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# Chronic work stress is associated with atherogenic lipids and elevated fibrinogen in middle-aged men

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**Abstract.** Siegrist J, Peter R, Cremer P, Seidel D. (University of Düsseldorf and Ludwig Maximilians University of Munich, Germany). Chronic work stress is associated with atherogenic lipids and elevated fibrinogen in middle-aged men. *J Intern Med* 1997; **242:** 149–56.

**Objectives.** To examine the association between a model of chronic work stress (high efforts in combination with low rewards) and two risk factors of coronary heart disease, low-density-lipoprotein (LDL)-cholesterol and fibrinogen.

**Design.** A cross-sectional study in a group of 179 healthy middle-aged (48.5 ± 4.5) male middle managers.

**Setting.** A large car-producing enterprise in Germany.

**Results.** After adjustment for relevant covariates, logistic regression analysis showed independent effects of a composite measure of high effort and low reward at work on the prevalence of elevated (upper tertile, i.e. ≥160 mg $dL^{-1}$) LDL-cholesterol (prevalence odds ratio (POR) = 3.57; 95% confidence intervals (CI): 1.24-10.20) and on elevated (upper quintile, i.e. ≥420 mg $dL^{-1}$) plasma fibrinogen (POR = 6.71 (CI: 1.57-28.76). Apart from this core measure, cigarette smoking, overweight and alcohol consumption were the covariates with the relatively strongest contributions to the multivariate model.

**Conclusions.** Results give preliminary evidence on an independent association of chronic work stress with atherogenic lipids and with elevated fibrinogen in an occupationally homogeneous group of healthy middle-aged men.

**Keywords:** fibrinogen, LDL-cholesterol, work stress.

## Introduction

An impressive number of prospective epidemiological studies documented elevated relative risks of fatal or nonfatal acute myocardial infarction in middle-aged men suffering from chronic psychomental or socio-emotional stress at work [for overview see 1–7]. Only part of this elevated risk was attributable to health-detrimental behaviours associated with stressful experience, such as heavy cigarette smoking, lack of physical exercise or faulty diet [3, 5, 8]. Experimental and clinical evidence indicates that pathophysiological pathways linking chronically-stressful experience to coronary artery disease involve enhanced activation of the autonomic nervous system and of different neuroendocrine and immune responses, which in the long run adversely affect the cardiovascular system [9–12]. Partly, these pathways affect important coronary risk factors such as atherogenic lipids [13, 14], elevated plasma fibrinogen [9, 15] or high blood pressure [12,16]. Yet, the epidemiological demonstration of associations between chronic work stress and elevated low-density-lipoprotein (LDL)-cholesterol [17, 18], plasma fibrinogen [19–23] or hypertension [24, 25] so far is limited.

This study was undertaken to test these associations in a socio-economically homogeneous group of middle-aged men experiencing different levels of chronic stress at work. Whereas results concerning the prevalence of hypertension were published elsewhere [26], this report presents the original findings with regard to low density lipoprotein (LDL)-cholesterol and plasma fibrinogen, two coronary risk factors whose clinical significance is widely accepted [27–29].

To introduce the notion of chronic work stress into a scientific framework, a standardized measurement

approach based on a theoretical concept is needed. In this respect the present study is focused on the model of effort–reward imbalance at work developed and tested in our group [5]. In summary, this model defines chronically stressful experience at work in terms of a mismatch between high costs spent and low gains received in occupational life. Two sources of effort are distinguished, an extrinsic source, the demands on the job, and an intrinsic source, the motivations of the individual worker in a demanding situation. In this latter regard, we introduced the concept of 'need for control' as a personal pattern of coping with the demands at work (see 'Data and methods'). These efforts are spent as part of a socially-organized exchange process where rewards are distributed by three transmitter systems: money, esteem, and job security or promotion prospects (so called occupational status control). Lack of reciprocity between costs and gains defines a state of emotional distress, with special propensity to autonomic arousal and cardiovascular risk.

In view of the rather high prevalence of these conditions in modern working life, it is important to know whether they are associated with the prevalence of coronary risk factors such as elevated atherogenic lipids or elevated plasma fibrinogen.

## Data and methods

*Study sample*

A cross-sectional study was conducted in a large car-producing enterprise as part of a cardiovascular screening offered to the total group of middle managers by the company's Occupational Health Department. Based on epidemiological information on prevalence of cardiovascular risk factors, we restricted our investigation to men aged 40–55 years. During the study period a total of 189 middle managers in this age category were screened. Roughly 95% (n = 179) of them agreed to participate in our investigation (48.5 ± 4.5 years). Of the remaining 10 men 6 refused to participate and 4 suffered from long-term sickness absence.

In this study middle managers have been chosen for two reasons. First, we decided to study a group as homogeneous as possible in terms of education, training, and occupational status to rule out the confounding effects of these variables [1, 2, 3, 4, 17–23]. Secondly, due to exposure to specific job characteristics, we expected a rather high proportion of middle managers to exhibit high chronic work stress in terms of high effort and/or low reward.

The present analysis is restricted to middle managers with complete data. This leaves 175 subjects for analysis with regard to LDL-cholesterol and 143 subjects for multivariate analysis with respect to plasma fibrinogen (97% and 79%, respectively, of the total study sample). When considering possible sample bias within the reduced study group we did not find systematic differences on core variables between the full and the reduced sample.

*Biomedical measures*

Independent blood pressure readings were taken by occupational physicians as part of the cardiovascular screening programme using sphygmanometry according to WHO criteria. In addition, body weight and height were assessed. Manifest hypertension was defined according to WHO criteria (160 mmHg systolic and/or 95 mmHg diastolic blood pressure).

Blood samples were obtained from subjects under standardized conditions, i.e. after 30 min of rest in supine position at fixed diurnal time. A fasting time of 12 h was not required for our measurement approach [30]. Plasma fibrinogen was determined by an immunochemical method using monospecific antisera and a nephelometer analyser BNA from Behring Werke, Marburg, Germany. The interassay variation coefficient of fibrinogen measures was as low as 2.5%. The fibrinogen measurement in this study was based on a standard material (Behring AG, Marburg, Germany) which, due to its former declaration by the manufacturer at that time, provided about 40% higher values as compared to the currently used standardization procedure of this method or to functional tests according to the Clauss method [31].

Total serum cholesterol and triglycerides were determined enzymatically. Lipoproteins were measured by commercially available techniques (Immuno Diagnostica, Heidelberg; Boehringer, Mannheim): quantitative lipoprotein electrophoresis [30, 32]; precipitation techniques with dextrane sulphate and sodium phosphotung-state/MgCI2, respectively. All analyses were performed blind by the Department of Clinical Chemistry. In addition, heart rate (resting EKG) and conventional laboratory parameters were assessed [32].

In this study, data analysis is based on continuous and on categorical clinical data. We are aware of the fact that international standardization of cut-off points defining abnormal levels of LDL cholesterol and of plasma fibrinogen is still under discussion. Therefore, our decisions concerning cut-off points of upper limits are justified by reference to recent prospective epidemiological studies indicating that these cut-off points define thresholds of clearly elevated incidence of coronary events: they are the upper quintile corresponding to $\geq 420$ mg $dl^{-1}$ with respect to plasma fibrinogen [31, for discussion see also 27, 33, 34] and the upper tertile ($\geq 160$ mg $dL^{-1}$) with respect to LDL-cholesterol [35].

*Psychosocial and behavioural measures*

The variables of the model of effort–reward imbalance at work were measured by a set of Likert-scaled items which were previously tested and which were assessed by means of a structured interview and a self-administered questionnaire [36, 37]. The experience of extrinsic effort (demands) was measured by assessing the frequency and intensity of being distressed by time pressure, frequent interruptions, inconsistency of demands, and severity of work problems. Factor scores based on these items were computed (Cronbach's alpha: ranging from .76 to .69).

Intrinsic effort was assessed by a self-administered questionnaire measuring 'need for control', a critical personal style of coping with work demands [37]. The questionnaire contains 29 dichotomous items describing excessive job involvement, positive and negative feelings and attitudes related to work commitment as measured by four unidimensional scales: (i) need for approval; (ii) competitiveness and latent hostility; (iii) impatience and disproportionate irritability; and (iv) inability to withdraw from work obligations. These four subscales were repeatedly found to load on one latent factor (Cronbach's alpha ranging from .70 to .63). In a previous study we found that persons scoring in the upper tertile of this scale were at risk of suffering from acute myocardial infarction [38].

Measures of occupational rewards covered the three dimensions of income, esteem and reciprocal support, and of occupational status control (job insecurity, poor promotion prospects, forced job change). Again, frequency and intensity were assessed by Likert-scaled items, and respective scores were computed (Cronbach's alpha ranging from .82 to .48).

According to our theoretical assumption, effort–reward imbalance is defined as the simultaneous manifestation of at least one dimension measuring high extrinsic or intrinsic effort and of at least one dimension measuring low reward. We do not expect all dimensions to be significantly related to the criteria under study, but we postulate independent effects of a three-categorical variable combining information on high effort and low reward on LDL-cholesterol and on fibrinogen, after adjusting for relevant confounders (see 'Statistical analyses').

Information on health-damaging behaviours (cigarette smoking, alcohol consumption, lack of physical exercise, lack of weight control, faulty diet, noncompliance with medication) was recorded from the structured interview using standardized, well-tested questions [32, 36].

*Statistical analyses*

In addition to bivariate analysis, multivariate statistical methods include analysis of variance (anova) for continuous data and logistic regression analysis for categorical data. In analysis of variance, F-test and mean values are displayed. In logistic regression analysis, the model fit of the most parsimonious model is tested by the likelihood ratio difference test in a bottom up procedure [39]. Regression coefficients, standard errors, multivariate prevalance odds ratios and the 95% confidence intervals are indicated in respective tables. For more detailed information on the statistical methods see [37]. A level of significance of $p \leq 0.05$ was accepted in all analyses. Calculations were performed on personal computers using SPSS PC for Windows for data analysis.

## Results

In Table 1, the study sample is characterized with respect to the main biomedical and behavioural variables (means and frequencies). The prevalence as well as mean values and standard deviations of coronary risk factors in this sample are well comparable to those observed in large, representative samples of the male German population in this age group [32, 40, 41].

According to the cut-off points mentioned in the 'Data and methods' section, the two subgroups of

**Table 1** Biobehavioural coronary risk factors in 179 middle managers

| Variable | Mean ± SD | | % |
|---|---|---|---|
| Age ( years) | 48.5 ± 4.5 | Regular cigarette smoking (>10 cig. day $^{-1}$) | 24.0 |
| BMI (kg/m$^2$) | 27.1 ± 3.4 | Lack of physical exercise (<once week $^{-1}$) | 59.0 |
| Systolic blood pressure (mmHg) | 136.1 ± 18.2 | Hypertension[a] | 30.0 |
| Diastolic blood pressure (mmHg) | 88.7 ± 11.4 | Hyperlipidaemia[b] | 32.0 |
| Total cholesterol (mg dL$^{-1}$) | 233.3 ± 40.2 | Elevated fibrinogen[c] | 22.3 |
| LDL-cholesterol (mg dL$^{-1}$) | 141.1 ± 37.6 | Frequency of alcohol consumption (regular)[d] | 29.6 |
| HDL-cholesterol (mg dL$^{-1}$) | 55.3 ± 13.8 | | |
| Fibrinogen (mg dL$^{-1}$) | 372.7 ± 63.7 | | |

[a]SBP: >160 mmHg and/or DBP >95 mmHg. [b]LDL-cholesterol: upper tertile, i.e. >160 mg dL$^{-1}$. [c]Fibrinogen: upper quintile, i.e. >420 mg dL$^{-1}$. [d]At least one 'regular' answer on three three-categorical scales (never, seldom, regular) measuring the frequency of beer, wine and spirit consumption. Values represent means and standard deviations (SD) (left side) and percentages (right side).

middle managers with normal or abnormal values of LDL-cholesterol and of fibrinogen, respectively, are compared in Table 2. From this table it is obvious that regular cigarette smoking is more prevalent in both subgroups at risk. Regular alcohol consumption is found to be more prevalent in middle managers with elevated LDL-cholesterol whereas overweight and younger age are more frequent in the group with elevated fibrinogen. Turning to the psychosocial data, the composite measure of effort–reward imbalance indicates that at least twice as many middle managers with abnormal values of LDL-cholesterol or plasma fibrinogen suffer from chronic work stress as compared to the group with normal values (20.0%

**Table 2** Biobehavioural and psychosocial factors associated with elevated LDL-cholesterol and elevated fibrinogen levels in middle-managers

| | Elevated LDL-cholesterol (upper tertile) | | Elevated fibrinogen (upper quintile) | |
|---|---|---|---|---|
| Variable | Yes (n = 55) | No (n = 115) | Yes (n = 30) | No (n = 113) |
| Age (>50 years) | 34.5% | 42.6% | 26.7%* | 51.3% |
| LDL-cholesterol (upper tertile) | | | 33.3% | 28.3% |
| Fibrinogen (upper quintile) | 32.0% | 20.4% | | |
| Hypertension (>160/95 mmHg) | 34.6% | 27.4% | 23.3% | 29.2% |
| Regular cigarette smoking (>10 cig. day–1) | 30.9% | 19.1% | 40.0%* | 21.2% |
| Frequency of alcohol consumption (regular) | 40.4% | 27.4% | 26.7% | 33.6% |
| Lack of physical exercise (<once week–1) | 66.7% | 55.8% | 66.7% | 55.8% |
| Body weight (≥28.8 kg/m2) | 26.9% | 19.5% | 33.3% | 17.7% |
| *High extrinsic effort* | | | | |
| workload (upper tertile) | 43.6% | 33.0% | 50.0% | 61.6% |
| *High intrinsic effort* | | | | |
| Need for approval (upper tertile) | 25.5% | 27.0% | 30.0%* | 14.2% |
| *Low reward* | | | | |
| Lack of reciprocal support (upper tertile) | 45.5%* | 30.4% | 70.0% | 55.8% |
| Low promotion prospects (upper tertile) | 30.9% | 23.9% | 33.3% | 22.3% |
| *Effort–reward imbalance index* | | | | |
| Neither high efforta nor low reward[b] | 30.9% | 46.1% | 20.0% | 38.1% |
| High effort[a] OR low reward[b] | 49.1% | 44.23% | 60.0% | 54.0% |
| High effort[a] AND low reward[b] | 20.0% | 9.6% | 20.0% | 8.0% |

*$P \leq .05$;. [a]'Workload' (LDL-cholesterol), 'need for approval' (fibrinogen); [b]Lack of reciprocal support (LDL-cholesterol and fibrinogen).

**Table 3** Logistic regression analyses: effort-reward imbalance associated with elevated LDL-cholesterol and elevated fibrinogen in middle-managers

| **Model I** Variable Elevated LDL-cholesterol | Multivariate prevalence odds-ratio Outcome (sample) | 95% CI |
|---|---|---|
| Regular cigarette smoking (>10 cig. day−1) | 2.19* | 1.01–4.75 |
| Frequency of alcohol consumption (regular) | 1.83 | 0.89–3.74 |
| *Effort-reward imbalance index* | | |
| Neither high effort[a] nor low reward[b] | 1.00 | |
| Either high effort[a] OR low reward[b] | 1.62 | 0.77–3.42 |
| High effort[a] AND low reward[b] | 3.57* | 1.24–10.20 |
| **Model II** Variable Elevated fibrinogen | Multivariate prevalence odds-ratio | 95% |
| Regular cigarette smoking (>10 cig. day$^{-1}$) | 3.46** | 1.34–8.89 |
| Body weight (>28.8 kg/m2) | 3.14* | 1.18–8.37 |
| *Effort-reward imbalance index* | | |
| Neither high effort[a] nor low reward[b] | 1.00 | |
| Either high effort[a] OR low reward[b] | 2.56 | 0.87–7.39 |
| High effort[a] AND low reward[b] | 6.71** | 1.57–28.76 |

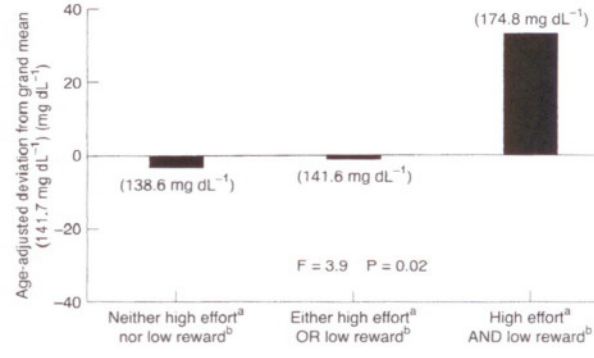
**$P = \leq .01$; *$P \leq .05$. [a]Workload (upper tertile); [b]lack of reciprocal support (upper tertile); [a]need for approval (upper tertile).

vs. 9.6% and 8.0%). Under both conditions, low reward is measured by the same indicator ('lack of reciprocal support'). However, in the case of LDL-cholesterol, high effort is measured by the factor score of extrinsic demands (termed 'workload') whereas in the case of fibrinogen, intrinsic effort as measured by the subscale 'need for approval' is part of the composite measure. In an inductive approach, these two different indicators of effort were chosen according to their discriminatory power.

Results of a statistical test of the study hypothesis are demonstrated in Table 3, using logistic regression analysis. In both logistic regression models, prevalence odds ratios (POR) of being at coronary risk are elevated in the subgroup of middle managers who suffer from effort–reward imbalance at work. This holds true after adjusting for relevant biomedical and behavioural confounders (e.g. cigarette smoking and alcohol consumption with regard to LDL-cholesterol, cigarette smoking and body weight with regard to fibrinogen). As not all possible confounders [42, 43] passed the Likelihood-ratio-difference-test of model fit (see 'Methods') age, hypertension, and lack of physical exercise had to be excluded from analysis.

Finally, as indicated in 'Data and methods', we present an analysis of continuous data, using LDL-cholesterol as outcome criterion. Again, a three-categorical variable is constructed using indicators of extrinsic effort and of low reward. In this case, the definition criterion of low reward is even more restricted as we included only those middle managers who suffered from lack of reciprocal support and from lack of promotion prospects simultaneously, thus defining a high-risk group in psychosocial terms. As can be seen from Figure 1, mean LDL-cholesterol, adjusted for the effect of age, is clearly elevated in this psychosocial high-risk group (174.8 mg dL$^{-1}$ as compared to the grand mean of 141.7 mg dL$^{-1}$; F = 3.9; P = 0.02).

Respective analyses with continuous data on fibrinogen were not indicated due to the fact that the distribution of fibrinogen values precluded the application of anova.




[a]Workload; [b]lack of reciprocal support, low promotion prospects.

**Fig. 1** Effort–reward imbalance and mean LDL-cholesterol levels amongst 168 middle managers.

## Discussion

In this cross-sectional study of a group of economically-active middle-aged male middle managers chronic work stress in terms of high effort and low reward is associated with significantly increased relative risks of having abnormal levels of LDL-cholesterol and plasma fibrinogen. Results are neither explained by important confounders such as cigarette smoking, overweight, age, lack of physical exercise or alcohol consumption [42, 43], nor are they influenced by social class, a variable which was shown to be inversely associated with fibrinogen [19–22] and, partly, with atherogenic lipids [8]. Current stress physiological evidence on epinephrine-induced platelet activation and increase in plasma fibrinogen [9, 15] and on sympatho-adrenergically enhanced endogenous lipid metabolism [12-14] offers a possible frame of interpretation of reported findings. Clearly, this study lacks direct information on an association between chronic work stress, catecholamine concentrations and level of fibrinogen or LDL-cholesterol.

Additional support in favour of a stress–physiological interpretation of the observed association is given by further results obtained from the same study population: middle managers suffering from high effort, in terms of time pressure and severe problems, in combination with anticipated forced job change (low reward) exhibited an increased relative risk of being hypertensive (multivariate odds ratios ranging from 1.86–2.94; [26]). Moreover, in a previous prospective investigation on cardiovascular risk and disease in a cohort of male blue-collar workers, indicators of effort–reward imbalance at work were associated with a high ratio of low-density-lipoprotein (LDL)- to high-density-lipoprotein (HDL)-cholesterol [17], and they predicted incident-fatal or nonfatal cardiovascular events [38].

Studies from other research teams using a somewhat different concept of measuring chronic work stress, the demand–control model of job strain [2, 3], reported similar findings with regard to fibrinogen [20, 23, but for negative results see 44].

### *Limitations of the study*

This cross-sectional study is based on a limited sample size and a limited range of measurements. Though unlikely, the observed statistical effects could be attributed to some covarying risk factor not measured in our protocol, such as coffee consumption [45] or genetic risk [29]. Alternatively, one may argue that persons suffering from cardiovascular risk may express higher levels of chronic work stress. This latter interpretation, however, is unlikely for two reasons: first, the majority of middle managers with elevated level of fibrinogen or LDL-cholesterol considered themselves as being healthy and were not pharmacologically treated.

Moreover, the robustness of reported findings may be limited as evidenced by large confidence intervals in logistic regression analyses. The fact that variables entering the composed measure of high effort and low reward were not exactly identical in all analyses needs some further comment. As mentioned in the 'Data and methods' section, we do not expect every core variable measuring the model to be a predictor of the criteria under study. Rather, the simultaneous manifestation of at least one condition of high effort (either extrinsic or intrinsic) and of at least one condition of low reward is hypothesized to account for the specific quality and intensity of stressful work-related experience which may underlie the observed cardiovascular risk. Nevertheless, in future studies composite measures of effort–reward imbalance will be required which define critical thresholds at study onset and which will be comparable across different investigations.

A further argument refers to the fact that some middle managers have suffered from high LDL-cholesterol and elevated fibrinogen simultaneously, and that accounting for this association may threaten the robustness of the reported findings. Therefore all analyses were repeated taking into account the 10 subjects who were at risk from both conditions. No significant changes were observed.

Due to deviation from normal distribution of criterion variables and due to unequal size of subgroups, multivariate statistical analysis in this report was confined to logistic regression analysis. The respective loss of information on a possible dose–response relationship between work stress and cardiovascular risk must be considered a major limitation. Some additional analyses using anova procedure were performed, and they give preliminary support in favour of such an assumption, at least when introducing continuous data on LDL-cholesterol (see Figure 1).

A further limitation of this study concerns the cut-off points on which analyses are based. For two reasons, the case of plasma fibrinogen may be

particularly critical. First, international consensus on clinically relevant thresholds is not yet as advanced as in the case of LDL-cholesterol. Secondly, standardization of measurement techniques used in epidemiological studies is still insufficient, thus rendering difficult direct comparisons across different study populations.

Despite these limitations, we maintain that reported statistical associations between theoretically-based measures of chronic work stress and elevated atherogenic lipids, as well as plasma fibrinogen, deserve further attention in epidemiological and clinical studies on cardiovascular risk and disease. This holds true especially in view of the high prevalence of stressful working conditions in terms of effort–reward imbalance in the current global economy, and in view of the high prevalence and clinical significance of the two cardiovascular risk factors under study, LDL-cholesterol and plasma fibrinogen. It may well be that future attention to the psychosocial conditions specified above contributes to further successes in reducing the burden of cardiovascular risk and disease.

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