Personality, Stress, Smoking, and Genetic Predisposition as Synergistic Risk Factors for Cancer and Coronary Heart Disease

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Abstract—Risk factors for cancer have been found in the past to act synergistically in a number of studies. However, these studies were not always designed to test the hypothesis of synergism, and have sometimes failed to equate for important variables, which might influence the results. The present study tests the hypothesis that psychosocial variables and physical ones (personality/stress, smoking, and genetic predisposition) interact in a synergistic fashion in the causation of lung cancer and coronary heart disease (CHD).

IT IS WELL KNOWN that there are many risk factors in diseases like cancer and coronary heart disease, and that in many cases these act *synergistically*, rather than *additively* (Kannel, Neaton, 1986; Kleinbaum, Kupper, & Morganstern, 1982; Koopman, 1981; Perkins, 1985, 1987, 1989; Rothman, 1974; Saracci, 1980, 1987; Walker, 1981). These studies usually look at physical factors of one kind or another, but there is accumulating evidence that psychosocial factors also interact synergistically with physical factors (Eysenck, 1991; Grossarth-Maticek, 1980, 1989; Grossarth-Maticek & Eysenck, 1990b, Grossarth-Maticek, Eysenck & Vetter, 1988; Grossarth-Maticek, Vetter, Frentzel-Beyme & Heller, 1988). If this hypothesis of synergistic interaction between psychosocial and physical risk factors is correct, it has tremendous implications for the analysis and interpretation of epidemiological data.

The hypothesis to be tested is that *single* risk factors, (e.g., smoking, drinking, stress, genetic predisposition) have relatively little influence on mortality from cancer or coronary heart disease (CHD), but that effects are synergistic, in the sense that these universal effects do not *add* (the additive hypothesis) but *multiply*. We have attacked this problem along several different lines, using different samples and different methods (Eysenck, 1991); some of these studies have been referred above. There are many different ways of attacking the problem, and different statistical tests; this variety raises problems some of which are discussed in this paper.

The term *synergism* may at first appear to be perfectly clear in its meaning; it is defined as the "combined effect of drugs, organs, etc. that exceeds the sum of their individual effects" (Concise Oxford Dictionary, 1976.) However, the precise operational definition of the term has given rise to many difficulties (Everitt & Smith, 1979), and apparently contradictory results have been obtained by workers using different models for identical data. We may use

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an *additive* model looking simply at *differences between proportions*, or a multiplicative one, which works with *ratios of proportions*, or relative risks. As Everitt and Smith point out, "it is quite possible for the two models to lead to seemingly conflicting results when applied to the same set of data" (p.582). They also point out, in answer to the question of which model is the correct one, that "unfortunately there is no absolute answer, and in practice the choice between them may depend on rather complex reasoning" (p.582).

Cornfield (1962) is credited with first introducing the multiple logistic function in his analysis of the factors related to the occurrence of coronary heart disease, and in 1968, Selikoff, Hammond and Chung (1968) showed that the combined exposure to tobacco smoking and to asbestos was associated with a lung cancer risk far exceeding that expected from the separate exposure to each of these agents, indicating the occurrence of an interaction between the two agents. Saracci (1987) has published a survey of interactions of tobacco smoking and other agents in cancer etiology, concluding that "a multiplicative relation of the relative risks for tobacco smoking and for another agent can at present be regarded either as an approximately satisfactory representation of the data, or, at the worst, as an upper limit of the strength of the interaction" (p. 190).

How is synergism measured? According to Saracci, we observe relative risks among subjects exposed to smoking alone (R), to the other agent alone (R) or to both agents (R), all relative risks here being calculated taking the subjects not exposed to either agent as reference. A *zero* difference between the observed value of R and the value of R + R - 1 defines zero interaction (i.e., a simple additive relation or model). A value greater than zero defines a positive interaction (synergism)—Rothman (1976), Saracci (1980).

Perkins (1989) uses a similar model. He states that the risk of CHD due to the interaction of smoking and elevated cholesterol is determined by the difference between the observed risk for those with both risk factors and the sum of the risk due to (a) smoking alone, (i.e., the observed risk for smokers without elevated cholesterol minus "background" risk, in absence of risk factor), (b) elevated cholesterol alone (observed risk for non-smokers with elevated cholesterol minus background risk), and (c) the background risks. He follows Kleinbaum, Kupper and Morganstern (1982) in not using "synergism" as a synonym for "interaction". As he points out, non-linear, multiplicate models, such as logistic regression, widely used in recent years,

> ...allow for simultaneous control of the effects of converging risk factors in order to determine the independent effect of an individual risk factor of interest, but they may also hide the existence of risk factor interactions as defined above, by deviations from additivity (Koopman, 1981; Rothman, 1974, 1976). Therefore, a primary reason that these interactions are unrecognized may be that most epidemiologic studies of CHD have used predictive models which are generally incompatible with the detection of such interactions. (p.3).

In other words, when synergism so defined is present, even on simple inspection of the four-fold table, this additive model is not the only one available (Cox, 1970; Darrocks, 1974; Galtung, 1967; Grizzle, Starmer, & Koch 1969; and Plackett, 1974). There is also a *multiplicative*, logistic model (Everitt, 1977) and the two models may give apparently different answers, as Everitt and Smith (1979) point out in discussing alternative interpretations of identical data by Brown and Harris (1978) and Tennant and Bebbington (1978).

We have used both types of approaches, wherever applicable, to a variety of data, some previously published, others not; the tables will be able to give evidence concerning syner-

gism, as defined by Saracci and Perkins, but are also adequately described by logistic models in which effects act independently. Final interpretation will then be left to the reader.

Study 1

In this study, we have re-analyzed data already published (Grossarth-Maticek, Eysenck, & Vetter, 1988), but not analyzed from this point of view. We reported on three prospective studies; one carried out on healthy elderly people in Yugoslavia, one on a random sample of healthy probands in Heidelberg, and one on a stressed but physically healthy sample in Heidelberg. The groups were tested at the beginning of each study, ascertaining data on smoking and various other physical risk factors such as blood pressure, cholesterol level, blood sugar, etc. In addition, probands were administered a stress/personality inventory assigning them to one of four types. Type 1 was cancer-prone, according to the theory tested, reacting to stress with inadequate coping behaviour, leading to the development of feelings of hopelessness, helplessness, and depression. Type 2 was CHD-prone, according to the theory tested, reacting to stress with feelings of anger, aggression, and hostility. Types 3 and 4 were relatively healthy mentally, and according to theory, unlikely to develop cancer or CHD. The study showed that mortality rates as ascertained 10 years later, and again after another 4 years, bore out these predictions, with Type 1 probands dying mostly of cancer, Type 2 probands dying mostly of CHD, and probands of Types 3 and 4 showing much lower mortality. Overall mortality data showed clear evidence of synergistic interaction between stress/personality and the physical risk factors included (Grossarth-Maticek, Eysenck, & Vetter, 1988).

In the present study we are concerned with the results for lung cancer for two reasons. First, overall mortality is such a broad concept that much important detail may be hidden, and no conclusions can be arrived at concerning specific diseases. Second, lung cancer is linked most closely with smoking, so our conclusion that stress/personality was over six times as predictive of mortality as all the other physical risk factors combined might not apply here. Neither, of course, might the theory of synergism, which emerged clearly from the original study.

The data in question, using death from lung cancer as the dependent variable, are shown in Table 1. "Stress" (absence or presence) is here defined as being of Type 1, as opposed to being of Type 2, 3, or 4. The term is used simply for convenience, and does not carry additional meaning. Thus, we have 4 subgroups; "stress" probands who either smoke or do not smoke, and "non-stress" probands who either smoke or do not smoke. We have added the probands from the Yugoslavian and the "stressed" Heidelberg samples. Those from the random Heidelberg sample had too few cases of lung cancer to make a worthwhile addition to the analysis.

The background factor is a mortality of .35% in the non-smoking, non-stress group. For

TABLE 1. Lung cancer mortality of no stress, no smoking; stress, no-smoking; no-stress, smoking, and stress, smoking probands. Groups from Yugoslavia and Heidelberg stressed sample.

Types	*No stress*	*Stress*	*Stress effect*
No smoking	0.35%	2.89%	(2.89% - 0.35%) = 2.54%
Smoking	0.80%	15.56%	
Smoking effect	(0.80% - 0.35%) = 0.45%		

Note: $N = 2374$

Real combined effect: (15.56% - 0.35%) = 15.21%
Additive effect: (0.45% + 2.54%) = 2.99%
Difference (Synergistic Effect) = 12.22%

the non-smoking, cancer-prone group, it is 2.89%, giving an excess of 2.54% (2.89%-.35%). For smoking in non-cancer-prone probands, the effect is .45% (.80%-.35%) (i.e., about a fifth of that of personality). The combined effect of smoking and personality is 15.21% (15.56%-.35%), which is five times the effect expected from a simple addition of the smoking and personality effects (.45% + 2.54% = 2.99%). This calculation takes into account 2,374 people, giving 77 cases of lung cancer mortality. The results are suggestive, but the number of deaths is not large enough to take the results as anything but a very rough-and-ready guideline. Also the bringing together of two different populations (Yugoslavian and German), differing in age and stress, might be criticized, although the results when analysed separately for the two groups are not dissimilar.

We now present a standard logistic model applied to the data. Table 2 shows the model.

For the Stress and Smoking model the estimated parameters are as follows:

Grand mean = -6.277 (0.4191)
Stress = 2.872 (0.3557)
Smoking = 1.689 (0.3078)
(Standard errors are given in parentheses.)

A comparison of observed, fitted and standardized residual values for this model indicates that the fit is extremely good. (See Table 3.)

Denoting the probability of dying from cancer as p, the model can be written out in detail as follows (ln = natural logarithm):

1. Non-smokers/no stress

$$\ln \frac{p}{1-p} = -6.277$$

2. Non-smokers/stress

$$\ln \frac{p}{1-p} = -6.277 + 2.872$$

3. Smokers/no stress

$$\ln \frac{p}{1-p} = -6.277 + 1.689$$

4. Smokers/stress

$$\ln \frac{p}{1-p} = -6.277 + 1.689 + 2.872$$

The model implies the following:

1. Being in the stress group rather than the non-stress group increases ln (odds in favour of dying from cancer) by 2.872 with an approximate 95% confidence interval (2.161, 3.585). Converting this to the 'odds' scale gives a confidence interval of (8.68, 35.98).

2. Being a smoker rather than a non-smoker increases ln (odds in favour of dying from

TABLE 2. Logistic model analysis of data in Table 1.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	167.85	3	0.000
Stress	42.20	2	0.000
Smoking	117.22	2	0.000
Stress & smoking	1.49	1	0.222

TABLE 3. Goodness of fit of model.

Types	*Observed*	*Fitted*	*Residual*
No smoking/no stress	3	1.50	1.11
No smoking/stress	10	11.41	-0.42
Smoking/no stress	6	7.41	-0.52
Smoking/stress	68	66.59	0.10

cancer) by 1.689 with an approximate 95% confidence interval (1.073, 2.305). Converting this to the 'odds' scale gives a confidence interval of (2.924, 10.242).

Lastly, and perhaps most importantly the model implies that smoking and stress act *independently*; so on this particular scale there is little need to postulate interactions between conditions.

Study 2

For this study, 1,914 men with an average age of 53 were selected on a random basis from a sample of over 5,000 subjects of our 1973 Heidelberg study when their smoking habits and their stress/personality characteristics were determined by means of an interviewer-administered questionnaire. The questionnaire used has been reproduced in detail elsewhere (Grossarth-Maticek & Eysenck, 1990a); it defines the same two types (Type 1 and Type 2), respectively cancer-prone and CHD-prone, as well as four other types. (See Study 3.) Mortality and cause of death were established in 1986 (i.e., 13 years after these healthy subjects had been interviewed and allocated to the smoking/no smoking and the stress/no stress categories). "Stress" is defined here as belonging to Type 1 (for our lung cancer comparison) or Type 2 (for our CHD comparison). For this reason in the tables to follow, the numbers of smokers and non-smokers remain identical, but the number of "stressed" individuals differs; this is because "stress" is differentially defined in the two cases.

Table 4 shows the results for lung cancer mortality. Here again the figures show a clear-cut and synergistic effect. The additive effect is 0.95%, while the real combined effect is 9.90%, giving a difference due to synergistic mechanisms of 8.95%. These effects are similar to those shown in Table 1, and may be considered to be a replication of our earlier study.

Table 5 gives similar data for CHD mortality, and it will be seen that, here too, there is a powerful synergistic effect of roughly the same size as in the case of lung cancer (10.36%).

We may conclude that Study 2 has replicated the results of our first study as far as lung cancer is concerned, and has extended the support for a synergistic model to CHD mortality.

TABLE 4. Lung cancer mortality of no stress, no smoking; stress, no smoking; no stress, smoking, and stress, smoking probands. Groups from 1973 Heidelberg study.

Types	*No stress*	*Stress*	*Stress effect*
No smoking	0.69%	2.09%	(2.09% - 0.69%) = 1.40%
Smoking	0.24%	10.59%	
Smoking effect	(0.24% - 0.69%) = 0.45%		

	Real combined effect:	(10.59% - 0.69%) = 9.90%
Note: N = 1914	Additive effect:	(1.40% + 0.45%) = 0.95%
	Difference (Synergistic Effect)	= 8.95%

TABLE 5. Coronary heart disease mortality of no stress, no smoking; stress, no smoking; no stress, smoking, and stress, smoking probands. Groups from 1973 Heidelberg study.

Types	*No stress*	*Stress*	*Stress effect*
No smoking	1.10%	5.30%	(5.30% - 1.10%) = 4.20%
Smoking	3.04%	17.50%	
Smoking effect	(3.04% - 1.10%) = 1.94%		

Note: N = 1914

Real combined effect:	(17.50% - 1.10%) = 16.40%
Additive effect:	(4.20% + 1.94%) = 6.14%
Difference (Synergistic Effect)	= 10.26%

How about interaction on a logistic regression model? Consider Table 6, which deals with the data from Table 4.

Here the independence model (Stress & Smoking) does not provide an adequate fit. Consequently, stress and smoking do not appear to act independently in this case. The estimated parameters for a model including an interaction parameter for Stress and Smoking (a model which fits the data perfectly because it has four free parameters), are as follows:

Grand mean	= -4.96	(0.502)
Smoking	= -1.064	(1.120)
Stress	= 1.119	(0.604)
Stress & smoking	= 2.776	(1.179)

Here there does appear to be some evidence of a genuine interaction effect of stress and smoking. Table 7 deals with the data from Table 5.

For the Stress and Smoking model the estimated parameters are as follows:

Grand mean	= -4.657	(0.279)
Stress	= 1.829	(0.254)
Smoking	= 1.265	(0.215)

The observed, fitted and residual values are as follows:

	Observed	*Fitted*	*Residual*
No smoking/no stress	6	5.11	0.40
No smoking/stress	25	25.89	-0.18
Smoking/no stress	13	13.89	-0.24
Smoking/stress	84	83.11	0.11

The model implies the following:

1. Being in the stress group rather than the non-stress group increases the ln (odds in favour of dying from cancer) by 1.829 with an approximate 95% confidence interval (1.320, 2.338). Converting this to the 'odds' scale gives a confidence interval of (3.743, 10.360).

TABLE 6. Logistic model analysis of data in Table 4.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	92.93	3	0.000
Stress	30.08	2	0.000
Smoking	61.94	2	0.000
Stress & smoking	7.17	1	0.007

TABLE 7. Logistic model analysis of data in Table 5.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	117.46	3	0.000
Stress	40.35	2	0.000
Smoking	71.51	2	0.000
Stress & smoking	0.25	1	0.617

2. Being a smoker rather than a non-smoker increases the ln (odds in favour of dying from cancer) by 1.265 with an approximate 95% confidence interval (0.835, 1.695). Converting this to the 'odds' scale gives a confidence interval of (2.305, 5.447).

Again the model suggests that smoking and stress act independently.

Study 3

This study began in 1973, when some 16,000 males, aged between 32 and 66 years, constituting a random sample of the male population between these age limits, were interviewed and asked if they had any relatives or friends characterized by the following risk factors for lung cancer. This group consisted of people who were heavy smokers, had one or more close relatives who had died, or were suffering from lung cancer, or who were suffering from severe bronchitis for more than 5 years. Persons suffering from only one of these risk factors for lung cancer could also be nominated. After consultation with the person so nominated, 798 were nominated, but 54 refused to participate, leaving 744 in all. This is our sample, the members of which are clearly far from random, but who are well suited to investigate the effects of single risk factors as compared with different combinations of two, three or four such risk factors.

Members of the group filled in a questionnaire as follows:

1. Of your parents or grandparents, are any ill with lung cancer, or have any died of lung cancer? If yes, how many? In which clinic was the diagnosis made? What treatment was administered? How long did your relatives live after diagnosis?
2. Do you smoke? If yes, how long have you smoked, and how many cigarettes did you smoke a day during the past 5 years?
3. Have you been suffering from bronchitis, as diagnosed by a physician, for more than 5 years?
4. Are you suffering form high blood pressure? What is the reading?
5. Are you suffering from high cholesterol levels? What is the reading?
6. Are you suffering from diabetes mellitus? If yes, for how long?

In addition, participants were administered a personality questionnaire that is reproduced in full elsewhere (Grossarth-Maticek & Eysenck, 1990a). This questionnaire is the same as that used in Study 2. The questionnaire gives scores to each person on six type-factors, of which three (factors 1, 2, and 5) are prognostic of stress induced disease, particularly cancer and coronary heart disease, while the other three (factors 3, 4, and 6) are prognostic of absence of disease. We used the formula: (1+2+5) - (3+4+6) >0 as our measure of (psychological) stress. We, thus, have four two-value (Yes Or No) risk factors: H (hereditary predisposition), C (cigarette smoking), B (bronchitis), and S (stress), as defined by answers

to the interviewer-administered questionnaires. Mortality was ascertained in 1986 (i.e., after 13 years). Cause of death was taken from the death certificates.

Results are shown in Table 8, giving mortality figures for lung cancer and all other causes, as well as the mean ages of the groups concerned. We compare mortality rates for groups having only one risk factor, two risk factors, three risk factors, or all four risk factors. It was not possible to find sufficient persons to fill all possible cells; thus there are no persons in the table suffering *only* from bronchitis. However, for all combinations of two, three, or four risk factors, we were able to find sufficient subjects to make up groups of reasonable size, the smallest consisting of 26 members.

What does Table 8 tell us? Looking at lung cancer first, we see that the risk factors taken singly do not lead to mortality. Bronchitis, as already mentioned, is missing, but it is not associated with mortality even when associated with other risk factors, so that we may be justified in assuming that it is innocent when present alone. Thus our four risk factors, taken one at a time, produce zero deaths in 209 subjects. For a combination of two risk factors, there are three deaths in 356 subjects (i.e., a rate of 1%). For three risk factors, we have 17 deaths, in a population of 127 subjects, giving a rate of 13%. For the 26 subjects showing all four risk factors, there are eight deaths, amounting to 31%. Thus, there is a steep rise in mortality as we go from one to two, three and four risk factors: 0%, 1%, 13%, 31%. This is far removed from an additive model, and indicative of synergistic actions.

We now turn to "other causes of death." Here for single risk factors we have 33 deaths for H, C, or S alone, for 209 subjects, or 16%. If we add half of the deaths from H + B, C + B, and B + S, to take the place of B alone, we have 13 additional deaths for 209 subjects (i.e., 16% overall). For combinations of two risk factors, we have 61 deaths for 356 subjects, equal to 17%. For three risk factor combinations, there are 29 deaths for 127 subjects, or 23%. Finally, for all four risk factors in combination, there are eight deaths for 26 subjects (i.e., 31%). Thus for "other causes of death" the progression is 16%, 17%, 23%, and 31%. This is very different from the progression in the case of deaths from lung cancer, suggesting quite a different pattern of interaction.

Table 8 also contains one group not mentioned thus far, namely the group of 26 subjects entered into the table as (H+C+B+S+BT.) Here BT stands for behaviour therapy, as defined for the prophylactic treatment of cancer-prone subjects elsewhere (Grossarth-Maticek, & Eysenck, 1991). These subjects were matched individually with the H+C+B+S group, so that on age, sex, and the four risk factors the two groups were matched. The only difference was

TABLE 8. Combination of risk factors for lung cancer and other causes of death.

Combination of risks	*N*	*Lung cancer*	*%*	*Other causes of death*	*%*	*Average age*
Only H	50	0	0	5	10	51
Only C	100	0	0	12	12	52
Only S	59	0	0	16	27	52
H + C	50	1	2	4	8	53
H + B	52	0	0	8	15	51
C + B	55	0	0	11	20	52
C + S	100	2	2	21	21	53
H + S	49	0	0	9	18	54
B + S	50	0	0	8	16	53
C + H + B	26	2	8	5	19	51
C + H + S	50	10	20	14	28	51
C + B + S	51	5	10	10	20	51
H + C + B + S	26	8	31	8	31	52
(H+C+B+S+BT)	26	3	12	4	15	52

the fact that the therapy group was subjected to a course of bibliotherapy, of a behavioural kind, supplemented with 4 hours of individual therapy devoted to changing their cancer-prone personality to a more healthy, autonomous type of personality. This type of therapy has been shown to be highly successful in preventing cancer (Eysenck, & Grossarth-Maticek, 1991), and it was felt that the two samples of 26 subjects each showing maximal involvement of risk factors would give a useful opportunity for testing the replicability of the earlier results.

As will be seen from Table 8, mortality for lung cancer is reduced form 31% to 12%. Similarly, for deaths from other causes, mortality is reduced from 31% to 15%. Overall, mortality is reduced from 16 to 7, a drop of over 50%. Statistically, this difference is significant by McNemar's test for paired observations.

Applying statistical procedures to the data, we find the following, treating the number of risk factors (NRF) as forming a kind of dose-response curve.

The results of fitting a series of logistic models for the cancer deaths are shown in Table 9.

The quadratic term significantly improves the fit and so is retained in the final model, which is therefore:

$$\ln \frac{p}{1-p} = -16.22 + 7.588\text{NRF} - 0.934\text{NRF} * \text{NRF}$$

This model is essentially a simple "dose-response" curve, which one would not normally think of in terms of synergistic effects, although it is clear that the odds of dying from cancer increases considerably as the number of risk factors increases.

For the deaths from 'other causes,' the equivalent results are shown in Table 10.

Here a simple "grand mean" model might suffice, although the introduction of the linear term for NRF does significantly improve the fit. The fitted model is:

$$\ln \frac{p}{1-p} = 2.022 + 0.26\text{NRF}$$

Clearly there is very much less pronounced relationship with NRF than in the cancer deaths example.

Study 4

In this study, we used a group of 360 males of similar age to those taking part in Study 3, selected from the same population and belonging to a group having prominent risk factors for cardiovascular disease (i.e., suffering from high blood pressure, high cholesterol level and/or diabetis mellitus, singly or in combination). Of the 392 persons provisionally included in this

TABLE 9. Dose-response type analysis of data in Table 8.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	69.85	3	0.001
NRF (Lin)	5.51	2	0.064
NRF (Quad)	0.03	1	0.862

TABLE 10. Significance tests of Table 9.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	5.242	3	0.155
NRF	0.665	2	0.717

sample, 32 refused to participate, leaving us with 360 probands. All were male, with an average age of 55.3 years.

The total group was divided into two groups, namely those suffering from and those not suffering from classical risk indicators for CHD, viz. high blood pressure, high blood sugar, high cholesterol level, overweight, and high consumption of cigarettes. Table 11 shows the comparison between the two groups. Within each group we distinguish between those who died of CHD (A) and those who did not (B). It will be seen that Group 1 differs profoundly from Group 2, but that within groups there is little difference between A and B.

We now consider the interaction between three risk factors other than those listed in Table 11. The first of these is high degree of sclerosis in the fundus of the eye; we have found this highly predictive of CHD (Grossarth-Maticek, Eysenck, Gallasch, Vetter, & Frentzel-Beyme, in press). This was judged on a 5-point scale, with grades 3 and 4 constituting the high level, grades 0, 1, and 2 the low level. Stress was defined as being of Type 2 (CHD-prone), with a high score also in Type 1. Finally, we looked at genetic predisposition, defined as having one or more relatives (parents or grandparents) suffering from, or having died of CHD. The ages of the subjects were almost identical when comparing the groups, and played no role.

Consider the first subjects in Group 1, those not suffering from classical risk factors. Table 12 shows the results. Clearly all risk factors are highly predictive. Concerning their interaction, we find that for Group 1, 11 subjects combine all three risk factors, 3 combine two risk factors, and there are none with 1 or no risk factors. For Group 2, there is only one subject with 3 risk factors, four with 2 risk factors, 33 with 1 risk factor, and 178 with none.

Table 13 show the results for Group 2, those who had high classical risk factors. Clearly all three of our risk factors are highly predictive. As regards to their interaction, we find that for Group 1, 27 combine three risk factors, 29 combine two risk factors, and two and one respectively have 1 or 0 risk factors. For Group 2, the figures are three for 3 risk factors, five for 2 risk factors, 28 for 1 risk factor, and 35 for none. Here again, there is a clear clustering of risk factors for Group 1, but not for Group 2.

Rewriting the data as shown in Table 14, we may fit logistic models with "groups" and "NRF" as explanatory variables.

The results from fitting a number of such models are shown in Table 15.

Here it is difficult to find a model that fits much better than the group and NRF model, although the chi-square value indicates that this is not a particularly good fit. Allowing the

TABLE 11. Classical risk factors and CHD mortality (A) and survival (B).

	Group 1 (no classical risk factors present)		*Group 2 (classical risk factors present)*	
	A	B	A	B
Blood pressure	140/80	135/80	220/115	225/120
Blood sugar	100	95	153	152
Total cholesterol	180	175	320	330
Weight	-3	-2	+5	+6
Cigarette consumption	15	17	20	27

TABLE 12. CHD mortality of probands not suffering from classical risk factors.

Group 1 (N=230)	*N*	*Sclerosis +*	*Stress +*	*Genetic predisposition +*
(A) Died of stroke or heart infarct	14	13 (93%)	14 (100%)	3 (21%)
(B) Did not die of stroke or heart infarct	216	14 (6%)	29 (13%)	1 (0%)

TABLE 13. CHD mortality of probands suffering from classical risk factors.

Group 2 (N=130)	*N*	*Sclerosis +*	*Stress +*	*Genetic predisposition +*
(A) Died of stroke or heart infarct	59	48 (81%)	57 (97%)	29 (49%)
(B) Did not die of stroke or heart infarct	71	20 (28%)	44 (62%)	1 (1%)

TABLE 14. Dose-response relations for number of non-classical risk factors.

Group 1 (no classical risk factors)

Number of other RF	*Number CHD deaths*	*Total*
0	0	178
1	0	33
2	3	7
3	11	12

Group 2 (classical risk factors present)

Number of other RF	*Number CHD deaths*	*Total*
0	1	36
1	2	30
2	29	34
3	27	30

TABLE 15. Logistic model analysis of data in Table 14.

Model	*Chi-square*	*d.f.*	*p*
Grand mean	274.87	7	0.000
Group	196.43	6	0.000
N risk factors	22.81	6	0.001
Group + NRF	12.91	5	0.024

slope parameter for number of risk factors to differ in the two groups does not significantly increase the fit, and neither does the introduction of a quadratic effect for a number of risk factors.

Examination of the observed, fitted, and residual values for the group and NRF model shows a relatively good fit apart from the Groups 2 and 3 risk factors cell. See Table 16.

The parameters estimates for this model are as follows:

Grand mean	=	6.53	(0.89)
Group	=	1.82	(0.61)
N Risk factors	=	2.88	(0.37)

Again denoting p as the probability of dying from CHD the group and NRF model implies the following:

1. Group 1

$$\ln \frac{p}{1-p} = -6.53 + 2.88 \times \text{NRF}$$

2. Group 2

$$\ln \frac{p}{1-p} = -6.53 + 1.82 + 2.88 \times \text{NRF}$$

The estimated 95% confidence intervals on the 'odds' scale for Group is 1.83., 20.65, and NRF is 8.47, 37.37 (i.e., each additional risk factor increases the odds in favour of dying from CHD by between 8 and 37).

Discussion and Conclusions

The data adduced in this paper are highly suggestive of a synergistic interaction of many different risk factors for cancer (particularly lung cancer) and CHD, although interaction effects in the logistic regression model are largely absent. If this is so, certain consequences follow. The major consequences would be that we should concentrate efforts for prevention on those groups combining different risk factors (e.g., smoking and stress) rather than on groups showing only one risk factor, such as smoking. Our decision as to what kind of intervention is indicated, and at which factor the intervention should be directed must be

TABLE 16. Fit of analysis given in Table 15.

Group	*RF*	*Observed*	*Fitted*	*Residual*
1	0	0	0.26	-0.51
1	1	0	0.83	-0.92
1	2	3	2.21	0.64
1	3	11	10.70	0.28
2	0	1	0.32	1.21
2	1	2	4.12	-1.13
2	2	29	25.14	1.51
2	3	27	29.42	3.20

determined by our knowledge available at the time. Eysenck (1991) has pointed out that quitting smoking has had little effect on mortality. On the other hand, behaviour therapy-directed stress management (autonomy training) has been very successful in prophylaxis (Eysenck & Grossarth-Maticek, 1991). Accurate ascertainment of risk factors their predictive value, and their interaction are vital for any application of preventive measures. Given the major importance of cancer and CHD in our mortality statistics, it is surprising that so little research has been devoted to this task, and that important psychosocial factors have been so frequently disregarded. Personality and stress exert a powerful effect on a person's likelihood of dying of cancer and CHD, and interact strongly with more widely studied risk factors, such as smoking. In future, research would be well advised to proceed along rather less restricted lines, and to take psychosocial factors into account to a greater extent than is customary at present. Obviously our data are subject to the need for independent replication, but there is already a large literature pointing in the same direction, and suggesting causal theories for the observed effects (Eysenck, 1991).

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