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Synergistic interaction of smoking and neuroticism as a risk factor in ischaemic heart disease: case-control study

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Abstract

Contemporary epidemiology and health psychology research has pointed out that single risk factors have relatively little influence on ischaemic heart disease (IHD), but that effects are synergistic. The possibility of such interactions has occasionally been noted and indeed might be expected, given the unexplained variance in IHD risk after accounting for the effects of IHD risk factors taken individually. Risk factors of smoking and neuroticism (emotional lability) were investigated simultaneously in groups of 187 male IHD patients and 187 controls. Initially, a logistic regression was used to compare the two groups on the two risk factors. Next, their interaction was tested by dividing the two samples into different subgroups according to the level of neuroticism and presence of smoking. The multivariate regression model and other methods supported both risk factors including a synergistic interaction between the two. The synergistic interaction of smoking and neuroticism plays an important role in predicting IHD. Different potential mechanisms of psychobehavioural pathogenicity have been suggested so far. The presence of a psychobiological synergistic interaction between neuroticism and smoking suggests the involvement of the former risk factor in sudden deterioration in the coronary flow due to vasoconstriction.

Keywords: Coronary artery disease; Case-control study; Smoking; Neuroticism; Coronary-prone personality; Synergistic interactions

1. Introduction

Contemporary epidemiology and health psychology research has pointed out that single risk factors have relatively little influence on morbidity or mortality from illnesses such as ischaemic heart disease (IHD), but that effects are synergistic, in the sense that these universal effects do not

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add but multiply. The possibility of such interactions has occasionally been noted and indeed might be expected, given the unexplained variance in IHD risk after accounting for the effects of IHD risk factors taken individually. Perkins (1989) reviewed selected studies of large samples which present incidence rates for subgroups that are relatively homogeneous with respect to the presence of none, one, or two of the major risk factors for IHD. It was concluded that interactions between smoking and cholesterol, and between hypertension and cholesterol may each as much as double the risk of IHD which might be expected if these factors acted only additively. Eysenck (1991) thought that psychobehavioural variables, and particularly personality type and stress, are important because of their relevance for sensitivity to biological risk factors.

Nevertheless, many studies have shown that smoking on its own has been associated with a twofold increased risk of IHD (Lakier, 1992). Wakefield (1988), however, pointed out that the relative risk is useful only for educational purposes rather than as a measure of the degree of association between two variables. Overall correlation coefficients of a size between 0.13 and 0.17, as discovered in the Wakefield (1988) analysis, are rather weak, particularly because univariate studies of this kind cannot adequately take into account other factors that may influence both the variables correlated: IHD and smoking. Thornton, Lee, and Fry (1994), and Seltzer (1989) have shown, that when even a small number of other variables are taken into account, the apparent correlation between smoking and disease tends to vanish. As an example, the majority of studies that have considered both smoking and psychobehavioural aspects of IHD have tended to show relationships and interactions between the two risk factors (Friedman, Fireman, Petitti, Siegelaub, Ury & Klatsky, 1983; Carney, Rich, teVelde, Saini, Clark & Freedland, 1988; Glassman, Stetner, Walsh, Raizman, Fleiss, Cooper & Covey, 1988; Eysenck, 1991; Forgays, Bonaiuto, Wrzesniewski & Forgays, 1993; Marušič, Gudjonsson, Eysenck & Starc, 1999).

Although it has been known that cigarette smoking exerts detrimental effects on the lipid profile and haemostatic factors (Farmer & Gotto, 1997), the exact mechanism by which it may accelerate the process of atherosclerosis remains poorly understood. According to one of the hypotheses, Winniford, Wheelan, Kremers, Ugolini, van der Berg, Niggemann, Jansen, and Hillis (1986) found increased coronary tone and enhanced vasoconstriction in IHD patients by inhalation of tobacco smoke. Later on, they reported that blockade of alpha1 receptors in patients with IHD attenuates the coronary vasoconstrictor response to cigarette smoking indicating that a possible effect of smoking is mediated by stimulation of these receptors (Winniford, Jansen, Reynolds, Apprill, Black & Hillis, 1987). Accordingly, other authors reported significantly increased risk for vasospasm in smokers (Nobuyoshi, Abe, Nosaka, Kimura, Yokoi, Hamasaki, Shindo, Kimura, Nakamura, Nakagawa, Shiode, Sakamoto, Kakura, Iwasaki, Kim & Kitaguchi, 1992; Sugiishi & Takatsu, 1993; Numata, Ogata, Oike, Matsumura & Shimada, 1998).

At the same time, an investigation of mechanisms that may mediate psychobehavioural influences on IHD has taken place. Apart from well known alterations in health-related behaviours (Ornish, Brown, Scherwitz, Billings, Armstrong, Ports, McLanahan, Kirkeeide, Brand & Gould, 1990; Wright, Murcer, Adams, Welch & Paris, 1994), some other mechanisms have been suggested. Of particular importance to us should be decreased coronary blood supply by precipitating vasoconstriction of atherosclerotic coronary arteries (Yeung, Ganz & Selwyn, 1993) or a temporary vasospasm (Numata et al., 1998), which may explain psychobehavioural pathogenicity, its relationship with smoking, and a possible synergistic interaction of these two risk factors. Neuroticism as a personality trait of emotional lability should be, therefore, of particular

importance as it has been suggested to be, at least to a certain extent, related to individual differences in excitability and emotional responsiveness, which are reflected in autonomic activation (Eysenck & Eysenck, 1985; Gramer & Huber, 1994) and increased reactivity to stressors (Friedman & Booth-Kewley, 1987). Moreover, neuroticism and chronically disturbing emotions have repeatedly been found to be associated with the presence of different forms of IHD (Jenkins & Zyzanski, 1980; Weiss & Richter-Heinrich, 1985; Fielding, 1991; Cramer, 1991).

In relation to the synergistic interaction between smoking and psychobehavioural coronary proneness, Friedman et al. (1983) measured psychobehavioural coronary-proneness in smokers and non-smokers, with or without myocardial infarction. The strength of smoking as a risk factor for myocardial infarction in men was strongly related to the way the subjects responded to the questionnaire, so much so that people with very low proneness scores were actually ''protected'' from myocardial infarction by smoking. The risk ratios for the very high, high, low, very low coronary proneness groups were, respectively, 4.4, 2.2, 1.1 and 0.4. On the basis of this and other above-listed findings and suggestions, we hypothesised that there exists a synergistic interaction of smoking history and neuroticism in predicting the presence or absence of IHD.

2. Methodology

A total of 374 subjects took part in the study. The IHD sample constituted 187 consecutive patients (56.8 years old; SD 9.5), who underwent coronary angiography at the Clinical Centre in Ljubljana. They had at least 50 percent narrowing of at least one coronary artery and/or had been diagnosed for myocardial infarction. The control sample constituted 144 inpatients from other departments in the same institution and 43 outpatients invited to a preventive medical examination elsewhere. Both subgroups were formed by the technique of systematic sampling. First, a list was drawn up of all the male outpatients registered in the chosen general practice. Next, the required number of outpatients was selected; each had the same chance of being selected. This was achieved by selecting individuals at regular intervals, the starting point being chosen at random. Similarly, the subgroup of inpatients was formed. In the latter the sampling frame was drawn up of all the inpatients admitted to certain other departments of the Clinical Centre. The patients were mainly from urology, neurology, gastrosurgery and traumatology units. None of these groups and the group of the outpatients formed the majority. Also, in all of the above units different patients with different diagnoses were included. Among the inpatients that were not included it is worth noting terminal patients, patients with head injury and patients with mental illness. There were no differences found when comparing the outpatient and inpatient subgroups of controls on the two testing variables. In 187 controls the diagnosis of IHD was ruled out by a close examination of medical records and history data and, if necessary (e.g. if clinical presentation was not clear enough), by clinical examination and specialised diagnostic procedures. They were well matched for age (Mean 56.5; SD 10.2) as well as for place of data acquisition and testing. In addition, any exclusions or restrictions made in the identification of the IHD cases applied equally to the controls and vice versa. The Clinical Centre in Ljubljana is the only University Clinic in Slovenia and therefore every department covers, to a certain extent, the whole country. Apart from these, to balance possible differences all the outpatients were collected outside Ljubljana. Due to the lower percentage of women with IHD only men were included in the

study (Farmer & Gotto, 1997). Among the exclusion criteria were a history of terminal illness, head injury and mental illness. A brief description of the study and its aims was given to all participants. All of them provided written informed consent prior to entry into the study. After being evaluated by laboratory tests and other special diagnostic procedures both IHD patients and controls were interviewed, clinically examined and psychologically tested by the physician and psychologist.

The outcome variable of the case-control study was *presence or absence of evidence of IHD*. Exploratory variables constituted smoking history and neuroticism:

1. *smoking history* was coded as present or absent; here, history of smoking tobacco rather than a current behaviour was important as a majority of IHD patients tended to quit smoking after the onset of their illness; history was coded as positive if a patient has smoked at least 1000 cigarettes in his life;
2. *neuroticism (N)* as a personality trait measured by the Slovene version of the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975), which has been standardised and widely used in Slovenia since the late 1970s (Lojk, 1979); the alpha coefficient for N in the present study (N = 393) was 0.87.

All statistical analyses of the present study were conducted by using SPSS for Windows. Initially, both variables were investigated by fitting the logistic regression models. The binary outcome variable (presence or absence of evidence of IHD) in a case-control study was fixed by stratification. In this type of study design samples of fixed size are chosen from the two strata defined by the outcome variable. The values of the independent variables are then measured for each subject. Based on the univariate results, we began to analyse the multivariate logistic regression model with both variables and their interaction. The entry of predictor variable was controlled by forward stepwise selection in which removal testing was based on the probability of the likelihood-ratio statistic (0.05 for entry and 0.10 for removal) based on the maximum partial likelihood estimates. Constants were always included in a model. Secondly, the interaction of the two studied variables was tested further by calculating percentages of IHD patients into each of four different groups determined as all possible combinations of positive and negative history of smoking on one hand, and high and low N score on the other. The synergistic effect can then be calculated by subtracting the additive effect from the real combined effect. The additive effect is by definition a simple sum of single risk factors' effects, which are differences between percentages of IHD patients in groups with and without a given factor. On the other hand, the real combined effect is determined by the difference between percentages of the double risk group and the group without any of two risk factors. Finally, the interaction was also investigated by measuring relative risks (Chi-square statistics) and associations (Phi coefficients) between smoking and IHD in three different subgroups, the first being defined by high N, the second by scoring on N somewhere around the mean, and the last one by low N.

3. Results

The present study contrasted the IHD patients' group with the comparison group of controls for smoking history and N. To start with, Table 1 shows frequencies for smoking history, and means for N. In IHD patients, smoking history was more frequent and N scores were higher.

Table 1
Frequencies for smoking history, and means with standard deviations (SD) for neuroticism (N) in the case-control study (N = 187 + 187)

Risk factors	IHD group	Control group
Smoking	82%	58%
Neuroticism (N)	13.3 (SD 5.2)	10.4 (SD 5.3)

Next, both exploratory variables were investigated as possible predictor variables by fitting the univariate logistic regression models in which the dependent variable is dichotomous, notably presence or absence of IHD. Both risk factors, smoking (Model Chi-square = 26.2; df = 1; $p < 0.0001$) and N (Model Chi-square = 27.9; df = 1; $p < 0.0001$), were found to be statistically significant predictors of the presence of IHD.

Based on the univariate results, we began to analyse the multivariate logistic regression model using the forward stepwise method with the two variables and their hypothesised interaction. As shown on Table 2, only the interaction of smoking and N, and N on its own were included in the final model, concluded when no variable in the equation was eligible for removal and no variable not in the equation was eligible for entry. The exposure variable of smoking history did not enter the model. The final Chi-square was 49.3 (df = 2; $p < 0.0001$) with an improvement of 14.9 (df = 1; $p = 0.0001$) after the addition of N as the second variable. Note that category variable of history of smoking has been recoded so that parameter estimates for logistic regression (1, −1) are not the same as for indicator variables (0, 1). Next, the classification table (Table 3) shows predictions and observed outcomes for the multivariate model (Table 2).

It appeared worth looking in more detail at the nature of this coaction. To begin with, all the subjects were subdivided into four different groups determined as all possible combinations of positive and negative history of smoking on one hand, and high and low N score on the other.

Table 2
Final multivariate logistic regression model using the forward stepwise method with both variables (smoking and neuroticism–N) and their interaction (Model Chi-square = 49.3; df = 2; $p < 0.0001$; N = 374)

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
Interaction	−0.04	0.01	20.45	1	< 0.0001	−0.19	0.96
Neuroticism	0.08	0.02	14.61	1	0.0001	0.16	1.09
Constant	−1.21	0.27	19.85	1	< 0.0001		

Table 3
Classification table for IHD using the multivariate model including the interaction (Table 2)

		Predicted IHD		Percent correct
		Absent	Present	
Observed IHD	absent	133	54	71
	present	69	118	63
Overall				67

Table 4
IHD as a function of smoking and neuroticism (N) score; synergistic effect is determined by the difference between the real combined effect and the simple additive effect of both variables[a]

N = 187 + 187	Low N (< 12)	High N (> 11)	N effect
No smoking	27%	35%	35% − 27% = 8%
Smoking	43%	69%	
Smoking effect	43% − 27% = 16%		

[a] Real combined effect: 69% − 27% = 42%; Additive effect: 16% + 8% = 24%; Difference (synergistic effect): 42% − 24% = 18%.

Table 5
Relative risk and significance of association between smoking risk factor and IHD in three different groups according to the neuroticism (N) score

14 < N trait	Smoking	No smoking	N = 130
IHD	72 (85%)	13 (15%)	Relative risk estimate = 4.0
No IHD	26 (58%)	19 (42%)	Phi = 0.30 ($p < 0.001$)
N trait = 9–14	Smoking	No smoking	N = 121
IHD	52 (84%)	10 (16%)	Relative risk estimate = 3.6
No IHD	35 (59%)	24 (41%)	Phi = 0.27 ($p < 0.01$)
N trait < 9	Smoking	No smoking	N = 123
IHD	29 (72%)	11 (28%)	Relative risk estimate = 2.0
No IHD	47 (57%)	36 (43%)	Phi = 0.15 ($p = 0.09$)

Table 4 gives data on the percentage of probands with IHD in each of these groups. The synergistic effect was finally calculated by subtracting the additive effect from the real combined effect. The additive effect is by definition a simple sum of single risk factors' effects or differences between the groups with and without a given factor, whereas the real combined effect is determined by the difference between the double risk group and the group without any of the two risk factors. The synergistic effect of smoking and N seems obvious (Table 4).

Another way of investigating the synergistic effect was by measuring associations between smoking and IHD in three subgroups with different N (Table 5). The relative risk estimate for smokers — when compared to non-smokers — to have IHD in the low N group was only 2.0. Also, the association was not significant. On the other hand, the relative risk estimates, Phi coefficient and their significance increase while moving from low N towards the group with high N, where the relative risk appeared to be 4.0.

4. Discussion

The possibility of synergistic interactions of risk factors in IHD has occasionally been noted (Kannel, 1978; Friedman et al., 1983; Stone & Thorp, 1985; Perkins, 1989; Eysenck, 1991) and indeed might be expected, given the unexplained variance in IHD risk after accounting for the

effects of all relevant biological and suggested psychobehavioural IHD risk factors taken individually. Eysenck (1991) showed a powerful synergistic effect of smoking and stress on mortality from IHD. Similarly, Friedman et al. (1983) reported that the risk to get a myocardial infarction in smokers when compared to non-smokers was related to actual psychobehavioural coronary-proneness. Evaluation of a given synergistic effect in both already-noted studies were repeated here by replicating their methodologies on the present data. At first, the synergistic effect was measured by calculating the percentage of IHD patients in each of the four groups according to the smoking history and low or high neuroticism (N) score. The synergistic effect was calculated to be almost twice as high as the simple additive one, which agrees with the data of Eysenck (1991), although this time N (not coronary-prone psychosocial type II) and morbidity (not mortality) of IHD were studied. In the other attempt, associations were measured between IHD and smoking in three groups, notably high, mean and low N scorers. Unlike the findings reported by Friedman et al. (1983), no protective effect from smoking was detected for the low N scorers. However, in this group it was truly impossible to confirm risk of smoking as far as IHD was concerned. On the other hand, association only became significant in the group with mean N scores. Higher, although not much, was the relative risk estimate in the high N scorers.

Three hypotheses of smoking-stress interrelation in exacerbating the risk of IHD were outlined by Epstein and Perkins (1988). First, stressors may increase the smoking dose. Second, smoking may increase exposure to stress by increasing a smoker's endurance of a stressor or altering the rate of habituation to the stressor. Finally, the co-occurrence of smoking and stressors may have additive or synergistic effects on cardiovascular reactivity. However, their hypotheses do not try to explain pathogenicity of a given interaction. According to the response-to-injury hypothesis, which is a generally accepted theory for the pathogenesis of atherosclerosis consistent with a variety of experimental evidence, an injury may occur to the lining endothelial cells at particular anatomical sites in the artery wall (Ross, 1997). Examples of types of injury include chemical injury, as in chronic hyperlipidaemia, and mechanical stress associated with hypertension. On the other hand, smoking and some other risk factors have not appeared to influence extent and severity of artery disease at angiography (Vlietstra, Kronmal, Frye, Seth, Tristani & Killip, 1982). Vlietstra et al. (1982) suggested that multistage development of IHD gives a potential for different risk factors involvement at different stages. Some of the factors that are related to the overall risk for IHD, but are not related to atherosclerosis extent and severity, are most probably risk factors for acute and sudden deterioration in coronary flow. For example, in myocardial infarction, coronary flow may be impaired by a thrombus (DeWood, Spores, Notske, Mouser, Burroughs, Golden & Lang, 1980; Antman & Braunwald, 1997) or by coronary vasoconstriction or spasm (Maseri, Parodi & Fox, 1983). In the former, fibrinogen and other haemostatic factors may play an important role (Hultin, 1991), whereas in the latter smoking (Winniford et al., 1986; Winniford et al., 1987; Nobuyoshi et al., 1992; Sugiishi & Takatsu, 1993) and psychobehavioural variables (Legault, Breisblatt, Jennings, Manuck & Follansbee, 1993; Yeung et al., 1993), or even their interactions, might be important.

In relation to the latter, Winniford et al. (1986) found increased coronary tone and enhanced vasoconstriction in IHD patients by inhalation of tobacco smoke. Later on, they reported that blockade of alpha1 receptors in patients with IHD attenuates the coronary vasoconstrictor response to cigarette smoking (Winniford et al., 1987). Hence, a possible effect of smoking may be mediated by stimulation of alpha1 receptors, which is presumably also the case with subjects

who score high on psychobehavioural proneness to IHD. Indeed, psychobehavioural factors were already suggested to be important in terms of temporary deterioration of coronary flow (Numata et al., 1998), and this should most probably be the case, knowing that intrinsic vasoactive substances and neurotransmitters, such as serotonin and acetylcholine, can provoke coronary artery spasm (Kanazawa, Suematsu, Ishida, Hirata, Kawashima, Akita & Yokoyama, 1997). As an example, Yeung et al. (1993) showed that mental stress can cause ischaemia by precipitating vasoconstriction of atherosclerotic epicardial coronary arteries. In subjects with stable angina, mental stress caused dilation of the arteries with normal endothelium but constriction of vessels with evidence of endothelial dysfunction (Yeung, Vekshtein, Krantz, Vita, Ryan, Ganz & Selwyn, 1991). A similar pattern of response has been observed with other stimuli that are also accompanied by activation of the sympathetic nervous system (Ganz & Braunwald, 1997).

Another approach to the investigation of the same interaction (Marušič et al., 1999) showed that almost all possible mechanisms by which cigarette smoking may accelerate the process of atherosclerosis, such as raised blood pressure (Trap-Jensen, 1988; Gerace, Hollis, Ockene & Svendsen, 1991), the detrimental effect on the lipid profile (Tiwari, Gode & Dubey, 1989; Kreitler, Weissler, Kreitler & Brunner, 1991; McCall, van der Berg, Kuypers, Tribble, Krauss, Knoff & Forte, 1994), and markedly increased uptake of fibrinogen by the arterial wall (Kannel, D'Agostino & Belanger, 1987; Allen, Browse & Rutt, 1989), could be explained by the variables that entered the multivariate logistic model of the case-control study independently of smoking and, interestingly enough, the apparent prediction of IHD by smoking and N did not vanish completely. Obviously, the above suggested mechanism that can explain the synergistic interaction between smoking and N should be also important.

To conclude with, personality-smoking interaction is, according to our data, more important than smoking itself. It is, hence, psychologically impermissible to look at smoking as the only meaningful risk factor in the relationship between smoking and emotional lability on one hand and IHD on the other. The interaction is synergistic in the sense that their universal effect does not add but multiply the individual effects. The major consequences would be that we should concentrate efforts for prevention on those groups combining both risk factors. However, further study of the relationships between smoking and emotional lability, and their relationships with IHD is warranted to improve our understanding of the smoking and neuroticism interaction's pathogenicity in IHD. A good start in terms of a pilot study could be the periodic assessment of IHD morbidity in the present control sample and the periodic assessment of IHD mortality in the present IHD group, both in relation to the two risk factors and their interaction. By means of longitudinal or prospective design it would be possible to clarify the already obtained findings. In other words, this study has established a predictive association between these risk factors' interaction and IHD. Future research should focus on improving our understanding of the causal mechanisms responsible for these findings.

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