Socio-economic status, cortisol and allostatic load: a review of the literature

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Background	The notion that chronic stress contributes to health inequalities by socio-economic status (SES) through physiological wear and tear has received widespread attention. This article reviews the literature testing associations between SES and cortisol, an important biomarker of stress, as well as the summary index of allostatic load (AL).
Methods	A search of all published literature on the PubMed and ISI Web of Knowledge literature search engines was conducted using broad search terms. The authors reviewed abstracts and selected articles that met the inclusion criteria. A total of 26 published studies were included in the review.
Results	Overall, SES was not consistently related to cortisol. Although several studies found an association between lower SES and higher levels of cortisol, many found no association, with some finding the opposite relationship. Lower SES was more consistently related to a blunted pattern of diurnal cortisol secretion, but whether this corresponded to higher or lower overall cortisol exposure varied by study. Approaches to collecting and analysing cortisol varied widely, likely contributing to inconsistent results. Lower SES was more consistently related to higher levels of AL, but primarily via the cardiovascular and metabolic components of AL rather than the neuroendocrine markers.
Conclusions	Current empirical evidence linking SES to cortisol and AL is weak. Future work should standardize approaches to measuring SES, chronic stress and cortisol to better understand these relationships.
Keywords	Socio-economic status, cortisol, allostatic load

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Introduction

Decreased socio-economic status (SES), whether measured by income, education or other indicators, is consistently associated with increased rates of morbidity and mortality.[1–3] Less certain are the mechanisms through which SES gets translated into biological risk after differentials in access to care and health behaviours have been taken into account.[4,5] Chronic stress has received widespread attention as a potential mechanism by which SES can 'get under the skin'.[6–9] Individuals with lower SES are hypothesized to have both increased exposure to stressful events in their lives as well as fewer social and material resources with which to buffer stressful events that occur.[7,10]

Research on the physiologically damaging effects of stress has focussed on the hypothalamic–pituitary–adrenal (HPA) axis, one of the systems that regulates the biological response to stimuli which is perceived as stressful. Whereas acute response to stress is adaptive, chronic activation of the system is thought to damage the feedback loops that return these hormones to their normal levels. Of the hormones released by the HPA axis, cortisol has received the most research attention, in part due to its widespread regulatory influences covering the central nervous system, the metabolic system and the immune system.[11] Chronically elevated levels of cortisol have been linked to a variety of pathogenic processes including cognitive decline, immunosuppression and insulin resistance,[12–15] although recent work suggests that cortisol deviations in both directions are potentially pathogenic.[11]

Cortisol can be assayed from saliva, plasma and urine, but the relative scientific merit of these respective measurements is still under debate; see refs[16,17] for recent reviews. Recent work has even explored the possibility of analysing longer-term cortisol production from hair.[18] Salivary cortisol represents free cortisol that has passively diffused into the salivary glands. Free cortisol represents the fraction of cortisol not bound to binding proteins, including corticosteroid-binding globulin (CBG). While free, unbound cortisol is commonly thought to represent the only biological active fraction and thus most appropriate for study, recent discoveries of the biological roles of binding proteins have called this assumption into question.[16] Urine collections of 12 or 24 h have been used to provide an integrated measure of HPA activity over a longer period of time. Urinary free cortisol is a function of not only cortisol production, but also cortisol metabolism by the liver and clearance by the kidneys, which may influence the association of urinary and other cortisol measures.[17] Correspondence between salivary and urinary measures has been mixed.[19] Whereas high correlations between salivary and free plasma cortisol levels have been found,[20] 30–50% of free cortisol in saliva is converted to cortisone by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2, leading to lower overall levels of cortisol in saliva.[16]

Cortisol secretion in humans follows a diurnal pattern that typically peaks early and declines progressively over the day, with an independent pulsatile secretion component that is superimposed on the underlying circadian rhythm.[16,21] Figure 1 illustrates this typical diurnal pattern. Due to this strong diurnal variation, combined with significant variation in the diurnal pattern across individuals and within individuals across different days, characterization of HPA-axis activity and its correlates has increasingly moved towards repeated measurements of cortisol over 1 or more days.[16,21–25] Salivary cortisol, which can be collected by study respondents themselves, has proved to
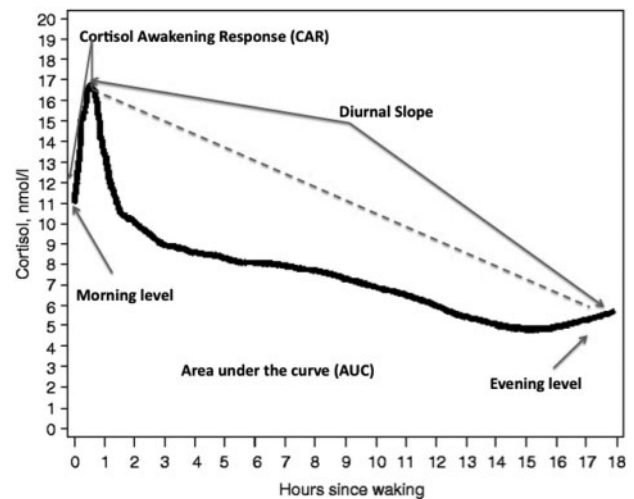

Figure 1 Example of diurnal pattern of cortisol secretion

be the most practical method of cortisol collection in naturalistic settings requiring repeated collections.

In modelling cortisol as an outcome, different features of the diurnal pattern have been examined including the slope of the diurnal curve from peak to trough, the size of the cortisol awakening response (CAR), levels of morning and/or evening cortisol and measures of total cortisol concentration over the day such as area under the curve (AUC). Research on the relationships between the CAR, stressors and health outcomes is ongoing. Whereas a lower CAR has been associated with chronic health problems, post-traumatic stress disorder, chronic fatigue syndrome and sleep disorders, a higher CAR has been related to over commitment to work, high job demands and social stress.[26–28] Inconsistent relationships have been found between the CAR and measures of depression and burnout.[28] It has been suggested that these inconsistencies might be related to the fact that the CAR is strongly related to the anticipation of demands, both positive and negative, providing the 'boost' needed to meet such demands.[23,28] Long-term chronic activation of the HPA-axis might ultimately lead to a blunted under-active HPA response.[23,28] Waking levels of cortisol and the slope of decline across the day are generally correlated with the CAR and likely capture related features of the diurnal pattern. A flatter or 'blunted' cortisol pattern is thought to indicate HPA-axis dysfunction with a steeper decline believed to indicate a normal rhythm, though a substantial fraction of individuals has more inconsistent patterns.[29–31]

Allostatic load (AL) has been suggested as a conceptual framework for the cumulative wear and tear on the body caused by the inefficient turning on or shutting off of physiological responses to stressors.[32] This gradual loss of the body's ability to maintain physiological parameters within normal operating ranges is thought to result from frequent and/or long durations

of adaptive stress response. Of the measures included in AL, cortisol and markers of sympathetic nervous system (SNS) functioning, epinephrine and norepinephrine are conceived as the 'primary mediators' in the cascade of events that ultimately affects 'secondary' outcomes such as blood pressure, glycosolated haemoglobin, abdominal obesity and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels, ending in the 'tertiary' outcomes of cardiovascular and other diseases.[32] It is thought that chronic overexposure to stress mediators such as those regulated by the HPA-axis and SNS ultimately leads to adverse effects on multiple organ systems, resulting in disease.

A growing literature has begun testing the idea that stress mediates the relationship between SES and health outcomes using biological data collected in epidemiological and social surveys. In order to critically assess current knowledge on this important topic, we conducted a review of existing literature on SES and cortisol, as well as papers examining SES and indices the authors define as 'AL'.

Methods

Reviewed articles were extracted from a larger systematic review examining all studies of the relationship between SES and biomarkers of multiple physiological systems up to June 2009. All published literature in PubMed and ISI Web of Knowledge were searched based on the following keywords found in the title or abstract: 'socio-economic position' OR 'socio-economic status' OR education OR occupation OR income OR wealth OR poverty OR schooling OR 'occupational status' OR 'occupational grade' OR 'employment grade' OR employment OR unemployment OR deprivation OR 'social class' OR 'social grade' OR 'occupational class' AND cortisol OR glucocorticoid* OR cortisone OR 'adrenocorticotropic hormone' OR ATCH OR 'corticotropin-releasing hormone' OR allostatic load, where * represents a Boolean operator that will identify all permutations of the base word. In addition, references from all relevant review articles were obtained and reviewed.

Non-human studies, letters, editorials, lectures, commentaries, replies and non-English language studies were removed prior to abstract review. All abstracts were read and studies were excluded if they did not report a direct association between an SES indicator and one or more biomarkers of interest as described in the keyword search. In addition, studies were excluded if they examined non-community-based populations, such as clinical or patient populations, or selected participant populations with existing illnesses. From the remaining abstracts, all full manuscripts were gathered and reviewed for key information: type and measurement of biological markers, type and measurement of SES markers, direction and significance of each

reported relationship and stratification and control variables.

Results

The search identified 26 studies meeting the inclusion criteria. The papers selected reported associations between an indicator of SES and cortisol, and/or AL.

Cortisol
SES and levels of cortisol
The SES and stress literature has emphasized chronic overexposure to cortisol as a risk to health. We first summarized results based on the association of lower SES with higher or lower reported levels of cortisol (Table 1). Of the 21 papers reporting associations of SES with cortisol, two analysed serum cortisol, five urinary cortisol and fourteen salivary cortisol. (Dowd and Goldman[43] and Gersten[44] report results from the same Taiwanese sample, and the samples from the two Lupien papers, 2000, 2001, analysing Canadian children partially overlapped. Steptoe et al.[41] and Kunz-Ebrecht[27] analysed the same Whitehall subsample, and Steptoe et al.[48] also used data from a follow-up of this sample. The sample of Evans et al.[36] is a follow-up of the sample analysed in Evans and Kim[35]. Of the 21 papers, seven reported a significant association between lower levels of SES and higher levels of cortisol,[33–39] four found mixed results,[27,40–42] eight studies found no relationship between SES and levels of cortisol[43–50] and two found a relationship between lower SES and lower cortisol.[51,52]

Among those studies finding lower SES associated with higher cortisol, Cohen et al. found that lower income and education were associated with higher levels of cortisol during the evening and at bedtime in a sample of 781 middle-aged adults in the CARDIA study.[34] In a different study, Cohen et al. found that lower levels of income and education were associated with higher levels of total cortisol concentration over the day in a recruited sample of 193 adults aged 21–55 years.[33] Data from 6335 participants in the 1958 British Birth Cohort Study with saliva collected at age 45 years found that lower lifetime SES was associated with a greater risk of extreme post-waking values and higher AUC measures.[37] In a sample of 217 school children aged 6–10 years in Canada, Lupien et al. found that lower family income was associated with higher morning levels of a single sample of salivary cortisol.[38] Evans and Kim reported a relationship between lower family income and increased levels of 12-h urinary cortisol in a sample of 287 children aged 8–10 years from rural parts of upstate New York State.[53] In a follow-up of this sample at the age of 13 years, Evans et al. found a significant relationship between duration of poverty and higher levels of overnight urinary cortisol,

Table 1 Studies examining SES and cortisol up to 2009

References	Country	SES indicator	Age range	n	Cortisol measure	Lower SES associated with higher levels?
Arentz et al.[39]	Sweden	Employment	Nr	354	Serum	Yes
Goodman et al.[45]	USA	Parental education, income	15–19	758	Serum	No
Evans and English[53a]	USA	Income	8–10	287	Urinary	Yes
Dowd and Goldman[43a]	Taiwan	Education and income	54–90	972	Urinary	No
Evans and Kim[35a]	USA	Duration of poverty	13	207	Urinary	Yes
Gersten[44a]	Taiwan	Education	54–90	880	Urinary	No
Rosero-Bixby and Dow[50]	Costa Rica	Education, wealth	60+	2256	Urinary	No
Brandstadter et al.[51]	Germany	Education, employment, income, occupation	35–65	767	Salivary	No (lower)
Decker[49]	Dominica	Education, income, wealth	17–49	31	Salivary	No
Lupien et al.[38a]	Canada	Family income	6–10	217	Salivary	Yes
Rosmond and Bjorntorp[47]	Sweden	Occupational grade	51	284	Salivary	No
Lupien et al.[40a]	Canada	Family income	6–16	284	Salivary	Mixed
Steptoe et al.[41a]	UK	Occupational grade	45–58	202	Salivary	Mixed
Kunz-Ebrecht et al.[62a]	UK	Occupational grade	45–58	181	Salivary	Mixed
Wright and Steptoe[42]	UK	Subjective social status, education, financial strain	65-80	81	Salivary	Mixed
Ranjit et al.[46]	USA	Material hardship	18–54	188	Salivary	No
Steptoe et al.[48a]	UK	Financial strain	49–57	144	Salivary	No
Chen and Patterson[52]	USA	Neighbourhood and family income, assets	14–19	212	Salivary	No (lower)
Cohen et al.[33]	USA	Income, education, composite	21–55	193	Salivary	Yes
Cohen et al.[34]	USA	Education and income	33–45	781	Salivary	Yes
Li et al.[37]	UK	Father, adult, lifetime social class	44–45	6335	Salivary	Yes

aStudies examining the same or overlapping samples, or follow-ups of the same sample.

controlling for wave 1 cortisol values.[35] In a sample of 354 blue-collar workers in Sweden, Arnetz et al. found that employed workers had significantly lower serum cortisol levels compared with unemployed workers.[39]

Four studies reported mixed results, with some groups in the sample showing a relationship between lower SES and higher cortisol, but other groups showing either no relationship or the opposite relationship.[27,40–42] Specifically, Steptoe et al. found higher levels of cortisol over the working day for men of lower occupational grade, but this relationship was reversed for women.[41] Kunz-Ebrecht et al. also found opposite associations for men and women in the same sample while examining the interaction of occupational grade and job control and job demands.[27] Lupien et al. found that lower SES children aged 6–11 years had significantly higher levels of salivary cortisol, but the relationship was not present and appeared reversed in children aged 12–16 years.[40] Wright and Steptoe found a relationship between lower subjective social status and higher CAR, but no relationship between level of education or financial strain and CAR in adults aged 65–80 years.[42]

Eight studies found no overall relationship between SES and cortisol.[43–50] Specifically, Decker found no association between education, income or wealth and mean levels of salivary cortisol in a sample of 31 Dominican men aged 17–49 years.[49] Dowd and Goldman[43] and Gersten[44] both found no relationship between education or income and 12-h overnight urinary cortisol in a sample of 972 Taiwanese adults aged 54–90 years. Rosero-Bixby and Dow[50] found that levels of education and wealth were not associated with the likelihood of high 12-h urinary cortisol levels in a sample of 2256 adults aged ⩾60 years in Costa Rica. In a sample of 188 women aged 18–54 years receiving welfare benefits in Michigan, Ranjit et al.[46] found that lower levels of material hardship were associated with a sharper morning rise in cortisol and a subsequent sharper decline throughout the day, but morning and overall levels did not significantly differ by material hardship.[46] In a sample of 167 Whitehall participants aged 49–59 years sampled twice over 3 years, Steptoe et al. found no relationship between financial strain at wave 1 and CAR, cortisol decline over the day or evening cortisol level.[48] Overall, improvement in financial strain between the two waves was not associated with change in the CAR. Broken down by sex, an improvement in financial strain was associated with a smaller increase in the CAR in wave 2 compared to those with worse strain or no change in men only.[48] Change in financial strain was not associated with the slope of cortisol decline over the day or evening levels of cortisol.[48] Rosmond and Björntorp found no association between SES and total salivary cortisol secretion over a day in a sample of 284 51-year old Swedish men,[47] and Goodman et al. found no relationship

between lower parental SES and serum cortisol in a sample of 758 children aged 15–19 years from a suburban Midwestern public school district.[45]

Two studies identified a relationship between lower SES and lower cortisol.[51,52] Brandstadter et al. found lower levels of morning salivary cortisol concentrations to be associated with lower levels of education and occupational status in a study of 767 adults aged 35–65 years in Germany.[51] In a sample of 212 children aged 14–19 years in the USA, Chen and Patterson found that lower neighbourhood and lower family SES were associated with lower mean salivary cortisol levels.[52] Overall, the evidence for a consistent relationship between lower SES and chronically higher levels of cortisol is weak. Next, we summarized associations between SES and patterns of cortisol secretion, which recent works suggest may be more important for health than basal levels.[11]

SES and patterns of salivary cortisol secretion

Table 2 summarizes the 14 studies reporting relationships between SES and parameters of diurnal salivary cortisol secretion. Within these studies, there was large variation in the number of samples collected and the parameters analysed in relation to SES.

Of the six studies that explicitly examined the CAR and SES, three found no relationship,[27,34,41] two found a relationship between higher or improved SES and a lower CAR[42,48] and one found a relationship between lower SES and a lower CAR.[46] Of the four studies that examined SES and the slope of cortisol decline over the day, two found a flatter slope for those with lower SES.[34,46] In the CARDIA study, this flatter slope resulted from less of an evening decline in cortisol, with no SES differences in morning levels or morning rise.[34] In contrast, the flatter slope identified by Ranjit et al. was found together with a lower CAR and no difference in evening levels,[46] suggesting heterogeneous profiles even within overall flatter patterns of diurnal cortisol. Li et al. collected two saliva samples on one day, one 45 min after wakening, and the second 3 h later.[37] They defined a 'normal' diurnal decline as having a time 1 measure in the top 95% of the distribution and a time 2 measure that was ⩾20% lower than the time 1 measure. Those with higher SES were more likely to have 'normal' declines by this definition.[37] Those with higher SES were also reported less likely to have 'extreme' time 1 cortisol defined as a measurement in the top or bottom 5% of the distribution.[37] Defined in this way, it is unclear whether lower morning levels or higher later-day levels underlie the association between lower SES and an 'abnormal' decline, but the significant association between low SES and higher AUC in this sample suggests the latter. Steptoe et al. found no association between improvement in financial strain and diurnal slope over the day.[48] Whereas Brandstadter et al. did not explicitly calculate diurnal slope in their study,

Table 2 SES and salivary cortisol

References	No. of daily measures	No. of days	Outcome of interest	SES association
Brandstadter et al.[51]	3	1	Morning, afternoon and evening levels	Higher SES associated with higher morning and afternoon cortisol levels, no association for evening levels
Decker[49]	Up to 2	Up to 15	Mean cortisol	No relationship
Lupien et al.[38a]	2	1	Mean morning cortisol	Lower SES associated with higher mean levels
Rosmond and Bjorntorp[14]	7	1	Mean cortisol	No relationship
Lupien et al.[40a]	4	1	Mean morning cortisol	Lower SES associated with higher mean levels for children aged 6–11, no association for children aged 12–16
Steptoe et al.[48a]	10	1	CAR, mean of all samples	No difference in CAR, mean level higher in low SES men, lower in lower SES women
Kunz-Ebrecht et al.[62a]	10	1	CAR, mean cortisol over the remainder of the day	No relationship for CAR, mean level higher in lower SES men, lower in lower SES women
Wright and Steptoe[42]	5	1	CAR	Lower subjective social status associated with higher CAR, no association for education or financial strain
Chen and Patterson[52]	1	1	Average level	Higher neighborhood SES associated with higher cortisol
Cohen et al.[33]	7	3	AUC, mean cortisol level	Lower SES associated with higher AUC, but not mean levels
Ranjit et al.[46]	Up to 4	1	Waking level and slopes of four regression splines	No difference in waking level, increased material hardship associated with flatter slopes of diurnal profile
Steptoe et al.[48a]	5	1	CAR, slope of cortisol decline, evening level	Men with improvement in financial strain had lower CAR, no association for women, no association for slope or evening level
Cohen et al.[34]	6	1	CAR, AUC, diurnal slope	No difference in CAR, lower income associated with higher AUC, flatter diurnal slope
Li et al.[37]	2	1	t1 level, slope of t1–t2, AUC	Lower SES associated with 'extreme' t1 values, 'abnormal' t1–t2 patterns, and higher AUC

[a]Same or overlapping samples.
t1–t2 = time 1 and time 2.

they found higher morning levels for those with higher SES, weaker evidence of higher afternoon levels for those with higher SES and no SES differences in evening levels.[51] This pattern suggests a flatter slope with lower morning levels for lower SES individuals, more similar to the findings of Ranjit *et al.* than those found in the CARDIA study.[34,46]

Three studies examined AUC as a measure of total free cortisol release, all three finding that lower SES was significantly related to a higher AUC.[33,34,37] As discussed above, in the CARDIA study, the higher AUC was a result of similar morning levels but higher evening cortisol levels for those with lower SES,[34] which appears to also be the case in the analysis of Li *et al.*[37] Cohen *et al.* found non-significantly higher levels of cortisol with lower SES for each of seven cortisol measurements throughout the day, attributing the AUC difference to small difference accumulating over the day.[33] There was no significant association between SES and slope, suggesting a uniformly higher pattern for those with lower SES.

The remaining studies of salivary cortisol and SES examined relationships with mean levels across the day. Decker collected morning and evening samples for up to 15 days, with the actual number of samples collected from each individual varying between 6 and 25.[49] After time-standardization, a mean *Z*-score was calculated for each individual depending on the distance of their cortisol value from the median value for the time interval in which it was taken.[49] No relationship between SES and this outcome was found. Chen and Patterson collected one saliva sample in the late afternoon, finding higher cortisol levels for children with higher neighbourhood SES.[52] Rosmond and Bjorntorp collected seven cortisol samples across the day, reporting the mean and variance of cortisol levels for each individual. Whereas mean cortisol was not significantly different across occupational groups, cortisol variance was significantly lower among manual workers, which may be consistent with a blunted diurnal pattern.[47] Both studies by Lupien *et al.* examined mean morning cortisol based on samples taken at the beginning (8 a.m.) and end (9 a.m.) of a neuropsychological session.[38,40] In both cases higher mean levels were found for lower-SES children aged 6–11 years, but the second study found no such association for children aged 12–16 years.[40] The two remaining studies that looked at mean cortisol as a parameter come from the same Whitehall sample, and found higher mean levels in low-SES men and higher mean levels in high-SES women, based on an average of 10 samples collected across 1 day.[27,41] Based on figures 4 and 5 in Steptoe *et al.*,[41] these mean differences appear to come from uniformly higher diurnal patterns, with some evidence of a convergence of values in the evening. Overall, these studies provide some evidence that lower SES is related to a blunted diurnal pattern of salivary cortisol secretion, but lacked consistency on whether this pattern

corresponded to higher or lower overall cortisol exposure over the day.

Allostatic load

Table 3 summarizes results from the seven studies reporting associations between SES and indexes referred to as allostatic load (AL) by the study authors. The original operationalization of AL by Seeman *et al.*[54] summed the number of markers for which an individual had a value in the highest risk quartile. The original 10 biological markers used for AL were systolic and diastolic blood pressure; waist–hip ratio; ratio of total to HDL serum cholesterol; plasma levels of glycosolated haemoglobin (HbA1c); serum dihydroepiandrosterone sulphsate (DHEA-S, a functional HPA antagonist); 12-h urinary cortisol and 12-h urinary epinephrine and norepinephrine.[54] Subsequent studies have added or subtracted to these measures based on data availability and the particular hypothesis being tested. Three of the seven AL studies reported results based on the same Taiwanese sample from the Social Environment and Biomarkers of Aging Study (SEBAS).[43,44,55] Interestingly, despite coming from the same sample, the analyses and results from these three studies differed slightly. Dowd and Goldman added interleukin-6 (IL-6), albumin and insulin growth factor 1 (IGF-1) to their index of AL. They found that increased education was negatively associated with the overall index of AL in women but not men, and income was not related to AL in either sex. Breaking down the AL index into neuroendocrine, cardiovascular and immune/inflammatory markers, they found that higher education was associated with worse scores only in the immune/inflammatory index for men, and the cardiovascular index for women.[43] Using the same sample, Gersten looked only at what he called 'neuroendocrine AL' comprised of cortisol, epinephrine, norepinephrine and DHEA-S, and found no relationship between education and this index.[44] Hu *et al.*, using the original 10 AL components, reported bivariate associations between lower education, lower income and greater AL, but did not report any direct results for SES and AL adjusted for age and sex.[55] In both Dowd and Goldman and Hu *et al.*, inclusion of AL did not reduce differences in health outcomes by education or income.[43,55]

Analysing data from the MacArthur Study of Ageing, Seeman *et al.* added markers of inflammation as well as renal and lung function to the original 10 components of AL.[56] They found a marginally significant bivariate association between years of education and AL ($P = 0.054$). They also found that inclusion of baseline AL reduced the effect of education on follow-up mortality by 35.4%. Breaking down the AL into subscales, the cardiovascular, inflammatory and lung function markers were the biggest contributors to a reduction in the education–mortality association, with the neuroendocrine markers contributing the least to

Table 3 Studies examining SES and AL up to 2009

References	Country	SES indicator	Age range	n	Markers included in AL	Lower SES associated with higher levels?
Singer and Ryff[57]	USA	Income, education, economic change	59–60	84	Original 10	Yes
Kubzansky et al.[58]	USA	Education	42–88	1217	Original 10 *minus* cortisol (2-h glucose in lieu of HbA1c)	Yes
Seeman et al.[59]	USA	Education	70–79	657	Original 10 *plus* IL-6, fibrinogen, albumin, CRP, creatinine clearance, peak flow	Marginal
Dowd and Goldman[43a]	Taiwan	Education and income	54–90	972	Original 10 *plus* IGF-1, IL-6, albumin	Mixed
Hu et al.[55a]	Taiwan	Education and income	54–90	1023	Original 10	Yes
Gersten[44a]	Taiwan	Education	54–90	880	Only neuroendocrine: cortisol, epinephrine, norepinephrine, DHEA-S	No
Seeman et al.[59]	USA	Education and income	20+	15 578	Original 10 minus cortisol, epinephrine, norepinephrine, DHEA-S, plus CRP, albumin, resting heart rate	Yes

aSame sample. Original 10 markers: systolic and diastolic blood pressure; waist:hip ratio; ratio of total to HDL serum cholesterol; plasma levels of glycosolated haemoglobin (HbA1c); serum dihydroepiandrosterone sulphate (DHEA-S); 12-h urinary cortisol; 12-h urinary epinephrine and norepinephrine.

this mediation.[56] In a subsample of 84 respondents from the Wisconsin Longitudinal Study, Singer and Ryff found that lower household income in high school as well as middle age was associated with greater AL using the original 10 markers.[57] Those with lower income in both periods as well as those with downward economic mobility from childhood to adulthood also had higher AL. Income in this study was dichotomized as above or below the median household income in Wisconsin during the year it was measured, and *P*-values were not reported.[57] In the Normative Ageing Study, Kubzansky et al. found that those with the lowest levels of education had significantly greater AL scores (original 10 minus cortisol) than those with the highest level of education.[58] They found that measures of hostility partially mediated the relationship between education and AL in this sample.[58] Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Seeman et al. analysed the relationship between education, income and AL as measured by nine markers of inflammatory, metabolic and cardiovascular risks, without any markers of neuroendocrine function.[56] They found significant associations between income, education and the three subscales as well as the overall AL index.[56]

Discussion

The role of stress in explaining observed relationships between SES and health is an important empirical question in literatures ranging from epidemiology and psychology to the social sciences. This review described what is currently known about the relationship between SES and cortisol, an important biomarker of stress, as well as AL, an index meant to capture cumulative stress-related physiological dysfunction. Overall, the findings were mixed, with little evidence that lower SES is consistently related to higher levels of cortisol. Lower SES was more consistently related to a blunted diurnal pattern of salivary cortisol, but whether this corresponded to higher or lower overall exposure to cortisol over the day varied by study.

Lower SES was more consistently related to higher levels of AL, though the biomarkers comprising AL differed across studies and did not always include measures of HPA-axis and SNS function. When AL was broken down into subscales of markers, relationships between SES and neuroendocrine markers were not found, whereas relationships between SES and cardiovascular and metabolic markers were stronger.[43,44,55,56,58,59] While the inclusion of metabolic and cardiovascular markers in AL derives from the theory that HPA and SNS dysregulation affects multiple physiological systems including the regulation of glucose, lipids and blood pressure, it is nonetheless difficult to interpret findings of SES associations with the 'secondary' outcomes in the allostatic cascade of events while finding no relationships

for the 'primary mediators' of cortisol and catecholamines themselves. Especially given the challenges in measuring cortisol secretion, one possibility is that there is less measurement error for metabolic and cardiovascular components of AL that do not have large diurnal variations compared with HPA and SNS markers, increasing the power of empirical tests to identify a significant relationship with metabolic and cardiovascular measures. But since metabolic and cardiovascular markers are by definition 'secondary' outcomes in the cascade of events leading from HPA and SNS dysregulation to poor health outcomes, they are more subject to influence by other physical and behavioural pathways well known to be associated with SES such as diet, physical activity and smoking. Whereas these behavioural pathways may also ultimately be linked to 'stress', the literature on AL has emphasized the physiological effects of activation of the HPA-axis due to stimuli perceived as stressful. Consequently, while the conceptualization of AL as dysregulation across multiple physiological symptoms is an important theoretical advance in the study of 'stress' and health, current empirical tests of AL that rely heavily on more general metabolic and cardiovascular measures make interpretation of these results with regards to stress difficult. Combining different physiological systems into a single empirical index rather than taking a system-specific approach involves important trade-offs,[60] and much work remains to bridge the empirical execution of AL with its theoretical underpinnings.

Cortisol has received extensive attention as a potential mediator in the SES–health relationship. This review documented that more studies to date have found no association of cortisol with SES than have found the hypothesized association between lower SES and higher levels of cortisol, with several studies identifying 'reverse' associations for the whole sample or subgroups. These results may point to genuine inconsistencies in the nature of these relationships, or current inconsistencies in the measurement and analysis cortisol and SES.

Intra-individual variation in patterns of cortisol secretion is known to be high, especially around time of awakening, making inter-individual comparisons based on a single day of collection likely to be noisy.[22] In fact, up to 6 days of sampling may be necessary to characterize an individual's mean awakening response.[24] Of the studies reviewed here that analysed salivary cortisol, only two collected measures for more than one day.[33,49] Neither of these utilized multi-level approaches to separate out variability within or across individuals.[22]

Another crucial factor in the measurement of salivary cortisol is the accuracy of collection time. Time of day accounts for a majority of the variation in observed cortisol values across a day.[61] The time between waking and recording a 'waking' cortisol sample has been shown to have important

implications for the CAR, with a delay of >10 minutes resulting in almost no CAR on average.[62] Differential adherence to timing could therefore lead to artificial blunting of the CAR in certain groups. New methods of compliance monitoring using microchips to record the opening of collection vials could help to minimize or adjust for these problems, although these technologies are currently expensive for use in large-scale population-based research.[23] Studies also varied in whether samples are collected at specific times of day or designated times based on waking time.

Suggestions for future directions
Taken together, there has been little consistency in cortisol measurement in the studies testing associations between SES and cortisol, making the broader interpretation of these findings difficult. Interest in the role of the stress, and especially the activity of the HPA-axis, in explaining socio-economic differences in health outcomes is high. Given the inconsistent results found in this review of current literature linking SES to biological markers of HPA activity, we offer several suggestions for future research directions in order to move these questions forward.

Measurement of cortisol
The standardization of collection procedures and agreement on relevant parameters for analysis of salivary cortisol offers great opportunities to clarify the nature of the relationship between SES and HPA functioning. Adam et al.[25] summarize recent statistical approaches to isolating separate aspects of salivary cortisol activity, including Latent-State-Trait modelling and hierarchical linear modeling (HLM) growth-curve modelling, which generally provides more robust associations between cortisol and parameters of interests. Despite the increased challenges of multiple days of cortisol collection, investigators should take seriously the evidence that little information on individual differences in cortisol secretion can be gleaned from a single day of collection.[22,24] Social epidemiologists need to closely follow emerging developments in psychobiology and neuroendocrinology documenting the nature of the relationship between HPA activity and chronic stress as well as HPA activity and specific health outcomes, which are not as clear-cut as they have been represented in the SES, stress and health literature.[11,16,21,23]

Research on AL that uses urinary rather than salivary cortisol has not adequately addressed how this difference might be important for their findings. Whereas 24-h urinary cortisol is thought to be a measure of the total amount of cortisol released by the adrenals over a complete circadian cycle, correlations between salivary cortisol and 24-h urinary cortisol have been shown to be weak.[19] Twelve-hour overnight urinary cortisol was used in all of the reviewed studies on AL. The advantages of 12-h

overnight collection are increased compliance and measurement of basal cortisol activity over a non-stimulated period.[63] Seeman *et al*. report a rank correlation of 0.81 between 12-h overnight and 24-h cortisol in pilot testing for the MacArthur Study of Successful Ageing.[63]

Research on SES and stress has both implicitly and explicitly suggested that higher total exposure to cortisol is detrimental, whereas neuroendocrine and psychological research has focussed more on deviations in both directions or alterations of the diurnal pattern as a marker of dysregulation. Future research on SES and cortisol should make clear which hypotheses are being tested. Currently, the lack of broad agreement on how parameters of the diurnal cortisol pattern are related to various outcomes has led to similar interpretations of different results regarding SES and cortisol. For example, papers reviewed here that found both a higher CAR[42,48] and a lower CAR[46] associated with lower SES, all interpreted these results as a relationship between low SES and chronic stress. Although this may not be inconsistent if more typical chronic stress leads to higher CARs in anticipation of demands and long-term stress leads to an inability to mount a response,[23] these distinctions have not been made clear in the SES-stress literature. Similarly, flatter diurnal slopes are generally interpreted as a marker of HPA-axis dysfunction, but within the reviewed papers a flatter diurnal slope was associated with both higher and lower overall cortisol levels as measured by AUC. In the SES and cortisol literature, there has been little discussion of the relative importance of a blunted profile versus greater overall exposure to cortisol, or their potentially different associations with stressors and health outcomes.[11]

Measurement of SES and stress

This review included studies that examined a specific marker of SES such as those typically used to characterize the overall socio-economic 'gradient' in health outcomes. The SES markers used in the reviewed studies were quite diverse and included education, income, occupational grade or status, subjective social status, wealth, financial strain, material hardship and duration of poverty, among others. Different components of SES have been shown to vary in their association with mortality risk for the same individuals, and the same is likely true for other markers of physiological function.[64] Thus, variation in the SES indictor used in these studies likely contributed to the inconsistency of results. Even if well measured, the use of general SES indicators such as income and education could obscure the specific dimensions of SES that are most related to stress and the health impacts of stress.

Better theory and measurement of the relevant components of SES should go hand-in-hand with increased clarity about different types of stressors, whether the discrete or 'acute' stress of the loss of a loved one, the 'chronic' or enduring stress of on-going financial hardship or the constant stress of 'daily hassles'.[65] The impact of stress on HPA activity has also been found to differ by factors such as time since the stressor onset and the controllability of the stressor.[11] The literature has already begun investigating more specific elements of SES and stress with regards to cortisol such as job demands, job control and relationship functioning.[26,27,49,61,66,67] Longitudinal collection of cortisol over multiple days and multiple time periods combined with daily diary information[65] would dramatically improve the ability to understand the day-to-day versus longer-term influences of one's material and psychosocial environment on cortisol patterns.

Mediators

Improving our understanding of the links between SES and cortisol will also depend on careful consideration of the mediating and moderating variables associated with both cortisol secretion and SES. Nicotine, for example, is a stimulator of the HPA-axis and regular nicotine consumption may contribute to chronically elevated cortisol and a less responsive HPA-axis.[68,69] Although several studies adjusted for smoking status in their analyses,[27,37,41,42,44,46] many did not. The studies of Cohen *et al*. were the only ones that explicitly reported a substantial mediation effect of smoking in the observed SES and cortisol relationships.[33,34] Obesity may be both a consequence of increased cortisol exposure and a contributor to continued elevated levels, in part through increased expression of 11β-HSD-11, an enzyme responsible for converting cortisol into its active form.[70,71] While smoking behaviour and obesity may themselves be the consequence of stress pathways, they are also distinct from a direct link between stress and cortisol secretion, so future work will need to more explicitly model these factors in relation to SES and neuroendocrine markers.

Life course

A growing literature suggests that early life experiences may play an important role in the development of the HPA-axis.[25] Results from animal studies suggest that early life deprivation can reduce neural plasticity to later-life stress and potentially permanently alter the expression of genes critical to stress response.[72,73] Early-life SES could potentially play an important role in determining whether responses to stress in later life result in a high- or low-cortisol response. Although the two studies by Lupien examined children as young as 6 years of age,[38,40] only one of the reviewed studies used childhood socio-economic variables to predict adult cortisol. Li *et al*. found that childhood SES was associated with extreme time 1 cortisol values, but after simultaneous adjustment, only adult SES had an effect. Lower lifetime SES was also associated with higher AUC and

increased likelihood of abnormal cortisol decline, with childhood SES seeming more important for men and neither childhood nor adult SES predominating for women. Life-course approaches such as this, as well as prospective studies measuring cortisol during these critical early periods will help shed light on the role of early life on cortisol patterns in adulthood.[23,35,61]

Cortisol reactivity to stressors

While this review focussed on studies looking at basal or non-stimulated levels of cortisol, some papers have looked at SES differences in cortisol response to laboratory-induced challenges.[47,74] While beyond the scope of this review, this is another potential tool for research on SES differences in HPA activity. The degree of cortisol elevation in response to a laboratory stressor and the delay in returning to pre-test levels has been considered signs of HPA-axis dysfunction. As in overall diurnal patterns, extremely high or extremely low responses and/or long delays returning to baseline are considered maladaptive, with healthy responses falling in the middle.[25] Research on cortisol reactivity has the advantage of holding constant the particular stress exposure as well as the timing of measurements. Its disadvantages include a necessary abstraction from more naturalistic stressors, as well as the cost of more intensive laboratory-based measurements. Cognitive stressors such as test-taking or public speaking may differ significantly in perceived stressfulness depending on factors of interests such as education level. Another option includes the use of dexomethasone challenges to test the associations of SES and cortisol at the glucocorticoid receptor level, which can illuminate the sensitivity of the HPA-axis' negative feedback circuit.[11] Although not specifically included in our search, our selected papers included one study that found less efficient dexamethasone inhibition in lower-SES men.[47]

Conclusion

The notion that chronic stress is an important mediator of the relationship between SES and health outcomes is widespread. Despite the strong intuitive appeal of this hypothesis, current evidence of a consistent relationship between SES and neuroendocrine biomarkers of stress is weak. Better theory and study design should help clarify the expected and observed relationships between SES and HPA-axis activity, as well as SES and AL. Future research on the diurnal pattern of cortisol secretion with multiple days of collection will likely yield a better understanding of how HPA activity is associated with physiological dysregulation, chronic stress and SES, in contrast to the historical focus on overexposure to cortisol.

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