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Self-perceived chronic stress and self-rated health as mediating markers for the association with cardiovascular disease risk: The Malmö Preventive Project

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Abstract

Cardiovascular (CVD) is one of the most common causes of mortality. Apart from known causal risk factors such as smoking, obesity, dyslipidaemia and hypertension, chronic psychological stress has been suggested as a possible independent risk marker, also because the CVD burden follows a social gradient. Another self-reported variable is self-rated health (SRH) which in many studies has ben shown to predict morbidity and mortality in otherwise healthy subjects.

Aims This study aimed to investigate a possibly interaction effect of self-perceived chronic stress and SRH on CVD risk. We also wanted to investigate if social class modified this effect.

Subjects and methods Data were analyzed from a population based cohort study consisting of 10,868 men and 2741 women from Malmö, southern Sweden, with a mean followed up time for 27 years. Subjects were screened at baseline for traditional biochemical and physical risk factors for CVD and filled a self-administered questionnaire containing ratings of psychological and lifestyle related factors. Subjects were then followed in both national and regional registries for first CVD event. The influence of self-perceived chronic stress and SRH were analyzed in a Cox regression model with stepwise adjustment for other risk factors. Interaction effects between stress/SRH were also tested.

Results In all, 3252 men and 320 women suffered a CVD event during follow-up. In the total cohort (n=13,609) the hazard ratio for CVD was 1.28 (95% CI; 1.06-1.55) among subjects reporting both chronic stress and poor SRH compared to the reference group (no stress, optimal SRH). Men who reported poor SRH with or without stress had a HR of 1.53 (CI 1.24-1.87) and 1.21 (1.03-1.41) respectively after full adjustments for other risk factors. There were no associations among women. No significant interaction effect between stress/SRH was found in either sex.

Conclusion Self-perceived chronic stress and poor self-rated health are both independent, long-term cardiovascular risk markers in middle-aged men, but not in women. The biological mediators of this increased risk pattern have still not been well characterized.

Key words: Cardiovascular disease, cohort, prospective, self-rated health, social class, stress

Introduction/Background

Cardiovascular disease (CVD) is one of the most common causes of mortality and morbidity on a global scale [1]. Besides traditional CVD risk factors such as smoking, hypertension, diabetes mellitus, dyslipidemia, a positive history of early onset CVD and sedentary lifestyle [2] psychosocial factors contribute to the disease burden [1]. Some of these non-traditional risk factors can be measured with rather simple questionnaires [3] and related to demographic statistics. For example global self-rated health (SRH) has been shown to have a strong predictive value for mortality and morbidity [4-7]. Socioeconomic status (SES) can contribute to further understanding of the disease pattern [4, 8]

The stress concept in medicine

Psychological stress has long been suspected to cause somatic diseases, although the assumptions have been lacking according to exact mechanism [9-11]. One of the greatest methodological problem is to separate the influence from traditional biochemical and physiological risk factors for the disease in question [2], for example in the case of CVD when psychological stress often cluster with other risk factors [1].

The concept of stress can be interpreted in a wide spectrum, and has in lay terms become a highly adopted metaphor for a broad spectrum of mental suffering [12]. Segerstrom [13] refers to Elliot & Eisdorfer´s (1982) taxonomy where stress is divided in five different categories based on the duration and course. The last category, long lasting chronic stress is of interest in this study.

Self-rated health as a predictor of events

It has been argued that modern medicine, with its high-technological approach to health care, risks to loose valuable information from the patient [7], for example self-reported symtoms, not often asked for, could reveal early reflections of disease (illness) that are not yet objectively measurable [3]. Several epidemiological studies argues for the valuable contribution of self-rated health to predict future mortality and morbidity [3, 4, 6, 7, 14] and many studies uses SRH as outcome variable in itself.

Socioeconomic factors and risk

There are inherent systematic differences and opportunities between people depending on their social position in the society [15]. The term socioeconomic status (SES) derives from the statistical descriptive system which aims to highlight the hierarchy within societal groups [16]. SES is a major predictor for health during an individual´s life, where higher position equals better health [8, 17].

Except for some malignant diseases like breast cancer and malignant melanoma [18], the disease gradient in SES is sloping downward. According to Weyers [19] SES also determines health behaviour in many aspect. He summarized European studies where low SES is associated with higher degree of health threatening behaviors such as smoking, poor dieatry habits and physical inactivity, and in addition uses Bourdieu´s social habitus model to explain this phenomenon [19]. Except for obvious relationships such as that between low SES and working in a health hazardous environment [8], and poor health behavior, much research has been done to investigate the links between low SES, health and chronic stress [20, 21].

Aims

The aim of this study is to investigate if SRH could be a mediating factor for the association between subjective chronic stress exposure and the prospective risk for cardiovascular disease.

Material and methods

Subjects

The Malmö Preventive Project (MPP), which started in 1974 at the Department of Preventive medicine, University Hospital, Malmö was used for this study. The originally purpose was to create a case-finding programme for intervention by screening a large strata of the middle aged population for CVD risk factors, impaired glucose tolerance, alcohol abuse and from 1980s also women and risk factors for breast cancer were included [22].

Subjects were invited to participate in health screening, including physical examination, blood sampling for laboratory testing, as well as filling an extensive self-administered questionnaire with 260 questions concerning medical and family history, lifestyle and social characteristics [23] including subjecting chronic stress and SRH. Although the questionnaire evolved during the years it also resulted in some inconsistencies. More detailed information concerning the screening and the main results from MPP has been previously published [22][24].

Between 1974 and 1992 a total of 22,444 males and 10, 902 females attended the MPP (71% attendance rate) where males dominated the first half of the period and women the second period, thus resulting in shorter mean follow-up times for the female population. Unfortunately questions regarding chronic stress were used only between 1974 -1980, a total of 13,609 individuals [25] based on data from 10,868 men (mean age of 46 years, median follow up time 27 years) and 2741 women (mean age 42 years, median follow-up time 28,9 years).

This cohort were later followed up in a re-screening session betweeen 2002-2006 with a participation rate of 72 % (n= 18,238) [26]. The re-screening included the same physical and laboratory mearsurements as at the baseline examination but a modified version of the questionnaire, including the original questions regarding chronic stress. Of the total of 13,609 individuals at baseline who were asked if they had experienced chronic stress only 6566 were followed up 2002 to 2006.

Questionnaire

We selected questions with highest relevance to chronic stress, SRH, lifestyle and social background characteristics, when some of the variables were transformed into new ones to better fit our models.

In accordance with earlier research on the same cohort (Öhlin et al) [25] and based on our interest in chronic stress, we selected the same two questions to create a combined stress score: (1) *"Have you experienced permanent stress (defined as feeling of tension, irritability, or anguish) during the last year?"* and (2) "Have you experienced permanent stress (defined as a feeling of tension, irritability, or anguish) during the last five years?" Reported stress from both or one of the questions resulted in a score of 1 and two negative answers gave 0 score (0= low stress, 1= stress). We gave both questions the same score in effort to further separate the subjects reporting chronic stress or not, no matter the duration.

The screening tool for global SRH were the single dichotomous question: "Do you feel completely healthy (yes/no) ?", later categorized as good or poor. To investigate a possible interaction effect between stress and SRH four value crosstab variables were created (1= optimal SRH, no stress, 2=optimal SRH, chronic stress, 3= poor SRH, no stress and 4= poor SRH, chronic stress).

In order to obtain some information regarding the subjects stress experience beyond baseline, we also did another four value cross tab variable, consisting of baseline stress and re-screening stress status (1=stress-, stress-, 2=stress-, stress+, 3=stress+, stress- and 4=stress+, stress+).

Lifestyle factors included questions (yes/no) regarding smoking habits and alcohol consumption. Smoking was dichotomized into current smoker and non-smoker. Alcohol consumption was based on the modified version of the brief Michigan Alcohol Screening Test (MAST). The Malmö version (Mm-MAST) is based on seven questions about drinking habits and consequences [23].

We used consumption categories proposed by Sillén et al [23] where "moderate alcohol habits" includes the following three questions: "Do you usually have a drink before going to a party?", "Do

you mostly drink alcohol, e.g. a bottle of wine. at weekends or holidays?", and "Do you drink a couple of beers, some glasses of wine or a drink to relax on a daily basis". "Heavy alcohol habits" includes the questions: "Do you tolerate alcohol better now than 10 years ago?", "Has it ever happened that after a party you do not remember how you got into bed?", and "Do you usually have bad consciousness after a party?". Affirmative answers on one or more questions in each category was considered as "yes", and we also added a third category "low alcohol intake" (no affirmative answer to any question) to Silléns model.

Social background included questions regarding marital status, educational attainment and SES. Marital status was dichotomized to "cohabiting" or "living alone". Level of educational attainment were obtained from the questionnaire based on three questions for different educational levels, later transformed to one variable with three scores (1=lower public school, 2=middle public school or 3=high school/college o higher studies).

SES was derived from self-reported job titles in the Swedish national censuses carried out in the years 1960, 1970, 1980, 1985, and 1990 (In Swedish: Folk- och Bostadsräkning, FoB) The Swedish classification for occupational categories was used (SEI, Statistics Sweden, 1982). The job titles were later converted into standardized social class categories in the MPP database, as follows [22]:

-Non manual employees: (high-level, medium level, low level); White collar
-Self-employed: (professional with or without employees, entrepreneurs, farmers); Other
-Manual workers: (skilled, unskilled); Blue collar

These were later simplified as three variables (1= White collar, 2= Other and 3=Blue collar) in the same order as above. Subjects outside the work force (retired, students and housewives) were excluded from further analyses.

Physical examination

All participants went through measurement of weight (kg) and height (m) and the body max index (BMI, kg/m^2) was calculated, as well as blood pressure (mmHg) and heart rate (beats/min). Systolic and diastolic blood pressures was measured in the right arm in supine position after 10 minutes rest, and a mean of two readings were recorded.

Laboratory investigations

A panel of fasting blood samples were analysed at standardized procedures at the Department of clinical Chemistry, Malmö University Hospital. The variables included serum cholesterol, triglycerides, blood glucose and liver enzymes.

Outcomes

All subjects attending MPP at baseline were followed up in local as well as national registries for total mortality, non-fatal ischemic heart disease (ICD-8 and ICD-9: 413; ICD-10 I 20) and non-fatal stroke (ICD-8 and ICD-9 codes 431, 43, 434 and 436) [25]. Registry data recorded up to end of June 2009 were used.

Ethics

The Malmö Preventive Project was approved by Ethics Committee of Lund University, Sweden, in 2004 (numbers LU244-02 and 85/2004).

Statistical methods

The statistical analyses were carried out with software SPSS for Mac, version 20.0 (2011).
Descriptive risk factor data, at baseline, are presented (table 1) stratified for stress/SRH and gender. Differences in means and proportions are tested with Student´s t-test or ANOVA for continuous variables and chi-square for categorical variables. 50 men and one woman had a reported prevalent CVD event at baseline, and were excluded from further studies.

The multivariate regression analyses were performed with the Cox´s proportional model to calculate hazard risk ratios (HR) and subsequent 95% confidence intervals (95% CI) with first reported cardiovascular event as clinical endpoints in relation to the four groups of stress/SRH where the combination of no stress and optimal SRH was used as reference.

Adjustments were made step wise, and there after adding a new model to the previous. Beginning adjustment with the non-modifiable risk factor age (Model A), followed by social factors: SES, cohabiting and level of education (Model B), behavioural and lifestyle factors: smoking and alcohol consumption (Model C) and finally standard biological risk factors BMI, BP, lipids (triglycerides were log-transformed for better normal distribution) and fasting glucose (Model D). Analyses were made in total cohort and separately for men and women. P-value <0.05 was considered statistically significant. Possible interaction effect between chronic stress and SRH were analyzed by including an interaction terms in the final model.

Results

Baseline characteristics

The 3252 men who suffered a CVD event were more likely to report chronic stressed rate their health as poor at baseline. They also tended to be less educated, and to be smokers. The 320 women later affected by CVD were more likely to be living alone, have low education level, and to be smokers. Among the biological risk factors, both men and women with later CVD had higher BMI, Blood pressure, cholesterol and fasting glucose compared to those did not suffer any CVD (Table 1).

There were significant trend differences between the four stress/SRH groups regarding SES, level of education, living arrangements, smoking and alcohol consumption, as well as for BMI, blood pressure and TG in both sexes (table 2-3).

Men who rated their health as poor, with or without chronic stress, were more likely be blue collar workers, to have achieved a lower educational level, more likely to live alone, to be a smoker and consume more alcohol. They also had a slightly higher BMI, blood pressure and TG levels compared to those who rated their health as optimal (table 2). Among women there were generally less clear associations. Subjects with chronic stress and poor health in combination were more likely to live alone, to smoke and to consume more alcohol. Among the biological factors BMI, cholesterol, TG and fasting glucose were elevated in this group (table 3).

Stress/SRH and in the total cohort

During follow-up time (mean of 27 years) in the total cohort of men and women (n= 13,609) those subjects who experienced both chronic stress and rated their general health as poor at baseline (n= 1219) had a hazard ratio (HR) of 1.28 (95% CI 1.06-1.55, p= 0.012) for suffering a cardiovascular event, compared to the reference group in the fully adjusted regression model D. That was the only significant difference among the four interaction groups.

Stress/SRH and CVD in males

The male cohort (n= 10,817) had 3252 CVD events during follow-up. There were no stastistical difference between the reference group and those who experienced chronic stress and rated their health as good. When comparing the reference group with the two other groups where subjects rated their health as poor, all adjustment models and group differences were significant (table 4) .

Comparing the reference group with the group reporting no stress but poor SRH and the group with both chronic stress and poor SRH, only adjusted for age (model A) the HR were 1.21 (95% CI: 1.10-1.32) and 1.46 (95% CI: 1.30-1.64) respectively. The HR were statistically significant through

all models and at full adjustment (Model D), the two groups had a HR of 1.21 (95% CI: 1.03-1.41) and 1.53 (95% CI: 1.24-1.87), respectively.

Stress/SRH and CVD in females

The female cohort (n=2740) experienced a total of 320 CVD events, but no significant associations were recorded for increased CVD risk in any of the chronic stress/SRH groups following adjustments (Models A-D) (table 5).

No statistically significant multiplicative interaction was observed for the stress/SRH variable (p=0.51 women, 0.46 for men).

Chronic stress consistency

6566 individuals (men=5006, women 1560) of the total MPP cohort were alive and available at the re-screening session after 20-25 years when the inclusion criteria consisted of being screened twice for chronic psychosocial stress. The subjects reporting chronic stress at baseline were almost twice as likely to also report chronic stress at re-screening, and this finding were significant for both men and women (table 6).

Discussion

The main findings of this large, long-term observational study of a middle-aged urban population was that subjects who at baseline reported chronic stress and rated their health as poor had a statistically greater risk of suffering a CVD event after full adjustment (HR of 1.28 (95% CI: 1.06-1.55, p= 0.012). When analyses were stratified for gender it was revealed that men in poor self- rated health had an increased HR irrespective of their stress status, although concurrent stress potentiated the outcome. The female subjects did not show any significant associations in any group or in any adjustment statistical models. There were no interaction effect between the chronic stress and SRH variables, thus the increased risk for CVD was merely based on the sum of influence of the two indedendent risk markers.

Comparison with previous studies

Several studies [7, 27, 28] have pointed out the value of SRH for predicting morbidity and mortality, including one previous prospective study from the MPP cohort [23]. Research on SRH predicting CVD is however not that common. A Norwegian study [29] found that both men and women with poor SRH had a higher risk of coronary mortality (HR 1.62 for women and 1.23 for men) after adjusting for other known risk factors. This cohort included 5808 individuals and was followed for 7.9 years, but the subjects were all over 70 years at baseline and the outcome was only calculated as

death from ischaemic heart disease (IHD), but not from other CVD causes or non-fatal events. A study from the US [30] reported that women with poor SRH had a two-fold risk to suffer a major CVD event compared to those with good SRH, although the number of subjects was only 900, and the subjects selected were suspected to have some prevalent heart disease at baseline making this a narrow selected cohort. Nevertheless our results points in the same direction, at least for men.

Chronic stress exposure and its association with CVD, on the other hand, have been more often studied through the years [1, 2]. Öhlin et al [25] study, based on the same selected cohort from the MPP, found that self reported chronic stress increased the risk of suffering various CVD events, especially for men and fatal stroke as outcome. Rosengren et al [31] performed a similar population-based prospective study where men (n=6003 no women included) who had experienced permanent stress were more likely to suffer coronary artery disease (CAD). In the INTERHEART case-control study of myocardial infarction, Rosengren [32] found that cases more often reported periods of stress at home or at work prior to their disease than controls. Although the study was of a case control design, running the risk of recall bias as questions were asked after the event, the material was large (n=24 767) and divided on 52 countries which gives an indication that simple stress questionnaires has some validity over regions and cultural borders on a global scale.

Stress at work or at home

Our definition of stress, and the part of the questionnaire that we used to construct our chronic stress variable, represents subjective stress at a general level. Most prospective studies of chronic stress as a risk factor for CVD is based on stress exposures primarily at work [33]. Two of the most applied methods of measurement is Siegrist ”effort-reward imbalance” [34] and Karaseks 2-dimensional ”job strain model” where the most harmful aspects of work is the combination of high demands, low sense of control and low social support, suggesting that chronic stress is more of a situation-based problem. Kivimäki et al [35] published 2006 a meta-analyses with quantitative estimates of a 50 % higher risk for CHD among subjects experiencing work-related stress. Steptoe [33] argues that the increased risk mediated from work-related stress is comparable with the CHD risk derived from leisure time stress such as social isolation and loneliness. Therefore one might argue that the same unhealthy stress mechanism is involved irrespective of the nature or background of the chronic stressors, or that stress at both work and generally is being experienced and reported as an integrated item by the individual.

SES, SRH and CVD

Many researchers argue that low SES constitutes one of the main explanations for the interaction between poor health and psychological stress influencing a pronounced gradient in CHD [36], although the causal direction is somewhat unclear [37]. In our male cohort, level of education had no effect on CVD but blue collar workers (low SES) had higher risk for CVD than white collar (high SES) although stress/SRH association remained significant after full adjustment. It is interesting that our material did not find any significant association with educational level in spite of the fact that other studies have reported that both occupation and educational level are strongly associated with mortality and especially the education gradient in terms of CVD as outcome [38]. Toivanen [34] studied cross sectionally the association between SES, SRH and stress, and reported a positive association between low SES and poor SRH, but no association to psychological stress. Researchers from the Whitehall study hypothesized that the linear relationship between SES and CVD could partially be explained by stress-induced inflammatory markers, but failed to display a concentration gradient [39]. Another study with similar hypothesis, detected higher levels of inflammatory markers in subjects living in poverty, although much of the detected difference in biomarkers were mediated by cigarette smoking and lack of exercise after further adjustments [40]. Unhealthy lifestyle is more prevalent in lower SES groups and subjects belonging to these groups probably face more everyday stressors in terms of risk of unemployment, financial problems and limitations of life and opportunities, compared to more privileged groups. Cigarette smoking, poor diet, alcohol and other short term treats is known to be a part of a maladaptive coping pattern found in stressed individuals [19]. Somehow the influence of low SES and risk behaviours did not profoundly affect our results, thus we could not by adjustment for known risk factors eliminate the stress/SRH association with CVD risk. This suggests that other unknown mediators could be of importance, not measures in our study, for example the influence of cardiovascular changes related to morphology (atherosclerosis) or functionality (arterial stiffness) constituting aspects of cardiovascular ageing [41].

We also showed that subjects who were stressed at baseline had an almost two-fold risk to be suffering from chronic stress also at the re-screening study, although that association should be interpreted carefully when more than 50 % had died before the re-screening examination. Although no further analyses were done, results propose that subjective feeling of chronic stress is fairly constant in this material.

Strengths and weaknesses

The main weakness in our study as has earlier been pointed out by Öhlin [25], is validity. The problem of validity is more pronounced for perceived stress because the very nature of SRH is and sup-

posed to be multidimensional. Chronic stress can involve many aspects of life, work-related or a general feeling of mental discomfort as discussed earlier, thus making it hard to differentiate if it is based on work or linked to stress-prone individuals or disadvantaged social groups. Questions could be raised if stress and SRH measured at baseline is a continuous risk exposure and valid over the years, and whether it is reasonable to use this variables or not without repeated measurements. As the original questionnaire contained specific work-stress related questions, it would have been of value to compare our chronic stress groups to those who experienced stress only at work, which could narrow down the stress concept.

The relatively rough measure of social class that we used could have diluted the SES gradient. If we had been able to differentiate those who studied at university for instance, adjustment for social class (based on education) might have had a larger impact in the regression models.

Females represented only a minority (26%) of the entire cohort by design, thereby reducing statistical power. They were also younger at baseline, which could partly explain a lower incidence of CVD during follow-up.

The main strength of our study are the characteristics of the cohort in terms of its size, consistency of outcome registries, long follow-up time and that it is population based. To our knowledge, no other study has simultaneously approached the field of chronic stress, SRH and CVD risk based on our design or statistically tested if there were any interaction effect.

Future research- possible interventions

We were not able to make further adjustments to completely eliminate the increased risk associated with chronic stress and poor SRH, implying that there must exist some other unmeasured biological pathways between cognitive domains (stress and SRH) and disease outcome. Even though research on psychological stress has been linked this as a risk factor for disease since the 1930´s, there is still a wide scepticism within the biomedical community against the hypothesis that psychological stress actually leads to somatic disease [42]. There is however some possible explanation models for the negative effect that the physical stress response might have on the cardiovascular system. McEwen [9] has developed the model of allostasis, the bodily response of chronic psychosocial stress. The allostatic response mobilizes us for handling stressors and the most common pathways act via the sympathetic nervous system to the hypothalamic-pituitary-adrenal (HPA) axis, ending with increased cortisol release [43]. If the stress hormones continue to be secreted in higher concentrations over time or becomes dysregulated it translates into an increased (negative) allostatic load [9]. Ex-

amples of pathophysiological load effects is seen in the cardiovascular and metabolic systems in elevated risk for myocardial infarction and diabetes, as well as hippocampal degeneration in the brain and dysregulation of the immune system [9]. Känel [1] summarized the literature and concludes that psychological factors are involved from the beginning of atherosclerosis formation to manifest disease. The chronic stress initiated dysregulation in the autonomous nervous system and HPA axis, leads to negative changes in the immune and hemostatic systems, resulting in down-stream events such as these leading to CVD [43].

Both SRH and stress were both independent risk factors for CVD, in spite the fact that they are multidimensional in nature, they did not measure the same underlying disease process. A number of different biochemical markers have been investigated through the years to objectively mediate psychological stress, but so far, none stands out as the most important candidate. Recent studies have suggested that vascular cell dysfunction leading to atherogenesis is a result of affected telomeres [44, 45] a marker of biological ageing that is linked to cardiovascular ageing. Tomiyama [46] combines the model of allostasis with research where psychological stress has been associated with shortened telomeres, and thus assumingly accelerates biological aging. That study found that dysregulated cortisol may be related to telomere shortening in chronically stressed individuals. This theory could provide an explanation for how chronic stress increases risk of CVD [44], due to allostatic load which in turn accelerates cellular aging, making the person more likely to suffer ischemic disease, similar conclusions has been made based on data from other studies on chronic stress [47, 48]. There is also evidence that certain individuals could be more vulnerable to chronic stress and thus more likely to become ill. Nilsson et al [49] studied the association between birth weight and stress susceptibility in young life. It was found that young males performed better when tested for general psychological functioning and stress tolerance with increasing birth weight [49]. Schlotz et al [50] used a similar hypothesis and found similar results when they investigated stress susceptibility in the 7th decade of life in relation to birth weight. There are several studies indicating that some factors occurring during early in life modifies disease patterns in adulthood. Individuals with a previous low birth weight or impaired fetal growth also seem to run an increased risk for later CVD because of the fetal programming resulting in a more susceptible body composition [51]. This is probably linked to less optimal neuro-cognitive developments resulting in maladaptive stress coping patterns as also influenced by the social situation during childhood.

Although no simple test can explain what biological mechanism the perception of chronic stress or poor SRH represents in the body at present, subjects with poor SRH and/or perceived chronic stress should be monitored carefully due to increased risk. In the future there might be a better understanding for the biological system involved and a more individualized panel of biomarkers or can-

didate genes for those at risk. Disease conditions such as CDV, being viewed in a life course perspective and including early life factors, childhood circumstances, education and adult occupation might gives us more clues what to look for.

In conclusion, this population-based, long-term observational study showed that self-perceived chronic stress and poor self-rated health were independent risk markers of prospective CVD risk in middle-aged men. There were no significant associations among the female subjects, which might be explained of their small sample size. Biological mediators of this risk are still to be better characterized.

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References

1. Känel, v., Psychosocial stress and cardiovascular risk - current opinion. Swiss Med Wkly, 2012. 142: p. 0.
2. Bairey Merz, C.N., et al., Psychosocial stress and cardiovascular disease: pathophysiological links. Behav Med, 2002. 27(4): p. 141-7.
3. Idler, E.L., L.B. Russell, and D. Davis, Survival, functional limitations, and self-rated health in the NHANES I Epidemiologic Follow-up Study, 1992. First National Health and Nutrition Examination Survey. Am J Epidemiol, 2000. 152(9): p. 874-83.
4. Bauer, G.F., et al., Socioeconomic status, working conditions and self-rated health in Switzerland: explaining the gradient in men and women. Int J Public Health, 2009. 54(1): p. 23-30.
5. Halford, C., et al., Self-rated health, life-style, and psychoendocrine measures of stress in healthy adult women. Ups J Med Sci, 2010. 115(4): p. 266-74.
6. Ahnquist, J., S.P. Wamala, and M. Lindstrom, Social determinants of health - A question of social or economic capital? Interaction effects of socioeconomic factors on health outcomes. Soc Sci Med, 2012.
7. Kaplan, G.A., et al., Perceived health status and morbidity and mortality: evidence from the Kuopio ischaemic heart disease risk factor study. Int J Epidemiol, 1996. 25(2): p. 259-65.
8. Fujishiro, K., J. Xu, and F. Gong, What does "occupation" represent as an indicator of socioeconomic status?: exploring occupational prestige and health. Soc Sci Med, 2010. 71(12): p. 2100-7.
9. McEwen, B.S., Protective and damaging effects of stress mediators. N Engl J Med, 1998. 338(3): p. 171-9.
10. O'Donovan, A., et al., Stress appraisals and cellular aging: A key role for anticipatory threat in the relationship between psychological stress and telomere length. Brain Behav Immun, 2012.
11. von, K., Psychosocial stress and cardiovascular risk - current opinion. Swiss Med Wkly, 2012. 142: p. 0.
12. Helman, C.G., Culture, Health and Illness. 2000(Fourth edition).
13. Segerstrom, S.C. and G.E. Miller, Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull, 2004. 130(4): p. 601-30.
14. Halford, C., I. Anderzen, and B. Arnetz, Endocrine measures of stress and self-rated health: a longitudinal study. J Psychosom Res, 2003. 55(4): p. 317-20.
15. Goldberg, T., Samhällsproblem. 2005. 6th edition. Studentlitteratur, Lund Sweden.

16. Samuelsson, C., Socioekonomisk indelning. Statistiska centralbyrån 2012(http://www.scb.se/Pages/List____257217.aspx).
17. Andersson, S., Ingmar, Hälsa och Psykologi. 2009. Studentlitteratur, Lund, Sweden.
18. Shack, L., et al., Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. BMC Cancer, 2008. 8: p. 271.
19. Weyers, S., et al., How does socio economic position link to health behaviour? Sociological pathways and perspectives for health promotion. Global Health Promotion, 2010. 17(2): p. 25-33.
20. Yang, T.C. and S.A. Matthews, The role of social and built environments in predicting self-rated stress: A multilevel analysis in Philadelphia. Health Place, 2010. 16(5): p. 803-10.
21. Orpana, H.M., L. Lemyre, and S. Kelly, Do stressors explain the association between income and declines in self-rated health? A longitudinal analysis of the National Population Health Survey. Int J Behav Med, 2007. 14(1): p. 40-7.
22. Berglund, G., et al., Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. J Intern Med, 2000. 247(1): p. 19-29.
23. Af Sillén, U., et al., Self-rated health in relation to age and gender: Influence on mortality risk in the Malm√∂ Preventive Project. Scandinavian Journal of Public Health, 2005. 33(3): p. 183-189.
24. Nilsson, P.M., et al., Social mobility, marital status, and mortality risk in an adult life course perspective: the Malmo Preventive Project. Scand J Public Health, 2005. 33(6): p. 412-23.
25. Ohlin, B., et al., Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. Eur Heart J, 2004. 25(10): p. 867-73.
26. Leosdottir, M., et al., The association between glucometabolic disturbances, traditional cardiovascular risk factors and self-rated health by age and gender: a cross-sectional analysis within the Malmo Preventive Project. Cardiovasc Diabetol, 2011. 10: p. 118.
27. Jakob Bue Björner, T.S.K., Kristina Orth-Gomér, Gösta Tibblin, Marianne Sullivan, Peter Westerholm, Self-rated health A useful concept in research, prevention and clinical medicine. Forskningsrådsnämnden, 1996. Report 96:9.
28. Miilunpalo, S., et al., Self-rated health status as a health measure: the predictive value of self-reported health status on the use of physician services and on mortality in the working-age population. J Clin Epidemiol, 1997. 50(5): p. 517-28.
29. Ernstsen, L., et al., The predictive ability of self-rated health on ischaemic heart disease and all-cause mortality in elderly women and men: the Nord-Trondelag Health Study (HUNT). Age Ageing, 2011. 40(1): p. 105-11.

30. Rutledge, T., et al., Self-rated versus objective health indicators as predictors of major cardiovascular events: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation. Psychosom Med, 2010. 72(6): p. 549-55.
31. Rosengren, A., G. Tibblin, and L. Wilhelmsen, Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. Am J Cardiol, 1991. 68(11): p. 1171-5.
32. Rosengren, A., et al., Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet, 2004. 364(9438): p. 953-62.
33. Steptoe, A. and M. Kivimaki, Stress and cardiovascular disease. Nat Rev Cardiol, 2012. Epub ahead of print.
34. Toivanen, S., Exploring the interplay between work stress and socioeconomic position in relation to common health complaints: the role of interaction. Am J Ind Med, 2011. 54(10): p. 780-90.
35. Kivimaki, M., et al., Work stress in the etiology of coronary heart disease--a meta-analysis. Scand J Work Environ Health, 2006. 32(6): p. 431-42.
36. Steptoe, A., et al., Socioeconomic status and subclinical coronary disease in the Whitehall II epidemiological study. PLoS One, 2010. 5(1): p. e8874.
37. Elovainio, M., et al., Socioeconomic differences in cardiometabolic factors: social causation or health-related selection? Evidence from the Whitehall II Cohort Study, 1991-2004. Am J Epidemiol, 2011. 174(7): p. 779-89.
38. Davey Smith, G., et al., Education and occupational social class: which is the more important indicator of mortality risk? J Epidemiol Community Health, 1998. 52(3): p. 153-60.
39. Steptoe, A., et al., Inflammatory cytokines, socioeconomic status, and acute stress responsivity. Brain Behav Immun, 2002. 16(6): p. 774-84.
40. Kershaw, K.N., et al., Socioeconomic position, health behaviors, and C-reactive protein: a moderated-mediation analysis. Health Psychol, 2010. 29(3): p. 307-16.
41. Safar, M.E., et al., Pulse Pressure, Arterial Stiffness, and End-Organ Damage. Curr Hypertens Rep, 2012.
42. Cohen, S., D. Janicki-Deverts, and G.E. Miller, Psychological stress and disease. JAMA, 2007. 298(14): p. 1685-7.
43. Fantidis, P., The role of the stress-related anti-inflammatory hormones ACTH and cortisol in atherosclerosis. Curr Vasc Pharmacol, 2010. 8(4): p. 517-25.
44. Fuster, J.J. and V. Andres, Telomere biology and cardiovascular disease. Circ Res, 2006. 99(11): p. 1167-80.

45. Samani, N.J., et al., Telomere shortening in atherosclerosis. Lancet, 2001. 358(9280): p. 472-3.
46. Tomiyama, A.J., et al., Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. Physiol Behav, 2011.
47. Wikgren, M., et al., Short telomeres in depression and the general population are associated with a hypocortisolemic state. Biol Psychiatry, 2012. 71(4): p. 294-300.
48. Wolkowitz, O.M., et al., Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety, 2010. 27(4): p. 327-38.
49. Nilsson, P.M., P. Nyberg, and P.O. Ostergren, Increased susceptibility to stress at a psychological assessment of stress tolerance is associated with impaired fetal growth. Int J Epidemiol, 2001. 30(1): p. 75-80.
50. Schlotz, W. and D.I. Phillips, Birth Weight and Perceived Stress Reactivity in Older Age. Stress Health, 2012.
51. Rinaudo, P. and E. Wang, Fetal programming and metabolic syndrome. Annu Rev Physiol, 2012. 74: p. 107-30.

Table 1. Baseline characteristics of the study population with means, standard deviations (SD) and proportions (%). Stratified for gender and cardiovascular events.

	Men				Women			
	All	**No CVD**	**CVD**	**p-value**	**All**	**No CVD**	**CVD**	**p-value**
N	10817	7565	3252		2740	2420	320	
Chronic stress (%)	2196	19.7	21.8	0.01	568	20.7	20.9	0.92
Poor SRH (%)	2967	26.5	29.7	0.001	702	25.4	27.2	0.49
Social position SES (%)								
- White collar	4751	72.0	28.0		1314	90.3	9.7	
- Other	937	69.8	30.2	0.001	89	88.8	11.2	0.12
- Blue collar	4717	68.3	31.7		1133	77.6	12.4	
Living alone (%)	2470	23.0	22.8	0.88	810	30.4	25.1	0.05
Education (%)								
- High	1303	74.4	25.6		595	89.6	10.4	
- Medium	946	71.7	28.3	0.045	414	89.4	10.6	0.001
- Low	1549	70.0	30.0		721	82.4	17.6	
- None #	213	68.1	31.9		87	82.8	17.2	
Lifestyle factors								
- Smokers (%)	5534	47.6	59.4	<0.001	1169	41.4	52.5	<0.001
Estimated alcohol intake (%)								
- Low	4337	70.9	29.1		1903	88.0	12.0	
- Moderate	2525	73.4	26.6	0.06	558	89.8	10.2	0.48
- Heavy	1824	70.8	29.2		279	87.8	12.2	
Biological factors								
- BMI, kg/m2		24.6 (3.3)	25.3 (3.4)	<0.001		22.9 (3.7)	24.4 (4.3)	<0.001
- BP syst, mmHg		127.7 (1.5.0)	132.5 (15.0)	<0.001		119.4 (14.6)	126 (1.0)	<0.001
- Chol, mmol/l		5.6 (1.0)	5.9 (1.2)	<0.001		5.3 (1.0)	5.6 (1.0)	<0.001
- TG, mmol/l		1.54 (1.1-2.0)	1.53 (1.0-1.8)	Median +IQR*		1.3 (0.9-1.6)	1.18 (0.8-1.4)	Median + IQR*
-Fasting blood glucose, mmol/l		4.9 (0.9)	4.98 (1.2)	0.002		4.8 (0.66)	5.0 (1.2)	<0.001

* Interquartile range.

No education reported in questionnaire.

Table 2. Baseline characteristics for men with means, standard deviations (SD) and proportions (%). Stratification made for chronic stress/SRH groups.

Men	**Stress-, SRH+ (n=6521)**	**Stress+, SRH+ (n=1198)**	**Stress-, SRH- (n= 1832)**	**Stress+, SRH- (n=854)**	**P for trend**
Age (years)	45.3 (5.4)	45.2 (5.3)	46.0 (4.7)	45.6 (4.9)	<0.001
Social position					
SES %					
- White collar	66.4	13.2	13.6	6.8	
- Other	59.0	16.5	15.8	8.6	<0.001
- Blue collar	59.6	8.8	22.0	9.5	
Education %					
- High	61.3	15.0	13.0	10.7	
- Medium	61.1	11.2	18.9	8.8	<0.001
- Low	63.7	8.8	19.6	7.8	
- None #	30.0	5.2	52.1	12.7	
Living alone %	20.4	25.1	25.4	32.5	<0.001
Lifestyle factors					
- Smoking %	49.6	52.3	51.9	58.8	<0.001
Alcohol intake					
- Low	64.0	9.1	19.6	7.4	
- Moderate	64.6	12.2	15.4	7.8	<0.001
- Heavy	53.1	16.9	15.6	14.4	
Biological factors					
BMI kg/m2	24.7 (3.23)	24.8 (3.25)	25.1(3.5)	25.2 (3.7)	<0.001
SBP, mmHg	128.8 (15.5)	129.1 (15.9)	130 (16.5)	130 (16.6)	0.01
Cholesterol, mmol/l	5.71(1.1)	5.7(1.1)	5.74 (1.1)	5.71 (1.6)	0.71
Triglycerides, mmol/l (*)	1.54 (1.0-1.8)	1.59 (1.0-1.9)	1.67 (1.0-1.9)	1.79 (1.1-2.1)	<0.001
Fasting glucose mmol/l	4.9 (0.92)	4.9 (0.99)	4.9 (1.2)	4.98 (1.1)	0.33

* Interquartile range.

No education reported in questionnaire.

Table 3. Baseline characteristics for women with means, standard deviations (SD) and proportions (%. Stratified for chronic stress/SRH groups.

Women	**Stress-, SRH+ (n= 1720)**	**Stress+, SRH+ (n= 318)**	**Stress-, SRH- (n= 452)**	**Stress+, SRH- (n= 250)**	**P for trend**
Age (years)	40.9 (8.5)	39.9 (8.1)	42.4 (8.7)	41.4 (9.3)	0.002
Social position					
SES %					
-White collar	67.0	11.9	13.1	8.0	
-Other	66.3	14.6	14.6	4.5	0.001
-Blue collar	60.5	11.3	19.4	8.7	
Education %					
- High	62.9	12.3	13.1	11.8	
- Medium	64.5	10.4	15.9	9.2	<0.001
- Low	62.3	10.0	17.9	9.8	
- None #	32.2	4.6	49.4	13.8	
Living alone %	27.3	36.5	27.9	41.5	<0.001
Lifestyle factors					
- Smoking %	39.6	50.3	42.5	54.4	<0.001
Alcohol consumtion					
- Low	62.8	10.0	18.2	9.0	
- Moderate	68.8	11.8	13.4	5.9	<0.001
- Heavy	50.5	21.9	11.1	16.5	
Biological factors					
BMI kg/m2	22.9 (3.7)	22.9 (3.6)	23.6 (4.1)	23.7 (4.5)	<0.001
SBP, mmHg	120.0 (14.8)	118.7 (13.6)	121.6 (16.4)	120.6 (16.1)	0.05
Cholesterol, mmol/l	5.3 (1.0)	5.2 (0.9)	5.4 (1.1)	5.4 (1.1)	0.04
Triglyerides, mmol/l (*)	1.17 (0.8-1.4)	1.16 (0.8-1.4)	1.2 (0.9-1.4)	1.4 (0.8-1.6)	<0.001
Fasting glucose mmol/l	4.8 (0.7)	4.8 (0.5)	4.9 (0.9)	4.9 (1.1)	0.008

* Interquartile range.

No education reported in questionnaire.

Table 4. Regression models with hazard ratios (HR) and confidence intervals (95% CI) for cardiovascular risk for *men*. Stepwise adjustments made for Models A-D.

Men (total n=	**Stress-, SRH+**	**Stress+, SRH+**	**p-value**	**Stress-, SRH-**	**p-value**	**Stress+, SRH-**	**p-value**
CVD-events *n*	1911	375		632		334	
Model A	Index	1.12 (1.0-1.23)	0.06	1.21 (1.10-1.32)	<0.001	1.46 (1.30-1.64)	<0.001
Model B	Index	1.16 (0.96-1.40)	0.13	1.25 (1.07-1.46)	0.005	1.56 (1.28-1.91)	<0.001
Model C	Index	1.14 (0.95-1.39)	0.17	1.24 (1.06-1.45)	0.007	1.52 (1.24-1.19)	<0.001
Model D	Index	1.14 (0.94-1.38)	0.19	1.21 (1.03-1.41)	0.018	1.53 (1.24-1.87)	<0.001

Table 5. Regression models with hazard ratios (HR) and confidence intervals (95% CI) for cardiovascular risk for *women*. Stepwise adjustments made for Models A-D.

Women (total n=2740)	**Stress-, SRH+**	**Stress+, SRH+**	**p-value**	**Stress-, SRH-**	**p-value**	**Stress+, SRH-**	**p-value**
CVD-events n	194	39		59		28	
Model A	Index	1.22 (0.86-1.72)	0.26	1.06 (0.79-1.42)	0.65	1.04 (0.70-1.55)	0.85
Model B	Index	0.97 (0.62-1.51)	0.88	0.91 (0.63-1.32)	0.61	0.74 (0.43-1.30)	0.30
Model C	Index	0.93 (0.60-1.46)	0.62	0.86 (0.06-1.25)	0.44	0.69 (0.40- 1.21)	0.20
Model D	Index	1.04 (0.66-1.63)	0.88	0.76 (0.52-1.10)	0.15	0.64 (0.37-1.12)	0.12

Model A: Age

Model B: A + Socioeconomic status, cohabiting and level of education.

Model C: A + B + smoking and alcohol consumption.

Model D (fully adjusted): A + B + C + Biological factors (BMI, BP, lipids and fasting glucose).

Table 6. Cross table comparing baseline and re-screening characteristics according to proportion of subjects reporting self-perceived chronic stress.

	Re-screening examination (2002-2006)					
	Men n=5006			**Women n=1560**		
Baseline (1974-1980)	Stress-	Stress+	p-value	Stress-	Stress+	p-value
Stress-, n (%)	3757 (90.9)	375 (9.1)	<0.001	1029 (81.0)	241 (19.0)	<0.001
Stress+, n (%)	691 (79.1)	183 (20.9)	<0.001	177 (61.0)	113 (39.0)	<0.001