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# POSITIVE AND NEGATIVE LIFE CHANGES AND LDL CHOLESTEROL

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**Summary.** Epidemiological studies have revealed that stressful changes in social environment increase the risk of cardiovascular mortality. In this study, the influence of major negative and positive life changes on serum cholesterol was examined in middle-aged men to determine a possible biochemical link between life changes and cardiovascular mortality. The results showed no influence of negative life changes on serum cholesterols. However, positive life changes significantly predicted a reduction in total and LDL (low-density lipoprotein) cholesterol levels after adjustment for the baseline cardiovascular health status, baseline cholesterol level, diet, body mass index, waist-to-hip ratio and cardiorespiratory fitness. The odds ratio for lowering LDL cholesterol was 5·2 in the men reporting positive events compared with those reporting none. The findings suggest a predictive value of positive life changes for atherogenic lipid profile in middle-aged men.

## Introduction

An association has been found between stressful life events and increased risk of cardiovascular morbidity and mortality (Theorell, 1992; Bosma *et al*., 1997), but it is not clear what factors underlie this association. One possibility is that serum lipids are a biochemical link between stressful life events and cardiovascular disease (Romm *et al*., 1991). It is well established that acute and chronic mental stress elevates serum lipid levels (Melamed, Kushnir & Shirom, 1992; Patterson *et al*., 1993; McCann *et al*., 1995; Muldoon *et al*., 1992, 1995). It has also been shown that stress reduction rapidly decreases serum lipids (Mitsibounas *et al*., 1992). Although a brief review of the literature reveals an association between stress and serum lipids (Niaura, Storey & Herbert, 1992), it has not been reported whether major positive and negative life changes affect lipid levels.

The purpose of this 1-year follow-up panel study was to assess in 152 middle-aged men whether major negative and/or positive life changes predict changes in cholesterol concentration in serum and lipoprotein fractions independently of social support and biomedical prognostic factors.



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## Methods

### *Subjects and procedure*

This study was part of the Kuopio Osteoporosis and Atherosclerosis (OPAS) study investigating the prevalence of carotid atherosclerosis and its biological, behavioural, and psycho-social risk factors in men aged 50–60 years (Rauramaa *et al*., 1995). Subjects gave written informed consent, and the study protocol was approved by the Ethical Committee of Kuopio University.

In 1992, a 6·2% random sample of Eastern Finnish men aged 50–60 years ($n = 4853$) living in the city of Kuopio (82%) and a nearby semiurban community (18%) were invited to participate in the OPAS study. Of the 300 men initially invited, 84% participated in the study. The final cohort comprised 212 men. The same panel was invited to the follow-up examination 12 months later. The participation rate was then 90% ($n = 186$). During the follow-up period, no attempt was made to influence the physical activity, diet or smoking habits of the subjects. At the baseline the drop-outs were heavier (body mass index 29·0 (SD 3·6) kg/m$^2$ vs 26·8 (3·6) kg/m$^2$; $p = 0{\cdot}001$) and smoked more (42·3 vs 18·8%; $p = 0{\cdot}006$) than the men who completed both examinations. However, serum total, LDL and HDL cholesterol concentrations, as well as education level, marital status, and social support levels, were similar in both groups.

In 1993, of the 186 men participating in both examinations, 152 (82%) provided information about major positive and 133 (72%) about major negative life changes that happened during the past year. The men with missing data did not differ from those with completed questionnaires in regard to serum lipids, body weght, smoking, education level, social network and support, marital status and cardiovascular health status.

### *Examinations*

A self-administered questionnaire, designed for this study, was used to keep track of major life changes. The questionnaire consisted of an equal number of questions about negative and positive changes. The three major positive changes requested were (yes/no): 'major positive changes in work conditions', 'major positive changes in close relationships' and 'major positive changes in living conditions (economy)'. The three major negative changes (yes/no) included the items 'remarkably worsened economical situation', 'loss of a job' and 'remarkably increased conflicts with a spouse or a cohabitant'. Two dichotomized variables – a positive life change indicator and a negative life change indicator – were designed. The positive life change indicator included subjects with one to three positive changes. The negative life change indicator included subjects with one to three negative changes. A positive life change was defined as a desirable event and a negative life change as an undesirable event. It was hypothesized that the changes were major enough to influence social support and psychosocial stress levels.

Venous blood samples were drawn without stasis between 07.30 and 10.00 h after a 12-h fast and 30 min rest in supine position. The men were advised not to drink alcohol for 1 week nor to take any inflammatory analgesics during the 2 weeks prior to blood donation. Also, in the case of any acute respiratory infection, blood samples

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were not taken until at least 1 week had elapsed after disappearance of the symptoms. For serum determinations, blood was allowed to clot at room temperature for 60 min whereafter the collection tube was centrifuged at $2000 \times g$ for 10 min at room temperature. Very low-density lipoproteins (VLDL) were separated from serum samples by ultracentrifugation for 16 h at $105{,}000 \times g$ (Kontron TGA-65 Ultracentrifuge, Kontron International, Zürich, Switzerland) after adjusting the density to 1·006 g/ml with NaCl (Carlson, 1973). High-density lipoprotein (HDL) cholesterol was measured in the supernatant obtained after precipitation of low-density lipoproteins (LDL) from the VLDL-free fraction by dextran sulphate ($M_r$ 500,000, Pharmacia, Uppsala, Sweden) and $MgCl_2$ (Magnesium chloride hexahydrate, Merck, Darmstadt, Germany) (Penttilä *et al.*, 1981). Cholesterol concentrations in serum and lipoprotein fractions were measured enzymatically using a commercial CHOD-PAP method (Boehringer Mannheim GmbH, Germany).

Dietary intake was measured in 1992 and in 1993 using 4-day food records. Recording days included three weekdays and Sunday. Portion sizes were estimated using a picture booklet (Pietinen *et al.*, 1988) or household measurement units. The dietician gave instructions to all subjects on how to fill in the records, and he also checked the records at the time of their return. All records were analysed using MicroNutrica software based on a nutrient file from Finnish food analyses (Rastas *et al.*, 1989). Subjects were weighed with a digital scale in light clothing without shoes.

The body mass index (BMI) is defined as weight/height$^2$ (kg/m$^2$). A BMI value of 25 or more was defined as first grade obesity, 30 or more as second grade obesity, and 40 or more as third grade obesity. Waist circumference was measured midway between the lower rib margin and the iliac crest, and hip circumference at the level of the greater trochanter.

Smoking habits were determined by an interview and current smoking was used as binary variable in the statistical analysis. Twenty-one per cent of the subjects were smokers.

To assess spousal support men were classified into men living alone (15%) (never married living alone, divorced living alone, widowed living alone) and men cohabiting (84%) (married, divorced cohabiting, widowed cohabiting). Social network and support level was assessed by a validated 22-item self-report questionnaire. The method has been described previously (Helminen *et al.*, 1995).

### *Statistical methods*

Net changes in cholesterol, BMI and waist-to-hip ratio in groups of positive (yes/no) and negative (yes/no) life changes were calculated as a difference between the individual values from years 1993 and 1992. Ninety-five per cent confidence intervals of the differences are shown. Differences in serum lipids between the men with or without positive or negative life events were tested with a t-test. In addition, analysis of covariance was used to test the differences in the changes in serum lipids with baseline values as covariances. Logistic regression analysis was used to assess the predictive association of positive life changes with the LDL difference, which was used as a dichotomous dependent variable. The crude odds ratio of lowering LDL for those with positive life changes compared with men without them is presented, as well as the

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odds ratio adjusted to the baseline LDL. In the final model, BMI in tertiles, education (low and high), marital status (living alone and cohabiting) and cardiovascular disease at the baseline (yes and no) are included (Norusis, 1990). Analyses relating serum lipids to baseline social support level (1992) were conducted. Similarly, analyses were undertaken relating life events to baseline education level and marital status.

## Results

Most of the 152 subjects were cohabiting (84%). Seventy-six per cent of the men had a low educational status, i.e. elementary school level or less. Twenty-nine (19%) men had experienced at least one to three major positive life changes whereas 123 (81%) had had none. Thirty-one (23%) men reported one to three major negative changes including eighteen men who had lost their jobs during the follow-up. There were five men who had experienced both negative and positive changes.

Negative life changes did not associate with cholesterol levels in serum or lipoprotein fractions while positive changes did. Table 1 shows the net changes in serum cholesterol, BMI and waist-to-hip ratio among the subjects with one to three positive life changes and subjects with none. The men with one to three positive life changes showed a significant decrease in total and LDL cholesterol, the net changes being 0·23 (95% CI 0·00; 0·47) mmol/l ($p = 0·050$) and 0·31 (95% CI 0·08; 0·54) mmol/l ($p = 0·010$), respectively. Analysis of covariance showed that baseline lipid levels, cardiovascular health status and saturated fat intake, as measured in 1992 and at the end of the follow-up in 1993, did not explain the difference. Marital status ($p < 0·124$) did not explain the difference in LDL between the two study groups either, while education level ($p < 0·016$) had some effect. Marital status was not significantly related to the positive changes in work ($p < 0·492$), close relationships ($p < 0·229$) or living conditions ($p < 0·097$). Of the single positive life changes 'close relationships' ($p < 0·013$) and 'living conditions (economy)' ($p < 0·002$) appeared to associate with LDL, while 'work conditions' ($p < 0·119$) did not. The number of subjects in each of these categories was too small to draw conclusions of the influence of these variables on cholesterols, separately.

The association of social support with baseline and net changes in cholesterol levels was studied with a t-test. The analysis showed that social support did not explain the differences in total ($p < 0·368$) and LDL ($p < 0·530$) cholesterol levels in 1992, nor did it explain differences in the net changes in total ($p < 0·420$) and LDL ($p < 0·602$) cholesterol levels in 1993 between the two study groups. Similarly, current smoking did not explain the differences in baseline total ($p < 0·550$) and LDL ($p < 0·981$) cholesterol levels, nor did it explain differences in net changes in total ($p < 0·267$) and LDL ($p < 0·107$) cholesterols at the end of the follow-up.

Table 2 indicates that positive life changes are associated with lowered LDL cholesterol. The odds ratio for lowering LDL cholesterol was 5·2 (95% CI 1·9; 15) in the men reporting positive events compared with those reporting none. In addition, baseline LDL level and BMI were related to the change in LDL cholesterol levels during follow-up. Men with a higher baseline LDL cholesterol level were more likely to have a lowered LDL cholesterol level at follow-up compared with men with a lower baseline LDL cholesterol level. Men who had a higher baseline BMI were less likely to have a decreased LDL cholesterol at follow-up than men with a lower baseline BMI.

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**Table 1.** Means and net changes in serum cholesterol, BMI and waist-to-hip ratio among subjects with one to three positive life changes ($n=29$) and subjects with no positive life changes ($n=123$) and among subjects with one to three negative life changes ($n=31$) and subjects with no negative life changes ($n=102$) during a 1-year follow-up

| Variable | 1992 Mean (SD) | 1993 Mean (SD) | Net change (95% CI) | *p* |
|---|---|---|---|---|
| Total cholesterol | | | | |
| Positive change: no | 5·46 (0·91) | 5·58 (0·96) | 0·23 | 0·050 |
| Positive change: yes | 5·30 (0·94) | 5·19 (0·89) | (0·00 to 0·47) | |
| Negative change: no | 5·41 (0·91) | 5·50 (0·93) | 0·07 | 0·572 |
| Negative change: yes | 5·60 (0·93) | 5·57 (1·08) | (−0·17 to 0·30) | |
| LDL cholesterol | | | | |
| Positive change: no | 3·70 (0·86) | 3·86 (0·91) | 0·31 | 0·010 |
| Positive change: yes | 3·59 (0·97) | 3·45 (0·77) | (0·08 to 0·54) | |
| Negative change: no | 3·67 (0·87) | 3·80 (0·86) | 0·05 | 0·672 |
| Negative change: yes | 3·79 (0·83) | 3·86 (0·92) | (−0·19 to 0·21) | |
| HDL cholesterol | | | | |
| Positive change: no | 1·21 (0·25) | 1·20 (0·25) | 0·02 | 0·620 |
| Positive change: yes | 1·20 (0·27) | 1·18 (0·29) | (−0·06 to 0·09) | |
| Negative change: no | 1·23 (0·24) | 1·21 (0·86) | −0·03 | 0·413 |
| Negative change: yes | 1·16 (0·25) | 3·86 (0·92) | (−0·10 to 0·04) | |
| VLDL cholesterol | | | | |
| Positive change: no | 0·54 (0·40) | 0·51 (0·41) | −0·09 | 0·169 |
| Positive change: yes | 0·51 (0·36) | 0·56 (0·38) | (−0·22 to 0·04) | |
| Negative change: no | 0·51 (0·39) | 0·49 (0·31) | 0·04 | 0·448 |
| Negative change: yes | 0·60 (0·43) | 0·54 (0·41) | (−0·07 to 0·16) | |
| BMI | | | | |
| Positive change: no | 26·4 (3·3) | 26·5 (3·44) | 0·2 | 0·227 |
| Positive change: yes | 28·3 (4·8) | 28·2 (4·28) | (−0·1 to 0·6) | |
| Negative change: no | 26·7 (3·7) | 26·8 (3·6) | 0·1 | 0·690 |
| Negative change: yes | 26·8 (4·5) | 26·9 (4·4) | (−0·3 to 0·4) | |
| Waist-to-hip ratio | | | | |
| Positive change: no | 0·968 (0·046) | 0·964 (0·050) | 0·001 | 0·938 |
| Positive change: yes | 0·983 (0·056) | 0·978 (0·058) | (−0·013 to 0·014) | |
| Negative change: no | 0·970 (0·049) | 0·964 (0·051) | −0·002 | 0·792 |
| Negative change: yes | 0·973 (0·051) | 0·969 (0·056) | (−0·015 to 0·012) | |

Similarly, men with a higher education level were less likely to have a lowered LDL cholesterol concentration than those with a lower education level.

## Discussion

This study was undertaken to identify if major positive or negative life changes influence serum cholesterol levels. The 1-year follow-up study found that serum total and LDL cholesterol levels were significantly lower in men who had one or more

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**Table 2.** The odds ratios of decreased LDL levels during 1-year follow-up in a logistic model

| Variable | Odds ratio | 95% CI for odds ratio | *p* |
|---|---|---|---|
| Positive life changes | | | |
| None ($n=123$) | 1·0 | | |
| One or more ($n=29$) | 5·2 | 1·9 to 15 | 0·0017 |
| Baseline LDL cholesterol | | | |
| First tertile (<3·3 mmol/l) | 1·0 | | |
| Second tertile (3·3 to 4·0 mmol/l) | 3·2 | 1·2 to 8·7 | 0·0193 |
| Third tertile (>4·0 mmol/l) | 8·0 | 2·9 to 22 | 0·0001 |
| Baseline BMI | | | |
| First tertile (<25 kg/m$^2$) | 1·0 | | |
| Second tertile (25 to 28 kg/m$^2$) | 0·29 | 0·11 to 0·76 | 0·0116 |
| Third tertile (>28 kg/m$^2$) | 0·14 | 0·048 to 0·41 | 0·0004 |
| Education | | | |
| 6 years or less | 1·0 | | |
| 7 years or more | 0·43 | 0·11 to 0·80 | 0·0162 |
| Marital status | | | |
| Living alone | 1·0 | | |
| Cohabiting | 0·43 | 0·14 to 1·3 | 0·1243 |
| Cardiovascular health status | | | |
| Absent | 1·0 | | |
| Present | 1·1 | 0·48 to 2·5 | 0·8135 |

positive life changes compared with those who had none. The clinical importance of these findings is difficult to estimate. However, earlier clinical trials have indicated that even a modest reduction, especially in LDL cholesterol level, is likely to lead to a reduction in coronary heart disease (Yosuf, Wittes & Friedman, 1988; Hollis *et al.*, 1990; Law, Wald & Thomson, 1994; Levine, Keaney & Vita, 1995; Hu *et al.*, 1997). An unexpected finding of the present study was that no association was observed between major negative life changes and serum lipids.

The influence of positive life changes on serum lipids could be artefactual, real, or a real effect due to confounding factors, for instance social support, smoking or dietary change after the baseline dietary record. However, smoking and saturated fat intake, measured at the baseline and at the end of the follow-up, did not explain the influence. In the present study, the influence of positive life changes on serum cholesterol levels was not confounded by social support, measured by marital status (spousal support) and overall social support. In this respect, these results differ from two previous studies which indicate a direct or indirect effect of social support on serum cholesterols. For instance, Thomas, Goodwin & Goodwin (1985) reported that elderly adults with high levels of perceived social support are more likely to have lower serum cholesterol levels than those without support. Gore (1978) observed that the effect of job loss on the level of total cholesterol is higher among workers with low levels of social support than those without support. Further, men with adequate levels of social support have been

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reported to be protected from high all-cause mortality associated with stressful life events (Rosengren *et al*., 1993). It has been suggested that social support buffers against harmful stress effects by altering the perception of stress (Thomas *et al*., 1985; Rosengren *et al*., 1993; Guillemin *et al*., 1995).

In this study the stress level of the subjects was not determined. Acute mental stress has been shown to increase serum total, LDL and HDL cholesterol levels (Patterson *et al*., 1993). However, this increase seems mainly to be due to stress-induced haemoconcentration rather than changes in lipoprotein metabolism and appears, therefore, to have little clinical relevance (Muldoon *et al*., 1995). Severe forms of real or perceived stress do appear to alter cholesterol levels (Niaura *et al*., 1992). From the results of the present study, it can be hypothesized that positive life changes strengthen one's ability to cope with perceived psychosocial stress, which in turn lowers cholesterol levels. In this sense these results are consistent with observations from a 1-year psychosocial intervention study which showed a significant decrease in serum cholesterol levels among post-acute myocardial infarction patients (Mitsibounas *et al*., 1992).

In the present study, negative life changes did not influence serum cholesterol levels. This was not anticipated, and is not in line with a previous study which indicated that work-related stress significantly increases LDL levels (Melamed *et al*., 1992). It is possible that the single negative life changes requested in the present study were not long-lasting or severe enough to have any effect on cholesterol levels. A negative life change as such does not generate stress. The effect depends on how a life change is interpreted and coped with (Arnetz *et al*., 1991). In this study, for instance, loss of a job, which objectively is regarded as a severe negative change, might have acutely been perceived neutrally, even positively. In 1991 a deep economical recession began in Finland. The unemployment rate in Kuopio rapidly increased from 10% to over 20%. The fact that high numbers of people lost their jobs simultaneously might have diminished the perception of stress. Further, the follow-up was too short to perceive the effects of severe economic hardship because in Finland unemployment benefits compensate for lost earnings resulting from a job loss, at least for one year.

The present panel study was based on a randomized population sample. Generalization of the results should be done with caution because the sample size was small. Major positive life changes were alterations of close relationships, work conditions and overall living conditions. Loss of a job, conflicts with a spouse or cohabitant and a worsened economy were the major negative changes documented. The exact time point and duration of these changes, which could have provided information about their magnitude or stability (Tausig, 1982), were not determined. On the other hand, the short follow-up might have reduced the confounding effect of some other environmental events of a longer follow-up (Theorell, 1992). The many physiological and behavioural factors that could modify or confound the association between life changes and LDL cholesterol remain uncontrolled (Folkman *et al*., 1986; Hardy & Smith, 1988; Ensel & Lin, 1991; Vilhjalmson, 1993; Waldstein *et al*., 1993; Kushnir & Kristal-Boneh, 1995). However, the predictive value of the positive life changes indicator is evident.

In conclusion, the data suggest a predictive value of life changes for atherogenic lipid profile. In middle-aged men, positive life changes are likely to predict a reduction

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in serum total and LDL cholesterol independently of social support and biomedical risk factors. Clearly, studies with larger sample sizes and longer follow-up time are needed to confirm the possible persistence of the association.

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