5 The biopsychosocial approach: a note of caution

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Summary

This chapter will provide a cautionary critique of whether the biopsychosocial (BPS) model is useful in understanding aetiological factors in chronic diseases. I will illustrate the arguments by referring to studies of peptic ulcer and ischaemic heart disease. I will show that bias and confounding can generate spurious findings and associations, especially in observational studies. When interventional studies have been used to examine the efficacy of a psychosocial approach the results have been disappointing.

Introduction

This presentation concerns one area where I feel we need to be cautious about the BPS approach. This is when considering the aetiological importance of some of the factors postulated within the BPS model. Choose whatever term you like: stress, psychosocial factors, social anxiety, and so on. They have similar resonance, and, in my view, problems. I am sure that these factors are related to a general sense of well-being, happiness, or quality of life and that through their effects on health-related behaviours, such as smoking, drinking, drug use, sexual behaviour, risk taking, and adherence to medical care, they will have an effect on mortality and major disease outcomes. However, I think the evidence is less good that psychosocial factors have a direct aetiological effect on diseases like peptic ulcer or coronary heart disease.

One illustration of how such factors are related to particular health outcomes comes from a study of differentials according to characteristics of areas.[1] We used an indicator of material deprivation, the Townsend Index, and an index of social fragmentation, the Congdon Index, and examined how these correlated with different causes of death. When we examined small areas across the UK, material deprivation correlated more strongly with overall mortality than social fragmentation (Table 5.1). Because social fragmentation

Table 5.1 Correlation between indices of social fragmentation and deprivation with standardized mortality ratios for all-cause and cause-specific mortality

	Simple correlations		Partial correlations	
	Townsend Index	Congdon Index	Townsend Index	Congdon Index
Women				
All cause	0.82	0.35	0.85	−0.50
Coronary heart disease	0.66	0.12	0.81	−0.62
Stroke	0.58	0.12	0.68	−0.46
Lung cancer	0.81	0.51	0.73	−0.12
Stomach cancer	0.60	0.15	0.69	−0.45
Suicide	0.38	0.58	−0.04	0.48
Cirrhosis	0.63	0.56	0.40	0.23
Men				
All cause	0.87	0.46	0.86	−0.40
Coronary heart disease	0.67	0.13	0.80	−0.60
Stroke	0.67	0.24	0.71	−0.40
Lung cancer	0.84	0.44	0.82	−0.34
Stomach cancer	0.60	0.15	0.69	−0.45
Suicide	0.58	0.71	0.18	0.53
Cirrhosis	0.70	0.67	0.45	0.36

From Reference 1.

is related to deprivation, it was also related to all-cause mortality. But if we took deprivation into account, the association between social fragmentation and all-cause mortality actually reversed (Table 5.1). However for outcomes that are plausibly related to social fragmentation—suicide and cirrhosis—social fragmentation stayed related to mortality.

The psychosocial environment does appear to be associated with those causes of death that common sense would suggest it should be related to, through its influence on dispositions and behaviours. But what is the evidence that psychosocial factors are direct aetiological factors in chronic diseases, acting through psychoneuroendocrinological (or other currently fashionable) mediating mechanisms? Is stress an important determinant of population health?

I would like to quote from an article George Engel wrote a year after his seminal *Science* paper,[2] where he talked about our need to think about psychosocial factors.[3] He said,

> Predicated on a systems approach, the BPS model dispenses with the scientifically archaic principles of dualism and reductionism, and replaces the simple cause and effect explanations of linear causality with reciprocal causal models. Health, disease and disability thus are conceptualized in terms of the relative intactness and functioning of each component system on each hierarchical level. Overall health reflects a high level of intra- and inter-systemic harmony.[3]

I would suggest that, contrary to the view that embracing complexity always gets us closer to the truth, much of what we know about disease actually suggests that the utilization of rather simple models of linear causality is often appropriate, particularly when we are considering ways of improving population health. In this regard Engel's quote has some historical resonance. During the first half of the nineteenth century the complex, highly theoretical language of those who opposed the view that diseases like cholera were contagious was contrasted with the crude, reductionist tone of the contagionists.[4]

The more we understand about many diseases, the simpler the models get. The extraordinary detail given in reports in the 1830s about factors related to cholera no longer appeared so mysterious once it was recognized that a proximal transmissible element—associated with a wide variety of factors—was a necessary cause.[4] Some of the factors considered in the complex models are ones that would have influenced whether or not people were exposed to the transmissible agent and in this sense they are acting as distal causes. However, if the chain of causation is broken, then the disease does not occur. For example, many psychological and social factors influence whether people smoke and thus indirectly lead to an increase in lung cancer risk. In different times and different places, though, different economic and psychological factors may influence smoking. The social class gradient of cigarette smoking has, for example, changed greatly in the UK over the last 50 years.[5] Ultimately social and psychological factors will only influence the risk of lung cancer through influencing smoking patterns. Take away the cigarettes, and these factors will not result in lung cancer.

Similarly, consider peptic ulcer or stomach cancer. If you come from a large family where there are poor facilities for maintaining hygiene, you have a much higher risk of acquiring *Helicobacter pylori* infection in childhood. Therefore in some sense these social factors are causally related to acquisition of *H. pylori* and if you acquire *H. pylori* then your risk of peptic ulcer and stomach cancer increases greatly. However, if you treat the infection, or interrupt the transmission route, the link between the underlying social factors and the risk of these diseases will be broken.

Of course not everyone who smokes cigarettes develops lung cancer and not everyone carrying *H. pylori* develops stomach cancer or peptic ulcer. Therefore it might be thought that investigating why certain people develop disease,

given these exposures, is the key issue. However, if no one smoked cigarettes in a population, the vast bulk of lung cancer would disappear. Thus in public health terms, cigarette smoking is the cause of the burden of disease and focusing on why some smokers get lung cancer and some do not may be a diversion from a public health intervention that could produce a dramatic improvement in population health.

Cautionary tales

Over the past 50 years many psychosocial factors have been proposed and accepted as important aetiological agents for particular diseases and then they have quietly been dropped from consideration and discussion. If this meeting had been held 15 years ago we would have discussed type A behaviour at great length. Type A behaviour will hardly be mentioned at this meeting, because it no longer appears to be an important cause of coronary heart disease. People versed in the history of epidemiology will know that conditions such as cholera, pellagra, beri beri, asthma, Down's syndrome, scurvy, yellow fever, typhoid, and peptic ulcer were all at one time seen as diseases that were importantly influenced by stress or (in earlier times) 'moral' factors. In 1832 William Beaumont, for example, considered that such factors underlaid 'the greater proportional number of deaths in the cholera epidemics'.[6] He would doubtless have considered the BPS model an ideal way of conceptualizing the causes of cholera, while pouring scorn over those studying the geographical distribution of cases and relating this to water supply.

An important critic of the BPS model—although she never explicitly talks about it—is Susan Sontag. She published a remarkable book, *Illness as metaphor*,[7] a year after Engel's 1977 article appeared. Sontag wrote about how in plague-ridden England in the late sixteenth and seventeenth centuries, it was believed that a happy man would not get the plague. She stated that,

> The fantasy that a happy state of mind would fend off disease flourished for all infectious diseases before the nature of infection was understood. Theories that diseases are caused by mental state and can be cured by willpower are always an index of how much is not understood about the physical basis of the disease. The notion that a disease can be explained only by a variety of causes is precisely the characteristic of thinking about diseases where causation is not understood.

Diseases that are thought to be multi-determined have the widest scope for becoming metaphors for what is felt to be socially or morally wrong. Sontag was writing at least partially in response to her own diagnosis with cancer. Her reason for being sceptical of the BPS model was that she saw it as a way of putting blame for disease on the people with disease. This metaphorical treatment of disease can lead to internalized blame and guilt. Sontag therefore wanted to strip these metaphors away and see disease principally as a biological, not psychological, phenomenon.

The peptic ulcer story will be well known to most of you. A large amount of epidemiological work, carried out over some 50 years, repeatedly suggested that stress was a major factor in the causation of peptic ulcer. One case–control study was published in 1937.[8] If the study had got the right answer this would be considered an important early classic of the genre. Davies and Macbeth Wilson studied 205 patients with peptic ulcer. They recruited a group of controls with hernias, because they recognized that having an illness would influence the way people reported life events and they matched for age, sex, and social class. They asked people about life events, with an interviewer blinded to the case or control nature of each patient. This was clearly a study that had been well planned and showed evidence of methodological sophistication absent from most such research of its time. They detailed life events that had preceded the diagnosis of disease and demonstrated very strong associations between life events and the risk of peptic ulcer. Using a statistical approach not available to them in 1937, we can now calculate an odds ratio among men of 20 (95% confidence interval (CI), 9–47; $P < 0.0000001$) and among women of 13 (95% CI, 4–41; $P < 0.0000001$). In retrospect it is almost certainly the case that, despite their attempt to account for a possible bias, the associations arose because people who were reporting symptoms of peptic ulcer also tended to over-report problems in other aspects of their lives.

Richard Doll was introduced to epidemiology by Francis Avery Jones, an epidemiologically minded gastroenterologist. Avery Jones was very attuned to thinking about epidemiological patterns of disease and was also someone who appeared convinced that stress was important in peptic ulcer. In his chapter in the 1948 book *Progress in clinical medicine*[9] Avery Jones said,

> There have not been any major advances in the treatment of gastroduodenal ulcer. A better appreciation of the natural history of the disease has directed the treatment away from the ulcer towards the individual as a whole ... ,

which was a fair summary of the BPS approach. He went on to state that,

> Most clinicians agree there is a particular personality associated with peptic ulcer. These patients are tense, possess unusual drive and are over-conscientious in their work. They tend to worry unduly, but do not give way to their emotions ... The recognition of the psychological aspects of peptic ulcer has the virtue of therapeutic application. If the tensed-up, over-active individual can relax, he can ease the strain on his digestion. If the doctor can listen to the unburdening of a tragic tale, often untold to other ears, he may relieve a nervous tension which has been reflected on the stomach. If the patient can learn to appreciate the inter-relation between mind and stomach, he may be able to minimise his dyspepsia at times of stress.

Regarding the management of ulcers, Avery Jones thought that,

> During convalescence the patient should be given a simple exposition of peptic ulcer. A clear understanding of the need for maintaining a calm outlook on life, and of the necessity for not exceeding his natural 'tempo' by accepting too much work or responsibility, will be much more valuable than routine medication. The patient has got to live with his ulcer-forming tendency and it is essential to give him all the information at our disposal ... There is little doubt that healing is accelerated and more commonly completed if real rest is taken, preferably away from home, where the extra work occasioned by the illness may add to the worry of the patient. A period away from home may add perspective to domestic difficulties.

The patient in these quotes was, of course, always a male patient and it would be interesting to know what the wives of these patients thought about 'perspective' being added to their 'domestic difficulties' through absence from home. Avery Jones went on to discuss dietary aspects of treatment:

> It is sufficient to have initial hourly or two-hourly milk feeds, a first diet with small two-hourly purée feeds, and a basic second diet when pain has subsided, still with two-hourly feeds ... The third diet re-directs the emphasis to ordinary meal-times, but maintains the bland characteristics.

This does not sound like an attractive diet. However such was Avery Jones's concern not to increase stress, he added that,

> The diet should be served in as colourful and attractive a way as possible. A bland insipid colourless diet may cause less psychic flow of gastric juice, but it makes the patient depressed and irritable. The sustained resentment is more harmful than the increased psychic secretion.

It is entertaining to look at these discussions with the benefit of hindsight. Perhaps what is not quite so entertaining is the realization that in 400 consecutive admissions for gastroduodenal bleeding to the hospital at which Avery Jones worked, 27 of them died under this regime. This was a disease that killed people. As the dismal pattern of morbidity and mortality due to peptic ulcer continued, many of the epidemiological studies—which should have identified potentially modifiable causes of the disease—continued to focus on stress as a major causal factor. Interestingly, looking at these studies now, they often found that people with peptic ulcers came from large families and had more siblings than people not developing ulcers.[10–13] We now think that this is because the transmission of infection by *H. pylori* is facilitated within large sibships. Indeed, epidemiologists would tend to interpret such data as a possible indicator of the particular dynamics of infection. However, because the belief that peptic ulcer was stress-related was strong, association with family formation were taken to reflect particular psychological exposures,[14,15] thus associations that could have served as an important clue to a modifiable—and

key—cause of the disease were unfortunately taken as yet more 'proof' of the pre-eminent role of stress in peptic ulcer.

Another clue to a modifiable cause of peptic ulcer should have come from the pioneering work of Mervyn Susser and Zena Stein in 1962.[16] These authors identified clear birth cohort patterns in the rise (and then fall) of peptic ulcer disease in the UK, with duodenal ulcer lagging approximately 10 years behind gastric ulcer in terms of the birth cohort with the peak disease rates. An analysis of data from 19 countries showed similar cohort patterns, with some variation between countries in precisely when the rises and falls started, but a consistent pattern being seen with respect to the difference between gastric and duodenal ulceration.[17]

The detection of birth cohort phenomena in disease or mortality rates gives important clues as to the disease aetiology—specifically, suggesting aetiological factors operating early in life. Thus other early cohort analyses demonstrated that tuberculosis mortality fell in a cohort-specific fashion,[18,19] which Springett interpreted as indicating that most tuberculosis causing death at older ages was acquired during earlier life.[19]

Despite the work of Springett and others, the initial interpretation of the birth-cohort trends in peptic ulcer rates was strongly influenced by the prevailing paradigm that peptic ulcer was a disease caused by stress. Thus the birth cohort patterns observed by Susser and Stein were interpreted as reflecting the particular experiences of the UK birth cohort demonstrating highest disease risks—the First World War as young adults, then the depression of the 1930s, and the Second World War in middle age[16,20]—rather than an important aetiological factor acting in early life. Now, of course, we would identify *H. pylori* acquisition in early life as this factor.[21]

There were a few vocal sceptics in the stress and peptic ulcer saga. One was Richard Asher. Commenting on a paper by Szasz and Robertson, regarding psychological factors in the aetiology of baldness,[22] Asher wrote, 'It is now fashionable to put forward mental causes for those illnesses where physical causes have not yet been found, such as peptic ulcer.'[23] Richard Doll relates how Asher gave him an article to read about peptic ulcer and its cause by psychological stress and asked, 'Do you think that's a fair account of what people think?' Doll replied, 'Well, it's a bit stilted language, Richard, but yes, it's a perfectly fair account.' Asher replied, 'Actually, it was written in 1850 about general paralysis of the insane. And I merely substituted peptic ulcer for general paralysis of the insane.'[24]

Jerry Morris, Director of the Medical Research Council Social Medicine Research Unit, was also not an enthusiast for stress as a cause of peptic ulcer. A member of his unit, EM Goldberg, carried out a detailed study into the social

and psychological background of duodenal ulcer[14] and in the introduction thanked 'Dr JN Morris, whose healthy scepticism, particularly in matters psychological, helped throughout to keep the team's feet on the ground.' Morris considered that time trends in peptic ulcer incidence made little sense if viewed within the stress framework. He stated that these trends

> would suggest to anyone in sympathy with 'psychosomatic' theories . . . that the type of personality disposed to the disease is less common—unfortunately not a testable proposition; [or] that the environment is less of a strain—which is scarcely conceivable.[25]

Finally, an anonymous writer in the *British Medical Journal* in 1959 said

> When future work has solved the riddle of chronic peptic ulcer, we may find that the facile explanation sometimes given today that it is a disease of civilization due to mental stress will seem as remote from the truth as the view that malaria is caused by foul vapours ascending from the swamps.[26]

Enter *Helicobacter pylori*

In 1983, *H. pylori* was introduced as a candidate cause of peptic ulcer. It could be said that as we did not know about *H. pylori* until 1983, what does it matter that until then we had a stress model, because it did not block the development of understanding of the causes of peptic ulcer? But this may not be the case. Spiral bacteria, which clearly were *H. pylori*, were described in the stomach in 1889[27] and the specific hypothesis that peptic ulcers were caused by bacteria had already been advanced, with evidence, in 1875.[27] These early findings were followed by repeated studies published in good journals isolating bacteria, from peptic ulcers, which would now be identified as *H. pylori*.[27] Doctors in Mount Sinai Hospital advocated antibiotic treatment for peptic ulcers, which they claimed worked, in 1948.[28] A patent for an antibiotic formulation for treating peptic ulcers was issued in 1961.[29] However, the stress model served to block people from building on this and moving towards an answer that would have led to a treatment that could have improved the quality of life, dramatically, for millions of people.

Various psychological treatments for peptic ulcer were advocated and large numbers of people were subjected to them. Of course the usual claims for dramatic success were made, but properly conducted randomized controlled trials demonstrated no benefit of such time-consuming and expensive treatments.[30–32] The conclusion of one well-conducted trial was that 'our study demonstrates a need for humility about the degree to which psychological interventions can effect powerful biological processes and impact on patient's lives.'[32]

Things may appear clear with hindsight, but people really were directed away from a treatment for peptic ulcers that worked—antibiotics—to ones that did not. All the pieces fitted together, including the identification of a bacterium, by the 1950s. But the answer that could have led to an effective treatment of the disease was missed because of a particular model—essentially the BPS model—and the mindset that it generated.

Observational studies of threats to health and the problem of confounding

Now I am going to address problems in observational data relating psychosocial factors to health outcomes. The two major issues are confounding and bias. Confounding is a general issue in epidemiology. It is not something that is of any greater importance in psychosocial epidemiology than in other fields of epidemiology. It is important in all areas where we are studying factors that are very strongly socially patterned. The antioxidant story is relevant here. The epidemiological evidence gave very strong suggestions that antioxidant vitamin intake reduced the risk of cardiovascular disease. Large cohorts of people were followed up and the risk of cardiovascular disease in relation to

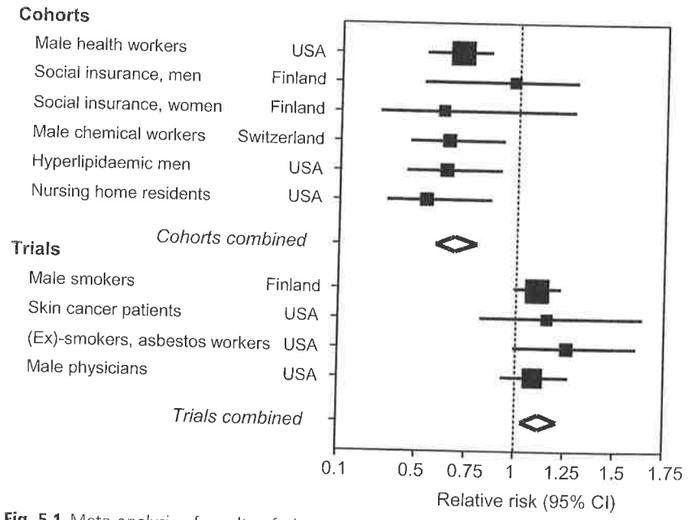

Fig. 5.1 Meta-analysis of results of observational cohort studies of β-carotene intake and cardiovascular mortality and of randomized controlled trials of the same issue. CI, confidence interval.

β-carotene intake or levels examined. Differences in β-carotene were associated with a large apparent reduction in the risk of cardiovascular disease (Fig. 5.1).[33] Some of these observational study results were adjusted for many potential confounding factors and this apparent protective effect was still shown. Large-scale randomized placebo-controlled trials of β-carotene for up to 13 years showed, if anything, slightly increased risk of cardiovascular disease in those given β-carotene (Fig. 5.1). The most striking finding was that in the first large randomized controlled trial, β-carotene was measured in the blood at baseline in the control group and it predicted cardiovascular disease just as in other observational studies. In the same study that showed that changing β-carotene level had no beneficial effect on cardiovascular disease risk, an observational analysis suggested apparent protection.

'Eating fruit halves the risk of an early death' a UK newspaper recently claimed,[34] in an excited response to a study showing a strong inverse association between blood vitamin C levels and coronary heart disease risk.[35] A subsequent randomized controlled trial of a vitamin supplement that raised

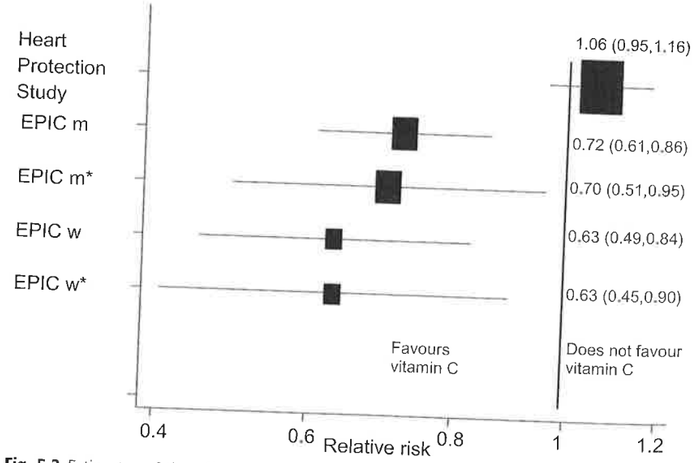

Fig. 5.2 Estimates of the effects of an increase of 15.7 μmol/l plasma vitamin C on coronary heart disease risk estimated from observational epidemiological EPIC (European Prospective Investigation of Cancer and Nutrition) study and randomized controlled Heart Protection study. EPIC m, men (age adjusted); EPIC m*, men (adjusted for systolic blood pressure, cholesterol, body mass index (BMI), smoking, diabetes, and vitamin supplement use); EPIC w, women (age adjusted); EPIC w*, women (adjusted for systolic blood pressure, cholesterol, BMI, smoking, diabetes, and vitamin supplement use).

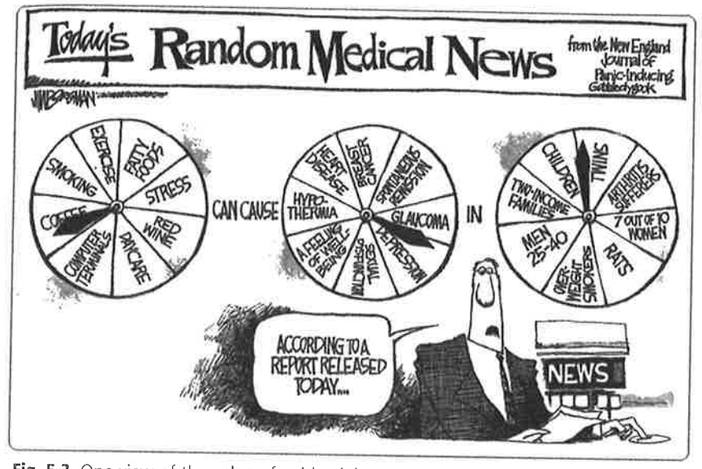

Fig. 5.3 One view of the value of epidemiology.

blood vitamin C levels by 15.7 μmol/l found 5-year coronary heart disease risk unchanged (relative risk, 1.06; 95% CI, 0.95, 1.16),[36] whereas the equivalent observational findings for this increase in blood vitamin C were coronary heart disease relative risks of 0.63 (95% CI, 0.49, 0.84) in women and 0.72 (95% CI, 0.61, 0.86) in men (Fig 5.2). Again the results from robust experiment and fallible observation are clearly not compatible. Similar stories could be told with respect to vitamin E intake and, famously, hormone replacement therapy (HRT), with observational data suggesting a strong protective influence on cardiovascular disease risk and randomized controlled trials ruling out such protective effects.[37] The repeated publication of claims from epidemiological studies—which get changed as better data accrue—have understandably led to cynicism among the public (Fig. 5.3).

Now I will give an illustration of how confounding can generate associations between socially patterned exposures and outcomes. In the first Whitehall study, Geoffrey Rose, Martin Shipley, and I completed a series of analyses on car ownership.[38] Car ownership was enquired about because Rose thought that if people had cars, they would do less exercise and would be at higher risk of coronary heart disease. Of course, by the time we came to look at the data in the late 1980s, we realized that car ownership would function as an indicator of social circumstances. Car owners had higher incomes and should live longer, and this is what we saw. People without a car had a 40 per cent higher risk of coronary heart disease mortality. If you adjusted for all of

the standard risk factors, a statistically robust residual effect remained, with people who did not have cars having a higher risk of mortality. If we randomized people to car ownership, would this reduce their coronary heart disease mortality? Probably not. But if, rather than asking people about car ownership, we had asked them about other socially patterned factors—for example, many of the stress measures we have heard about at this meeting—we would get exactly the same finding. Confounding generates these sorts of associations and conventional approaches for statistically 'controlling' for it do not work.[39,40]

In a study in the west of Scotland set up in the 1970s—known as the Collaborative study—a then popular stress measure called the Reeder Stress Inventory was elicited from nearly 6000 men.[41] It is predominantly a 'psychological' measure of perceptions of negative feelings and, in the few contemporary studies where comparisons can be made, scores on other measures of feelings are highly correlated with those of the Reeder Stress Inventory.[42] In contrast currently popular psychosocial measures—popular, perhaps, because they appear to predict disease—are often more 'social'. That is, they are measures of aspects of the social environment (such as work conditions) that are assumed to provoke negative feelings. Consequently estimates of the effects of these latter measures are inevitably prone to confounding—because poor social environment is likely to be characterized by several potentially health damaging factors in addition to any negative feelings it engenders in the person experiencing it.

An indication that the measure has some meaning was that the people who reported high stress were more likely to be heavy smokers or heavy drinkers, to do less leisure time exercise, and to have worse sleep patterns.[41] The stress measure was related to behavioural risk factors in the way that you would expect. But because of the sort of questionnaire it was, and the context of the time, it was actually associated with a higher socioeconomic position—better-off people reported more stress. If you adjusted the associations of stress with smoking, drinking, and exercise for measures of socioeconomic position, the associations got stronger.[41] This measure was telling us something about how people were feeling, which was reflected in their behavioural patterns.

You would imagine that this stress measure should be associated with higher risk of mortality—it was associated with smoking, heavy drinking, and other risky behaviours. The remarkable thing was that because it was associated with higher socioeconomic position, stress was apparently protective in this study.[43] All-cause mortality was lower in the people with high stress, as was cardiovascular disease mortality. Interestingly, smoking-related cancers

were lower in the people with high stress, presumably because of the confounding by socially patterned risk factors. The point here is that if stress is socially patterned the 'wrong way' then it appears that stress is protective. This is perhaps analogous to the way that type A behaviour ceased to predict coronary heart disease once diagnosed coronary heart disease was no longer a disease apparently of the affluent. In our study, psychiatric hospital admissions were much higher in people with high stress. This stress measure meant something. 'High stress' people also got admitted to hospital more for haemorrhoids, varicose veins, and other non-mandatory admissions.[44] Stress influenced the way they presented to hospital. It did not influence the onset of cardiovascular disease, however.

How can we get round confounding in observational epidemiology? One way is to reinstate one of Bradford Hill's causal criteria: specificity. If you think that stress processes influence cardiovascular disease, then they should not be related to other outcomes, as most diseases have only a finite number of causes. When exposures are associated in a general way with a wide variety of outcomes it is likely that confounding by socially patterned behavioural and environmental factors are at play. Early on in the HRT debate, Diana Petitti and colleagues pointed out that HRT use apparently protected against accidental and violent deaths in observational studies as much as against coronary heart disease and that given the lack of a plausible biological link between HRT and accidental/violent death both associations may have been confounded,[45] a suggestion later confirmed by the randomized controlled trials.[46]

The great shame in much of the stress literature is that only one endpoint—cardiovascular disease—is usually reported. If in the same study it was shown that stress was related to stomach cancer, or lung cancer, to the same degree as cardiovascular disease, this would suggest that confounding may well be generating the associations. Studies should report multiple outcomes.

Bias

Finally, I'm going to address the issue of bias, with an illustration of how bias can generate associations in observational studies. In the Collaborative study, the men were followed up after 5 years and Rose's angina questionnaire was given out. There was a 2.5-fold higher risk of incident angina among the men who reported more stress, but no effect on incident ischaemia,[47] or, as we have seen, cardiovascular disease mortality (Table 5.2). Indeed ischaemia and cardiovascular disease mortality showed reversed effects, presumably because the people reporting more stress experienced more favourable social circumstances. The large apparent influence of stress on incident angina was

Table 5.2 Odds ratios (95% confidence intervals) for incident angina and ischaemia at second screening by reported stress category at first screening (low stress as baseline, mean follow-up period of 5 years 2 months)[47]

	Incident angina		Incident ischaemia		Coronary heart disease mortality	
	Adjusted for age only	Adjusted for age, socioeconomic position, screening interval, and risk factors*	Adjusted for age only	Adjusted for age, socioeconomic position,screening interval, and risk factors*	Adjusted for age, only	Adjusted for age socioeconomic position, and risk-factors*
High stress	2.32 (1.43–3.78)	2.66 (1.61–4.41)	0.63 (0.34–1.15)	0.67 (0.36–1.26)	0.86 (0.67–1.12)	0.96 (0.74–1.25)
Medium stress	1.22 (0.82–1.82)	1.37 (0.91–2.08)	1.04 (0.73–1.48)	1.03 (0.71–1.49)	0.86 (0.72–1.03)	0.97 (0.81–1.16)
Low stress	1.00	1.00	1.00	1.00	1.00	1.00
P for trend	0.002	<0.001	0.27	0.37	0.14	0.72

* Risk factors: smoking, alcohol consumption, weekly hours of exercise, cholesterol concentration, diastolic blood pressure, body mass index, forced expiratory volume in 1 second.

Table 5.3 Incident angina, according to level of perceived psychological stress at baseline, with and without adjustment for reporting tendency[48]

Perceived stress	Mean reporting tendency score	Incident angina* (odds ratio (95% confidence interval))	
		Adjustment A—age, socioeconomic position, smoking, alcohol consumption, weekly exercise, blood pressure, cholesterol, body mass index, lung function	Adjustment B as in A, plus reporting tendency score
High (n = 739)	0.77	2.63 (1.59–4.33)	2.28 (1.37–3.80)
Medium (n = 3017)	0.52	1.36 (0.90–2.05)	1.27 (0.84–1.92)
Low (n = 1821)	0.41	1.00	1.00
P for trend	<0.001	<0.001	0.003

probably seen because the people who reported high stress also reported other forms of discomfort in their lives, including chest pain. This was obviously not due to there being any actual stress-related coronary disease, otherwise it would have been revealed in incident ischaemia and cardiovascular disease mortality. We had a good indicator of reporting tendency in this study. A series of symptoms were queried, which were thought to be symptoms of diabetes, but most of these symptoms did not predict mortality.[48] If you want a marker of reporting tendency you want something that does not predict mortality. This measure was quite strongly related to stress reporting. It was also related to reporting other factors, such as low job satisfaction, that we had in the study and seemed to be a marker of a tendency to report high rates of symptoms. It was related to Rose angina, but if you adjusted for reporting tendency, this made very little difference to the results (Table 5.3).[48] The point is that adjustment for measures of negative affectivity in studies does not actually control for reporting tendency. We could have published the 2.5-fold increased risk of angina independent of confounders and reporting tendency, because studies of stress have got into major journals reporting on just this outcome and with similar effect sizes (Table 5.4). Rather than this, we reported these results as demonstrating how it is possible to get misleading findings on stress and disease from observational epidemiology. It is interesting to compare our results using the Reeder questionnaire with the Whitehall study findings for job control (Table 5.5).[49] The two studies got very similar results with a subjective measure—Rose angina. In both studies there was no asso-

Table 5.4 Recent studies reporting relationships between subjective exposures and subjective health outcomes

Study	Subjective exposure	Health outcome	Effects described	Comments
Collaborative study	Global perceived stress	Odds ratio for incident Rose angina	High stress, 2.28 (1.37–3.80); medium stress, 1.27 (0.84–1.92); low stress, 1.00	Results adjusted for age, cardiac risk factors, occupational class and reporting tendency
Bosma *et al.* (1997)[49]	Job control	Odds ratio for incident Rose angina	Low control, 2.02 (1.22–3.34); intermediate control, 1.44 (0.86–2.39); high control, 1.00	Results adjusted for age, cardiac risk factors, employment grade and reporting tendency
Bosma *et al.* (1999)[58]	Psychological attributes	Odds ratio for self-reported adult 'poor general health' by childhood social class	Odds ratio of 1.67 (1.02–2.75) associated with lowest childhood social class reduced to 1.45 (0.87–2.43) on adjustment for locus of control	Results adjusted for age, marital status, urbanisation, religious affiliation and adult social class
Evans *et al.* (2000)[59]	Worry about pressure at work	Self-reported quality of life (SF-36) scores	Trend of decreasing health status with increasing worry about pressure at work for all eight dimensions of SF-36	Results adjusted for age, sex, ethnicity, marital status, education, occupational class, employment status, disease risk factors, environmental hazards
Cheng *et al.* (2000)[60]	'Job strain' (job control, job demands, and work-related social support)	Change in self-reported quality of life (SF-36) scores	Physical functioning deteriorated more and mental health improved less in subjects with low compared to high job strain (change in physical functioning with high control, −3.12 (−4.37 to −1.87), low control, −3.76 (−4.95 to −2.57))	Results adjusted for age, disease risk factors, marital status, educational level, presence of confidant and job insecurity

Table 5.5 Associations odds ratios (95% confidence intervals) between perceived stress and job control and subjective and objective outcomes in the West of Scotland Collaborative study and the Whitehall II study[47,49,61]

Outcome type	Effects in Collaborative study	Effects in Whitehall II study
*Fully subjective**		
High exposure	2.66 (1.61–4.41)	2.02 (1.22–2.34)
Medium exposure	1.37 (0.91–2.08)	1.44 (0.86–2.39)
Low exposure	1.00	1.00
Fully objective†		
High exposure	0.67 (0.36–1.26)	1.17 (0.8–1.8)
Medium exposure	1.03 (0.71–1.49)	1.16 (0.8–1.7)
Low exposure	1.00	1.00‡

* Rose angina in both studies, †Electrocardiogram abnormalities (Minnesota coding system) in both studies, All estimates adjusted for age, social position, and cardiovascular risk factors except for ‡, where only unadjusted estimates were reported in the paper.[61]

ciation between job control and the non-subjective measure of electrocardiogram (ECG) ischaemia. There is a remarkable parallelism between the findings.

In observational epidemiology, we need to take both confounding and bias into account. If a stress measure is not confounded with social position and other behavioural factors, then one needs to consider bias. If it is both related to reporting tendency and confounded, then both need to be considered. Every time we see an epidemiological result, the β-carotene, vitamin C, and HRT examples should come to mind.

Evidence from experimental studies and non-human primates

The preceding discussion of approaches to interpretational difficulty in observational data aside, the most powerful strategy to minimize the possibility of confounding is random allocation of exposure level within an experimental study. In this way any confounding factors (measured or unmeasured) should be evenly distributed across the different levels of exposure such that any effect seen is truly that of the exposure. To allow this approach, exposure level must be modifiable through an intervention amenable to random allocation. Arguably, this provides the strongest and most practically relevant evidence on causality, because a positive treatment effect demonstrates both the existence of a causal relation and the effectiveness of an intervention based on this relation.

The number of experimental studies of the effects of psychosocial intervention on objective measures of heart disease is relatively small. Most have assessed effects on prognosis amongst individuals with established heart disease. The factors determining prognosis in people with heart disease may not be the same, or may not have the same relative importance, as those determining disease development. Nevertheless this evidence is still useful as an indicator of the potential of psychosocial interventions to improve population cardiovascular health. In most published examples 'stress reduction' interventions were delivered as part of an intervention package targeting multiple risk factors such as smoking, diet, and exercise and aiming to improve case management. Reviews of these studies have suggested small but significant effects on prognosis, but have not been able to disaggregate the effects of the psychosocial component of the intervention from that of other components.[50,51]

A 'pure' psychosocial intervention was assessed in the recently completed Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial, a study considerably larger than any of those included in the preceding reviews.[52] Depression is perhaps the psychosocial factor with the strongest candidature for a causal relation with heart disease.[53] Because of this, ENRICHD assessed the effect of depression reduction (through cognitive behavioural therapy—with adjunctive use of sertraline at physicians' discretion) on the prognosis of established heart disease. The intervention was effective in reducing depression, but heart disease prognosis was the same amongst controls as in the intervention group. Indeed, lead investigators on ENRICHD acknowledged that the association between depression and heart disease may not be causal and have emphasized that the principal justification for treating depression is improved quality of life, more than reduction in mortality[54]

Patel and colleagues described perhaps the most convincing demonstration of an effect of a psychosocial intervention on coronary mortality amongst subjects without clinical heart disease at study recruitment.[55] Following a stress reduction intervention (relaxation therapy) amongst a group of subjects at high coronary risk, one control subject out of 81 died from heart disease and five out of 81 had ECG changes compatible with myocardial infarction, whereas no intervention subjects died from heart disease and only one out of 88 had ECG changes compatible with myocardial infarction, during a 4-year follow-up. The authors at the time suggested that, 'If the results of this study could be obtained in a larger study the financial and health care implications would be enormous.' Based on their preliminary results this seems a reasonable assertion—however it is noteworthy that almost 20 years later nobody has reported replication of these findings in a larger study.

Finally, primate models of psychosocial stress and coronary heart disease have been used to support the plausibility of various claims about stress and this condition. However, the totality of evidence demonstrates considerable heterogeneity—because as many studies exist that appear to demonstrate effects in one direction as show the opposite. Authors choose to cite the studies that support their hypothesis, ignoring those that run in the exactly opposite direction.[56] As in other areas of epidemiology, biological plausibility, when used in this way, is a very weak criteria for causality and animal evidence should be treated with as much respect as evidence from humans—through systematic reviewing, rather than the current and highly unsatisfactory pick-and-mix approach.[57]

Coda: which type of doctor?

In this presentation I have suggested that the epidemiological evidence supporting important contributions of psychosocial factors as direct causes of disease is limited. However, it might be suggested that despite this, a doctor who is influenced by the BPS is the sort of doctor one would like to consult when sick. I am not so certain about this. When writing about a myocardial infarction patient whom he had seen, Engel stated, 'In the end, whether the patient lives or dies, the biopsychosocial model further provides the physician with the conceptual tools to clearly think and plan the implications of the cardiac arrest.'[3] If I have a heart attack, I want to be treated by a doctor who cares about whether the patient lives or dies. I'm not really concerned about whether the doctor has the above-mentioned conceptual tools, I would rather have a doctor who keeps up to date with the best evidence on somatic treatments and gives me morphine, a thrombolytic, and aspirin, then puts me on appropriate long-term treatments.

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Discussion

Wessely: That was a powerful and uncomfortable paper. We should remember a couple of things, though. You presented a strong argument against hubris and accepting fashionable trends, merely because they are fashionable. There will undoubtedly be many people, including, for example, those who one might call 'CFS activists', who would have loved every word you were saying. There is a popular and seductive Whiggish view of medical history in which we move implicitly from unknown diseases which are thought to be psychiatric and as we become brighter, better scientists they are finally accepted in the pantheon of real diseases. You should remember that there is an opposite trend as well, which you didn't mention. You ignored the history of visceral proptosis, floating kidney, autointoxication, or focal sepsis, for example. There are also lots of other things that are seen as very clearly organic and which switch the other way.

Stansfeld: I realize that we have to take into account both negative affectivity and confounding. This is really important but do they really explain away all the effects of psychosocial factors. Are you saying, then, that psychosocial factors are going to have no impact on the aetiology of physical illness? For example, George Brown and others have worked on symbolic loss, in terms of events like not being promoted to a job, or if your partner is unfaithful, in relation to mental illness. The evidence for psychosocial factors as causal factors in mental illness, particularly depression, is quite strong. If I didn't feel that, I would get another job. But in relation to physical illness I wonder about work like Jane Ferrie's on job insecurity, where she has shown effects of perceived job insecurity on indices of coronary heart disease risk. What do you think about the possibility of these sorts of effects? If psychosocial influences don't lead directly to physical illness, what about effects on ageing, for example?

Davey Smith: First, I certainly think psychosocial factors are plausible contributors to mental illness. I have no doubt this is the case. Psychosocial factors are also importantly related to how people rate their quality of life, which is probably more important in countries with high longevity than is merely living longer. My main point was about disease aetiology. As a disease epidemiologist I want to get the right answers about this. As an aside, I think we know massively more about disease aetiology now than we did in 1977. The constant quoting of nihilistic statements about us having 'lost the war on cancer' and so on is wrong. We know the causes of some 70% of world-wide cancers. This is remarkable.

As I said, with mental illness I think psychosocial factors are aetiologically important. They are also clearly aetiologically important in many other illnesses, but as factors which influence the distribution of known exposures,

not as direct causes, in my view. Most illness is related to specific exposures. The example I started off with was cholera. People in epidemiology are generally taught about John Snow and cholera. The Whiggish view is that Snow came along, found that cholera was transmissible by water and dealt with it. What is remarkable about Snow's writings was that he had an extraordinarily nuanced view of how exposures came about.[1] First, he didn't just think that cholera was waterborne, but that it could also be faecally–orally transmitted. Where he worked, as a general practitioner during the 1832 outbreak, was near a mining community, and he noticed that miners had a high rate of cholera. He went down the pit and observed the conditions in which they had to eat and excrete. He noticed how these conditions ensured that transmission would occur. Snow's recommendation for dealing with cholera in miners was to give them work breaks so they could use proper toilet facilities. This is a beautiful and overlooked exposition of a simple model. Social factors were of key importance, but in the end they worked through influencing the distribution of exposures. In my view susceptibility has been overplayed and exposure has been under-appreciated in social epidemiology.

Marmot: I would emphasize Simon Wessely's point. It is easy to look back and say, 'Gosh how silly they were in the past to think all these silly thoughts; aren't we clever now!' There are many examples of people being silly all over the place, not just in the past. Your logic seems to be to seize on the notion of stress and say that people were silly about it before, therefore we should never think about stress ever again. I have a problem with your logic. The fact that not all diseases that were thought to be due to autoimmunity are so, does not mean that none is. The question is not could diseases be influenced by stress, of course they could, but instead what is the evidence for it? Research has advanced beyond the examples you cite because there have been many advances in conceptualization and measurement of psychosocial factors. Given those advances, I find it curious that you chose to illustrate the fallibility of self-reported stress measures with the Reeder scale. We conducted a systematic review of psychosocial factors and coronary heart disease using only studies that passed through a quality filter.[2] Not a single article linked the Reeder scale with incidence of coronary heart disease. To show then that in your data the Reeder scale is not related to hard evidence of coronary disease is hardly surprising. If your point is that it illustrates that if the reported stress is self reported and the disease outcome is self reported, there could be bias, my answer is, of course. The fact that there could be a spurious association does not mean there is. Yes, of course there can be reporting bias. The fact that you can illustrate it does not mean that either it is the whole story in the studies you cite (my own, for example), or in the wealth of other literature on

this subject. That's why in my chapter I spent some time discussing the systematic review of the evidence that actually looked at validated endpoints. Self-reported measures of psychosocial factors predict validated diagnoses of heart disease and mortality.

Your other criticism is confounding—a problem recognized by the founders of epidemiology, by Durkheim, by philosophers, by most scientists. We know confounding can occur. What one could take away from what you said is the message that controlled trials get it right, while observational studies get it wrong. You used the well-known example of the failure of the trials of β-carotene to prevent disease. Observational studies suggest a protective effect. Trials do not. One suggestion is that that β-carotene might be a marker for dietary intake, but it is not the β-carotene that has the protective effect. Your conclusion, though, was that if the trials didn't give the same results as the observational studies then the latter must have had incomplete control for confounding. In a technical sense that is true if the exposure is carotene. It is confounded by other dietary elements. If, however, the exposure is diet—fruit and vegetables perhaps—then the mistake the trials made was to intervene on an indicator, rather than the real exposure. The trouble is to do a dietary trial of prevention of heart disease does not solve the confounding problem. Enrol people in a dietary trial and they mess you up by taking up jogging. Trials are *an* answer to some questions. They are not *the* answer to all questions. You have delighted and stimulated your many admirers with a raft of observational studies about the life course, including parents' social class, education, childhood growth, voting patterns, social disruption, and disease. Are you now saying that all these studies of yours are wrong because they were observational studies, not controlled trials and therefore had incomplete control for confounding? Surely not? One of course needs to be careful in controlling for confounding. As an example, take the Finnish study that I cited that showed a link between low control and coronary mortality.[3] Reporting bias is unlikely with death as an endpoint. Would your other criticism of confounding by social class apply? It showed exactly what you would expect: that the association between job control and heart disease weakens when you control for social class and social position. This is what you would expect if low control were on the pathway between low social position and coronary disease. The association weakens but it doesn't go away.

Davey Smith: For medical treatments such as hormone replacement therapy (HRT) the randomized trials with long-term follow-up do get the right answer. Doctors told women that HRT reduced the risk of cardiovascular disease on the basis of observational data producing about the same relative risk as seen in the Finnish study of job control you refer to. The relative risks

in the observational HRT studies changed in about the same way on adjustment for confounding factors as do the relative risks in the job control studies. However there were massively more observational data on HRT, consistently suggesting that it was protective against coronary heart disease. If any doctors are now giving advice on the basis of this observational data, I think they are doing their patients a disservice. The randomized trials of HRT give the right answer to the question 'will my patients experience reduced coronary heart disease risk if they take HRT?' The answer is 'no'.

In the β-carotene example, of course β-carotene is a marker of something else—this is the definition of confounding! Millions of people in the USA were taking β-carotene supplements on the basis of the observational studies. The best test of the effect of β-carotene supplements comes from randomized trials, which do give evidence on cause and effect. I think epidemiology as a whole needs to revisit the issue of the importance of confounding. There are approaches to data analysis such as sensitivity analysis that could really help observational epidemiology. This is now a tractable approach. The specificity issue is also key: I'd really like to see reports of other outcomes than coronary heart disease in many of these observational studies of psychosocial factors. There are also novel ways of using genetic markers as ways of testing causal effects of environmental exposures.[4] So we can get more robust evidence from observational studies, but these approaches have not really been utilized in the psychosocial field.

Elwyn: You raised very interesting issues about aetiology. We have heard other presentations about interventions. We may have to differentiate in the biopsychosocial model between aetiology, where it is a weaker kind of model and intervention for complex diseases such as back pain, cardiac syndromes, and depression. We have yet to grapple with the design of interventions.

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6 Can neurobiology explain the relationship between stress and disease?

Stafford Lightman

Summary

Events that have occurred early in life, perhaps during a period of prolonged stress, may affect biological processes, sometimes permanently. The central nervous system (CNS) is the prime candidate for both being the sensor for these and also the major controller of the response to both physiological and pathological stimuli. There is good evidence that these responses include changes to midbrain neurotransmitter concentrations, the hypothalamic–pituitary–adrenal (HPA) axis, and the autonomic nervous system. These are both determined and differentiated by acute and chronic stressors, particularly those experienced at an early age. I will use animal models of stress to demonstrate these changes.

The stress response

Extreme stress can bring about intense emotion, which causes a variety of physiological reactions. There is central activation of the hypothalamus, which will have two major outputs. One is direct neural activation through both the sympathetic nervous system, affecting blood vessels and the adrenal medulla and the parasympathetic nervous system. The second is a humoral route through which the hypothalamus releases corticotrophin-releasing hormone (CRH) and arginine vasopression (AVP). These act on the anterior pituitary, which then releases adrenocorticotrophin (ACTH), which acts on the adrenal glands to secrete cortisol, which then circulates around the body. This is the output of stress.

I will focus firstly on what is controlling this output, rather than the output itself. I should add here that I do not like the word 'stress' and what I am really referring to are 'stressors' that impact on the CNS. All sorts of stressors in the internal or exterior environment can affect us by activating the brainstem,