How Stress Gets Under Your Skin: psychobiological studies of social status, stress and health

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- Whitehall and Whitehall II epidemiological studies
- English Longitudinal Study of Ageing (ELSA)
- Health Survey for England
- National Child Development Study (1946)
- Psychosocial factors in Eastern Europe (HAPIEE)
- Ethnic minority psychiatric illness rates (EMPIRIC) study
How stress gets under your skin

- Psychosocial factors and physical illness
- Psychobiological processes
- Methods of investigation
- Psychobiological responses and health outcomes
Premature mortality rates (deaths per 100,000) by social class in men aged 20-64
Psychosocial factors related to the development of physical disease

- **Chronic life stress**
  High demand/low control at work; effort-reward imbalance; financial strain; marital conflict; caregiving

- **Social environment**
  Social isolation; emotional support; social cohesion

- **Psychological factors**
  Depression, anger/hostility, anxiety/distress
Prevalence of Conventional Risk Factors in Men with Coronary Heart Disease (n=87,869)

- No Risk Factors: 19.4%
- 1 Risk Factor: 43.0%
- 2 Risk Factors: 27.8%
- 3 Risk Factors: 8.9%
- 4 Risk Factors: <1%
Work stress and cardiac mortality

25 year follow-up, adjusted for age, sex, smoking
Physical activity, blood pressure, cholesterol, body mass

Kivimäki, 2002
Social support and CHD

Social integration
Emotional attachment

15 year follow-up, adjusted for smoking, blood pressure, cholesterol, triglycerides, BMI, waist/hip ratio, diabetes, family history, social class, stress

Rosengren, 2004
Depression and CHD incidence

10 year follow-up. Adjusted for poverty, smoking, diabetes and body mass index (Ferketich et al, *Arch Intern Med* 2000)
Metabolic syndrome markers (ATPIII)

Three or more of:

- Waist circumference $> 102$ cm (men) or $88$ cm (women)
- Fasting triglyceride $\geq 150$ mg/dl
- Fasting HDL-cholesterol $< 40$ mg/dl (men), $< 50$ mg/dl (women)
- Blood pressure $\geq 130 / 85$ mmHg
- Fasting glucose $\geq 110$ mg/dl
Marital satisfaction and the metabolic syndrome

11.5 year follow-up adjusted for baseline MS, age, race, education, smoking, physical activity, alcohol, depression, anxiety

Troxel et al, 2005
Arch Intern Med
Psychosocial factors and illness

- Chronic challenges, not acute life events
- Influences on long-term development
- Not the cause, but a contribution to risk
Psychosocial factors and illness

• Mechanisms?
Psychosocial factors and illness

- Behavioural processes
  Smoking, food choice, physical exercise, alcohol consumption
Psychosocial factors and illness

• Behavioural processes
  Smoking, food choice, physical exercise, alcohol consumption

• Psychobiological processes
  Stress-induced modifications in neuroendocrine, cardiovascular, autonomic, immunological and other physiological responses
<table>
<thead>
<tr>
<th>Psychobiological responses</th>
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<tbody>
<tr>
<td><strong>Neuroendocrine</strong></td>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td><strong>Inflammatory</strong></td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td><strong>Haemostatic</strong></td>
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<tr>
<td><strong>Immune</strong></td>
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</tbody>
</table>
Some effects of cortisol

- Stimulation of glucose production in the liver
- Release of free fatty acids from fat stores
- Regulation of water balance
- Stimulation of anti-inflammatory responses
- Immune regulation
Sympathetic Nervous System

Increased Heart Rate
Increased Blood Pressure
Increased Breathing Rate
Increased Blood Clotting
Increased Adrenaline & Noradrenaline
When are psychobiological responses hazardous?

- Repeatedly elicited in conditions of everyday life
- Some people show heightened reactions or failure of post-stress adaptation
Some effects of high cortisol

Potentially damaging effects

- Increased lipid (LDL-cholesterol) in the blood
- Suppression of immune function
- Decalcification of bone
- Deposition of abdominal fat
- Damage to the hippocampus
- Muscle wasting
- Impaired reproductive function
How stress gets under your skin

- Psychosocial factors and physical illness
- Psychobiological processes
- Methods of investigation
- Psychobiological responses and health outcomes
Types of study

- Experimental or clinical studies
- Naturalistic monitoring studies
Psychophysiological Stress Testing

Set-up 50 min
Baseline 30 min
Tasks 20 min
Recovery 45 – 120 min

Physical Measures
Venous Cannula
BP set-up

Baseline
BP Stress rating

Task
BP Stress ratings

Recovery
BP Stress ratings

Blood sample
Blood sample
Blood sample
Blood sample
Laboratory mental stress testing

• Do responses in biological measures relevant to health vary with psychosocial risk profile?
C-reactive protein

- Acute phase protein synthesized in liver
- Increases in response to inflammatory stimuli (cytokines), infection and tissue damage
- Antimicrobial, clears apoptotic cells, enhances phagocytosis
- Marker of chronic low grade inflammation
- Risk marker for CVD, functional significance debated
Hansson, *NEJM*, 2005
Work stress study

- 105 healthy nonsmoking men, mean age 32.1 years. Full-time employment
- Measures of effort-reward imbalance
- Responses to simulated public speaking and mirror tracing tasks
- Blood samples for C-reactive protein before and after tasks
Effort-reward imbalance and C-reactive protein stress responses

Adjusted for baseline C-reactive protein, age and BMI
Socioeconomic factors and illness

• Do socioeconomic inequalities stimulate biological processes relevant to cardiovascular risk?
Psychobiological responses and SEP

Participants

- 238 members of the Whitehall II (prospective) cohort aged 47-59 years in full-time employment.
  Sampled by grade of employment:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>49</td>
<td>41</td>
<td>90</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44</td>
<td>37</td>
<td>81</td>
</tr>
<tr>
<td>Lower</td>
<td>36</td>
<td>31</td>
<td>67</td>
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Conditions

- Cardiovascular, neuroendocrine, cytokine and hemostatic responses to colour/word and mirror tracing tasks.
  Blood drawn at baseline, immediately post-task, and 45 minutes later.
Systolic BP by occupational grade

Euro Heart J, 2002
Socioeconomic position and incomplete recovery 45 min post-stress

Odds of incomplete recovery adjusted for gender, age, baseline value and reaction to tasks
Interleukin 6

An ‘endocrine’ cytokine associated with
- Coronary heart disease
- Type 2 diabetes, insulin resistance, obesity
- Depression
- Disability
- Cognitive decline
IL-6 and depressed mood

3024 men & women aged 70-79

Penninx et al, *Biol Psychiat* 2005
Stress and plasma interleukin-6

Brydon et al
Brain, Behav Immun, 2004
Types of study

• Experimental or clinical studies

• Naturalistic monitoring studies
Naturalistic monitoring

- Dynamic responses in everyday life
- Covariation of biology, events and reactions

Ambulatory blood pressure
Salivary cortisol
Adjusted for gender, age, occupational grade, smoking, BMI, and physical activity

Steptoe & Willemsen
J Hypertension, 2004
Cortisol profile over working day

Cortisol in nmol/l

Wake +30 min 8.00-8.30 10.00-10.30 12.00-12.30 14.00-14.30 16.00-16.30 18.00-18.30 20.00-20.30 22.00-22.30
Cortisol and job control

Men, age-adjusted

Kunz-Ebrecht et al
Measurement of happiness

- Repeated sampling every 20 minutes from morning (07:30 – 09:30 start) until evening (22:30) on a working day
- Happiness on 5-point scale:
  1 = very low to 5 = very high
- Division into 1-3 vs 4-5
- Proportion of happy ratings (4-5) over the day
Happiness in men and women

Steptoe et al
*PNAS, 2005*
Salivary cortisol – working day

8 samples (08:00 – 22:30)
Adjusted for gender, age, occupational grade, smoking, bmi, and GHQ

P = .009
Happiness ratings - 3 years

Happiness quintiles (baseline)

% happy rating:

Men  Women

Happiness quintiles (baseline)

1 Low  2  3  4  5 High
Cortisol and happiness – 3 year

Happiness quintiles

N = 144
Adjusted for gender, age, occupational grade, work at follow-up, smoking, bmi, GHQ

P = .064
Systolic BP and happiness – 3 year

Adjusted for gender, age, occupational grade, work at follow-up, smoking, bmi, GHQ. N = 160

P = .030
Problems of interpretation of cortisol data:

- Variation over the day; single readings of limited value
  - Cortisol awakening response
  - Levels over the day, slope
Cortisol waking response

Work day

Weekend

Kunz-Ebrecht et al
PNEC, 2004
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Stress responses and the development of disease risk

Do more responsive individuals show more rapid progression of disease risk, independently of original risk profile?

- Assessment of psychobiological responses and disease risk
- Repeat assessment of disease risk 3 years later
Cholesterol response to acute stress

Adjusted for socioeconomic status, age, body weight, smoking, and alcohol
Cholesterol stress response and cholesterol 3-years later

Adjusted for gender, socioeconomic status, age, body weight, smoking, alcohol and baseline cholesterol

Steptoe & Brydon
Health Psychol, 2005
Metabolic syndrome markers (ATPIII)

Three or more of:

- Waist circumference $> 102$ cm (men) or $88$ cm (women)
- Fasting triglyceride $\geq 150$ mg/dl
- Fasting HDL-cholesterol $< 40$ mg/dl (men), $< 50$ mg/dl (women)
- Blood pressure $\geq 130 / 85$ mmHg
- Fasting glucose $\geq 110$ mg/dl
Adjusted for baseline ATP III metabolic syndrome markers, gender, BMI, physical activity SES, age, smoking, alcohol consumption, medication, and baseline diastolic BP
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Psychosocial Factors
- Adverse Work stress Neighbourhood Financial Domestic
- Protective Social networks Coping responses Self-esteem

Health-compromising behaviours

Psychobiological processes

Psychological well-being

Physical disease risk

Affective disorders

Social position
- Occupation Education Income
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  Professor Clemens Kirschbaum

• University of Glasgow
  Professor Gordon Lowe, Dr Ann Rumley

Medical Research Council
British Heart Foundation
Cortisol waking response

Heightened response
- Depressive symptoms (Pruessner 2003)
- Patients with clinical depression (Bhagwagar 2003)
- Chronic work stress (Steptoe 2000)
- Working vs weekend days (Schlotz 2004)
- Loneliness (Steptoe 2004, PNEC)
- Abdominal adiposity (Steptoe, 2004, IJO)

Reduced response
- Chronic fatigue (Roberts 2004)
- Some physical illness groups (Kudielka 2003)
IL-6 and cognitive impairment

4 year follow-up of 2632 men and women aged 70-79 years

Cognitive impairment, adjusting for baseline cognitive score, age, education, race, depression, alcohol, stroke and statins

• High inflammation RR: 1.66 (1.19 – 2.18)
• Low inflammation RR: 1.08 (0.89 – 1.30)

Yaffe et al
JAMA 2004
Heart rate variability

- Beat-to beat variation in heart rate
- Interplay between sympathetic and parasympathetic (vagal) branches of autonomic nervous system

Assessed in the
- Time domain (R-R variability)
- Frequency domain (spectral analysis)
  - High frequency (parasympathetic)
  - Low frequency (sympathovagal balance)
  - Low/High (sympathovagal balance)
Low heart rate variability

- Higher risk of death or recurrent events in patients with CHD (Atrami study, 1998)
- Incident CHD in apparently healthy cohorts (Liao, 1997)
- Future hypertension (Schroeder, 2003)
- Post-stroke mortality (Makikillio, 2004)
- Depressive symptoms (Lim, 2005)
Low heart rate variability

• Poorer cognitive executive function (Hansen et al, 2003)

• Less effective impulse control in children (Allen et al, 2000)

• More negative moods in alcohol abuse (Ingjaldsson et al, 2003)

• Reduced sleep efficiency (Hall et al, 2004)
Whitehall autonomic function study

Low heart rate variability related to:

- Low employment grade
- Lower job control
- Smoking, inactivity, high alcohol intake
- Metabolic syndrome

Hemingway et al
Circulation, 2005
Low heart rate variability

- Social isolation (Horsten, 1999)
- High effort/reward imbalance (Vrijkotte, 2000)
- Depressive symptoms (Lim, 2005)
- Depression in post-MI patients (Carney, 2001)
Heart rate variability by grade

RMSSD (msec)

Higher

Lower
Whitehall Psychobiology Follow-up

• Assessment of 209 participants 3 years after mental stress testing (92% response rate)

• Measurement of
  ➢ resting blood pressure
  ➢ fasting lipid profiles
  ➢ BMI, waist and hip circumference
  ➢ Ambulatory BP in a subset (153)
3 year systolic BP increase $\geq 5$ mmHg

Adjusted for baseline BP, age, gender, grade of employment, hypertensive medication, BMI, and smoking

Adjusted odds ratio

Steptoe & Marmot

*J Hypertension, 2005*
Some effects of sympathetic activation

- Increased blood pressure and heart rate
- Reduced gut motility and salivation
- Stimulation of clotting processes
- Acute immune activation
- Release of free fatty acids from fat stores