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Longitudinal analysis of the relation between moderate long-term stress and health

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Summary
*The main goal of the present work was to longitudinally examine consequences of long-term moderately elevated levels of stress for various health outcomes. To address this issue, data covering 10 years was used from the ongoing Swedish population-based prospective Betula Study. Based on the ratings on a validated self-reported stress scale, matched subsamples between 40 and 65 years of age were divided into a high (*n = *137) and low (*n = *211) stress group. The reported incidence of cardiovascular, diabetes, psychiatric, tumour and musculoskeletal diseases was assessed 5 and 10 years after baseline (baseline = 1993–1995) without contaminating effects of past health history. The incidence of diseases 5 years after baseline assessment showed no differences between the groups. After 10 years, there was a significantly higher incidence of psychiatric diseases, mainly depression in the high-stress group as well as a significant effect for tumours, although the number of cases was low. Although moderately elevated stress level may have a possible impact on psychiatric diseases especially depression and some tumours, it seems that prolonged moderate stress does not appear to be harmful to other stress-related diseases. Copyright © 2007 John Wiley & Sons, Ltd.*

Key Words
cardiovascular; depression; diabetes; musculoskeletal; tumours

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Introduction

Increased level of stress is known to be the beginning of an ongoing process that when it proceeds, it leads to allostatic load (McEwen, 2000). Allostatic load during long periods are known to negatively affect cognitive ability and health (Seeman, McEwen, Rowe, & Singer, 2001). According to the *glucocorticoid cascade hypothesis* (Sapolsky, Krey, & McEwen, 1986), physical and psychological stress factors affect the hypothalamic-pituitary-adrenal (HPA) axis production of adrenal steroids, mainly cortisol. Normally, the HPA axis maintains basal cortisol levels, but increased levels are produced by the adrenal medulla to meet acute stress situations. Hippocampus, which has special receptors for plasma cortisol, has a depressing effect on further cortisol production. However, in situations of long-term stress, this feedback system may change structurally (Lupien et al., 1998; McEwen, 2000), with health and cognitive problems as potential consequences. Hypertension, an increased risk of coronary heart disease, and metabolic changes, including insulin resistance, high cholesterol values and obesity, are diseases coupled to dysregulation of the HPA axis over time (Epel et al., 2004; Kopp & Réthelyi, 2004; Korte, Koolhaas, Wingfield, & McEwen, 2005; Öhlin, Nilsson, Nilsson, & Berglund, 2004). Dysfunction of the HPA axis is also suggested to explain psychiatric diseases such as depression (de Kloet, Joëls, & Holsboer, 2005; Kopp & Réthelyi, 2004; Pedersen, Wan, & Mattson, 2001; Reiche, Nunes, & Morimoto, 2004). Long-term high stress can lead to suppressed immune defense that may promote the initiation and progression of some type of tumours (Reiche et al., 2004). Further, chronic stress can lead to lowered pain threshold that may promote progression of muscular skeletal pain disorders (Blackburn-Munro & Blackburn-Munro, 2001). Less extremely elevated stress levels may also have negative implications for health (Åkerstedt et al., 2002; Bergdahl, Larsson, Nilsson, Riklund Åhlström, & Nyberg, 2005; Krantz, Berntsson, & Lundberg, 2005; Möller, Theorell, de Faire, Ahlbom, & Hallqvist, 2005), but this relation has been less explored than conditions of higher stress.

The main goal of the present work was to examine long-term consequences of moderately elevated levels of stress for various health outcomes that have been linked to dysregulation of the HPA axis; cardiovascular and metabolic conditions (Epel et al., 2004; Kopp & Réthelyi, 2004; Korte et al., 2005; Öhlin et al., 2004), immune system and pain-related syndromes (Blackburn-Munro & Blackburn-Munro, 2001; Reiche et al., 2004) and depression (de Kloet et al., 2005; Kopp & Réthelyi, 2004; Pedersen et al., 2001; Reiche et al., 2004). To address this issue we used data from an ongoing population-based prospective study (Nilsson et al., 1997, 2004). The design of this study made it possible to examine whether elevated stress levels led to increased frequencies of health problems 5 or 10 years after initial assessment.

Subjects and methods

Participants

This study is based on three test waves of the Betula Study: 1993–1995 (T2), 1998–2000 (T3) and 2003–2005 (T4). Non-clinical population-based samples were used for longitudinal study of various parameters of health and memory (for further description, see Nilsson et al., 1997, 2004). The examination was conducted in two test sessions, each approximately 90 min. The first test session included health variables and the second test session memory variables. Two samples, sample 1 (S1) and sample 3 (S3), with an age ranging from 40 to 95 years, took part in three test occasions, T2, T3 and T4. S1 (N = 1,000) was tested for the first time, 1988–1990 (T1) and S3 (N = 983) participated for the first time in T2. In this study, subsamples of individuals between 40 and 65 years of age (N = 565) from S1 and S3 in T2 (baseline) were included. By using a stress scale the participants were divided into a high and low-stress group. Complete sets of data were not available in all participants and after matching for age, gender and education level, the high-stress group finally included 137 subjects and the low-stress group 211 subjects (Table I).

There were no differences at baseline (T2) between the two groups regarding tobacco and alcohol habits as well as sick leave frequency. The high-stress group reported sleeping problems (χ^2 = 5.641, p = 0.018), fatigue (χ^2 = 19.981, p < 0.001), anxiousness (χ^2 = 35.251, p < 0.001) and mood symptoms (χ^2 = 18.423, p < 0.001) more frequently than the low-stress group at baseline (T2). The high-stress group also reported higher frequency of psychiatric (χ^2 = 6.977, p = 0.008)

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Table I. Distribution of gender, mean age, and years of education at baseline (T2) in the high- and low-stress group.

Group	*N*	Females *n* (%)	Males *n* (%)	Mean age mean ± SD	Years of education mean ± SD
High	137	78 (56.9)	59 (43.1)	46.57 ± 5.9	13.27 ± 3.6
Low	211	119 (56.4)	92 (43.6)	46.71 ± 5.6	13.35 ± 2.7

and musculoskeletal ($\chi^2 = 4.419$, $p = 0.036$) diseases than the low-stress group at baseline (T2). The higher frequencies of sleeping problems, fatigue, anxiousness and mood symptoms in the high-stress group still persisted when subjects with psychiatric diseases at T2, T3 and T4 were excluded.

A repeated measure of stress level and diseases was performed in three test occasions: T2, T3 and T4. The incidence of diseases 5 years (T3) and 10 years (T4) after baseline (T2) was recorded. The participants who reported a specific disease at baseline were excluded when that specific disease was recorded 5 years (T3) after baseline. Furthermore, the participants who reported a specific disease at baseline or 5 years after baseline were excluded when that specific disease was recorded 10 years (T4) after baseline. This procedure made it possible to study whether health problems emerged over time, without contaminating effects of past health history.

Assessment of background variables and diseases

An extensive health questionnaire was administered measuring the background variables such as age, gender and years of education. The participants completed the questionnaire at home before the testing session and were further interviewed in the subsequent test session. In the interview, the presence of stress-related symptoms (yes or no), such as sleeping problems, fatigue, anxiousness and mood symptoms was measured.

Further, the interview included several items but in the present study only information about treatment of diseases during the last 5 years was recorded. The participants were asked: '*Have you sought for medical care, or been in hospital, for any of these diseases?*' In this study the following diseases were registered at baseline (T2), 5 (T3), and 10 years (T4) after baseline: cardiovascular, diabetes, tumours, psychiatric, and musculoskeletal. The prevalence of diseases at baseline (T2) provided information of all previous diseases from the age of 20 up to the interview at baseline.

Assessment of general stress

Perceived general stress was measured in the health test interview by using the question '*Are you stressed in general?*' and the subjects had to rate their stress level on a scale from 0 to 10 with the endpoints 0 = not stressed at all and 10 = very stressed. The participants who rated perceived general stress from 0 to 4 at baseline (T2) and 5 years after baseline (T3) were included in the low-stress group and those who rated from 5 to 10 were included in the high-stress group. The cut-off between value 4 and 5 was based on the mean value of stress rating among the total sample (S1 and S3), plus the standard deviation in T2 ($N = 1727$; $M = 3.17 \pm 2.17$) and in T3 ($N = 1487$; $M = 2.89 \pm 2.24$).

In order to validate the stress measure in the health test interview, a Pearson correlation analysis was performed between the stress scores and the scores on an additional stress measurement, the General Perceived Stress Questionnaire (PSQ, Levenstein et al., 1993) that was administered in T4. The PSQ emphasizes cognitive perceptions more than emotional states or specific life events and has been shown to be superior to alternative measures for predicting healthy outcomes. The PSQ has been reported to have high validity and reliability (Bergdahl & Bergdahl, 2002; Levenstein et al., 1993; Martin & Soon, 1993). The stress ratings administered in the present study were significantly correlated with the ratings on the PSQ ($N = 342$; $r = 0.670$; $p < 0.001$) indicating that the assessment of stress level in the health test interview was valid. A mean PSQ index = 0.22 [standard deviation (SD) ± 0.12] have been reported as normal stress level in a Swedish population (Bergdahl & Bergdahl, 2002). PSQ index cut-off scores for moderate stress were calculated to >0.34–≤0.46 and high stress to >0.46. The PSQ

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index measured at the test wave T4 showed that the high-stress group scored a mean PSQ index = 0.35 and the low-stress group a mean PSQ index = 0.20. This indicates that the high-stress group could be characterized as having moderately elevated stress level and the low-stress group normal stress level.

Statistical methods

Chi-square tests were performed to study differences between the groups regarding background variables at baseline and the incidence of diseases 5 and 10 years from baseline. Fisher's Exact Test was used when expected frequencies in cells were <5. The *p*-values < 0.05 were considered significant. SPSS 13.0 were used in all statistical analyses.

Results

Table II shows that the perceived general stress level was continuously elevated over time in the high-stress group, although a slight reduction was noticed 10 years after initial assessment. The low-stress group demonstrated a constant (low) stress level over time.

The incidence of diseases 5 years after baseline assessment showed no differences between the high and low-stress group, but a tendency of higher incidence of psychiatric diseases was observed in the high-stress group (Table III). Ten years after baseline there was a significantly higher incidence of psychiatric diseases in the high-stress group (Table III). There was also a significant effect for tumours, although the number of cases was low (Table III). According to the interview records, the tumour group included both benign and malign tumours. Among psychiatric diseases, conditions such as depression and burnout were the most common.

The cumulative incidence of diseases across the test events 5 and 10 years from baseline is displayed in Figure 1. A pattern of higher incidence of diseases over time was present in the high-stress group for all five diseases examined.

Table II. Mean values and standard deviations (SD) of perceived general stress in the high- and low-stress group at baseline (T2), 5 (T3) and 10 years (T4) from baseline.

Group	*N*	General stress baseline (T2) mean ± SD	General stress 5 years (T3) mean ± SD	General stress 10 years (T4) mean ± SD
High	137	6.40 ± 1.1	6.69 ± 1.3	4.53 ± 2.2
Low	211	2.39 ± 1.2	2.29 ± 1.2	2.13 ± 1.7

Table III. Incidence of diseases in high- and low-stress groups T3 and T4. Chi-square (χ^2), Fisher's Exact Test and *p*-values.

Disease	Group	*N* T3	Incidence in T3 (%)	χ^2	*p*	*N* T4	Incidence in T4 (%)	χ^2	*p*
Cardiovascular	High	87	14 (16.1)	2.533	0.111	73	16 (21.9)	0.441	0.507
	Low	152	14 (9.2)			138	25 (18.1)		
Diabetes	High	137	1 (0.7)		1.000*	136	5 (3.7)		0.492*
	Low	206	1 (0.5)			205	4 (2.0)		
Tumour	High	127	4 (3.1)		0.773*	123	9 (7.3)		0.004*
	Low	202	8 (4.0)			194	2 (1.0)		
Psychiatric	High	123	8 (6.5)		0.083*	115	13 (11.3)	5.145	0.023
	Low	204	5 (2.5)			199	9 (4.5)		
Musculoskeletal pain	High	55	19 (34.5)	1.731	0.188	36	7 (19.4)	0.000	0.993
	Low	109	27 (24.8)			82	16 (19.5)		

* Fisher's Exact Test.
T3: 5 years from baseline; T4: 10 years from baseline.

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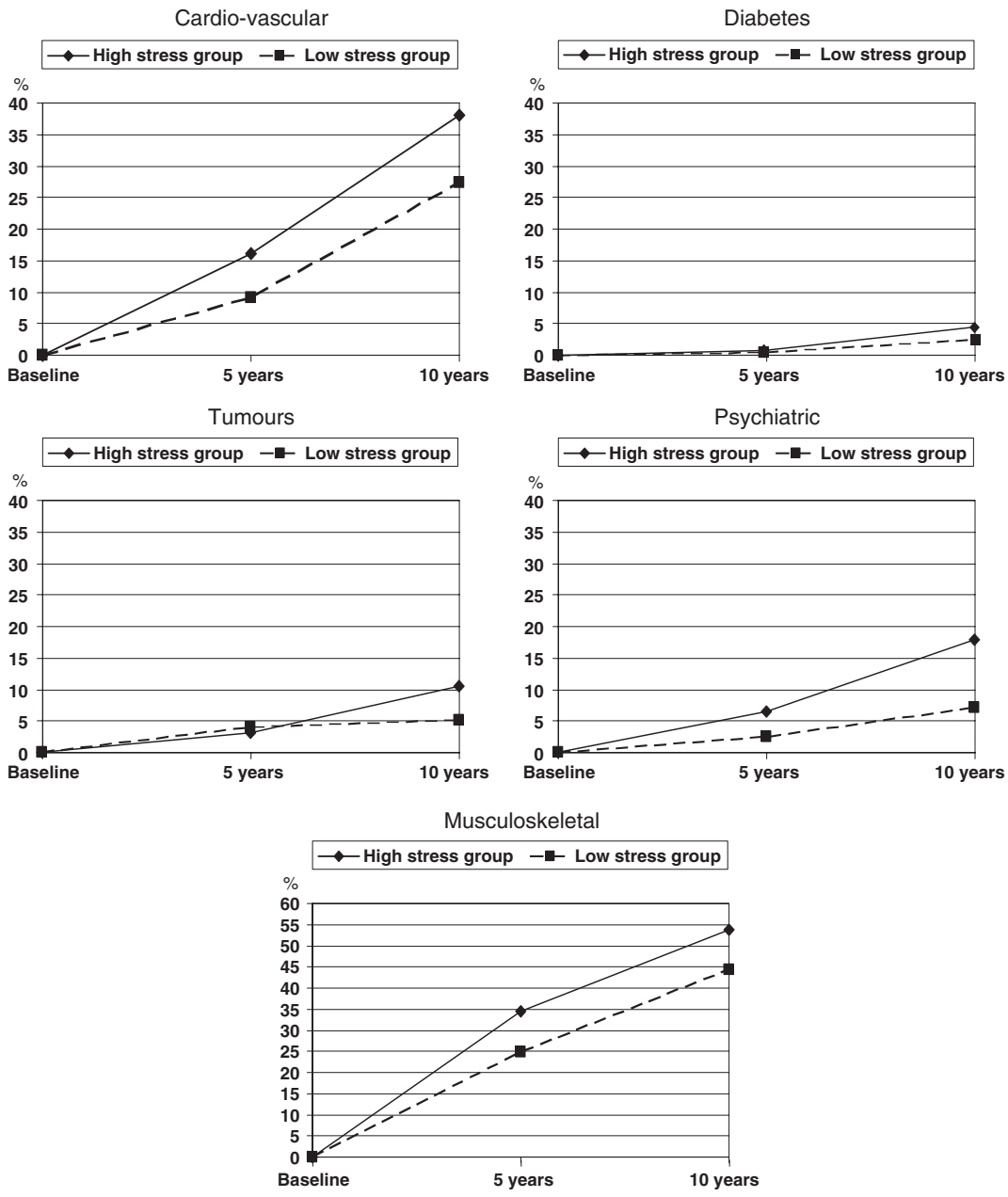

Figure 1. Cumulative incidence of diseases 5 and 10 years from baseline.

Discussion

The main objective of the present research was to longitudinally examine whether moderately elevated stress in a population-based sample was related to higher incidences of various health problems. We defined a group with elevated stress levels based on their self-reported stress levels. We found that these ratings were correlated with scores on the PSQ although the correlation coefficient was not especially high ($r = 0.67$), but we considered the association was sufficiently high to validate the stress measure. Because there was no available data on stress level before the initial assessment, we could not determine whether the stress was acute or chronic, but one can assume

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that the major part of the participants probably had a chronically elevated stress level at the baseline assessment. The stress level in the high-stress group was characterized as moderate, which was confirmed with the PSQ assessment in test wave T4. Furthermore, the group that reported higher levels of stress also reported more symptoms related to stress, such as sleeping problems and mood symptoms. Mental symptoms such as sleeping problems, fatigue, anxiousness and mood symptoms can be stressful themselves (Rasul, Stansfeld, Hart, Gillils, & Smith, 2002) and the higher frequency of these symptoms in the high-stress group could therefore be a prodrome of future psychiatric disease. Critically, we could not find any association with these mental symptoms in T2 and psychiatric diseases in T2, T3 and T4 indicating that the inclusion of the subjects in the high-stress group were not due to early signs of psychiatric disease.

Five years after initial assessment, we found no significant differences in health outcomes between the groups, although a tendency was apparent for some conditions showing that the high-stress group had had more health problems. Similarly, 10 years after initial assessment, the groups did not significantly differ for three of the assessed health outcomes (cardiovascular, diabetes, musculoskeletal), although some tendencies in the same direction as at the 5-year measurement were apparent (see Figure 1). At this time, however, significant group differences were noted for two conditions, psychiatric (mainly depression) and tumours.

These findings are supported by several other studies (Blackburn-Munro & Blackburn-Munro, 2001; de Kloet et al., 2005; Kopp & Réthelyi, 2004; Reiche et al., 2004) suggesting that prolonged stress is detrimental for health especially for the development of depression. It seems that the HPA axis and the sympathetic nervous system play an important role in the stress–poor health interaction. The HPA axis and the sympathetic nervous system are the major neural pathways that activate by elevated stress levels. The HPA axis is responsible for both the cognitive appraisal of the stressor as well as the behavioural and endocrine adaptation to stress (Sapolsky, Romero, & Munck, 2000). Prolonged stress may disturb the HPA axis so extensively that the adaptive responses of the HPA axis may become maladaptive (Blackburn-Munro & Blackburn-Munro, 2001). This can lead to symptoms of depression and anxiety, which can be an explanation to the high incidence of depression in the present study. Depletion of central serotonin may lead to an increase in ascending nociceptive transmission. The pain threshold may therefore be so extensively lowered in patients suffering from depressive illness that it manifests as part of the pathology of depression. On the other hand, depressive symptoms may manifest in chronic pain patients as a consequence of indirect, long-term nociceptive activation of the HPA axis. Chronic stress-induced HPA dysfunction can be a potential link uniting chronic pain and depressive illness (Blackburn-Munro & Blackburn-Munro, 2001). The cumulative incidence of musculoskeletal diseases in the high-stress group (Figure 1) may suggest a possible link between psychiatric diseases, that is, depression and musculoskeletal diseases, although no significant differences were found between the high and low-stress group regarding musculoskeletal diseases.

Other studies have suggested that stress and depression can result in an impairment of the immune response and may promote the initiation and progression of some type of tumours. Through HPA activation, the mediators released during chronic stress suppress some non-specific and specific parts of the immune response compromising the most important effectors of the immune response against tumours. The plasma concentration of adrenaline seems to be inversely related to specific immune functions of lymphocytes and monocytes. Corticosteroids have been suggested to have important immunosuppressive effects on the functions of lymphocytes and macrophages (Reiche et al., 2004). In the present study, the diseases in the tumour group were very heterogenic including both benign and malign tumours and therefore we can not put forward any specific tumour that dominated this group. This heterogeneity together with the rather few registered cases of tumour diseases made it difficult do draw any further conclusion regarding the association with chronic stress.

Several studies have confirmed the close relation between stress and cardiovascular diseases (Kopp & Réthelyi, 2004). The cumulative incidence of cardiovascular diseases was higher in the high-stress group compared to the low-stress group (Figure 1) although no significant differences were found between the high and low-stress group (Table III). One explanation to the non-significant result could be the too small number of subjects. Other possible explanations could be that we focused on effects of moderately elevated

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stress level and that the follow-up period was too short. This study included subsamples of the Betula Study ($N = 348$), which does not seem to be enough to reach acceptable number of subjects reporting stress-related diseases.

In this study the participants were interviewed regarding treatment of diseases during the last 5 years. This procedure is not optimal and therefore is a limitation of the study. More objective medical data such as medical records would provide more accurate information of manifest diseases over the last 5 years. We have therefore clustered the reported diseases into major diagnostic categories such as cardiovascular diseases, diabetes, psychiatric diseases, tumours and musculoskeletal disorders. Because of the diagnostic heterogeneity in each of the major diagnostic category we can not draw any further conclusions on specific diagnoses. Further studies should therefore include more objective medical data in order to differentiate between various specific diagnoses.

We could not find any pronounced differences between the high and low-stress group over time regarding the incidence of stress-related diseases. This can be explained by the fact that the stress level in the high-stress group was moderately elevated. Compared to chronic high-stress level, moderately elevated chronic stress seem to be harmful only to mental health, especially depression, over a 10-year period but perhaps it can be detrimental to other stress-related diseases when the moderate stress load is longer than 10 years.

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