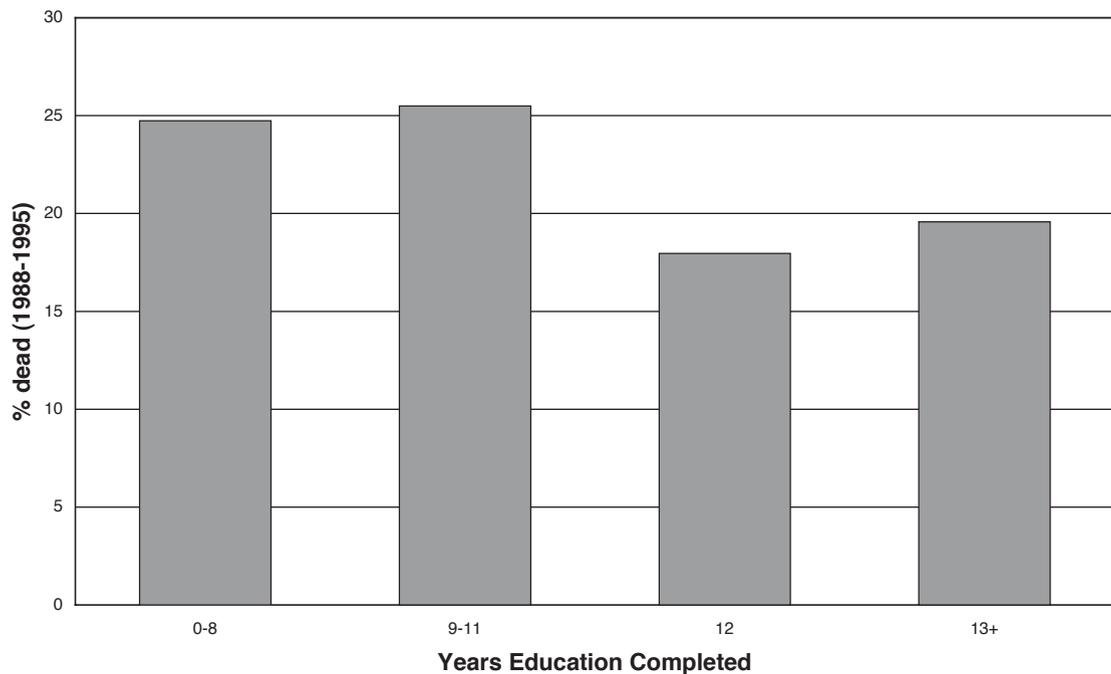


Fig. 1. Association between education and 7.5 year mortality (1988–1995) in the MacArthur Successful Aging Study.

mortality to that seen for the groups who completed HS or more. Those who completed less than HS experienced 25% mortality as compared with 18% mortality for those who completed HS or more ($\chi^2 = 4.18$, $p = 0.04$). This dichotomous designation for education (<HS

versus HS or more) was used in subsequent analyses to evaluate the potential mediating influence of allostatic load.

For allostatic load to serve as a mediator, it must be related both to education and mortality. Examination of

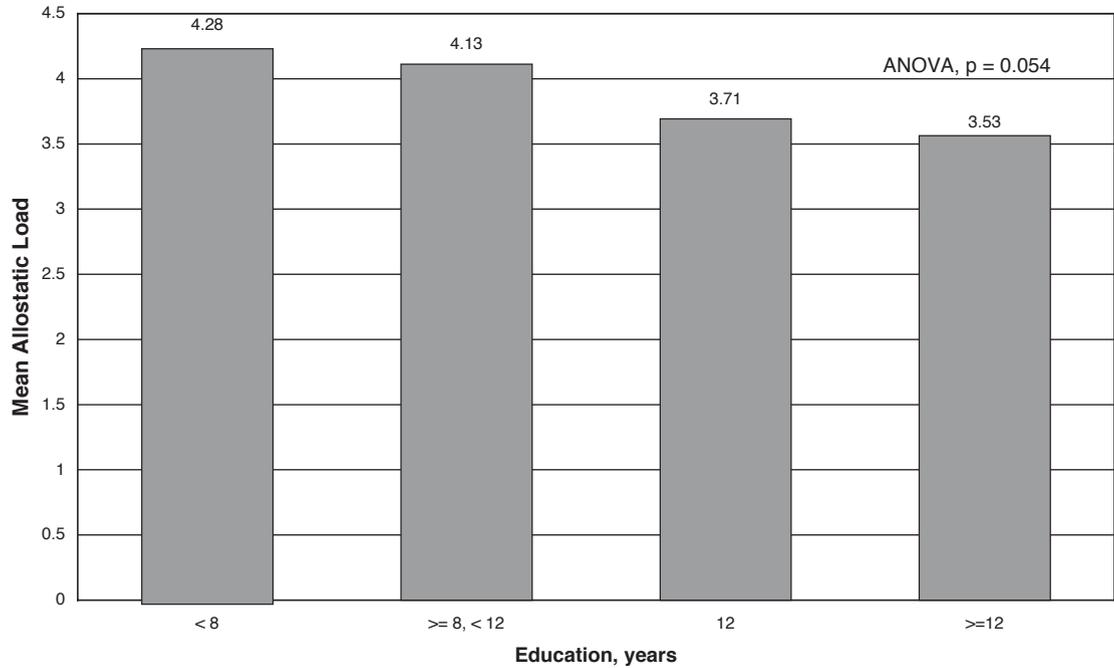


Fig. 2. Association between baseline (1988) allostatic load and educational attainment in the MacArthur Successful Aging Study.

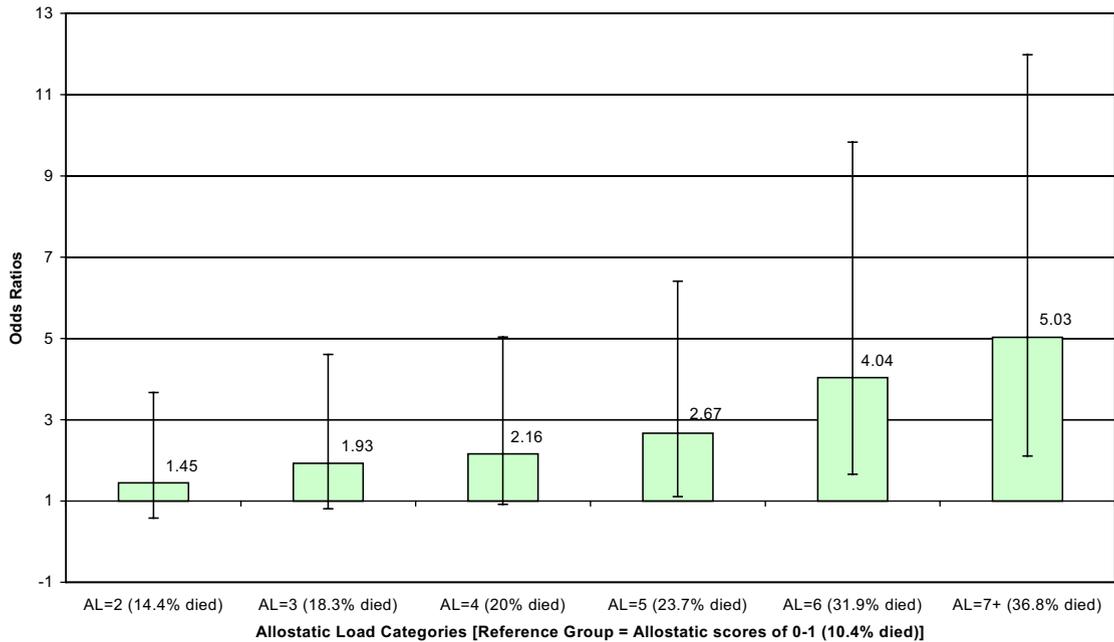


Fig. 3. Association between baseline (1988) allostatic load and 7.5 year mortality (1988–1995) in the MacArthur Successful Aging Study.

the relationship between educational attainment and allostatic load revealed that, as hypothesized, those with higher educational attainment exhibited lower allostatic loads at baseline (see Fig. 2). Higher

allostatic load scores were also associated with a gradient of increasing 7.5-year mortality. Fig. 3 illustrates the trend, showing increasing OR's for mortality with increasing levels of allostatic load; actual death

Table 3

Hierarchical logistic regression models testing role of allostatic load as a mediator of educational differences in 7.5-year mortality risks (1988–1995) in MacArthur Successful Aging Study ($N = 657$)

Variables	Model 0 ^a		Model 1 ^b		Model 2 ^c		Model 3 ^d		Model 4 ^e	
	OR	95% CI								
Education (HS or more vs. <HS; 0/1)	1.48	1.02, 2.17	1.48	1.00, 2.19	1.31	0.88, 1.97	1.43	0.96, 2.13	1.29	0.86, 1.94
Allostatic load										
2					1.50	0.58, 3.87			1.29	0.50, 3.36
3					1.75	0.72, 4.27			1.65	0.68, 4.04
4					2.11	0.88, 5.04			1.91	0.80, 4.59
5					2.67	1.09, 6.53			2.47	1.00, 6.09
6					3.83	1.54, 9.56			3.36	1.34, 8.46
7+					4.99	2.04, 12.2			4.45	1.81, 10.95
<i>P</i> for trend					< 0.0001					
Other demographics										
Age in 1988 (yrs)			1.06	0.99, 1.14	1.05	0.98, 1.13	1.06	0.99, 1.13	1.05	0.98, 1.13
Gender (1 = male; 2 = female)			0.38	0.26, 0.56	0.37	0.24, 0.55	0.37	0.24, 0.55	0.35	0.24, 0.53
Ethnicity (0 = White; 1 = Black)			1.18	0.72, 1.93	1.24	0.75, 2.06	1.21	0.74, 2.00	1.27	0.76, 2.11
Baseline morbidity										
Chronic conditions (#)							1.36	1.12, 1.66	1.32	1.08, 1.62

^a Model 0: Unadjusted effect of education.

^b Model 1: Adjusting for other demographics (i.e., age, gender, ethnicity).

^c Model 2: Adding allostatic load to model 1.

^d Model 3: Baseline morbidity as alternative to allostatic load.

^e Model 4: Adding allostatic load to Model 3—assessing its contribution to mediating education differentials, independent of baseline morbidity.

rates are reported along the horizontal axis (see Fig. 3; p for trend < 0.0001).¹

In order to test the role of allostatic load as a mediator of the observed education-related differences in mortality, a series of hierarchical logistic regression models were examined (see Table 3). Models using the linear allostatic load scores and those using the dummy-coded indicator variables for the increasing levels of allostatic load revealed comparable results in terms of estimated mediation of educational differences in mortality. Results for the dummy coded indicators of levels of allostatic load are presented in Table 3 as these provide more detailed information about relationships between increasing allostatic load and mortality risk. As shown in Model 0 in Table 3, comparison of those who completed less than HS vs. those completing HS or more revealed that the less educated group experienced 48% greater mortality (OR = 1.48, 95% confidence interval [CI]: 1.02, 2.17). Adjustments for other standard socio-demographic characteristics (age, gender and ethnicity) did not alter this association (see Model 1, Table 3).

¹ Parallel analyses based on the original 10-item index of allostatic load reveal these same patterns of association (e.g., p for trend = 0.0004 for mortality).

When baseline allostatic load was added to this latter model, the independent effect of education is reduced by 35.4% and was now non-significant (OR = 1.31; 95% CI: 0.88, 1.97; see Model 2 vs. Model 1 in Table 3). As also shown in Model 2, increasing levels of baseline allostatic load continued to be significantly associated with increased mortality risk, independent of education and other demographic characteristics (p -trend < 0.0001).²

A secondary set of analyses considered the question of whether our measure of allostatic load serves simply as an alternative measure of morbidity or whether it contributes independent information regarding biological pathways through which education impacts on mortality risks.

As shown in Model 3 (Table 3), baseline morbidity was found to mediate only 10.4% of the education differential (as compared with the 35.4% reduction in education differentials seen with adjustments for our measure of allostatic load). Indeed, addition of allostatic

² Again, parallel analyses based on the original 10-item index of allostatic load yielded comparable, though somewhat weaker, results with a 20.8% reduction in the education effect and a p -trend for allostatic load of 0.005).

Table 4

Logistic models assessing effects of individual biological component of allostatic load on 7.5 year mortality risks and their contribution to mediating education-related differences in mortality in MacArthur Successful Aging Study cohort ($N = 657$)

	Biological risk factors		Education	
	OR	95% CI	OR	% Chg from base model
Base model = education (adjusted for age, gender, ethnicity)			1.48	
<i>Individual biological factors^a</i>				
Cardiovascular risk index	1.16	1.01–1.35	1.42	–12.5%
High diastolic BP	1.40	0.92–2.12	1.47	–2.1%
High Systolic BP	1.37	0.90–2.08	1.46	–4.2%
High glycosylated hemoglobin	1.34	0.87–2.05	1.45	–6.2%
Low HDL cholesterol	1.31	0.86–1.99	1.46	–4.2%
High total/HDL cholesterol ratio	0.87	0.56–1.36	1.49	+2.1%
High waist–hip ratio	1.27	0.82–1.98	1.47	–2.1%
Stress hormone index	1.27	1.04–1.54	1.46	–4.2%
High urinary free cortisol	1.14	0.73–1.77	1.48	0.0%
Low DHEA-S	1.39	0.89–2.17	1.48	0.0%
High Urinary norepinephrine (NE)	1.49	0.96–2.30	1.47	–2.1%
High urinary epinephrine (EPI)	1.38	0.89–2.16	1.45	–6.2%
Inflammation index	1.18	0.99–1.41	1.43	–10.4%
Low albumin	0.86	0.55–1.36	1.47	–2.1%
High Il-6	1.41	0.92–2.16	1.43	–10.4%
High C-reactive protein	1.67	1.10–2.55	1.41	–14.6%
High fibrinogen	1.28	0.83–1.99	1.46	–4.2%
Low best peak	2.68	1.69–4.26	1.36	–25.0%
Low creatinine clearance	2.22	1.33–3.71	1.50	+4.2%

^aModels = education, age, gender, ethnicity + individual biological factor (or sub-scale).

load to the model including baseline morbidity resulted in a further 32.6% reduction in the education differential in mortality and allostatic load itself continued to have a significant impact on mortality, independent of baseline morbidity (see Model 4, Table 3).

In a final set of analyses, we examined the relative, individual contributions of each of the 16 biological components of our allostatic load index to mediation of education-related differences in mortality risks. We also examined the impact of the three major sub-scales reflecting cardiovascular risk factors, markers of inflammation and stress hormones (see Table 4). Analyses reported in Table 4 show the impact of each individual biological measure on mortality where each is considered separately in a model that also includes education, age, gender and ethnicity (i.e., comparable to Model 2 in Table 3). The final column in Table 4 also indicates the extent to which that individual biological measure mediates the effect of education on mortality. Three of the individual parameters (high CRP, low peak flow and low creatinine clearance) and two of the sub-scales (cardiovascular risk factors, stress hormones) were significantly related to mortality. With the exception of

low peak flow, which mediated 25% of the education effect, none of the individual components nor any of the sub-scales mediated more than 15% of the education effect on mortality. Because peak flow alone appeared to mediate a considerable portion of the education effect on mortality, we examined an alternative index of allostatic load which did not include peak flow to ascertain whether the earlier analyses of allostatic load largely reflected the influence of peak flow. Even without peak flow, this alternative index of allostatic load was found to mediate some 27% of the education effect on mortality. In sum, the largest percent mediation of education effects (35.4%) is explained by the most comprehensive measure of biological dysregulations—i.e., the summary measure of allostatic load.

Discussion

The analyses reported here show that socio-economic status, as measured by educational attainment, continues to be a significant predictor of differential

mortality risks in a cohort of older men and women. That this is seen for the MacArthur Successful Aging cohort, which was initially selected to represent the top tertile of those aged 70–79 in terms of physical and cognitive functioning, suggests that SES effects on mortality are not confined to those who have substantial burdens of disease or disability.

Most importantly, the observed SES-related differences in mortality risk were shown to be partially explained/mediated by baseline biological risk profiles as measured by our summary index of allostatic load. Approximately one-third (35.4%) of the education effect on mortality was mediated by our summary measure of biological risk. Notably, this effect was also shown to be largely independent of baseline morbidity (as measured by doctor-diagnosed conditions).

Our findings suggest that a cumulative measure of biological dysregulation can provide additional information on sources of SES-related differentials in mortality risk. A portion of the increased mortality seen for those with lower SES appears to derive from their greater cumulative burden of physiological dysregulation—dysregulation that is not completely reflected in their known burdens of diagnosed disease. This latter finding clearly points to the need for further efforts to elucidate the sources of such SES-related dysregulations. Given the likely cumulative nature of the observed biological dysregulations, a life history perspective may offer important insights into SES-related differentials in life experiences that result in differential accumulation of biological wear and tear.

The dysregulations captured by our measure of allostatic load were generally not of such magnitude as to be considered clinically significant nor were they (with a few exceptions) individually associated with significant, independent effects on mortality. Only high CRP, and low lung and renal function, were individually associated with increased mortality. Indeed the findings reported here suggest that for a relatively high functioning group of older adults, dysregulations in specific individual parameters generally do not confer significantly increased mortality risk. Nor do these individual parameters serve to mediate much of the observed education-related differences in mortality. By contrast, the cumulative total of these physiological dysregulations (as reflected in the summary measure of allostatic load) was associated with significant differences in mortality and explained a considerably larger proportion of the education-related differential in mortality. These findings suggest that a summary measure of biological risk may provide important explanatory information regarding differential mortality risks among older adults, information that is not provided either by individual biological parameters or by other more traditional measures of health status based on “doctor-diagnosed” disease.

Several limitations to the data reported here should be acknowledged. First, the cohort was selected initially to represent those in the top third of the age group (70–79) with respect to physical and cognitive functioning. Thus, the generalizeability of our findings to the broader population of older adults remains to be demonstrated. One might postulate that effects seen here may underestimate the potential role of cumulative biological risk profiles as our selection criteria resulted in a “healthier” cohort with a somewhat restricted distribution of biological risk profiles (Seeman et al., 1997). In the broader population of older adults, greater variability in biological risk profiles might lead to greater potential explanatory power with respect to SES differences in mortality.

Another potential limitation is our reliance on a single, relatively crude, assessment of SES—educational attainment. The MacArthur Study did not include adequate assessment of financial resources to permit a more thorough investigation of how economic aspects of SES might relate to biological risk profiles and mortality. Future analyses will need to evaluate possible differential effects of dimensions of SES on mortality and differential mediation of these effects through biological risk profiles. Finally, our measure of cumulative biological risk was constrained by our reliance on secondary data that were not originally collected with the goal of assessing cumulative biological risk profiles. To the extent that our measure of allostatic load does not include assessment of other biological parameters that may contribute to overall health risks (e.g., insulin resistance, immune function, parasympathetic activity), our measure of allostatic load may underestimate the extent to which overall, cumulative biological risk profiles mediate SES differences in mortality.

Despite these potential limitations, our findings suggest the potential value of taking a more comprehensive view of biological mediation of SES differences in mortality. Though past epidemiological research has clearly shown the value of understanding the role of individual biological parameters with respect to SES-related differences in health and longevity, the findings presented here highlight the potential value of taking a broader, more comprehensive view of biological risk profiles as represented by the concept of allostatic load. Indeed, a more comprehensive view of biological pathways may be particularly important when seeking to understand the mechanisms through which a fundamental, but multi-faceted, factor such as SES impacts on health and longevity. Because differences in SES are associated with a multitude of differential physical, behavioral, social and psychological exposures and experiences, which in turn impact a range of physiological regulatory systems, it is likely that the biological “signatures” for these different life experiences and exposures will be reflected in multiple (rather than

single) physiological systems. Thus, an approach that takes a more comprehensive, multi-systems view of biological functioning—as contrasted with our historical bent toward focusing on the individual effects of specific biological parameters—may be more useful and appropriate as we seek to understand the multiple and cumulative pathways through which differences in SES result in disparities in health and longevity. Such a multi-system view of biological risk may also contribute to more effective efforts to reduce or prevent health risks across the life cycle by pointing to the need to consider (and target) multiple contributing biological systems rather than targeting individual risk factors.

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