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Review Article

The role of psychobiological pathways in socio-economic inequalities in cardiovascular disease risk

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Introduction

Socio-economic inequalities in mortality and morbidity occur in most countries in the modern world, and are of major concern to public health authorities[1,2]. Research on socio-economic status and health has become a priority for the National Institutes of Health, the European Science Foundation and other funding agencies. Coronary heart disease is perhaps the most prominent and best established disorder for which socio-economic inequalities have been observed in the U.K.[3], U.S.A.[4] and other countries[5]. Effects are graded, with a progressively higher incidence with lower socio-economic position as defined by occupational status, income or education[6,7]. With appropriate classifications of socio-economic status, the differences in premature coronary heart disease appear as great in women as in men[5]. Variations by socio-economic status in subclinical coronary artery disease have also been documented[8,9].

This article concerns the pathways through which social inequalities are translated into differential disease risk, highlighting the likely role of psychobiological processes. Psychobiological processes can be defined as the pathways through which psychosocial factors stimulate biological systems via central nervous system activation of automomic, neuroendocrine and immunological responses[10]. We are particularly concerned with the pathways responsible for the gradient in ill health and coronary heart disease; that is, the differences between high and medium status individuals, as well as high compared with low status groups. These pathways may be different from those mediating the effects of poverty and absolute deprivation. The processes outlined here are based on a social causation model, and health selection will not be discussed. This is not to say that health selection (differences in social status resulting from ill health) does not occur, but that it does not account for the major part of the social gradient in coronary heart disease[11].

The criteria for defining socio-economic status vary in the studies reviewed here. There is debate over the extent to which social class, educational attainment, wealth and other constructs overlap[12]. It has been argued that the concept of socio-economic status confuses descriptions of social position as defined by economic circumstances (income and wealth), with those based on prestige or status[13]. This overview is constrained by the socio-economic classifications applied in psychobiological studies, so a range of different criteria is included. We also discuss the use of different research strategies for investigating psychobiological processes, highlighting the value of laboratory and naturalistic methods as complementary to animal research and epidemiological approaches. Our focus is on the aetiology of coronary heart disease and associated cardiovascular disorders, and not of the triggering of acute ischaemia or dysrhythmic events in people with pre-existing coronary artery disease[14].

It will become apparent in this review that work to date on psychobiological processes and socio-economic status is not conclusive. This is due in part to the ways in which psychobiological factors have been investigated, and also to confusion about what types of stress-related biological response relate to increased cardiovascular disease risk. We will therefore propose a conceptual framework in which testable predictions concerning socio-economic status, cardiovascular disease and psychobiological responsivity can be evaluated.

Pathways linking socio-economic status with coronary heart disease

Explanations of social inequalities in health can be elaborated at several levels, and models emphasizing

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cultural, economic, material and psychosocial factors have all proved illuminating[15,16]. Nevertheless, influences on cardiovascular disease risk must ultimately impact on the biology of the individual. In this respect, six pathways may theoretically contribute to socio-economic inequalities in coronary heart disease and cardiovascular disease risk.

Genetic factors

Coronary heart disease has a strong hereditary component. There also appear to be genetic influences on some of the psychosocial factors that relate to cardiac risk, such as aggressive dispositions[17] and cardiovascular stress reactivity[18]. Theoretically, it is possible that some of the social gradient in cardiovascular disease might be due to accumulation of higher risk genes in lower status groups. However, one reason why genetic factors are likely to play only a limited role is the marked and rapid changes over time in the social distribution of coronary heart disease, both nationally and internationally[19]. If the genetic substrate is important to the social gradient, this may be because differential psychosocial or physical exposures lead to variations in gene expression.

Perinatal and childhood factors

Parental occupational status is associated with cardiovascular disease and risk factors in offspring, independent of contemporary socio-economic status[20]. Social position early in life is also a determinant of adult behavioural and psychosocial risk factors such as smoking, physical inactivity, hostility, job strain and poor psychological well-being[21,22]. Low socio-economic status increases risk of adverse experience early in life, and animal studies indicate that early experiences influence later physiological stress reactivity[23]. There is growing evidence that size at birth is related to later cardiovascular disease, with lighter or smaller babies being at higher risk of adult coronary heart disease, and associated risk factors such as raised fibrinogen, low density lipoprotein cholesterol and blood pressure[24]. While the association of low birth weight with coronary heart disease has been shown to be statistically independent of socio-economic status, the fact that low birth weight is more common in lower status groups suggests that these mechanisms may combine to increase risk of coronary heart disease in later life.

Exposure to infection and hazard

Most diseases of poverty arise from infections or exposure to hazards related to poor water supplies, unhygienic living conditions and industrial pollution. These factors may be relevant to a limited extent to social inequalities in coronary heart disease. For example, exposure to carbon disulphide occurs in some blue-collar workers in the textile industry, and is associated with elevated low density lipoprotein cholesterol and blood pressure[25]. Modern concepts of atherogenesis emphasize the role of inflammation of the vascular endothelium in the early stages of the disease[26], and this has raised the possibility that infections contribute to coronary heart disease[27,28]. Chronic infections may be more prevalent in low social status groups, and could therefore contribute to the high rates of cardiovascular disease associated with poverty. They are unlikely, however, to be responsible for the gradient in coronary heart disease that occurs across the full spectrum of socio-economic status.

Access to health care

There is debate about access to quality health care by different social groups, with evidence for differential rates at several stages in the development of cardiovascular disease. An analysis of 'avoidable' hospitalizations for conditions such as malignant hypertension showed higher rates of hospitalization in lower income groups in the U.S.A., a difference that may be due to poorer quality primary health care[29]. Social factors have also been shown to influence delays in hospitalization with heart attack symptoms, with longer delays in lower status groups[30]. In addition, socio-economic status has been found to affect access to invasive cardiac procedures such as angiography and revascularization, even in countries with universal health care systems[31]. Differential access to health care may therefore contribute to socio-economic variations in coronary heart disease mortality, though it is less likely to play a role in the development and progression of cardiovascular disease.

Health behaviours

There are pronounced socio-economic gradients in many countries in behaviours relevant to cardiovascular disease, including cigarette smoking, alcohol consumption, physical activity and nutrition[32,33]. Cigarette smoking plays a clear role in the social gradient of coronary heart disease, and the prevalence and differential changes in smoking uptake and cessation across social groups over time parallel the socio-economic patterning of cardiovascular mortality and morbidity[34]. There is also a relatively consistent social gradient in overweight and obesity, particularly among women, and population attributable risks for fatal and non-fatal coronary heart disease have been estimated at 25–28%[35,36]. The situation is more complicated for other health behaviours. There is no clear association between dietary fat consumption and socio-economic status in the U.S.A. or U.K., although fruit, vegetable and fibre intake is greater in higher status groups[37,38] Vigorous physical activity in leisure time is more common in

higher status groups[39], but may be offset to some extent by occupational physical activity in lower status men. Moderate alcohol consumption is protective of coronary heart disease, and in the U.K. is more common in higher status groups[40].

There have been a number of attempts to determine the extent to which health behaviours account for social inequalities in mortality and coronary heart disease. A common strategy is to model the impact of health behaviour statistically, and assess whether the social gradient persists after they have been taken into account[41]. Analyses of this type indicate that health behaviours are responsible for some of the variance in cardiovascular deaths due to socio-economic status, but that attenuated social gradients persist after lifestyle factors have been taken into account[3,42,43]. Another approach is to analyse subsets of the population. For example, in the Whitehall study, the social gradient in coronary heart disease is still present when smokers are excluded from the analysis[3,44].

Psychobiological processes

The sixth mechanism through which socio-economic status may influence cardiovascular disease risk is via stimulation of neuroendocrine, autonomic and immune processes. These psychobiological processes can be investigated with a number of research strategies, including epidemiological surveys, animal experiments, laboratory and naturalistic studies, as detailed below.

It is difficult to make a direct comparison of the importance of these potential pathways to socio-economic inequalities in cardiovascular disease risk. Existing evidence suggests that genetic factors, exposures to hazard, and differential access to health care, are unlikely to make a major contribution to the gradient in risk across the socio-economic spectrum. Early life factors may operate in part through psychobiological pathways. Since social gradients in cardiovascular disease survive adjustment for health behaviours in many studies, it is plausible that psychobiological pathways are of major significance.

Biological risk factors for coronary heart disease and the social gradient

Epidemiological studies provide the cornerstone for knowledge concerning socio-economic gradients in cardiovascular disease, and for identifying the biological factors that might be involved. Although the results from different cohorts vary, lipid profiles tend to be unfavourable in lower socio-economic groups as defined by occupation, education and income in both men and women, with increased low density lipoprotein[45,46] and decreased high density lipoprotein[47] in lower status groups. Abdominal obesity and markers of the metabolic syndrome such as impaired glucose tolerance and hypertriglyceridaemia are inversely associated with socio-economic status in men and women[45,47,48]. There is a socio-economic gradient in both the prevalence and mortality from diabetes mellitus[49]. Haemostatic factors are related to socio-economic status, with higher levels of plasma fibrinogen in lower status men and women[50,51], and a socio-economic gradient in Factor VIII has been described[52]. Social gradients in blood pressure have been observed[53], although a recent meta-analysis concluded that the differences in blood pressure between high and low status individuals were typically small[54]. There is preliminary evidence that anabolic pathways are positively related to socio-economic status, with higher levels of nocturnal growth hormone in higher status individuals[55].

Many of the biological risk factors for coronary heart disease that vary with socio-economic status are influenced by neuroendocrine and autonomic processes. Epidemiological studies have also established correlations between biological markers of cardiovascular disease risk and psychosocial factors such as adverse work characteristics, social isolation, depression and hostility[56–59]. These associations can therefore be taken as positive evidence for the role of psychobiological pathways in mediating differences in risk. However, two other factors must be taken into account. Firstly, biological risk factors for coronary heart disease are affected by social background and early environment, and these effects are somewhat independent of adult social disadvantage[60,61]. Secondly, biological risk factors are also affected by health behaviours that are differentially distributed across the social gradient. For example, the association observed in the Whitehall II study between employment grade and levels of apolipoprotein A1 was substantially reduced once smoking, alcohol, exercise, diet and body mass index had been taken into account[62]. Educational differences in LDL-cholesterol in middle-aged Swedish women were no longer significant after adjusting for physical activity, alcohol intake, smoking and dietary factors[46]. The social gradient in blood pressure found in a number of studies is eliminated after adjustment for body mass index and age[54]. Haemostatic factors such as fibrinogen, plasminogen activator inhibitor-1 activity and von Willebrand factor are associated with smoking, alcohol consumption and physical activity[63]. Thus the presence of socio-economic differences in biological risk factors does not necessarily provide compelling evidence for the role of psychobiological pathways. To make the case, other types of research are required.

Animal models

The influence of stress on the cardiovascular system and coronary heart disease risk has been studied extensively in animal models. It has been established that atherosclerosis can be promoted by social stress in primates[64], and that the extent of coronary pathology is correlated

with autonomic reactivity to emotional stress[65]. The early stages of cardiovascular pathology such as vascular endothelial dysfunction are also affected by behavioural stress[66], as is abdominal fat deposition[67]. Adverse emotional experiences early in life are associated with substantial increases in physiological stress reactivity in adult monkeys[23].

Animal studies have also shown that psychobiological responses are associated with dominance hierarchies. Sapolsky's[68] work with wild olive baboons has established that basal cortisol levels are higher in subordinate animals, and similar patterns have been observed in other primates and some rodent species. In female cynomolgus monkeys, social subordination leads to stimulation of the hypothalamic–pituitary–adrenocortical axis, and is associated with increased coronary atherosclerosis[69].

These findings clearly indicate that social status can be linked with neuroendocrine and metabolic factors, and with cardiovascular disease. However, the analogy with social gradients in humans can be pursued only cautiously. As Kaplan and Manuck[70] have pointed out, there is nothing inherently pathogenic in either dominant or subordinate social status in animals. Thus in male cynomolgus monkeys, coronary atherosclerosis is greater in dominant rather than subordinate animals under unstable social conditions, in contrast to the pattern in female monkeys[64]. In a number of rat strains, socially dominant animals have lower corticosteroid levels but also higher blood pressure[71]. In baboons, the pattern of higher cortisol in subordinates is only present under stable conditions, and not when social hierarchies are disrupted[68]. In addition, dominance hierarchies in social animals are established through success in direct interactions with conspecifics, and are maintained on a daily basis by competition, eye contact and other behaviours. The biological responses elicited under these circumstances may be very different from those observed in humans, where socio-economic status is related to economic advantage and prestige, and is not necessarily maintained by day to day contact between individuals of different social ranks.

Strategies for investigating psychobiological pathways in humans

Two methods for investigating psychobiological pathways are commonly in use: laboratory or clinical studies of acute physiological stress responses to behavioural challenge, and naturalistic studies involving repeated measures of physiological function in relation to ongoing behavioural states in everyday life. The advantages and limitations of these two strategies have been discussed in detail elsewhere[72,73]. Briefly, laboratory and clinical studies have the advantage that measurement of complex physiological and biochemical parameters can be carried out during exposure to precisely defined stimuli under controlled conditions. Confounding factors can be monitored or eliminated, and the experimental manipulation of stimuli allows the causal factors responsible for physiological responses to be determined. The disadvantage is that clinical and laboratory studies are acute, and typically involve reactions to artificial stimuli that rarely occur in the real world. In addition, laboratory studies are not helpful in investigating differences in the frequency of exposure to stressors, but only differences in the magnitude of responses, as detailed below.

Naturalistic or field psychobiological studies were for many years confined to self-monitored blood pressure and urinary assays of neuroendocrine parameters. However, the development of ambulatory electronic apparatus and the use of saliva samples for assessing neuroendocrine function have greatly increased the potential of naturalistic investigations. Naturalistic studies allow the investigator to explore the dynamic covariation of biological processes, psychosocial factors and events in everyday life. The range of biological parameters that can be studied remains much smaller than in clinical laboratory studies. Fluctuations in biological activity in everyday life are also influenced by confounding variables such as time of day, temperature, nutritional status, physical activity and posture. These need to be measured, and sophisticated statistical models applied so as to allow psychosocial influences to be identified. In addition, the monitoring process itself may have an impact on ongoing behaviour, leading people to restrict their activities in comparison with the normal situation[74].

Both laboratory and naturalistic methods can be used to investigate psychophysiological pathways related to socio-economic status in two ways. Firstly, direct comparisons can be made of cardiovascular and neuroendocrine responses in people varying in social status. Secondly, physiological responses can be assessed in relation to psychosocial factors that are differentially distributed across the social gradient. Several damaging and protective psychosocial factors vary in prevalence with socio-economic status[75]. Adverse work characteristics such as job strain, effort–reward imbalance and low job control are more prevalent in people working in low status jobs[76,77]. Hostility is greater on average in low socio-economic status respondents[78,79], while sense of control, mastery, and perceived control are greater among high status individuals[80,81]. Social isolation is more common in low status groups[82]. Early literature on stressful life events showed inconsistent associations with social position[83], but there is accumulating evidence that higher levels of chronic life stress are experienced by adults of lower socio-economic status[84,85]. Depression, hopelessness and low self-esteem are inversely associated with socio-economic status[86,87]. These psychosocial factors have in turn been linked with the development of coronary heart disease (for recent reviews see[14,88]). The observation of consistent psychobiological correlates of such psychosocial factors would support the notion that these pathways are relevant to social inequalities in coronary heart disease.

Table 1 Cardiovascular stress reactivity and socio-economic status (SES)

Study	Sample size	Age (years)	Tasks	SES criterion	Findings
Children and adolescents					
Gump *et al.*[153]	147 children and adolescents	8–10 and 15–17	Mirror tracing Cold pressor	Family SES (education and occupation) Neighbourhood SES	Cardiovascular reactivity greater in low family SES black and white participants, and in low neighbourhood SES black participants
Jackson *et al.*[154]	272 male and female adolescents	13·5 ± 2·6	Video game Stress interview Parent-child interaction	Neighbourhood SES	Systolic pressure reactivity greater in lower SES white participants Systolic pressure reactivity greater in higher SES black participants
Wilson *et al.*[155]	76 male and female black adolescents	13–16	Video game	Family SES (education and income) Neighbourhood SES	Diastolic pressure reactivity greater in adolescents from low SES families who live in low SES neighbourhoods
Adults					
Carroll *et al.*[98]	1091 male civil servants	43·6 ± 5·9	Raven's matrices with aversive noise	Grade of employment	Systolic pressure reactivity greater in higher status participants
Carroll *et al.*[99]	1657 men and women	23–63	Mental arithmetic	Employment	Diastolic pressure and heart rate reactivity greater in participants with non-manual occupations
Lynch *et al.*[97]	882 men	42–60	Anticipation of exercise test	Education, income and childhood SES	High systolic pressure reactivity more common in less educated men
Owens *et al.*[96]	49 men and women	40–55	Speech task	Education	Systolic, diastolic pressure and heart rate reactivity greater in lower SES participants

Laboratory mental stress studies

Laboratory studies involve the measurement of biological processes in response to behavioural tasks or emotional stressors. Biological stress responses have several components: the magnitude of reactions to events, the duration of responses (whether they are sustained throughout stimulation or diminish after the initial impact), and the rate of post-stress recovery back to reference levels. The laboratory paradigm is not suitable for studying all biological risk factors for coronary heart disease, since some evolve slowly over time and may not be susceptible to the influence of acute stimulation. Nevertheless, many of the biological processes implicated in coronary heart disease can be influenced by emotional stressors. Thus acute behavioural tasks or stressors have been shown to influence vascular endothelial function[89], platelet activation[90], lipid levels[91], blood pressure and heart rate[92], baroreceptor reflex sensitivity[93], sympathetic nervous system activation[94], and cortisol release[95].

Socio-economic inequalities in acute stress responses

If psychobiological processes are involved in mediating socio-economic inequalities in cardiovascular disease, then it can be hypothesized either that reactions in biologically-relevant parameters are greater in low compared with high socio-economic status groups, or that reactions are more frequent in low status groups. Laboratory mental stress testing has been used to investigate the first of these possibilities. Research relating acute physiological stress responses directly with socio-economic inequalities has largely been confined to well established variables such as blood pressure and heart rate. Results are summarized in Table 1. Three studies have been carried out with children or adolescents, classifying participants on the basis of their parents' socio-economic status or the characteristics of the neighbourhoods in which they live. These studies have generally shown greater cardiovascular stress reactivity in lower status groups, although there are variations

related to race. The four studies with adults published thus far present a mixed picture. Two studies involving American men and women[96], and Finnish men[97], have both documented higher stress reactivity in lower socio-economic status participants. But the reverse has been observed in studies from the U.K. involving large epidemiological samples[98,99]. In both these investigations, cardiovascular reactions were larger in higher status individuals. Both studies used challenging problem solving tasks, mental arithmetic and an adaptation of an intelligence test, to stimulate reactions. Carroll *et al.*[98] speculate that the anomalous pattern of results might have arisen because of greater engagement in the intellectually demanding task from higher status participants.

These studies highlight an important issue in studying socio-economic differences in reactivity to standardized mental stressors, namely the importance of utilizing 'status free' challenges. If one social group is more familiar than others with the types of demand elicited by tasks, then these individuals might exert more effort to succeed and their physiological reactivity may be enhanced. The role of task engagement in stimulating psychophysiological responses has long been recognized[100]. In the two British studies, the behavioural tasks were likely to have been rather unfamiliar to lower status individuals, who may have not therefore have become so involved. On the other hand, in the study from Finland, men were preparing to carry out physical exercise[97]. This challenge might have engaged the predominantly rural lower status men to a greater extent than higher status individuals. Ratings of engagement or involvement are helpful in determining whether different social status groups vary in their appraisal of tasks.

Studies of physiological stress reactivity in different socio-economic status groups have been confined to markers of cardiovascular activation, although a lack of adaptation in cortisol responses to repeated stress in women who classify themselves as being of lower social status has recently been described[101]. Measures of cytokine release, haemostasis, platelet activation and other parameters that are more directly relevant to the pathogenesis of cardiovascular disease will generate important additional information.

Acute stress responses and psychosocial factors related to socio-economic status

Physiological responses to standardized mental stress tests have been evaluated in relation to many of the psychosocial factors that are associated with socio-economic status, including work characteristics, hostility, social support and chronic life stress.

Job strain and job control

Blumenthal *et al.*[102] reported no differences in cardiovascular stress responses in relation to job strain in a sample of mild hypertensives. Studies evaluating job stress in terms of effort–reward imbalance have actually recorded greater cardiovascular and neuroendocrine reactivity among the less stressed workers[103]. However, a factor that must be taken into account is the nature of the challenge imposed on the individual, since not all stimuli are relevant to the experience of job strain or low job control. In two studies, high job strain was positively associated with systolic blood pressure reactions to uncontrollable tasks[104,105], but not with responses to more controllable tasks. The implication is that it is necessary for acute challenges to mimic the particular types of stressor that trouble participants in everyday life.

Hostility

Hostile people typically show larger blood pressure and heart rate responses than less hostile individuals to situations in which their psychological traits are activated by provocation or harassment[106,107]. For example, hostile men showed greater blood pressure increases during a problem-solving task than non-hostile men, but only when they were harassed by the experimenter at the same time[108]. These findings endorse the role of situational factors in determining physiological reactions. Hostility has also been linked with heightened stress reactivity in catecholamines[108], and blood platelet activation[109].

Social support

Results of the investigations that have assessed physiological stress reactions in relation to trait measures of social support have been inconclusive[59]. Social support has also been modelled in the laboratory in a number of experiments, comparing physiological reactions in people tested in isolation, or in the presence of supportive others. Results appear to depend on the participant's relationship with the supporting individual, with reduced physiological responsivity when support is active and encouraging, rather than being conveyed passively by mere presence during testing[110]. The relevance of these laboratory analogues for real life experience of social support and social isolation has yet to be established.

Chronic life stress

Laboratory studies of physiological reactivity in relation to chronic life stress have generated mixed findings. Heightened sympathetic reactivity[111], null effects[112,113] and diminished cortisol reactivity[114] have been reported in adults experiencing chronic life stress. Gump and Matthews[115] argue that heightened reactivity occurs when background stressors are ongoing at the time of laboratory testing, but not when life stress is indexed by recent adverse events that have been resolved. The duration of life stress may also be important. This topic requires further investigation.

Other psychosocial factors

There has been limited research focused on physiological stress reactivity and other psychosocial factors related

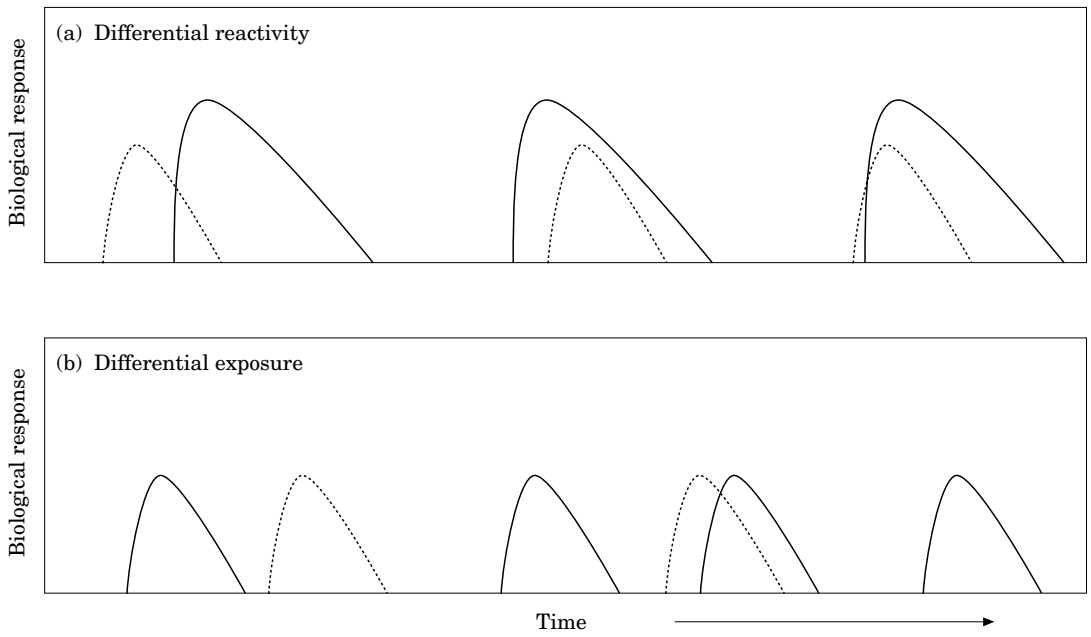

Figure 1 **Schematic outline of two ways in which biological responses to everyday events might differ in higher and lower socio-economic status groups. Response magnitudes and timings are arbitrary, and similar patterns might apply to a variety of biological processes. According to the differential reactivity model (a), socio-economic status groups might differ in their biological reactions to everyday events (shown here as larger and more sustained responses). The alternative differential exposure model (b) suggests that reactions do not differ in magnitude, but that lower status individuals experience more events that elicit biological reactions, so the frequency of reactions is greater in lower than higher status groups. ——=low social status; · · · ·=high social status.**

to socio-economic status. However, depression has been associated with heightened blood pressure, norepinephrine and cortisol responses to behavioural tasks[116,117], while high levels of self-esteem are inversely related to hypothalamic–pituitary–adrenocortical stress responses[118,119].

Conclusion

The literature relating acute physiological stress reactivity to psychosocial factors emphasizes the importance of the precise conditions under which reactivity is tested. Reaction patterns in relation to job strain, hostility and social support depend on the nature of the demands as well as upon the individual. However, given appropriate challenges, the consensus of evidence is that physiological reactivity is associated with psychosocial factors that are differentially distributed across the social gradient.

Naturalistic studies

Naturalistic studies of physiological activity in everyday life are used for a number of research and clinical purposes. Their relevance to understanding the psychobiological pathways mediating socio-economic inequalities in cardiovascular disease risk arises from the possibility of differences in three phenomena:

(1) Differences in level of function. Socio-economic status groups may differ in the level of activity in a physiological parameter in everyday life in ways that are related to disease risk. For example, blood pressure recorded with ambulatory techniques has been shown to predict cardiovascular disease independently of office or clinical blood pressure levels[120]. Similar patterns might exist for socio-economic status.

(2) Differences in rhythm. A second possibility is that low socio-economic status disturbs the diurnal rhythm of physiological function under naturalistic conditions. For example, the pattern of high corticosteroid output in the morning, diminishing to low levels late in the day, may be modified with chronic stress to a profile of heightened or diminished variability[121,122]. Such effects might be indicative of socio-economic disruption of normal regulatory function, and reflect persistent challenge to adaptive mechanisms or chronic 'allostatic load'[123].

(3) Differences in response to events. The third possibility is that socio-economic status stimulates differences in biological responses to psychosocial events under everyday life conditions. A phenomenon of this kind could be manifest either with differences in reactivity or differences in exposure, as is illustrated schematically in Fig. 1. Figure 1(a) shows the pattern that might arise if socio-economic status groups differed in their reactivity to everyday life

experiences, with larger or more sustained responses in low status individuals. The alternative is that the magnitude of responses is the same across the social gradient, but that there are differences in the frequency with which responses occur (Fig. 1(b)). Low status individuals may experience more events in their everyday lives that elicit physiological responses, because higher chronic stress, failures of coping, or reduced psychosocial resources may be translated into more frequent experience of daily hassles and minor stressors. The contrast between these two patterns resides in whether socio-economic status groups differ in reactivity to events, or exposure to events.

Naturalistic studies of socio-economic status and biological responses

Few naturalistic studies to date have systematically compared psychobiological measures under everyday life conditions in people of varying socio-economic status. Marmot and Theorell[124] analysed self-monitored blood pressure over the day and evening from civil servants in a pilot study for the Whitehall II survey, and showed that the decrease in the evening was smaller in the lower grade participants. However, a study of ambulatory blood pressure monitoring with 99 mild hypertensives found that levels over the working day and evening were greater in higher socio-economic status patients[125]. In another study of ambulatory blood pressure monitoring, pressure levels at work were marginally greater in low than high status normotensive men[125]. Among women, ambulatory pressure was elevated in high status women who also reported high levels of active striving and efforts to cope. A more recent study assessed blood pressure and heart rate from 100 men and women occupying high status (professional/managerial) and lower status (technical/clerical) jobs in a University[126]. No differences in blood pressure were observed between higher and lower status individuals over working or non-working days. However, heart rates were greater in participants with lower prestige jobs, particularly if they tended to experience negative moods over the recording period. In the one large scale neuroendocrine study yet to have been published, it was found that cortisol levels were greater over the day in individuals of high than low socio-economic status, with differences being particularly prominent early in the day[127].

The data thus far show no consistent associations between socio-economic status and variations in biological function over the day. Important differences between men and women may be present, but patterns vary with different biological responses. However, the majority of studies have involved post hoc division of samples into higher and lower status groups, and have not employed systematic sampling across the social gradient. Only tentative conclusions can therefore be drawn from this literature.

Psychosocial factors related to socio-economic status

Job strain and job control

Many studies have related ambulatory blood pressure and heart rate with job strain conceptualized according to the demand/control model. A pattern of elevated blood pressure in individuals working in high strain (high demand/low control) jobs has been confirmed by a large number of studies with men[128], although effects are less striking in women[129]. Within the working day, periods during which participants state that they have more control are associated with lower systolic and diastolic blood pressure[130]. High job strain has also been associated with a smaller reduction in blood pressure in the evening after work, indicative of a failure to unwind[105]. The impact of job strain on neuroendocrine function may be manifest through changes in rhythm, or responsivity at particular times of day. Saliva free cortisol is elevated early in the day in people experiencing high job strain and work overload, but not at later times of the day or evening[131,132].

Hostility

Associations have been described between psychobiological responses in naturalistic settings and different measures of hostility. Scores on the Cook-Medley cynical hostility scale were positively associated with systolic blood pressure over the working day in studies of male fire-fighters and students[133,134], while Raikkonen *et al.*[135] found that ambulatory blood pressure was positively associated with high hostility measured by interview in a sample of 100 working adults. Cortisol excretion during the day is greater in individuals with high scores on the Cook-Medley scale[136].

Social support

Research linking social support with psychobiological responses in naturalistic settings has been limited. One important study performed 24-h heart rate monitoring in 148 individuals from seven different professions ranging from physicians to saw-mill workers[137]. Social support at work was negatively correlated with heart rate during sleep, work and leisure time. Low social support has also been associated with diminished heart rate variability over the day[138].

Chronic life stress

Major life events and severe chronic stressors may lead to long-term disruption of biological function during everyday life[139,140]. At a more mundane level, negative moods and events in daily life are associated with biological responses. For instance, ambulatory monitoring studies have shown that blood pressure may be elevated during periods of stress within the day[141,142]. Cortisol sampled periodically over the day is also elevated in response to stressful events or problems,

independently of time of day, exercise and other factors[143]. Ockenfels *et al.*[121] reported that the chronic stress of unemployment was associated with a change in diurnal rhythm of cortisol, with higher morning and lower evening levels than were found in employed people. Social support buffers the impact of stress on blood pressure recorded in men and women over the working day[144].

Depressed mood

The association between clinical depression and function of the hypothalamic–pituitary–adrenal axis is well-recognized[145]. Negative moods states such as depression and anxiety have been associated with elevations in blood pressure during ambulatory monitoring[146] and with higher cortisol output over the day[147]. Patients with coronary artery disease who are depressed also show low heart rate variability[148], while elevated levels of inflammatory cytokines have been reported in patients experiencing 'vital exhaustion'[149]. Work in this area has largely involved measurement in clinical situations, and it will be important to establish whether similar processes are also observed during monitoring in everyday life.

Synthesis and future directions

Studies of the psychobiological processes relevant to the social gradient in coronary heart disease risk require the integration of disciplines that have traditionally worked to separate priorities, including behavioural and cardiovascular epidemiology, psychophysiology, psychoneuroendocrinology and clinical medicine. Research is at an early stage, and the promising leads identified in some studies have yet to be elaborated. Little prospective work has been carried out, and many methodological issues in the design, analysis and interpretation of laboratory and naturalistic studies remain to be resolved. Differences between men and women and between ethnic groups have been observed in several studies, but it is not yet certain how these relate to differences in coronary heart disease risk. Nevertheless, there are strong indications that psychobiological responses form one of the pathways through which socio-economic inequalities are translated into differential coronary heart disease risk.

From the present state of the evidence, we conclude that disturbed psychobiological reactivity (as assessed acutely in laboratory or clinic mental stress testing) in lower socio-economic status adults is present for some stimuli but not others. It is difficult to establish standardized challenges that are appraised in the same way by people across the social spectrum. Nevertheless, researchers should not be discouraged by the variability in results that have emerged thus far, but use these differences the better to understand the nature of the demands that elicit socially graded biological responses. Laboratory and clinical studies will continue to play a major role because of the wide range of biological parameters that can be recorded in such settings, in comparison with field studies.

We suggest that differences in exposure to psychosocial factors associated with coronary heart disease risk, that in turn have biological correlates, will prove as important as differences in reactivity per se. Enhanced stress reactivity may be necessary but not sufficient to increase cardiac risk. Such a conclusion means that greater emphasis needs to be placed on naturalistic studies in which exposure to adverse experiences that elicit biological responses can be examined. For example, Everson *et al.*[150] have shown that progression of carotid atherosclerosis over 4 years was greatest among middle-aged Finnish men from the Kuopio Study who were high stress responders, and had also been exposed to the chronic stress of high work place demands. The interplay between stress reactivity and socio-economic status has also been analysed in the Kuopio study[97]. The progression of carotid atherosclerosis over 4 years was greatest in low socio-economic status men who were high blood pressure stress responders, after adjustment for age, baseline atherosclerosis, lipid levels, body mass index, blood pressure, smoking and alcohol intake. These results are consistent with the model in Fig. 1 that emphasizes differential exposure to adverse life experience across socio-economic groups.

Ultimately, the significance of psychobiological pathways in contributing to socio-economic inequalities in coronary heart disease risk must be evaluated according to the scientific principles that are applied to other pathophysiological processes. Merely demonstrating that mechanisms are plausible and show the expected associations with cardiovascular risk profiles is not sufficient. From the epidemiological perspective, prospective studies are required that evaluate the associations between socio-economic status, disturbances of psychobiological function, and coronary heart disease incidence. Such investigations require the findings from laboratory and naturalistic studies to be integrated into large scale cohort studies. Establishing links with brain function is also vital. Brain imaging has recently been used to assess differences in cerebral activation during mental stress in relation to hostility[151]. There is preliminary evidence that central serotonergic responsivity is blunted in lower socio-economic status individuals, and this might be related to cardiovascular and neuroendocrine dysregulation[152]. From the clinical perspective, causal significance must be further tested by intervention studies in which putative psychobiological dysfunctions are corrected. The endeavour to understand how the central nervous system links the social and psychological experiences of people of different social rank with objective cardiac pathology is complex and multifaceted, but deserves our attention for its significance in correcting imbalances in disease risk across society.

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