THEORY AND METHODS

Do biomarkers of stress mediate the relation between socioeconomic status and health?

Jennifer Beam Dowd, Noreen Goldman

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See end of article for authors' affiliations

Correspondence to: Dr J B Dowd, Center for Social Epidemiology and Population Health, University of Michigan,1214 South University Avenue, 2nd Floor, Ann Arbor, MI 48104–2548, USA; jennbeamdowd@yahoo.com

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Objectives: To test the relation between socioeconomic status (SES) and biomarkers of chronic stress, including basal cortisol, and to test whether these biomarkers account for the relation between SES and health outcomes.
Design: Cross sectional study using data from the 2000 social and environmental biomarkers of aging study (SEBAS).
Setting: Taiwan.
Participants: Nationally representative sample of 972 men and women aged 54 and older.
Main outcome measures: Highest risk quartiles for 13 biomarkers representing functioning of the neuroendocrine system, immune/inflammatory systems, and the cardiovascular system: cortisol, adrenaline (epinephrine), noradrenaline (norepinephrine), serum dihydroepiandrosterone sulphate (DHEA-S), insulin-like growth factor 1 (IGF1), interleukin 6 (IL6), albumin, systolic blood pressure, diastolic blood pressure, waist-hip ratio, total cholesterol-HDL ratio, HDL cholesterol, and glycosylated haemoglobin; self reported health status (1–5) and self reported mobility difficulties (0–6).
Results: Lower SES men have greater odds of falling into the highest risk quartile for only 2 of 13 biomarkers, and show a lower risk for 3 of the 13 biomarkers, with no association between SES and cortisol. Lower SES women have a higher risk for many of the cardiovascular risk factors, but a lower risk for increased basal readings of adrenaline, noradrenaline, and cortisol. Inclusion of all 13 biological markers does not explain the relation between SES and health outcomes in the sample.
Conclusions: These data do not support the hypothesis that chronic stress, via sustained activation of stress related autonomic and neuroendocrine responses, is an important mediator in the relation between SES and health outcomes. Most notably, lower SES is not associated with higher basal levels of cortisol in either men or women. These results place an increased burden of proof on researchers who assert that psychosocial stress is an important pathway linking SES and health.

Much attention has been paid to the relation between socioeconomic status (SES) and health, but the mechanisms linking the social and the physical are not well understood. With the seeming inadequacy of either differences in medical care or health related behaviours to explain the gradient, psychosocial stress has emerged as a leading contender for translating low social status into poor health.[1–3] It is postulated that lower status people are more likely to experience both chronic and acute stressors in their lives, and numerous studies have provided empirical support for the idea that lower SES is associated with more reported life stress.[4–6] Studies of non-human primates have shown that lower status animals often show raised basal cortisol levels, lower levels of HDL cholesterol, more signs of coronary heart disease, and more susceptibility to infection.[7–10] Proponents of the idea that stress mediates the SES-health relation suggest that the physical pathways through which low status harms health operate in much the same way in humans as they do in other primates. It is postulated that the experience of low social status elicits sustained activation of stress related autonomic and neuroendocrine responses, with chronically increased levels of cortisol the most commonly mentioned mechanism through which low status damages health.[11–13]

While substantial work has linked lower SES to several cardiovascular risk factors such as blood pressure, waist to hip ratio, cholesterol, and fibrinogen,[14] much less work has related neuroendocrine markers of stress to SES in humans, and the results have been mixed. An analysis of 200 Whitehall participants found that resting blood pressure, heart rate, and salivary cortisol did not differ by employment grade, while average cortisol over the workday was significantly higher for lower grade men but significantly lower for lower grade women.[15] A study of 767 adults in Germany found positive associations between morning salivary cortisol concentrations and levels of education and occupational status,[16] while a study of 150 men from Lithuania and Sweden found that low social class was related to high early morning levels of salivary cortisol.[17] In a sample of 217 Canadian children, children of low SES were found to have significantly higher morning salivary cortisol levels than children with high SES.[18] These mixed results could be attributable to the small and specially selected samples, as well as the fact that there is high intraindividual variation in cortisol measured throughout the day, resulting from variation in activity and exposure to stimuli. The variability across studies may also represent actual variations across populations, which have been found for other biomarkers. For example, Martikainen *et al* found higher employment grade associated with lower BMI and higher HDL cholesterol among English men, whereas they found the opposite relation for Japanese men.[19]

Exposure to stressors can have both immediate and long term effects on physiology. In this paper, we focus on the longer term, rather than acute, consequences of stressful

Abbreviations: SES, socioeconomic status; DHEA-S, dihydroepiandrosterone sulphate; IGF1, insulin-like growth factor 1; IL6, interleukin 6; AL, allostatic load; SNS, sympathetic nervous system; HPA, hypothalamic pituitary-adrenal; SEBAS, social and environmental biomarkers of aging study

Table 1 Cut off points and summary measures for highest risk quartile of individual biomarkers in 2000 SEBAS

Biomarker	Cut off point	Mean (SD)
Neuroendocrine markers		
Cortisol (μg/g creatinine)	⩾30.0	28.63 (53.05)
Adrenaline (μg/g creatinine)	⩾3.7	2.65 (2.64)
Noradrenaline (μg/g creatinine)	⩾27.1	21.83 (9.88)
DHEA-S (μg/dl)	⩽40.8	81.17 (59.14)
Immune/inflammatory markers		
IGF1 (ng/ml)	⩽69.5	105.14 (48.3)
IL6 (pg/ml)	⩾1.41	1.84 (8.30)
Albumin (mg/dl)	⩽4.4	4.48 (0.29)
Cardiovascular risk factors		
Systolic blood pressure (mm Hg)	⩾150	138.45 (20.68)
Diastolic blood pressure (mm Hg)	⩾90	82.14 (11.08)
Ratio of total cholesterol to HDL	⩾5.1	4.37 (1.44)
HDL cholesterol (mg/dl)	⩽38	49.10 (13.71)
Glycosylated haemoglobin (%)	⩾5.8	5.75 (1.34)
Waist-hip ratio	⩾0.93	0.88 (0.07)

For IL6 and adrenaline, a large number (about 33% and 20%, respectively) of readings fell below assay sensitvity, but our analysis looks at the top quartile for each of those measures.

experiences. The cumulative effects of chronic stress form the foundation of the framework of allostatic load (AL), which describes how a person's biological response to chronic stressors can, over time, result in dysregulation of multiple interrelated physiological systems. This dysregulation is reflected by a change in the set-point of physiological markers, such that basal levels of the markers fall outside the optimal range, and, if they remain there for prolonged periods, ultimately lead to deteriorations in health.[20–22] Findings suggest that higher AL is associated with lower levels of education in the MacArthur studies of successful aging, and that this association accounts for roughly a third of the relation between education and mortality in that sample. Importantly however, this relation seems to be driven primarily by the cardiovascular risk components and inflammatory markers comprising AL rather than the neuroendocrine markers.[23 24]

Most of the above studies have come from small or specially selected samples that may not be representative of the population at large, and all have been from Western populations. This paper will test the relation between SES and a broad set of markers that have been proposed to reflect the physiological effects of stress in a representative sample of middle aged and elderly persons in Taiwan. We then examine whether these biomarkers can explain part or all of the observed relation between SES and health outcomes. The biomarkers include measures of sympathetic nervous system (SNS) and hypothalamic pituitary–adrenal (HPA) axis functioning, immune/inflammatory markers, and cardiovascular disease risk factors. In contrast with most previous studies relating SES to daytime salivary cortisol, we use a 12 hour overnight urinary measure of cortisol, capturing a time when most people are at rest.

METHODS

Study population

Data for this study come from the 2000 social environment and biomarkers of aging study (SEBAS), made up of a random subsample of the participants in the ongoing survey of health and living status of the near elderly and elderly in Taiwan. This longitudinal survey began in 1989 with a nationally representative sample, including the institutionalised population, of persons 60 years and older. The survey was expanded in 1996 to include a new sample of middle aged (aged 50 to 66) persons. In SEBAS, elderly respondents (71 and older in 2000) were over sampled relative to the near elderly (54 to 70 in 2000), as were persons in urban areas. The survey procedures were approved by the institutional review boards at Princeton University, Georgetown University, and the Bureau of Health Promotion, Department of Health, Taiwan, and conformed to the principles embodied in the Declaration of Helsinki. Among the 1713 respondents randomly selected, a total of 1497, constituting 92% of the survivors, were interviewed. Of this group, 1023 completed the physical examination portion of the survey that included physician evaluation and collection of blood and urine samples. Excluding respondents with missing data on one or more variables of interest leaves a final sample of 972. Older respondents were less likely to participate in the examination portion of the survey, but measures of SES were not significantly related to participation. Because of higher non-participation rates among both the healthiest and the least healthy people, persons who received the medical examination reported the same general health status, on average, as those who did not.[25] Each participant in the medical examination was asked to fast overnight, collect a 12 hour overnight urine sample (for integrated measures of neuroendocrine function), and proceed to the medical examination the next morning at a nearby hospital where a physician or nurse obtained blood from the participant and took blood pressure and other measurements.

Measures

Our biomarkers include the 10 measures used in the first empirical implementation of AL: serum dihydroepiandrosterone sulphate (DHEA-S, a functional HPA axis antagonist); urinary cortisol (an integrated measure of 12 hour HPA axis activity); urinary adrenaline (epinephrine) and noradrenaline (norepinephrine) (integrated measures of 12 hour SNS activity); systolic and diastolic blood pressures (indices of cardiovascular activity); waist-hip ratio (an index of metabolism and adipose tissue deposition); serum HDL cholesterol and the ratio of total to HDL serum cholesterol (indices of risk for cardiovascular disease); and blood plasma levels of glycosylated haemoglobin (HbA1c, an integrated measure of glucose metabolism over the previous 30–90 days). Recent work has expanded the empirical measure of AL to include information on inflammatory markers and immune function.[22] We include three additional markers meant to capture dysregulation in immune/inflammatory function: interleukin 6 (IL 6, a proinflammatory cytokine), insulin-like growth factor 1 (IGF1, aids in muscle growth and bone repair), and albumin (low levels associated with inflammation). Measures of cortisol, adrenaline, and noradrenaline were

Table 2 Odds ratios based on logistic models of the probability of falling into the highest risk quartile of each neuroendocrine and immune/inflammatory marker, by education, income, and sex (95% CI)

	Cortisol	Noradrenaline	Adrenaline	DHEA-S	IGF1	IL6	Albumin
Men							
SES variables							
No formal education	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Primary education	1.1 (0.61 to 1.98)	0.74 (0.41 to 1.36)	1.13 (0.61 to 2.07)	0.87 (0.49 to 1.53)	0.85 (0.50 to 1.44)	0.70 (0.42 to 1.16)	1.0 (0.61 to 1.63)
Secondary education	1.01 (0.53 to 1.94)	0.83 (0.43 to 1.57)	1.97 (1.04 to 3.74)	0.33 (0.16 to 0.69)	0.61 (0.33 to 1.12)	0.48 (0.27 to 0.85)	0.78 (0.45 to 1.34)
Lowest income quartile	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2nd income quartile	1.49 (0.77 to 2.88)	0.99 (0.48 to 2.06)	0.59 (0.31 to 1.13)	0.99 (0.53 to 1.86)	0.71 (0.39 to 1.28)	1.65 (0.91 to 2.99)	1.35 (0.78 to 2.34)
3rd income quartile	1.08 (0.55 to 2.10)	1.51 (0.77 to 2.98)	0.69 (0.37 to 1.28)	0.55 (0.28 to 1.09)	0.74 (0.42 to 1.32)	1.44 (0.80 to 2.61)	0.99 (0.58 to 1.72)
Highest income quartile	1.32 (0.67 to 2.60)	1.62 (0.80 to 3.27)	0.85 (0.46 to 1.58)	0.66 (0.32 to 1.35)	0.59 (0.31 to 1.10)	1.04 (0.54 to 1.98)	1.08 (0.61 to 1.91)
Women							
SES variables							
No formal education	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Primary education	1.18 (0.73 to 1.91)	1.07 (0.67 to 1.72)	1.42 (0.87 to 2.33)	0.99 (0.62 to 1.56)	0.76 (0.45 to 1.27)	0.84 (0.50 to 1.41)	0.6 (0.35 to 1.04)
Secondary education	1.98 (1.02 to 3.85)	0.98 (0.49 to 1.96)	2.93 (1.48 to 5.79)	0.30 (0.13 to 0.67)	0.89 (0.43 to 1.86)	0.94 (0.44 to 1.98)	0.70 (0.32 to 1.52)
Lowest income quartile	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2nd income quartile	1.09 (0.61 to 1.95)	1.24 (0.70 to 2.23)	1.06 (0.58 to 1.93)	0.79 (0.45 to 1.38)	0.86 (0.47 to 1.56)	0.83 (0.45 to 1.53)	0.64 (0.34 to 1.22)
3rd income quartile	0.80 (0.42 to 1.52)	1.82 (0.98 to 3.39)	1.01 (0.53 to 1.94)	0.81 (0.44 to 1.50)	0.88 (0.46 to 1.68)	0.89 (0.46 to 1.73)	1.15 (0.59 to 2.22)
Highest income quartile	0.90 (0.45 to 1.81)	1.12 (0.55 to 2.27)	0.73 (0.35 to 1.54)	0.91 (0.46 to 1.82)	0.76 (0.36 to 1.60)	0.74 (0.34 to 1.58)	0.85 (0.39 to 1.84)

All models control for age.

derived from 12 hour overnight urine specimens and are reported as ''micrograms per gram creatinine'' to adjust for body size. Measures of DHEA-S, IGF1, IL6, albumin, ratio of total to HDL cholesterol, HDL cholesterol, and glycosylated haemoglobin were taken from fasting blood specimens. Systolic and diastolic blood pressures were calculated using the average of two seated blood pressure readings taken about a minute apart, and waist-hip ratio was calculated based on waist circumference (measured at its narrowest point between the ribs and iliac crest) and hip circumference (measured at the maximal buttocks). Blood and urine samples were analysed by Union Clinical Laboratories (UCL) in Taipei. In addition to routine standardisation and calibration tests performed by the laboratory, during the early stages of fieldwork nine people outside of the sample contributed triplicate sets of specimens: two sets were submitted to UCL and a third was sent to Quest Diagnostics in the USA. The resulting data show high interlaboratory and intralaboratory reliability (intraclass correlations >0.80 for UCL; interlaboratory correlations >0.76 for UCL compared with Quest Diagnostics).[26]

Individual biomarkers are coded as 1 when the respondent falls in the highest risk quartile of the distribution of that biomarker (highest risk quartiles can be either high or low depending on the biomarker). Results were substantively the same with linear specifications of each biomarker. Table 1 gives cut off values for each biomarker.

AL is scored as the number of risk factors for which the respondent falls in the highest risk quartile. AL, based on the original 10 biomarkers, was found to be a strong predictor of new cardiovascular events, decline in cognitive and physical functioning, and mortality in a seven year follow up in a sample of the elderly from the MacArthur successful aging study, even controlling for health status and other factors at baseline. This was true even when the risk factors were not individually predictive. Other criteria for calculating AL, such as a stricter 10% cut off for scoring or the use of average z scores for each parameter, yielded similar results in regard to health decline, with the quartile cut off criterion showing the strongest effect.[21 27 28] Three subscales will also be used to look at the separate effects of SNS and HPA axis functioning (cortisol, adrenaline, noradrenaline, and DHEA-S); immune/inflammatory markers (IL6, IGF1, and albumin); and cardiovascular risk factors (blood pressure and cholesterol measures, waist-hip ratio, HbA1c). As with the overall AL score, these subscales count the number of respective biomarkers for which the respondent is in the highest risk quartile.

Table 3 Odds ratios based on logistic models of the probability of falling into the highest risk quartile of each cardiovascular measure, by education, income, and sex (95% CI)

	Waist-hip ratio	Systolic BP	Diastolic BP	HDL Chol	Ratio Chol/HDL	HbA1c
Men						
SES variables						
No formal education	1.0	1.0	1.0	1.0	1.0	1.0
Primary education	0.86 (0.53 to 1.41)	1.31 (0.74 to 2.30)	0.96 (0.57 to 1.62)	1.40 (0.80 to 2.44)	1.23 (0.70 to 2.18)	1.33 (0.70 to 2.54)
Secondary education	0.96 (0.56 to 1.65)	1.26 (0.68 to 2.33)	0.68 (0.38 to 1.23)	1.63 (0.89 to 2.97)	1.82 (0.99 to 3.35)	2.24 (1.14 to 4.42)
Lowest income quartile	1.0	1.0	1.0	1.0	1.0	1.0
2nd income quartile	0.63 (0.36 to 1.08)	1.0 (0.53 to 1.87)	1.38 (0.75 to 2.57)	0.97 (0.54 to 1.74)	0.83 (0.46 to 1.50)	1.33 (0.68 to 2.59)
3rd income quartile	0.86 (0.51 to 1.45)	1.21 (0.67 to 2.21)	1.95 (1.09 to 3.51)	0.79 (0.45 to 1.40)	0.70 (0.39 to 1.25)	1.0 (0.52 to 1.92)
Highest income quartile	0.61 (0.35 to 1.06)	1.06 (0.57 to 2.00)	1.32 (0.70 to 2.47)	0.93 (0.52 to 1.67)	0.75 (0.42 to 1.37)	0.99 (0.51 to 1.95)
Women						
SES variables						
No formal education	1.0	1.0	1.0	1.0	1.0	1.0
Primary education	1.10 (0.55 to 2.20)	0.93 (0.55 to 1.57)	0.85 (0.52 to 1.41)	1.05 (0.59 to 1.87)	0.91 (0.54 to 1.54)	0.61 (0.37 to 0.99)
Secondary education	0.08 (0.01 to 0.63)	0.65 (0.29 to 1.45)	0.34 (0.14 to 0.83)	0.57 (0.20 to 1.61)	0.68 (0.30 to 1.56)	0.45 (0.21 to 0.94)
Lowest income quartile	1.0	1.0	1.0	1.0	1.0	1.0
2nd income quartile	0.48 (0.20 to 1.19)	0.41 (0.21 to 0.78)	0.73 (0.39 to 1.38)	1.1 (0.54 to 2.22)	1.41 (0.74 to 2.68)	1.21 (0.68 to 2.17)
3rd income quartile	0.99 (0.40 to 2.43)	0.96 (0.50 to 1.82)	1.29 (0.67 to 2.48)	1.43 (0.69 to 2.99)	1.30 (0.64 to 2.61)	1.52 (0.81 to 2.86)
Highest income quartile	1.87 (0.71 to 4.92)	0.64 (0.30 to 1.38)	1.02 (0.48 to 2.15)	0.39 (0.14 to 1.11)	0.86 (0.38 to 1.96)	1.08 (0.52 to 2.21)

All models control for age.

SES is measured by education and income. Education is divided into three categories: no formal education, primary education, or secondary education. Income is measured as the respondent's and spouse's combined reported income in 1999 and is divided into quartiles. Results were substantively the same using a linear specification of education and log-linear specification of income.

Health outcomes include self reported health on a five point scale, with 1 = excellent, 2 = good, 3 = average, 4 = not so good, 5 = poor, as well as the number (0–6) of mobility difficulties the respondent reports with regard to the following activities: squatting, walking up two to three flights of stairs, lifting or carrying 11–12 kg, walking 200–300 metres, standing continuously for 15 minutes, and grasping or turning objects with fingers.

Statistical analysis

Analyses are run separately on men and women, because of potentially important sex differences in the biology of stress.[29 30] For individual biomarkers, logistic regression models were used to calculate the odds ratios of falling into the highest risk quartile of each biomarker. For AL, the three biomarker subscales, self reported health status and the number of mobility difficulties, ordinal logit models were used to calculate the odds ratios of moving one point higher on each of the scales. Each model includes a linear control for the age of the respondent (a quadratic term for age was not significant). Controls for marital status, ethnicity, and employment status were included in preliminary models but did not affect the results. Education and income are included jointly in all models to estimate their independent effects. Running models with education and income included separately yielded identical substantive results on all but one biomarker for men (noted below). All analyses were performed using STATA version 8.0 (StataCorp, College Station, TX).

RESULTS

Tables 2 and 3 show the associations between education, income, and the physiological measures obtained during the examination and laboratory portions of SEBAS, separately for each biomarker and sex. Overall, the number of significant associations between measures of SES and the biomarkers is quite modest, particularly in light of the large number of models estimated here.

Table 2, which presents estimates for the neuroendocrine and immune/inflammatory markers, shows that education is significantly associated with more favourable readings for men for only one of the four indicators of SNS and HPA axis activity, DHEA-S, and one of the three immune/inflammatory markers, IL6 (when education is included without income, higher education is associated with more favourable readings for IGF1). Somewhat counter-intuitively, higher levels of education are significantly associated with higher readings for adrenaline. Income is not significantly related to any of the neuroendocrine or immune/inflammatory markers in men. Table 2 also shows some unexpected results for women, with more education significantly associated with more favourable (higher) readings for DHEA-S but less favourable (higher) readings for adrenaline, and interestingly, cortisol. No significant associations are found for income.

Table 3, which examines the cardiovascular measures, shows some unexpected findings for men. More education is significantly related to higher readings of glycosylated haemoglobin and higher income is associated with higher diastolic blood pressure, although the estimates do not increase monotonically with increasing levels of income. The results for women are more consistent with expectation: additional years of education are associated with a lower risk of unfavourable readings for waist-hip ratio, diastolic blood pressure, and glycosylated haemoglobin. Table 4 presents odds ratios pertaining to the biomarker scales. The results show that lower education is significantly associated with worse scores in men only for the collective immune/inflammatory markers, with no significant relation seen for neuroendocrine markers, cardiovascular risk factors, or the overall AL score. For women, less education is significantly associated with higher scores for the cardiovascular risk factors as well AL, but is not significantly associated with the neuroendocrine marker or immune/inflammatory subscales, consistent with the findings for the individual biomarkers.

Next, we test whether these biomarkers can account for all or part of the relation between SES and health outcomes in our sample. Controlling only for age, we see an association between higher SES and better health outcomes in the SEBAS sample (model 1, table 5), although not all coefficients for a given health measure are significant. For men, higher education levels are associated with better self reported health status as well as fewer mobility restrictions, while more income is independently associated with fewer

Table 4 Odds ratios based on ordinal logit models of the probability of having more risk factors in highest quartile for each biomarker index, by education, income and sex (95% CI)

	Neuroendocrine	Cardiovascular	Immune/inflammatory	Allostatic load
Men				
SES variables				
No formal education	1.0	1.0	1.0	1.0
Primary education	0.97 (0.62 to 1.50)	1.17 (0.77 to 1.77)	0.78 (0.50 to 1.21)	0.97 (0.65 to 1.46)
Secondary education	0.93 (0.57 to 1.51)	1.38 (0.87 to 2.18)	0.53 (0.33 to 0.86)	0.95 (0.61 to 1.49)
Lowest income quartile	1.0	1.0	1.0	1.0
2nd income quartile	1.12 (0.68 to 1.85)	0.92 (0.58 to 1.46)	1.25 (0.76 to 2.04)	1.02 (0.64 to 1.60)
3rd income quartile	1.05 (0.65 to 1.70)	1.0 (0.64 to 1.56)	1.03 (0.64 to 1.65)	0.91 (0.59 to 1.42)
Highest income quartile	1.24 (0.75 to 2.07)	0.85 (0.53 to 1.35)	0.89 (0.55 to 1.46)	0.82 (0.52 to 1.30)
Women				
SES Variables				
No formal education	1.0	1.0	1.0	1.0
Primary education	1.30 (0.87 to 1.95)	0.77 (0.52 to 1.15)	0.72 (0.47 to 1.10)	0.84 (0.57 to 1.24)
Secondary education	1.39 (0.76 to 2.52)	0.33 (0.18 to 0.61)	0.94 (0.52 to 1.71)	0.55 (0.31 to 0.96)
Lowest income quartile	1.0	1.0	1.0	1.0
2nd income quartile	1.06 (0.65 to 1.72)	0.83 (0.50 to 1.37)	0.71 (0.43 to 1.19)	0.66 (0.40 to 1.07)
3rd income quartile	1.04 (0.61 to 1.79)	1.46 (0.86 to 2.51)	0.89 (0.51 to 1.56)	1.17 (0.69 to 1.99)
Highest income quartile	0.86 (0.48 to 1.56)	0.90 (0.50 to 1.63)	0.69 (0.37 to 1.29)	0.69 (0.39 to 1.23)

All models control for age.

Table 5 Odds ratios based on ordinal logit models of the probability of reporting worse health or more mobility difficulties, by education, income, and sex (95% CI)

	Men		Women	
SES variables	**Self rated health**	**Mobility difficulty**	**Self rated health**	**Mobility difficulty**
Model 1				
No formal education	1.0	1.0	1.0	1.0
Primary education	0.77 (0.50 to 1.19)	0.73 (0.46 to 1.15)	0.71 (0.47 to 1.08)	0.68 (0.44 to 1.03)
Secondary education	0.56 (0.35 to 0.91)	0.40 (0.23 to 0.68)	0.49 (0.27 to 0.92)	1.02 (0.57 to 1.84)
Lowest income quartile	1.0	1.0	1.0	1.0
2nd income quartile	1.09 (0.68 to 1.73)	0.96 (0.59 to 1.58)	0.64 (0.40 to 1.05)	0.55 (0.34 to 0.89)
3rd income quartile	0.86 (0.55 to 1.36)	0.52 (0.31 to 0.88)	0.80 (0.47 to 1.38)	0.55 (0.32 to 0.95)
Highest income quartile	0.62 (0.39 to 1.01)	0.79 (0.46 to 1.38)	0.50 (0.27 to 0.92)	0.34 (0.18 to 0.63)
Model 2				
No formal education	1.0	1.0	1.0	1.0
Primary education	0.72 (0.47 to 1.12)	0.72 (0.46 to 1.15)	0.71 (0.47 to 1.09)	0.66 (0.43 to 1.00)
Secondary education	0.50 (0.31 to 0.82)	0.39 (0.22 to 0.67)	0.51 (0.27 to 0.95)	1.04 (0.57 to 1.88)
Lowest income quartile	1.0	1.0	1.0	1.0
2nd income quartile	1.1 (0.69 to 1.76)	0.97 (0.59 to 1.60)	0.64 (0.39 to 1.04)	0.52 (0.32 to 0.85)
3rd income quartile	0.84 (0.53 to 1.32)	0.53 (0.31 to 0.90)	0.80 (0.46 to 1.37)	0.52 (0.30 to 0.90)
Highest income quartile	0.60 (0.37 to 0.98)	0.81 (0.47 to 1.42)	0.50 (0.27 to 0.93)	0.34 (0.18 to 0.63)
Model 3				
No formal education	1.0	1.0	1.0	1.0
Primary education	0.77 (0.50 to 1.19)	0.72 (0.46 to 1.14)	0.72 (0.47 to 1.09)	0.7 (0.46 to 1.06)
Secondary education	0.56 (0.35 to 0.91)	0.39 (0.22 to 0.66)	0.5 (0.27 to 0.93)	1.11 (0.61 to 2.00)
Lowest income quartile	1.0	1.0	1.0	1.0
2nd income quartile	1.09 (0.68 to 1.73)	0.96 (0.58 to 1.58)	0.64 (0.39 to 1.05)	0.54 (0.33 to 0.88)
3rd income quartile	0.86 (0.55 to 1.36)	0.52 (0.31 to 0.88)	0.8 (0.46 to 1.37)	0.52 (0.30 to 0.90)
Highest income quartile	0.63 (0.39 to 1.01)	0.83 (0.48 to 1.45)	0.5 (0.27 to 0.93)	0.35 (0.19 to 0.65)

Model 1: adjusted for age. Model 2: adjusted for age and three subscales for stress, immune, and cardiovascular markers. Model 3: adjusted for age and allostatic load index. Self reported health: 1 = excellent, 2 = good, 3 = average, 4 = not so good, 5 = poor. Mobility difficulty: the number (0–6) of mobility difficulties the respondent reports with regards to the following activities: squatting, walking up two to three flights of stairs, lifting or carrying 11–12 kg, walking 200–300 metres, standing continuously for 15 minutes, and grasping or turning things with fingers.

mobility restrictions. For women, a higher level of income is significantly related to both health measures, and more education is associated with better self reported health. Our sample is thus consistent with the large literature in many countries finding significant relations between various measures of SES and health outcomes, and consistent with previous literature finding educational gradients in Taiwan.[31 32] Readers interested in the direct relation between the biomarkers and health outcomes are referred to other papers that explicitly examine these relations.[26 33]

Model 2 in table 5 shows results adjusting for the three biomarker subscales, whereas model 3 adjusts for the summary index of AL (the estimates in model 2 are similar to those controlling for each individual biomarker). We see that inclusion of the biomarker scales does not diminish the observed effect of education and income on these health outcomes for either men or women. These results are not surprising given the weak associations between education, income, and the biomarkers presented in our previous tables.

What is already known on this topic

- Socioeconomic status is associated with a wide variety of health outcomes. Thus far, mechanisms such as access to health care and health related behaviours have failed to explain this association.
- Psychosocial stress has been posited as a possible pathway linking low social status to poor health, through sustained exposure to stress hormones such as cortisol.
- Few studies have tested the relation between socioeconomic status and biological markers of stress in humans, and the results have been mixed.

DISCUSSION

Overall, these results provide only weak evidence for the idea that stress, particularly through sustained activation of the autonomic and neuroendocrine responses, is one of the primary pathways linking SES to health outcomes. While lower education is significantly related to several risk factors for women, these are not the stress hormones through which the story of psychosocial stress is so often told. Associations between SES and cardiovascular measures in women may be confounded by other risk factors including poor nutrition, inactivity, and smoking, which are known to increase cardiovascular risk. While the relations between education and IL6 and DHEA-S are intriguing, the lack of associations in the expected direction between SES and the markers of HPA-axis and SNS activity leaves us without a smoking gun linking education or income to what are deemed the primary mediators of the body's stress response.

Most notably, lower SES is not significantly related to higher basal levels of cortisol, the stress hormone most commonly implicated in the literature on SES, stress, and health. For the stress hypothesis to remain viable, researchers would need to find consistent evidence of sustained activation of the HPA-axis and SNS in low SES people. This study finds mixed evidence of increased physiological dysregulation

What this study adds

- Lower socioeconomic status is not associated with higher basal levels of stress hormones, including cortisol, in our nationally representative sample of the middle aged and elderly in Taiwan.
- These results challenge the conventional wisdom that psychosocial stress, via sustained activation of autonomic and neuroendocrine responses, is an important pathway linking low social status and poor health.

attributable to chronic stress in lower SES people, and no evidence that biological markers of chronic stress explain the SES gradient in health. These results are partially inconsistent with those of Seeman and colleagues, whose analysis of the MacArthur study of successful aging suggests that AL explains roughly a third of the association between education and seven year mortality in their sample.[23] While their study examines the relation between education and the summary measure of AL, it does not directly test education's association with individual biomarkers or categories of biomarkers. Their results for mortality show that the attenuation of the effect of education on mortality is largely driven by the effects of the cardiovascular risk factors and immune/inflammatory markers, with the neuroendocrine markers accounting for only a 4% attenuation. Thus while there is mounting evidence that lower SES is associated with biological dysregulation in several systems including the cardiovascular system, metabolic functions, and inflammation processes, evidence linking SES to dysregulation in the SNS and HPA axis is scarce.

Study limitations

Potential limitations to this work include the fact that this is a middle aged and elderly sample, representing cohorts with low average education and comprised of many retirees. If the relation between psychosocial stress and SES occurs primarily through characteristics of one's job,[34 35] we may not see strong links between neuroendocrine markers and SES in our sample. Additionally, income may be a less reliable measure of social status in a retired population. Despite these potential problems, we do see health gradients by education and income in our sample, suggesting that education and income are measuring important differences in SES. Furthermore, as income is correlated over time and the effects of SNS and HPA axis dysregulation are cumulative, we should expect these relations to be present even in non-working populations if they are the indeed the primary driver of SES gradients in health.

It is possible that while the SES gradients in health seen here are similar to those in other countries, the pathways linking SES and health may be different in Taiwan, where cultural norms regarding social relationships and status are distinct from Western countries.[36] For example, co-residence of the elderly with a married child has been the desired living arrangement in Taiwan, and such a safety net could plausibly weaken relations between SES and stress in Taiwanese elderly persons. Recent work also suggests that both very high and very low values of the biological parameters comprising AL, including cortisol, are important for health outcomes.[26] Future work would benefit from looking in more detail at the relation between SES and both extremes of the distribution of neuroendocrine markers. Another potential limitation of this work is the contemporaneous measurement of biomarkers and health outcomes, which makes it difficult to identify the direction of the relation between the two. In addition, measurement error associated with measurements at one point in time could attenuate our results. Availability of follow up health and mortality data for SEBAS will mitigate these problems in the future. Finally, research into the dynamic and complex interactions comprising the body's stress response is ongoing; there is much we do not know, or do not know how to measure. Future research should incorporate new knowledge of the physiological processes and measurement of chronic and acute stress, so that a better consensus regarding the role of stress in the SES-health gradient can be found.

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CONTRIBUTORS

JBD designed the paper, carried out the statistical analysis and interpretation, and drafted the initial paper. NG contributed to design, collection, and acquisition of the data and collaborated on subsequent drafts of the paper. JBD accepts full responsibility for the work, had access to the data, and controlled the decision to publish.

Authors' affiliations

J B Dowd, Mathematica Policy Research, Washington, USA
N Goldman, Office of Population Research, Princeton University, Princeton, USA

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