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Does Autonomic Function Link Social Position to Coronary Risk?

The Whitehall II Study

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Background—Laboratory and clinical studies suggest that the autonomic nervous system responds to chronic behavioral and psychosocial stressors with adverse metabolic consequences and that this may explain the relation between low social position and high coronary risk. We sought to test this hypothesis in a healthy occupational cohort.

Methods and Results—This study comprised 2197 male civil servants 45 to 68 years of age in the Whitehall II study who were undergoing standardized assessments of social position (employment grade) and the psychosocial, behavioral, and metabolic risk factors for coronary disease previously found to be associated with low social position. Five-minute recordings of heart rate variability (HRV) were used to assess cardiac parasympathetic function (SD of N-N intervals and high-frequency power [0.15 to 0.40 Hz]) and the influence of sympathetic and parasympathetic function (low-frequency power [0.04 to 0.15 Hz]). Low employment grade was associated with low HRV (age-adjusted trend for each modality, $P \leq 0.02$). Adverse behavioral factors (smoking, exercise, alcohol, and diet) and psychosocial factors (job control) showed age-adjusted associations with low HRV ($P < 0.03$). The age-adjusted mean low-frequency power was 319 ms^2 among those participants in the bottom tertile of job control compared with 379 ms^2 in the other participants ($P = 0.004$). HRV showed strong ($P < 0.001$) linear associations with components of the metabolic syndrome (waist circumference, systolic blood pressure, HDL cholesterol, triglycerides, and fasting and 2-hour postload glucose). The social gradient in prevalence of metabolic syndrome was explained statistically by adjustment for low-frequency power, behavioral factors, and job control.

Conclusions—Chronically impaired autonomic function may link social position to different components of coronary risk in the general population. (***Circulation*. 2005;111:3071-3077.**)

Key Words: disparities ■ metabolism ■ psychosocial factors ■ social factors ■ stress

Lower position in the social hierarchy is associated with a higher incidence of coronary disease.[1,2] Part of this effect is explained by behavioral factors such as smoking, with an additional contribution made by psychosocial factors.[3,4] In the context of a working population, low job control predicts coronary disease incidence[5] and may mediate the relationship between low social position and coronary disease.[6] Laboratory and clinical studies suggest that the autonomic nervous system may link such distal influences to metabolic and physiological processes more proximal to coronary disease.[7,8] Among nonhuman primates, the accelerated atherosclerosis of social stressors is prevented by β-blockade.[9] Among healthy humans subjected to acute laboratory stressors, those with low social position demonstrate impaired recovery of heart rate variability (HRV).[10] High heart rate and low HRV, both measures of cardiac autonomic status, predict coronary disease incidence[11] and prognosis.[12]

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However, the relation between sympathetic and parasympathetic function and social position in the healthy populations is uncertain. Educational level may be associated with heart rate (inversely)[13,14] and HRV (directly),[11] but the extent to which this is explained by behavioral or psychosocial factors has not been addressed.[15] Low social position is associated with an increased prevalence of the metabolic syndrome,[16] components of which explain much of the social gradient in coronary events.[17] In a case-control study, 30 men with the metabolic syndrome had lower HRV than control subjects.[8] Autonomic dysfunction may lead to cases of insulin resistance,[18–23] but the relations of HRV to central obesity, postload glucose, blood pressure, HDL cholesterol, and triglycerides across the continuous range of values are not known.

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We therefore sought to determine the extent to which (1) HRV differs by social, behavioral, and psychosocial factors; (2) components of the metabolic syndrome differ by HRV; and (3) social differences in the metabolic syndrome are explained by these behavioral, psychosocial, and autonomic factors. The Whitehall II Study offers a unique opportunity to address this question with its precise measure of social hierarchy (civil service employment grade), range of psychosocial factors, oral glucose tolerance tests, and power spectral measures of HRV.

Methods

Participants

All nonindustrial civil servants 35 to 55 years of age working in the London offices of 20 departments were invited to participate in this study; 10 308 (6895 men) were recruited between 1985 and 1988. At phase 5 of the study (1997 to 1999), all participants known to be alive and in the country were invited to the screening clinic; 4646 men (67% of original sample) attended. HRV recordings were performed on 2344 men. Because of the availability of clinic staff, no HRV recordings were made on any men on 69 days during screening, which accounted for most of the missing HRV data. To address potential confounding by ethnicity, we confined all analyses to the 2197 white Europeans with HRV measurements. The University College London ethics committee approved the study, and written informed consent was obtained from each participant.

Employment Grade and Psychosocial Factors

Participants completed a questionnaire detailing job title and behavioral and psychosocial factors, as described previously.[24] Using salary and work role, the civil service defines a hierarchy of employment grades, which we analyzed in 3 levels: unified grades 1 to 7 (high), executive officers (medium), and clerical and support staff (low). There were 1220 men in the high, 871 in the medium, and 106 in the low grades. Minor psychiatric morbidity was assessed with the 30-item General Health Questionnaire and a 4-item depression subscale identified on the basis of factor analysis and comparison with the items of the depression subscale of the 28-item General Health Questionnaire. Social networks were measured with a 4-item scale of frequency and number of contacts with friends, relatives, and participation in a social group. Job control was measured with a 15-item scale.

Behavioral Factors

Smoking, exercise, diet, and alcohol were assessed by questionnaire. Participants were asked how often they took part in vigorous exercise; those undertaking <1 hour per week were defined as getting little or no exercise. In addition, MET hours per week of total physical activity was derived from a 20-item questionnaire on the amount of time spent walking and cycling, in sports, in gardening activities, on housework, and on house maintenance.[25] Diet was assessed by 3 items: frequency of fruit and vegetable consumption (8 levels ranging from never to $\geq$2 per day), the type of bread (3 levels: white, wheat meal, whole meal), and type of milk (3 levels: whole milk, semiskimmed, skimmed). Food frequency data were found to have acceptable validity.[26] Repeatability (weighted κ) for the 3 diet items, assessed in a subset (n=286) of participants who repeated the questionnaire, ranged from 0.57 to 0.82. A summary index of poor diet was defined if 2 or all of the following applied: most frequently used bread was white, usually used milk was whole, and fruit or vegetables were eaten less often than daily. Alcohol consumption in the last week was expressed in units of alcohol (1 U=8 g); $>$28 U/wk was categorized as high on the basis of UK government recommendations.

HRV Assessment

HRV measurement was carried out in accordance with current standards[27] and is described in detail elsewhere.[25,28] Five minutes of beat-to-beat heart rate data were sampled at 500-Hz frequency with a dedicated personal computer and software (Kardiosis) to obtain digitized recording of R waves. HRV was analyzed both in the time domain (SD of all intervals between R waves with normal-to-normal conduction [SDNN]) and in the frequency domain with the autoregressive method. Frequency domain components were computed by integrating the power spectrum within 2 frequency bands: low frequency (LF), 0.04 to 0.15 Hz (in ms^2), and high frequency (HF), 0.15 to 0.4 Hz (in ms^2). The LF power reflects both parasympathetic and sympathetic modulations; the HF component is a function of the variation in parasympathetic tone.[27] Heart rate was estimated from standard resting ECG among those participants who did not undergo HRV recordings.

Components of Metabolic Syndrome

Systolic and diastolic blood pressures, waist circumference, fasting and 2-hour post–oral glucose load plasma glucose, HDL cholesterol, and triglyceride levels were determined as previously reported.[16] Cases of metabolic syndrome were defined by use of the ATP-III definition.[29]

Statistical Analysis

SDNN, LF, and HF were transformed by natural logarithm because their distributions were skewed and are expressed as geometric means with 95% CIs. Age-adjusted proportions of participants with the metabolic syndrome were calculated with a Cochrane-Mantel-Haenszel test for trend across heart rate and HRV quartiles. For the continuous components of the metabolic syndrome, age-adjusted means and tests for trend were obtained from linear regression (proc GLM in SAS). Similarly, age-adjusted means and tests of differences were calculated for heart rate and HRV by behavioral and psychosocial factors.

To estimate how much of the employment grade gradient in metabolic syndrome was mediated by health-related behaviors, psychosocial factors, and HRV, we fitted linear regression models, assuming the grade effect to be linear across its 6 levels. Because previous studies suggest a link between the sympathetic nervous system and stressors related to social position, we chose to model LF power on a priori grounds as a marker of the balance between sympathetic and parasympathetic activity. We estimated the odds ratios of having the metabolic syndrome for low versus high employment grade by fitting logistic regression models, with employment grade as a single linear term. A higher percentage reduction in the employment grade coefficient on adjustment for 1 or a combination of these variables denotes stronger evidence that they play a mediating role. Adjustments were made for smoking (3 levels: never, ex-, current smoker), alcohol (6 levels), exercise (4 levels based on METS of vigorous exercise), diet score (4 levels), and job control (3 levels). Among the 1398 participants who were still in work and had a measure of job control and metabolic syndrome, data were missing on $\geq$1 covariates for 120 (9%). To examine whether working participants with complete data (n=1278) were representative of all working participants (n=1398), we carried out both a complete case analysis and an analysis using multiple imputation of missing values. Imputed data sets were generated with the NORM program. Five data sets were randomly selected, and because the analyses of these data sets gave very similar results, the mean is presented.[30]

Results

Employment Grade–HRV

Employment grade was inversely associated with heart rate and positively associated with HRV in men (Table 1). Thus, SDNN (P for trend=0.004), LF power (P for trend=0.02), and HF power (P for trend=0.002) were all lower among

TABLE 1. Age-Adjusted Mean* Heart Rate and HRV According to Civil Service Employment Grade

Employment Grade (n=2197 men)	Heart Rate, bpm	SDNN, ms	LF Power, ms^2	HF Power, ms^2
High (n=1220)	67.9 (67.3–68.5)	34.7 (33.9–35.6)	333 (316–351)	120 (113–128)
Medium (n=871)	70.0 (69.3–70.7)	33.5 (32–6–34.5)	317 (297–337)	109 (102–117)
Low (n=106)	71.1 (69.1–73.2)	30.8 (28.4–33.4)	261 (219–312)	87 (71–107)
P for trend	<0.001	0.004	0.02	0.002

Values in parentheses are 95% CIs.
*Geometric means are shown for HRV because these measures are skewed.

men in the low employment grades. The difference between low and high grades in mean heart rate was 3.2 bpm. These grade effects were independent of history of prevalent coronary heart disease. The participants who did not undergo HRV recordings did not differ in age, employment grade, educational level, job control, smoking status, marital status, history of coronary heart disease, body mass index, triglycerides, or 2-hour postload glucose compared with those who did undergo HRV recordings. There were small (<0.12 SD) differences in heart rate, waist circumference, HDL, and systolic blood pressure between these groups. Those participants without HRV measurements exhibited the same inverse grade–heart rate relationship; the mean heart rates for high-, medium-, and low-grade men were 65.6, 66.9, and 68.0 bpm (*P* for trend=0.002).

Behavioral and Psychosocial Factors–HRV

Adverse health-related behaviors were associated with adverse heart rate and HRV (Table 2). Thus, current smoking, little or no vigorous exercise, poor diet, and high alcohol consumption were associated with lower age-adjusted means of SDNN, LF power, and HF power. Participants in the low (adverse) tertile of job control had higher mean heart rates and lower SDNN, LF power, and HF power than participants in the middle and top tertiles. For LF power, the age-adjusted means were 319 ms^2 (95% CI, 286 to 355) and 379 ms^2 (95% CI, 360 to 399), respectively (*P*=0.004). This effect remained after further adjustment for employment grade (330 versus 376 ms^2; *P*=0.05). The highest heart rates and lowest HRV were consistently found in those with depression and low social networks (*P*=0.03 to 0.30).

Metabolic Syndrome–HRV

There were strong linear associations between the mean values of each component of the metabolic syndrome and heart rate and HRV (Table 3) (*P* for trend <0.001 for all except HDL cholesterol). After exclusion of cases of metabolic syndrome, the association of systolic blood pressure, waist circumference, triglycerides, and 2-hour postload glucose with HRV remained in men. Based on correlation coefficients, the strongest association with HRV was observed for waist circumference. The age-adjusted prevalence of the metabolic syndrome across the quartiles of LF HRV was 5.2% (top quartile), 7.7%, 14.6%, and 21.5% (bottom quartile; *P* for linear trend <0.001). Among participants who did not undergo HRV recordings, the age-adjusted prevalence of metabolic syndrome across quartiles of heart rate was 5.5% (bottom quartile), 8.6%, 10.2%, and 16.5% (top quartile; *P* for linear trend <0.001).

Effects of Behavioral, Psychosocial, and Autonomic Factors on Social Differences in the Metabolic Syndrome

There was an employment grade gradient in the prevalence of the metabolic syndrome among the subset of participants with HRV and psychosocial measures (as in the whole cohort); for each grade level lower in the social hierarchy, the prevalence of metabolic syndrome increased (Table 4). The proportion of variation in job control explained (age adjusted r^2) by employment grade was 0.29. For the imputed data sets, the age-adjusted odds ratio for having the metabolic syndrome in the low versus high employment grade was 1.71 (*P*=0.05). This age-adjusted grade gradient was reduced by adding LF power (40%), behavioral factors (52%), and job control (55%) separately to the models. Adding LF power to the job control or behavioral models removed virtually all the employment grade gradient in metabolic syndrome. These findings were consistent when the analysis was confined to participants with complete data for all covariates, with respective attenuations of 61%, 92%, and 61%. When analyses were carried on the working and nonworking population combined, the model including age, behavioral factors, and LF power reduced the grade effect by 65%.

Discussion

Lower social position in men was associated with higher heart rate and lower HRV. The high coronary risk of low social position is mediated by behavioral and psychosocial factors and components of the metabolic syndrome.[3,4,16] Here, we demonstrate that each of these factors was associated with low HRV. Furthermore, the relationship between social position and metabolic syndrome[16] was mediated by low LF power, behavioral factors, and low job control. This provides population evidence for the hypothesis that disturbances of the autonomic nervous system are involved in mediating the excess coronary risk associated with low social position.

Social Position

High heart rate[31,32] and low SDNN,[11,33–36] LF power,[11,33,37] and HF power[11,33,38] are associated with increased risk of coronary disease or all-cause mortality in healthy populations. We found that each measure of HRV was associated with low social position and found little evidence to support specific effects with LF power, which denotes sympathet-

TABLE 2. Behavioral and Psychosocial Factors and Age-Adjusted Means of Heart Rate and HRV

	Participants, n	Heart Rate, bpm	SDNN, ms	LF Power, ms^2	HF Power, ms^2
Behavioral factors					
Current smoker					
No	1991	68.7 (68.2–69.2)	34.5 (33.8–35.1)	332 (319–346)	118 (112–123)
Yes	193	70.6 (69.1–72.2)	31.6 (29.7–33.5)	271 (237–309)	96 (82–112)
P		0.02	0.007	0.004	0.01
Vigorous exercise					
Some	714	66.4 (65.6–67.2)	36.1 (34.9–37.2)	363 (338–389)	131 (121–142)
little / none	1329	70.3 (69.7–70.9)	33.2 (32.4–34.0)	308 (292–324)	108 (102–114)
P		<0.001	<0.001	<0.001	<0.001
High alcohol consumption					
No	1758	68.4 (67.8–68.9)	34.7 (34.0–35.4)	338 (324–353)	121 (116–128)
Yes	391	71.2 (70.1–72.3)	32.0 (30.6–33.4)	278 (253–306)	93 (84–104)
P		<0.001	<0.001	<0.001	<0.001
Poor diet					
No	1610	68.3 (67.7–68.8)	34.6 (33.9–35.4)	336 (321–351)	120 (113–126)
Yes	488	70.9 (69.9–71.9)	33.0 (31.7–34.3)	300 (276–326)	105 (96–116)
P		<0.001	0.03	0.02	0.02
Psychosocial factors					
Depression					
No	1424	68.6 (68.1–69.3)	34.5 (33.8–35.3)	335 (319–351)	119 (112–125)
Yes	701	69.2 (68.4–70.1)	33.6 (32.6–34.7)	313 (292–335)	112 (103–122)
P		0.3	0.18	0.12	0.27
Low social networks					
No	1482	68.5 (67.9–69.1)	34.5 (33.7–35.2)	332 (317–348)	120 (113–127)
Yes	584	69.5 (68.6–70.4)	33.4 (32.3–34.6)	307 (284–331)	107 (98–117)
P		0.07	0.15	0.09	0.03
Low job control*					
No	1190	68.1 (67.5–68.7)	36.3 (35.5–37.2)	379 (360–399)	133 (125–141)
Yes	271	70.8 (69.6–72.1)	33.7 (32.0–35.4)	319 (286–355)	114 (101–130)
P		<0.001	0.006	0.004	0.03

Values in parentheses are 95% CIs.
*Job control was estimated only in those 1461 participants still working.

ic:parasympathetic balance, as opposed to markers of parasympathetic function (SDNN and HF power). The biological pathways linking the social, autonomic, and metabolic disturbances are not clear but may involve central serotonergic and hypothalamo-pituitary adrenal pathways. Reduced serotonergic activity is associated with individual components of the metabolic syndrome,[39] autonomic function,[40] and a diverse array of behaviors.[41]

Psychosocial Effects–Job Control

Autonomic responses to acute psychosocial stressors are well described, but associations with the chronic psychosocial stressors associated with risk of coronary disease have been less widely investigated.[42–44] An important source of psychosocial stress is the workplace, and we found that low job control was associated with higher heart rate and low HRV independently of civil service employment grade. Other work characteristics were not associated (data not shown). Psychosocial work characteristics are associated with cardiovascular mortality[45] and morbidity,[3] but the biological mechanism by which such psychosocial exposures operate has been elusive. A previous small study found no association with job stress and HRV.[46]

Behavioral Effects on HRV

Smoking, exercise, diet, and alcohol were each associated with low HRV. Behavioral factors contributed to the grade differences in the metabolic syndrome. Although low job control and other psychosocial factors may lead to adverse behavioral responses,[47] both behavioral and psychosocial factors independently contributed to explanations of grade differences in metabolic syndrome. The findings in relation to exercise have been reported more fully elsewhere.[25] Few previous studies have reported on diet and alcohol in relation to HRV.[48] Our results suggest a role for autonomic dysfunction among the biological mechanisms that mediate coronary risk of health-related behaviors.

TABLE 3. Components of the Metabolic Syndrome by Quartiles of HRV: Age-Adjusted Means and Correlation Coefficients

	Components of the Metabolic Syndrome						
	Waist Circumference, cm	Systolic blood pressure, mm Hg	HDL Cholesterol, mmol/L	Triglycerides, mmol/L	Fasting Glucose, mmol/L*	2-Hour Postload Glucose, mmol/L*	Metabolic Syndrome, %
Heart rate, n	1853	2190	2073	2179	1880	1891	2094
Quartile 1 (lowest)	89.2	118.4	1.39	1.24	5.08	5.67	6.6
Quartile 2	91.7	121.6	1.36	1.41	5.13	5.69	9.5
Quartile 3	93.1	123.8	1.36	1.42	5.17	6.11	12.6
Quartile 4 (highest)	96.3	128.2	1.35	1.67	5.30	6.24	18.4
P for trend	<0.001	<0.001	0.11	<0.001	<0.001	<0.001	<0.001
Correlation coefficient†	0.23‡	0.22‡	0.03	0.12‡	0.15‡	0.13‡	
SDNN							
Quartile 1 (lowest)	96.1	127.1	1.34	1.69	5.24	6.22	20.8
Quartile 2	92.7	123.7	1.35	1.45	5.21	5.94	13.0
Quartile 3	91.7	121.6	1.38	1.39	5.14	5.81	9.7
Quartile 4 (highest)	89.9	119.6	1.38	1.22	5.10	5.76	5.3
P for trend	<0.001	<0.001	0.03	<0.001	<0.001	<0.001	<0.001
Correlation coefficient†	−0.17‡	−0.15‡	0.002	−0.13‡	−0.09‡	−0.08‡	
LF power							
Quartile 1 (lowest)	96.2	126.6	1.32	1.65	5.25	6.14	21.5
Quartile 2	93.2	124.1	1.36	1.53	5.17	5.97	14.6
Quartile 3	91.4	121.5	1.38	1.35	5.15	5.85	7.7
Quartile 4 (highest)	89.7	119.7	1.39	1.23	5.12	5.77	5.2
P for trend	<0.001	<0.001	0.001	<0.001	<0.01	<0.001	<0.001
Correlation coefficient†	−0.19‡	−0.14‡	0.04	−0.11‡	−0.07‡	−0.04	
HF power							
Quartile 1 (lowest)	97.0	127.2	1.33	1.64	5.27	6.17	20.1
Quartile 2	92.5	123.5	1.37	1.47	5.16	5.97	11.8
Quartile 3	91.4	121.5	1.36	1.37	5.13	5.82	9.7
Quartile 4 (highest)	89.6	119.6	1.39	1.26	5.11	5.78	6.9
P for trend	<0.001	<0.001	0.03	<0.001	<0.001	<0.001	<0.001
Correlation coefficient†	−0.21‡	−0.16‡	0.01	−0.12‡	−0.08‡	−0.08‡	

*Known diabetics were excluded from the oral glucose tolerance test.
†Correlation coefficients are expressed after exclusion of diabetics and patients with metabolic syndrome.
‡For correlation coefficient, $P<0.001$.

Explaining Social Differences in Metabolic Syndrome

We found strong, linear associations between each component of the metabolic syndrome and low HRV. These relationships extended into the normal range, below the cutoff values used to define the syndrome. LF power and low job control each offered important explanatory power for social differences in metabolic syndrome. In broad terms, these findings are consistent with the proposal[7] that autonomic dysfunction brought about by chronic stressors may in turn have adverse metabolic consequences.[8,18–20] However, the finding that job control influenced social differences in metabolic syndrome independently of LF power suggests the importance of other pathways beyond cardiac autonomic function, including the hypothalamo-pituitary adrenal axis.[49] The allostatic burden of low social position may involve the factors that cluster together as the metabolic syndrome. Increasingly recognized as a disease entity in its own right,[29] the metabolic syndrome is more prevalent as the social hierarchy is descended.[16] Low HRV predicts the onset of impaired fasting glucose,[21] new diabetes,[18] and hypertension.[50] In the ARIC study, lower HF power, LF power, and SDNN was observed in the presence (compared with the absence) of hypertension and fasting measures of glucose tolerance.[22]

Metabolic Syndrome Explaining Social Differences in HRV

The causal pathway between autonomic function and metabolic disturbance may operate in both directions, with insulin resistance, an underlying disturbance in the metabolic syndrome, leading to sympathetic activation.[51] Consistent with

TABLE 4. Employment Grade Differences in the Metabolic Syndrome and the Effect of Adjustment for HRV and Behavioral and Psychosocial Factors

Adjustments	OR of Having Metabolic Syndrome in Low vs High Employment Grade*† (95% CI)	Attenuation‡ %
Age	1.71 (1.0–2.9)	
Age+LF power	1.38 (0.8–2.4)	40
Age+behavioral factors	1.30 (0.7–2.3)	52
Age+job control	1.27 (0.7–2.4)	55
Age+LF power+behavioral factors	1.11 (0.6–2.0)	80
Age+LF power+job control	1.02 (0.53–1.9)	97

Each row represents a separate statistical model.

*The sample is based on those 1398 participants still working who had a value for job control and metabolic syndrome.

†The odds ratio (OR) is estimated from the linear trend across 6 levels of employment grade.

‡Percentage attenuation of the employment grade effect compared with the age-adjusted model.

this, we found that components of the metabolic syndrome explained 27% of the social gradient in LF power. However, in a cross-sectional study, it is not possible to establish the relative importance of each causal direction.

Study Limitations

These findings are based on white, male civil servants. Further studies are required in other ethnic groups, women, nonworking populations, and people in developing countries. However, the results are consistent with findings of a study of the general population not selected on the basis of occupation in which low HRV was related to educational level in women and men.[11] It is also possible that the subset of the Whitehall II population in whom HRV was assessed may be biased. However, evidence against this comes from the consistent relationships between heart rate and grade and between heart rate and metabolic syndrome among those without and with HRV assessments. We confined our analyses to men because women have higher heart rates and lower HRV than men[48] and because the patterns of social and psychosocial stressors show gender differences.[43] Although 5-minute HRV recordings are highly repeatable,[52] 24-hour recordings, especially involving naturalistic psychosocial exposures, may offer better characterization of these relationships.

Study Implications

Follow-up of the Whitehall II study, including women, is underway to test longitudinal associations between autonomic function and psychosocial, behavioral, and metabolic factors and ultimately to assess whether disturbances in autonomic function mediate the relation between social position and coronary events. If it does, prospective studies are required to identify interventions, for example, to improve control in the workplace.

Conclusions

In this occupational cohort, disturbances of autonomic function may link "distal" (behavioral and psychosocial) and more "proximal" (components of the metabolic syndrome) causes of social differences in coronary disease.

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