Psychobiology of Health and Disease: Integrating Laboratory and Population Studies in Whitehall II

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Pathways underlying psychosocial influences on health outcomes

**Lifestyle**
- Smoking, food choice, physical exercise, alcohol consumption, healthy weight, adherence to treatment

**Biology**
- Modifications in neuroendocrine, cardiovascular, inflammatory, immunological and other physiological responses
Pathways underlying psychosocial influences on health outcomes

- **Neuroendocrine**
  - cortisol, adrenaline, testosterone, noradrenaline

- **Cardiovascular**
  - Blood pressure, heart rate, heart rate variability

- **Immune**
  - Lymphocyte counts and activity, natural killer cells, immunoglobulins

- **Inflammatory**
  - C-reactive protein, interleukin (IL) 6, fibrinogen

- **Metabolic**
  - Lipids (cholesterol), glucose, insulin
Psychobiological processes and health risk

Levels of study

• Animal studies
• Psychophysiological stress testing
• Clinical studies
• Naturalistic monitoring
• Epidemiological studies
Psychophysiological stress testing

- Mentally challenging tasks:
  Problem solving, emotional interviews, simulated public speaking

- Measurement of:
  Blood pressure, heart rate, hormones, cholesterol, blood clotting, inflammation, muscle tension

- Comparison of:
  Clinical groups
  People high or low on psychosocial characteristics relevant to health
Psychophysiological stress testing

- Sophisticated biological measures
- Evaluation of dynamic responses
- Control of confounders
- Experimental manipulation of conditions
- Can establish causal links between stress-related factors and biology
Why study these processes within the Whitehall II study?

- Well-characterised study sample
- Participant recruitment in relation to a documented indicator of cardiovascular risk (occupational status)
- Tracking of health outcomes allows stress-related biology to be linked to future health outcomes
- Investigations of associations with other processes (genetics, cognitive function, diet, arterial stiffness, etc)
Psychobiology study

Participants (2000-2001)

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

Sampled by grade of employment:

- Higher: Men 49, Women 41, Total 90
- Intermediate: Men 44, Women 37, Total 81
- Lower: Men 36, Women 31, Total 67

Conditions

- Cardiovascular, neuroendocrine, cytokine and haemostatic responses to colour/word and mirror tracing tasks.
- Blood drawn at baseline, immediately post-task, and 45 minutes later.
- Salivary cortisol assessed 8 times over the day, along with momentary assessments of mood.
Findings

• Psychosocial factors are associated with a broad range of health-related dynamic biological responses to mental challenge
Stress, endothelial and haemostatic responses

Von Willebrand factor

Factor VIII

Plasma viscosity
Stress, endothelial and haemostatic responses

Von Willebrand factor

High BP responder

Low BP responder

Factor VIII

Plasma viscosity
Stress and plasma IL-6 response

![Graph showing the change in plasma IL-6 levels over time. The x-axis represents time in minutes (Base, 30 min, 75 min, 120 min), and the y-axis represents pg/ml. The graph shows a gradual increase in IL-6 levels from baseline to 120 minutes.]
Stress and IL-1β gene expression

Brydon et al
Brain, Behav Immun, 2005
Findings

- Psychosocial factors are associated with a broad range of health-related dynamic biological responses to mental challenge
- Impaired post-stress recovery characterises higher risk groups
Acute biological responses to mental stress

- Size of the response
- Rate of recovery
Systolic BP by grade of employment

Euro Heart J, 2002
Systolic BP by grade – heart scan study

Baseline Tasks 40-45 min 70-75 min

SBP (mmHg)

Lower
Intermediate
Higher

SBP (mmHg)

Baseline Tasks 40-45 min 70-75 min
Findings

- Psychosocial factors are associated with a broad range of health-related dynamic biological responses to mental challenge
- Impaired post-stress recovery characterises higher risk groups
- Individual differences in biological responses predict disease development
IL-6 stress responses

IL-6 45 min – baseline pg/ml
3 year ambulatory systolic BP

Adjusted for T1 ambulatory BP, age, gender, grade of employment, medication, BMI, smoking, baseline IL-6, and SBP responsivity/recovery
Heart scan study

Phase 1 (2006-2008)
- 543 men and women from Whitehall II cohort
- No history of CHD and no diabetes or hypertension
- Measurement of psychobiological responses to colour/word and mirror tracing tasks
- Salivary cortisol assessment over a single day
- Assessment of coronary artery calcification using electron beam computed tomography

Phase 2 (2009-2011)
- Repeat assessment of coronary artery calcification
- Accelerometry for 7 days
Heart Scan Study

Coronary artery calcification (CAC) measured using electron beam computed tomography (EBCT)
# Predictors of progression in subclinical coronary artery disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.01 – 1.10</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.11</td>
<td>1.23 – 3.63</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.25</td>
<td>1.01 – 1.56</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.47</td>
<td>1.20 – 1.81</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.50</td>
<td>1.06 – 5.89</td>
</tr>
<tr>
<td><strong>Cortisol stress response</strong></td>
<td><strong>1.27</strong></td>
<td><strong>1.02 – 1.60</strong></td>
</tr>
</tbody>
</table>

Hamer et al.  
PLoS One, 2012
Combining studies to assess clinical health outcomes

- Do individual differences in stress-related responses predict incident cardiovascular outcomes?
- Combination of Psychobiology and Heart Scan studies
- 736 (94.4%) assessed in Phase 11
- Exclusion of participants with high resting BP during stress testing – 636 analysed
- Hypertension defined as BP ≥ 140/90 or medication
## Stress responses and incident hypertension

<table>
<thead>
<tr>
<th>Exposure variable</th>
<th>Category</th>
<th>Incident hypertension (%)</th>
<th>Adjusted odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP task</td>
<td>Low</td>
<td>16.5%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>22.3%</td>
<td>1.35 (0.78 – 2.32)</td>
<td>0.28</td>
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<tr>
<td></td>
<td>High</td>
<td>29.3%</td>
<td>2.02 (1.17 – 3.48)</td>
<td>0.012</td>
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<tr>
<td>Systolic BP recovery</td>
<td>Low</td>
<td>19.4%</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>Medium</td>
<td>25.1%</td>
<td>1.74 (1.03 – 2.94)</td>
<td>0.037</td>
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<tr>
<td></td>
<td>High</td>
<td>23.7%</td>
<td>2.06 (1.19 – 3.57)</td>
<td>0.010</td>
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<tr>
<td>Fibrinogen task</td>
<td>Low</td>
<td>21.9%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>18.5%</td>
<td>1.99 (0.83 – 4.98)</td>
<td>0.12</td>
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<tr>
<td></td>
<td>High</td>
<td>26.2%</td>
<td>2.64 (1.11 – 6.30)</td>
<td>0.029</td>
</tr>
</tbody>
</table>
Other investigations

- Biological processes
  Endothelial function, vascular stiffness, telomeres, heat shock proteins, pericardial fat, infectious disease burden, corticosteroid receptor sensitivity, troponin, lipid metabolism

- Psychosocial factors
  Work stress, financial strain, neighbourhood factors, early life adversity, marital roles, social isolation, self-esteem, depression, loneliness, attachment, positive wellbeing, optimism

- Health and behavioural outcomes
  Diabetes, objective physical activity, metabolic syndrome
Professor Sir Michael Marmot
Professor Mika Kivimäki
Professor Jane Wardle
Professor Mark Hamer
Dr Lena Brydon
Dr Romano Endrighi
Dr Sabine Kunz-Ebrecht
Dr Katie O’Donnell
Dr Gonneke Willemsen
Ruth Hackett
Bev Murray
Livia Urbanova

Professor Elizabeth Backburn
Professor John Deanfield
Professor Julian Halcox
Professor Brian Henderson
Professor Avijit Lahiri
Dr Jennifer Beam Dowd
Dr Vidya Mohamed-Ali

British Heart Foundation
Medical Research Council