

Psychobiological Processes: Pathways Linking Social Factors with Disease

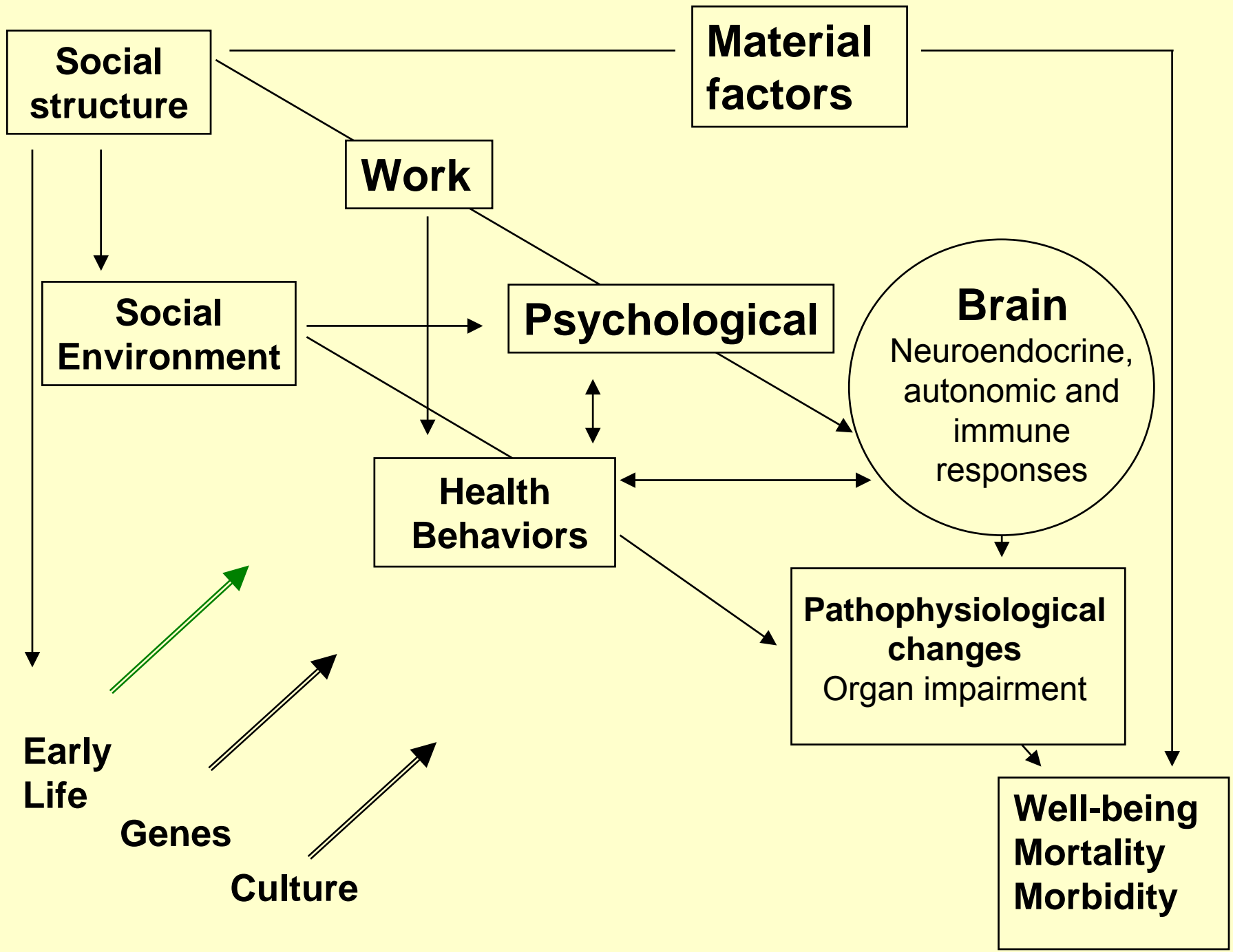
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<http://www.ucl.ac.uk/psychobiology/>

Department of Epidemiology and Public Health

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

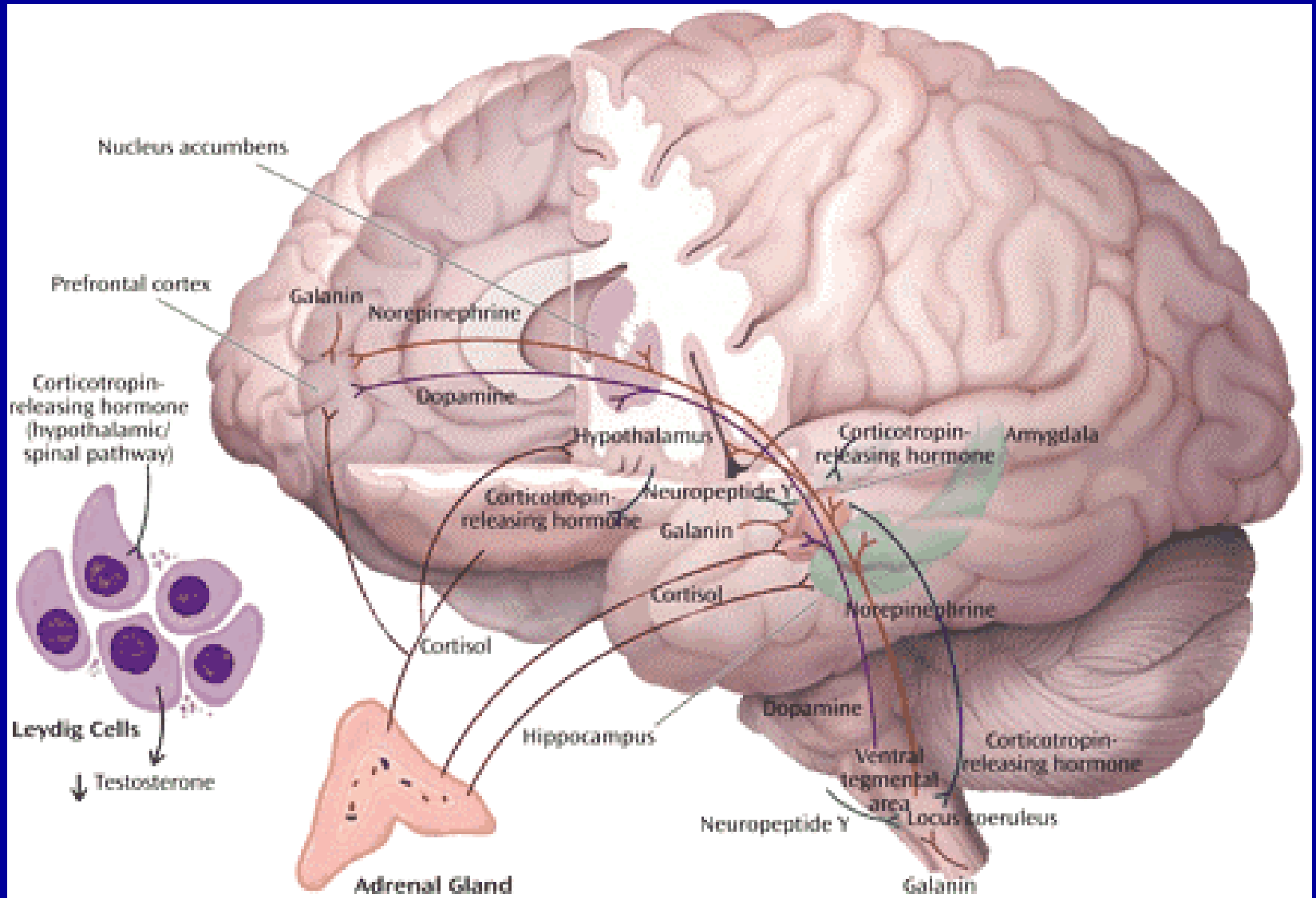


Issues:

- What are psychobiological processes?
- Why are they relevant?
- What types of study?
- What measures are useful in health care research?

Psychobiological pathways

The pathways through which psychosocial factors stimulate biological systems via central nervous system activation of autonomic, neuroendocrine and immunological responses



Charney, 2004

Psychobiological responses

Neuroendocrine	cortisol, epinephrine, testosterone, norepinephrine
Cardiovascular	Blood pressure, heart rate
Inflammatory	C-reactive protein, interleukin (IL-6) fibrinogen
Metabolic	Lipids, glucose, insulin
Hemostatic	Platelets, coagulation factors
Immune	Lymphocyte counts and activity, natural killer cells, immunoglobulins

**Hypothalamic-
Pituitary-Adrenal
Axis (HPA)**

Hypothalamus



CRF

Pituitary gland



ACTH

Adrenal cortex



Cortisol

**Sympatho-Adrenal
Axis**

Brain
Hypothalamus



Adrenal medulla



Epinephrine

**Sympathetic
nervous system
Norepinephrine**

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

Some effects of sympathetic activation

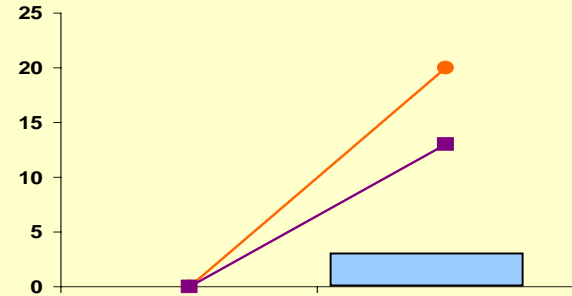
- Increased blood pressure and heart rate
- Reduced gut motility and salivation
- Stimulation of clotting processes
- Acute immune activation
- Release of free fatty acids from fat stores

When are psychobiological responses hazardous?

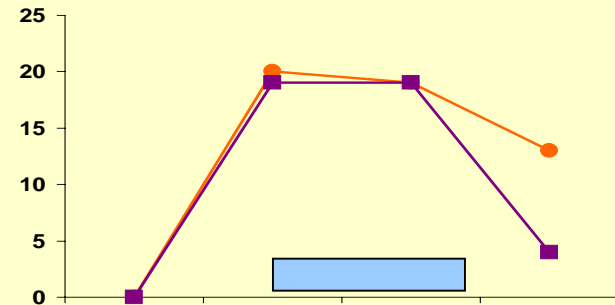
- Heightened reactions or failure of post-stress adaptation

Biological stress responsivity

- Size of the response



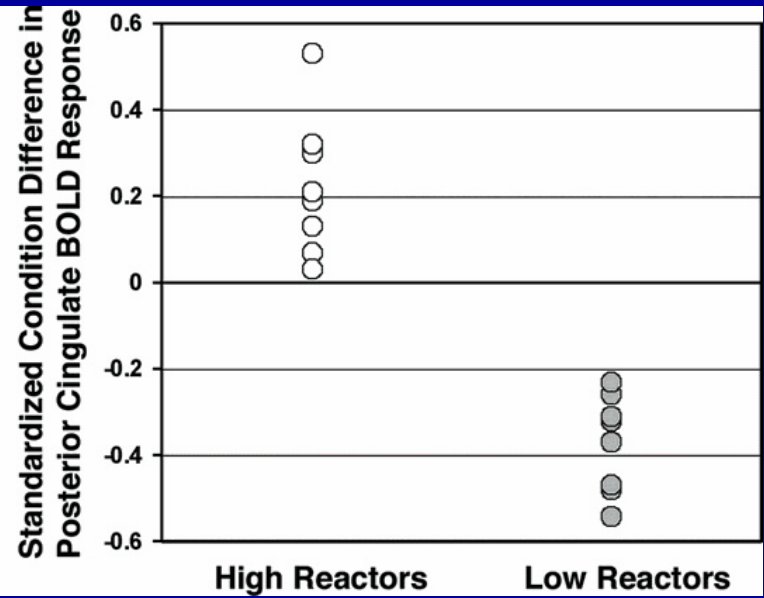
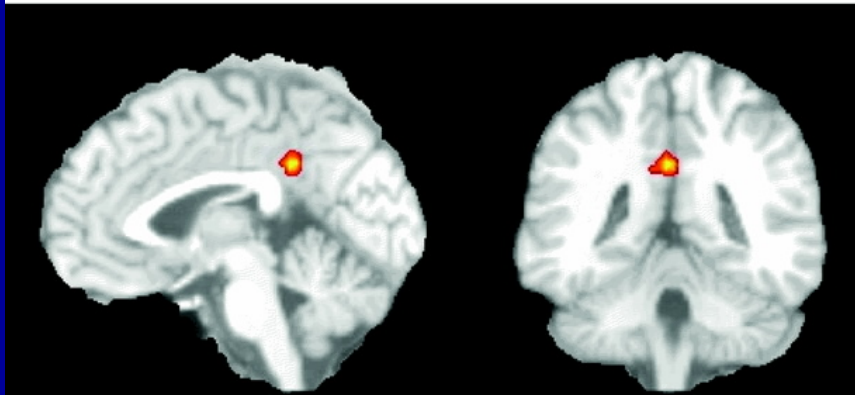
- Rate of recovery



Origin of variation in psychobiological responses

- Genetic factors
- Early life experience
- Adult life factors – adversity, temperament
- Appraisal and coping factors

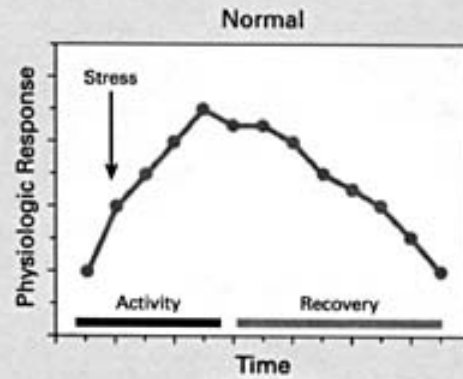
Posterior Cingulate Cortex



Gianaros,
Psychosom Med
2005

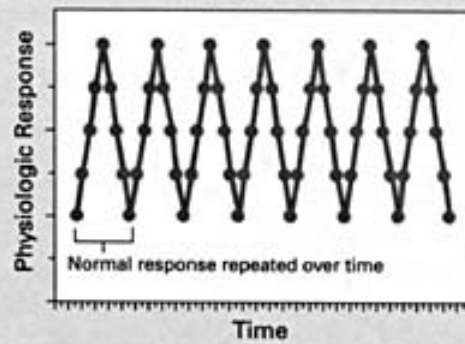
When are psychobiological responses hazardous?

- Heightened reactions or failure of post-stress adaptation
- Sustained or repeated exposure to conditions eliciting responses

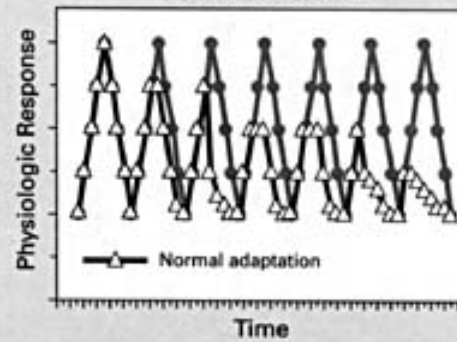


Allostatic load

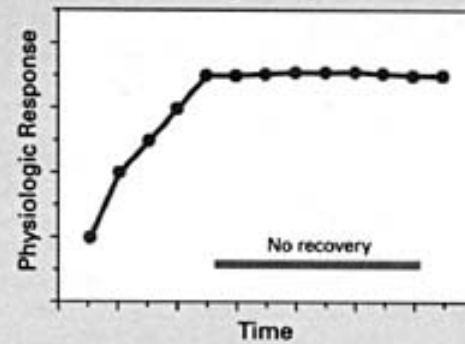
Repeated "hits"



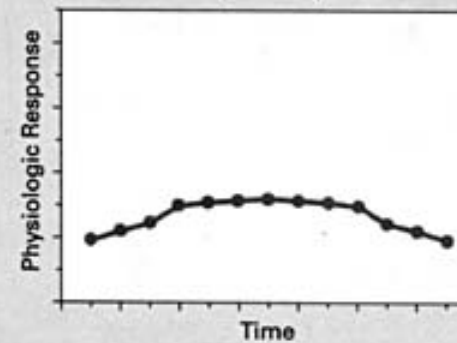
Lack of adaptation



Prolonged response



Inadequate response



McEwen,
NEJM
1998

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

Issues:

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Psychosocial factors associated with disease incidence or progression in prospective observational cohort studies

- Chronic life stress

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

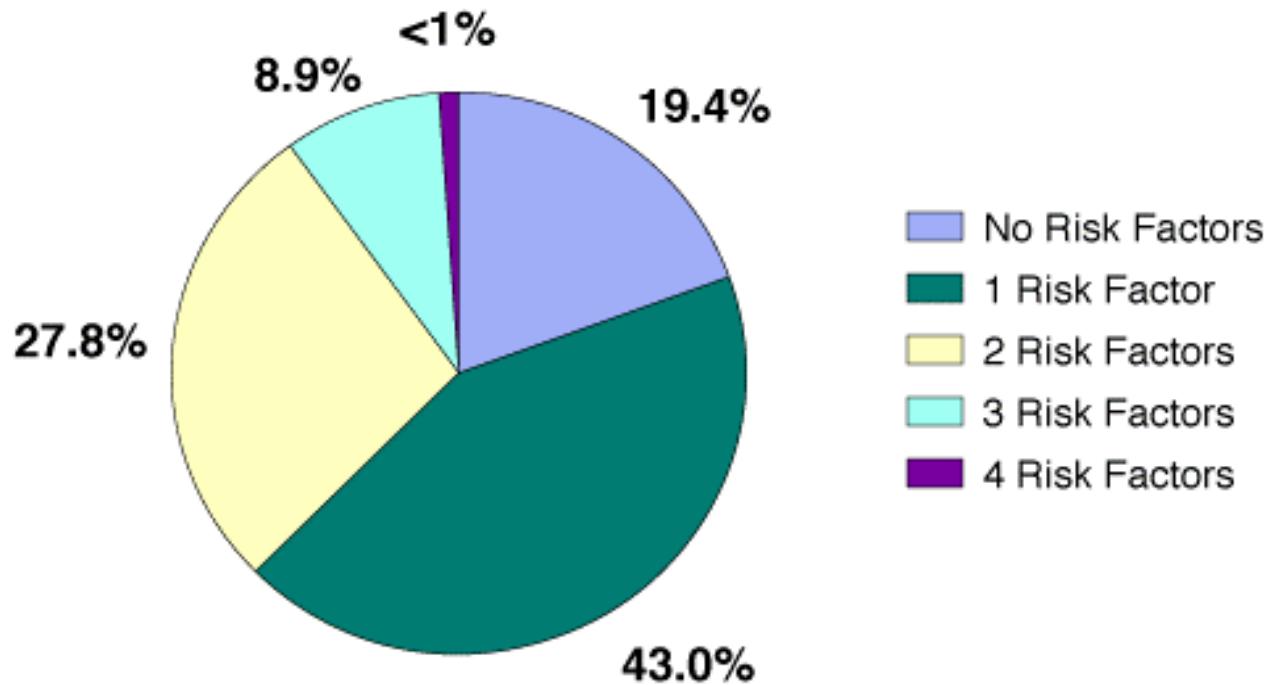
- Social environment

Social isolation; emotional support

- Psychological factors

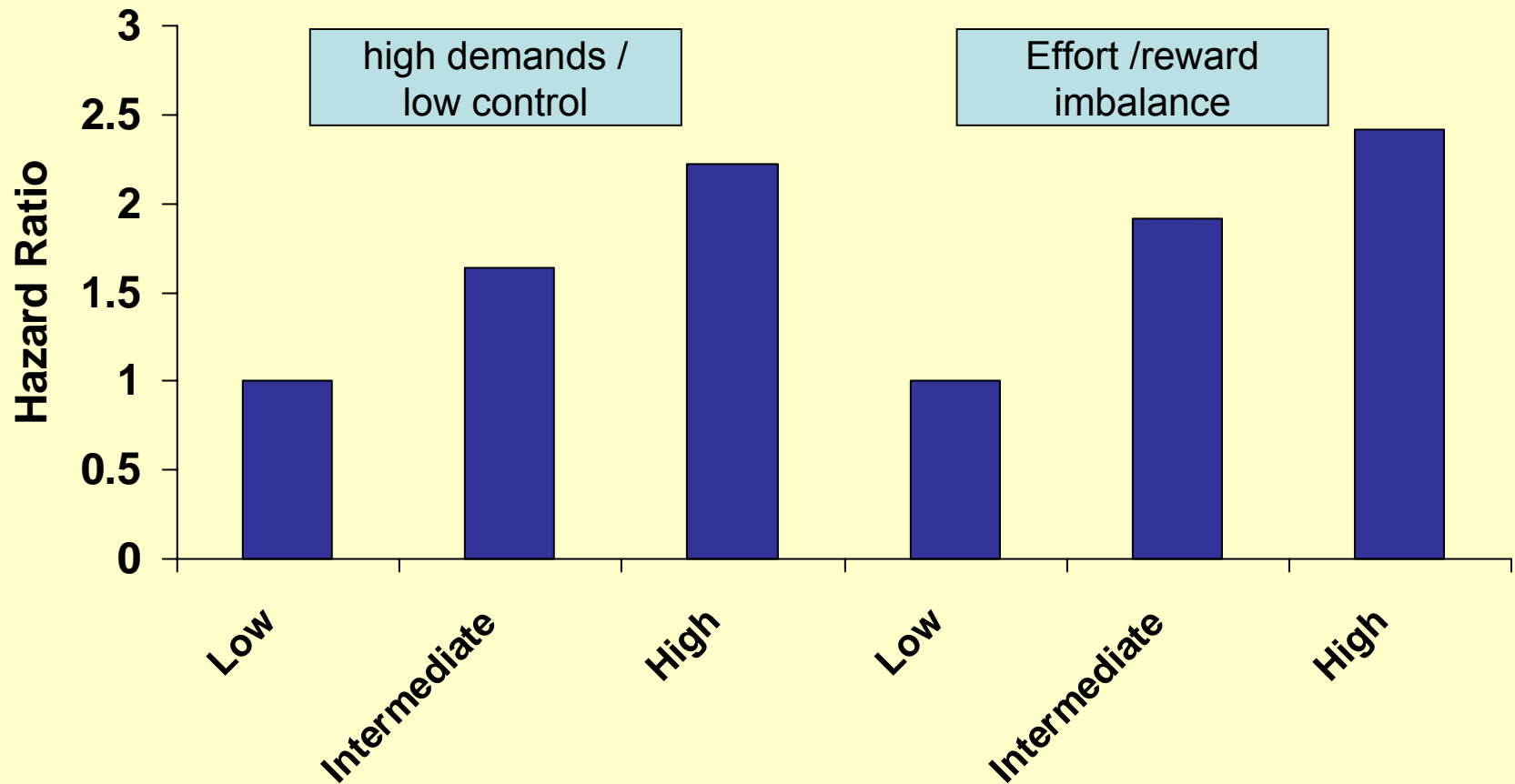
Depression, anger/hostility, anxiety/distress

Prevalence of Conventional Risk Factors in Men with Coronary Heart Disease (n=87,869)



Khot et al, 2003
JAMA

Work stress and cardiac mortality



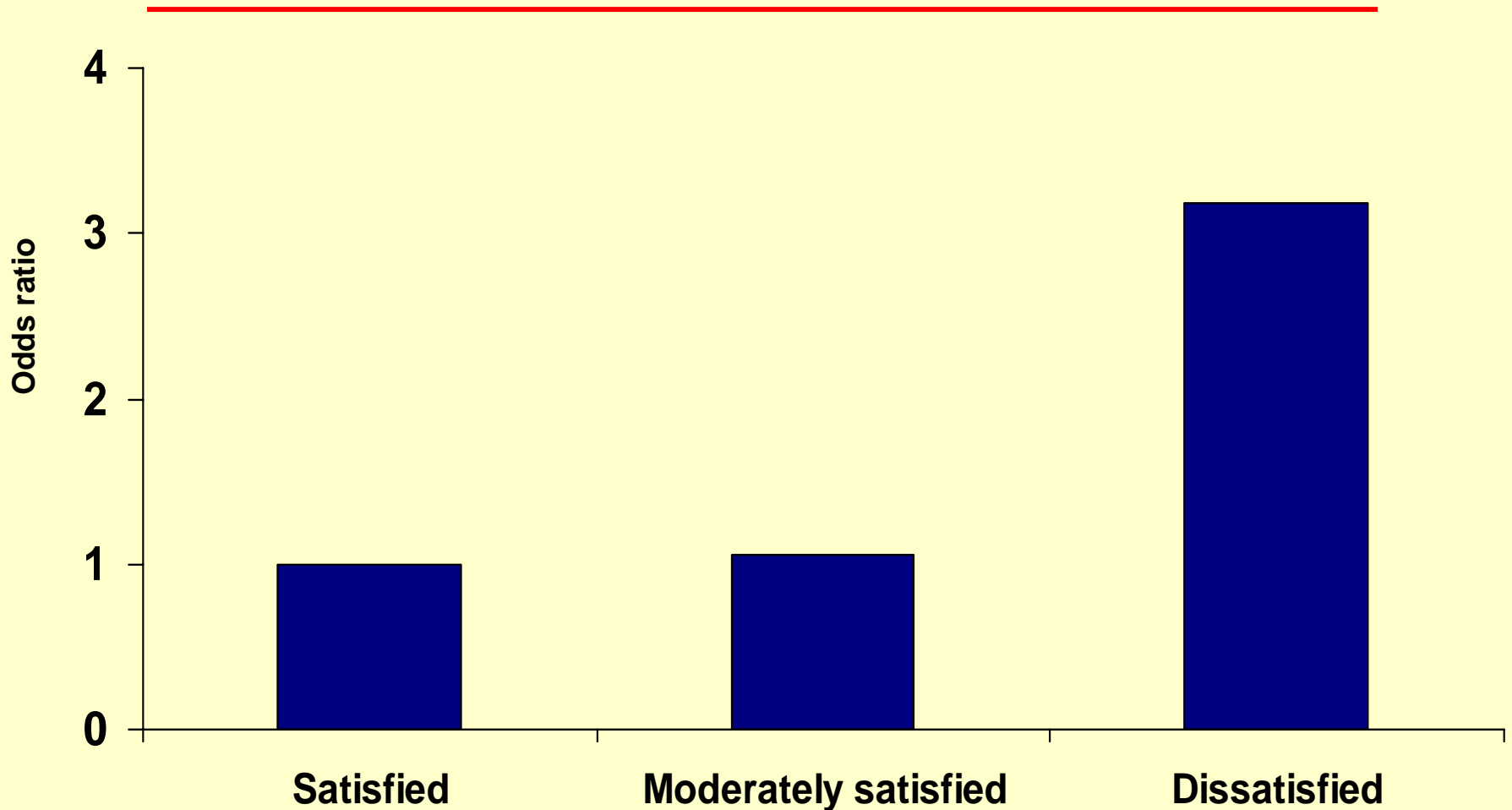
25 year follow-up, adjusted for age, sex, smoking
Physical activity, blood pressure, cholesterol, body mass

Metabolic syndrome markers (ATPIII)

Three or more of:

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

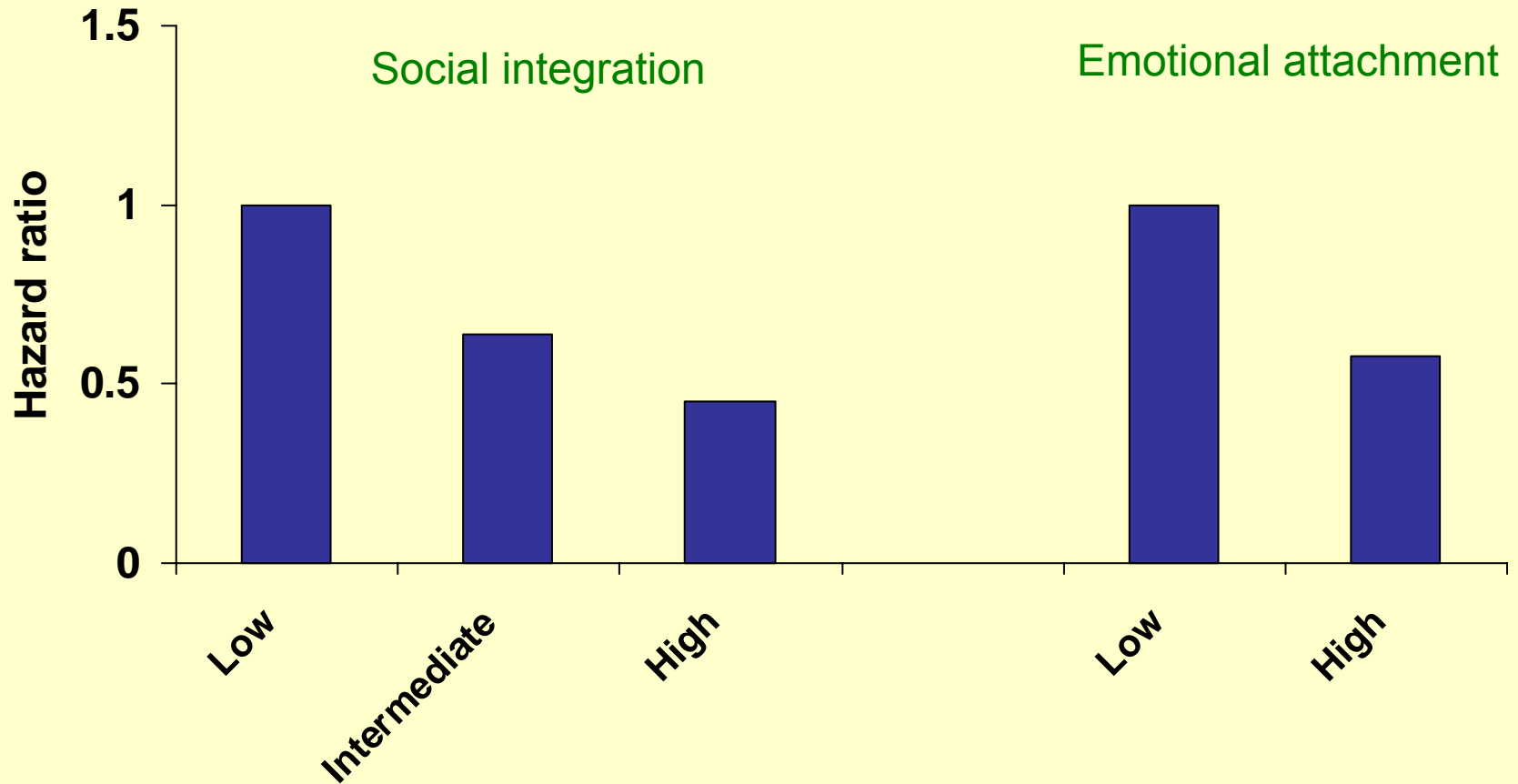
Marital satisfaction and the metabolic syndrome



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

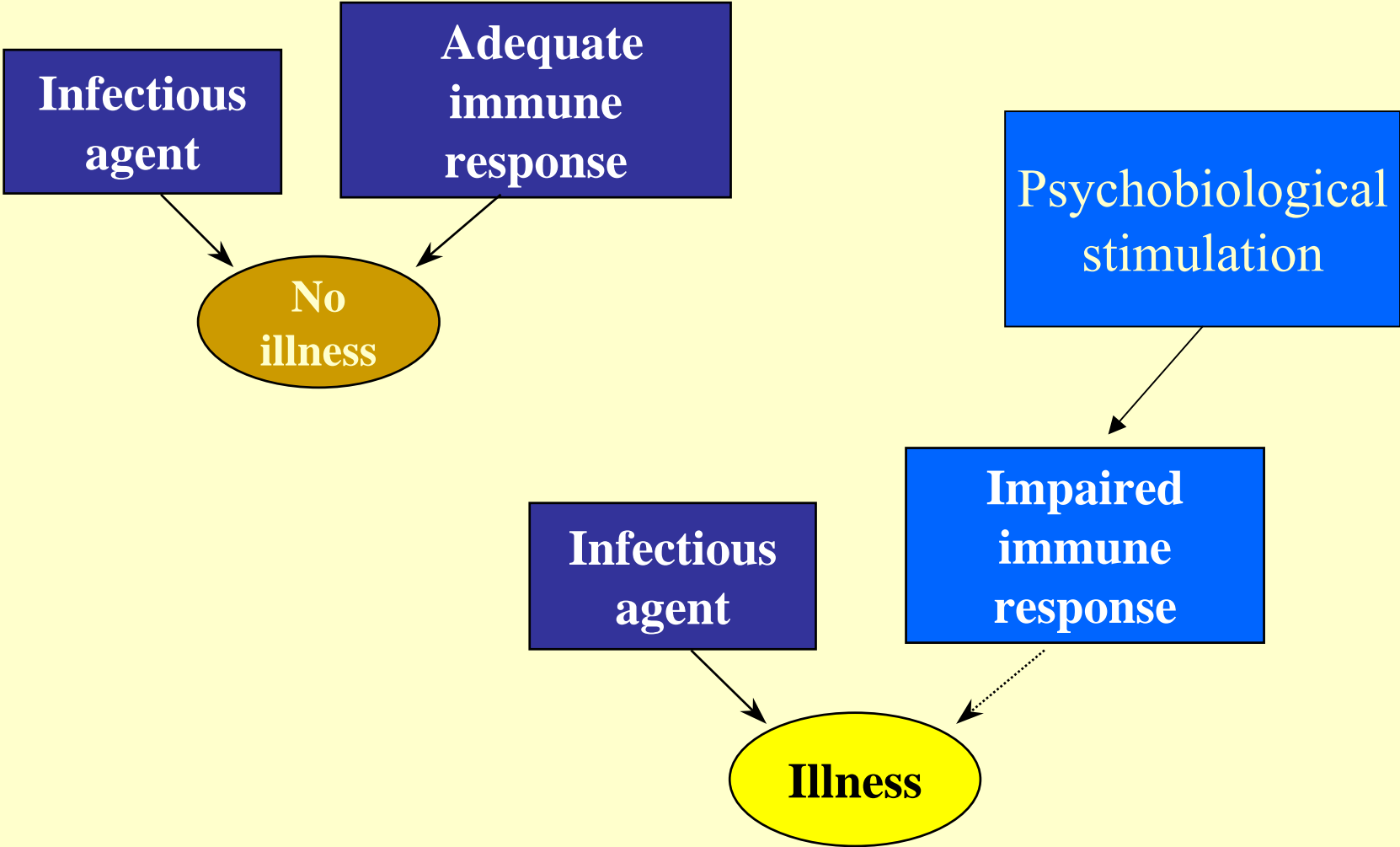
Troxel et al, 2005
Arch Intern Med

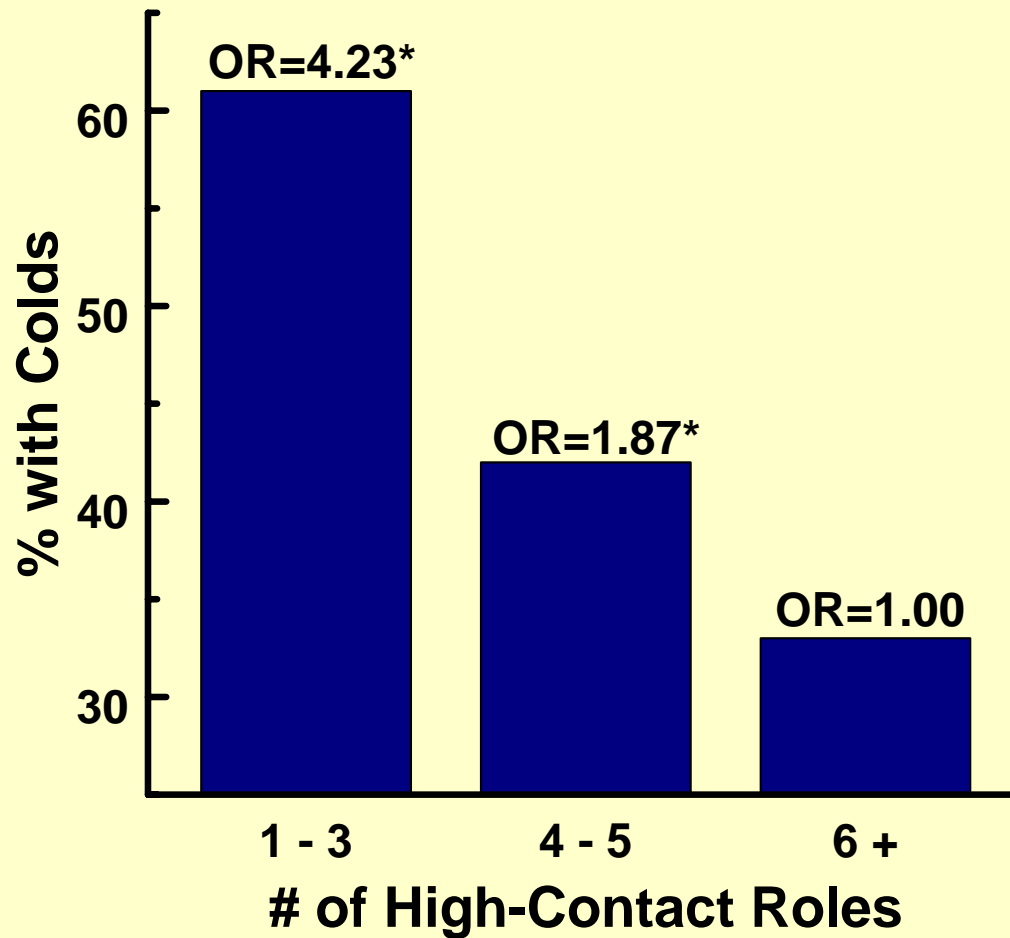
Social support and CHD



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

Psychobiology and Infection





(Odds ratios are adjusted for control variables.)

Cohen et al, *JAMA*, 1997

Depression and physical illness

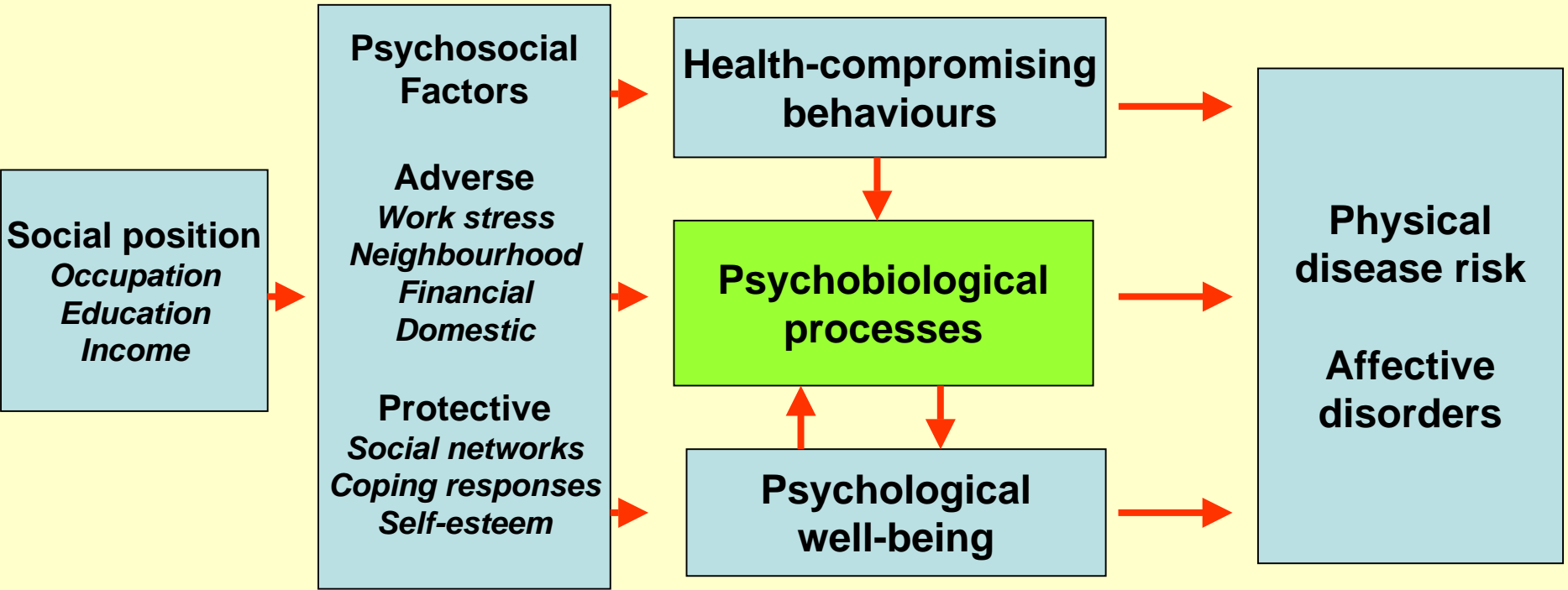
- Premature mortality
- Coronary heart disease
- Diabetes
- Disability
- Multiple sclerosis
- Rheumatic conditions
- Metabolic syndrome

Depression and Physical Illness
CUP, in press

Socioeconomic position and psychosocial factors

Lower socioeconomic position associated with

- Greater exposure to chronic stress (domestic, neighborhood)
- Greater financial strain
- Lower job control, higher job demands, effort-reward imbalance
- Greater social isolation and lower social support
- Lower sense of control
- Greater hostility
- Less use of active coping and planning responses
- More depressed mood, lower optimism



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Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies

Epidemiological surveys

- Large samples
- Disease endpoints
- Prospective designs

Fibrinogen

Inflammatory and thrombogenic factor

Increases blood viscosity, stimulates atherogenic cell proliferation, platelet aggregation

Associated with:

- Low SES
- Low control at work, high effort/reward imbalance
- Social isolation

Epidemiological surveys

- Large samples
- Disease endpoints
- Prospective designs

Single measures under resting conditions

Limited information about mechanisms

Confounding issues in psychosocial studies

Experimental studies

- **Stress-inducing 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;
Experimental conditions inducing low or high control, social support, etc

Laboratory mental stress testing

- Sophisticated biological measures
- Control of confounders
- Experimental manipulation of conditions

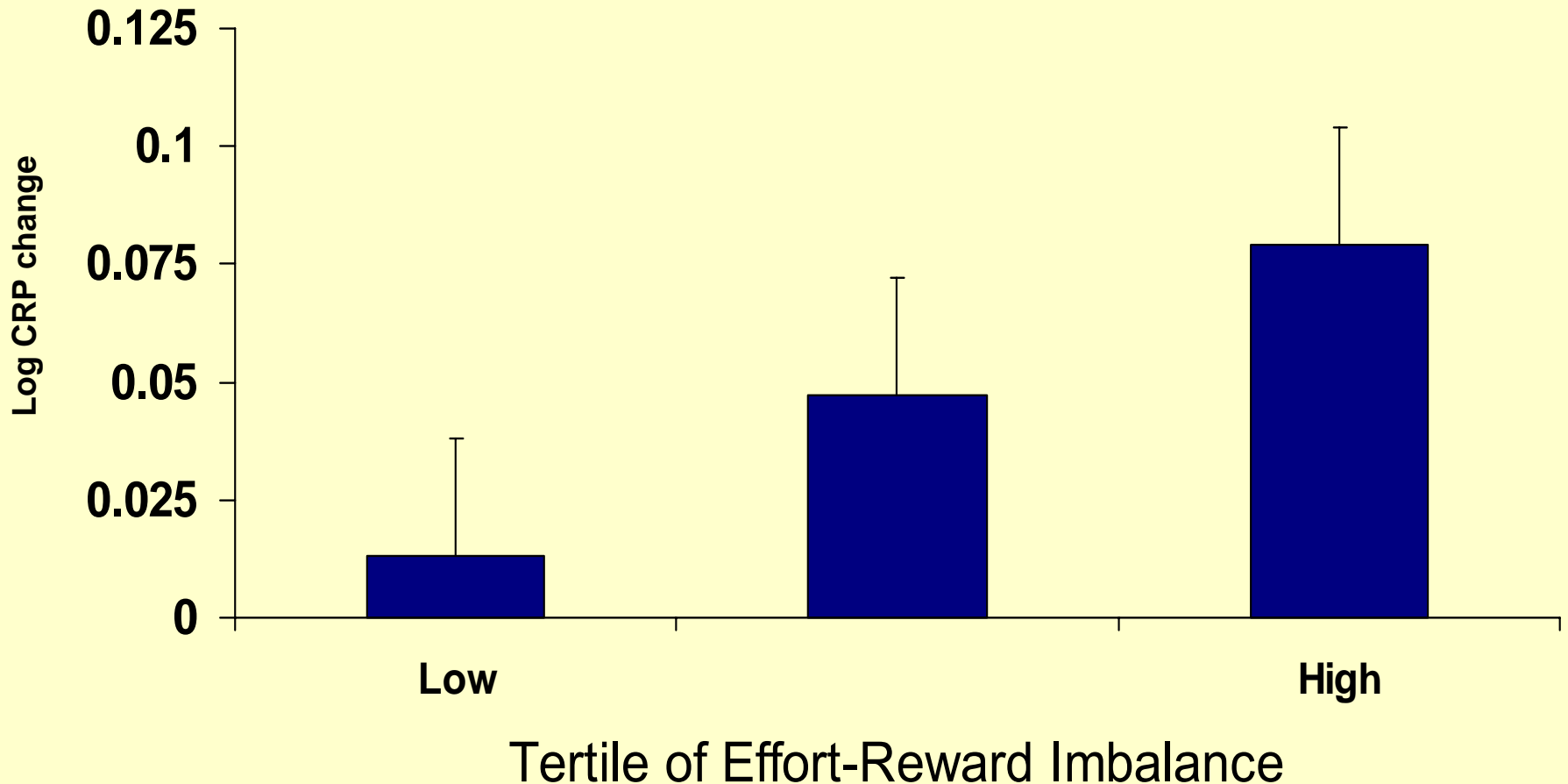
C-reactive protein

- 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

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

Psychobiological responses and SEP

Participants

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

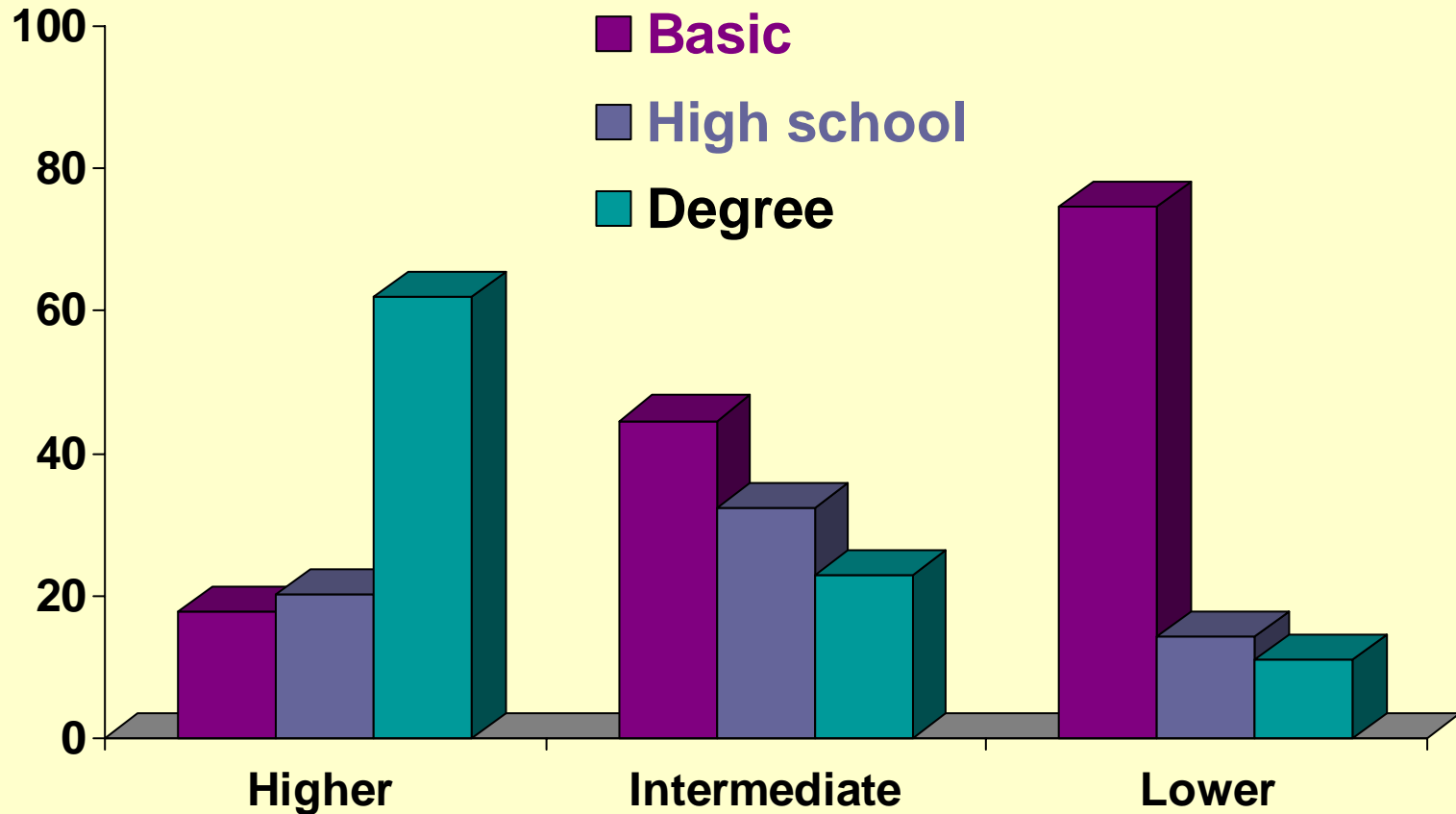
Sampled by grade of employment:

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

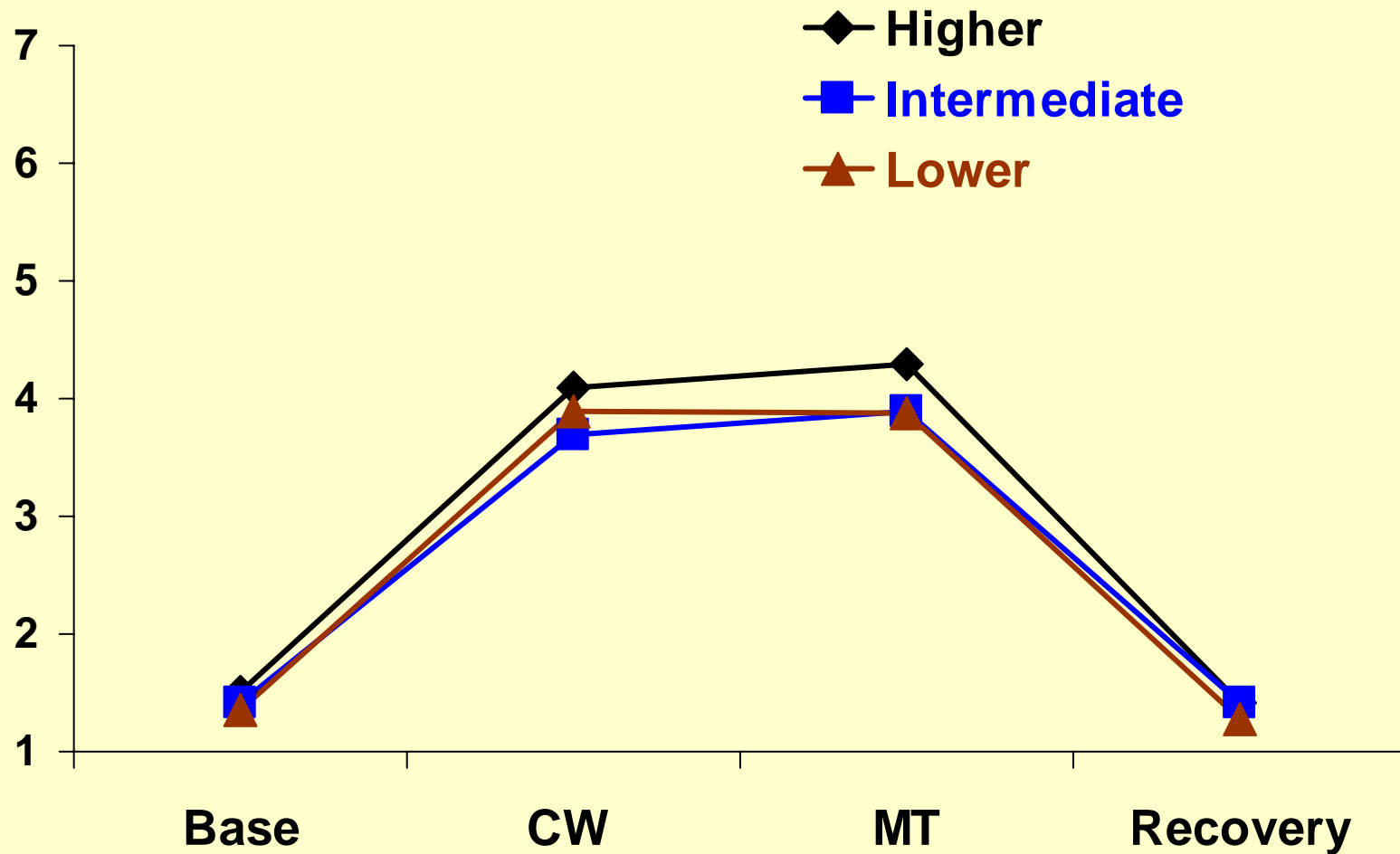
Conditions

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

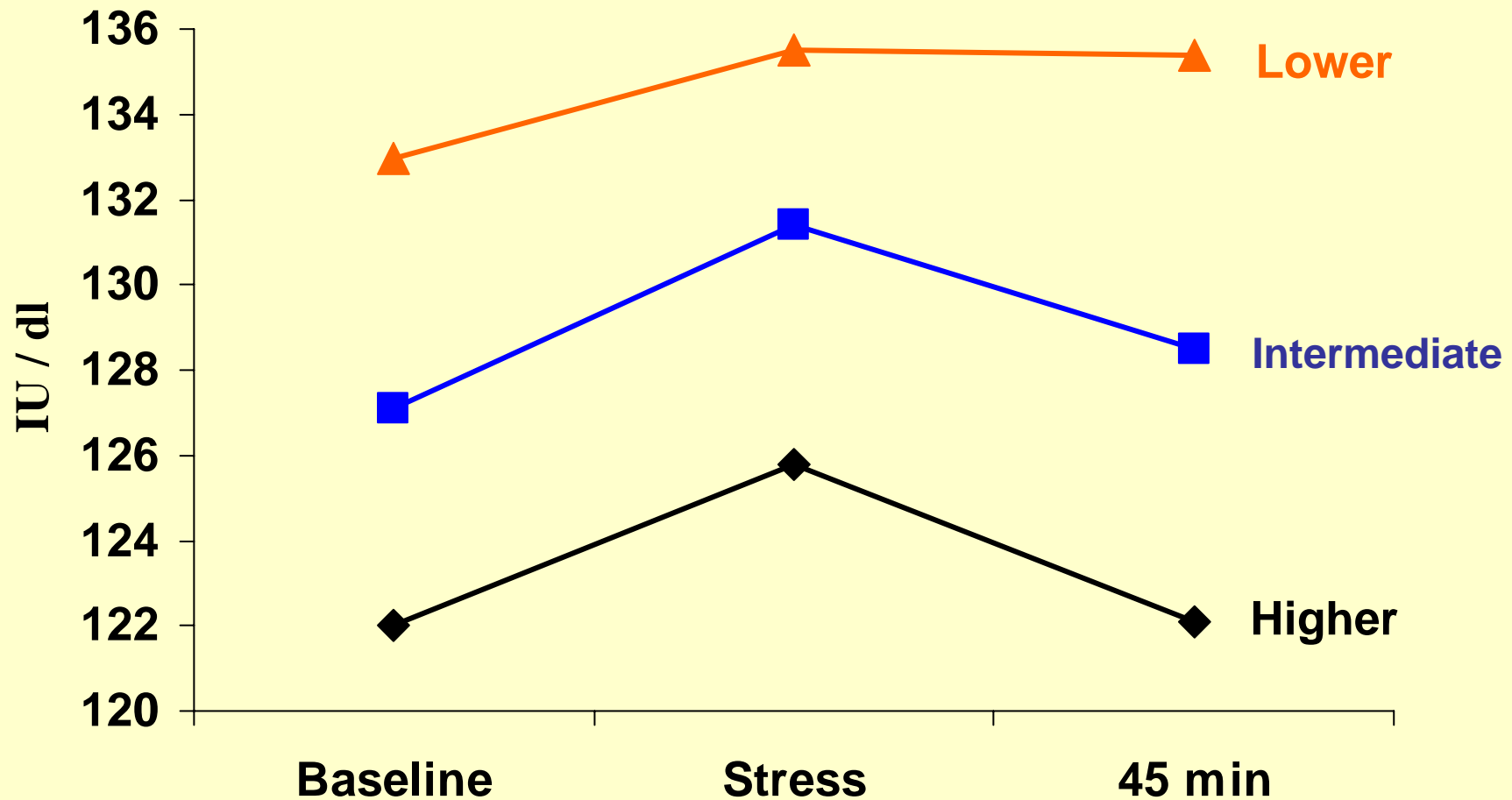
Occupational grade and education



Stress ratings by SEP



Factor VIII, Stress, and SEP



Step toe et al
Thromb Haemo, 2003

Laboratory mental stress testing

- Sophisticated biological measures
- Control of confounders
- Experimental manipulation of conditions

Small acute responses

Generalisation of acute responses into everyday life

Prediction of future health risk

Blood pressure reactivity and atherosclerosis

TABLE 3. Prediction of Mean/Maximum Carotid IMT and Plaque Scores From SBP Reactivity

Source Variable	Mean IMT		Maximum IMT		Plaque Score	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
Age	0.056	0.047	0.077	0.016	0.085	0.020
Education	-0.041	0.103	-0.042	0.158	-0.059	0.085
Triglycerides	-0.047	0.099	-0.023	0.474	-0.004	0.916
Fasting glucose	0.025	0.344	0.016	0.598	0.015	0.671
LDL cholesterol	0.032	0.211	0.037	0.211	0.069	0.041
HDL cholesterol	-0.025	0.377	-0.038	0.232	-0.056	0.127
Resting SBP	0.024	0.511	0.056	0.189	0.090	0.066
Resting DBP	0.041	0.070	0.050	0.226	0.046	0.334
Smoking status	0.087	0.001	0.104	<0.001	0.139	<0.001
Previous carotid measure	0.699	<0.001	0.586	<0.001	0.384	<0.001
SBP reactivity	0.059	0.026	0.084	0.006	0.093	0.008
Total <i>df</i>	12 675	...	12 675	...	12 675	...
<i>R</i> ² for model	0.583	...	0.453	...	0.268	...

Shows adjustment for cardiovascular risk factors and carotid measures taken 7 y earlier.

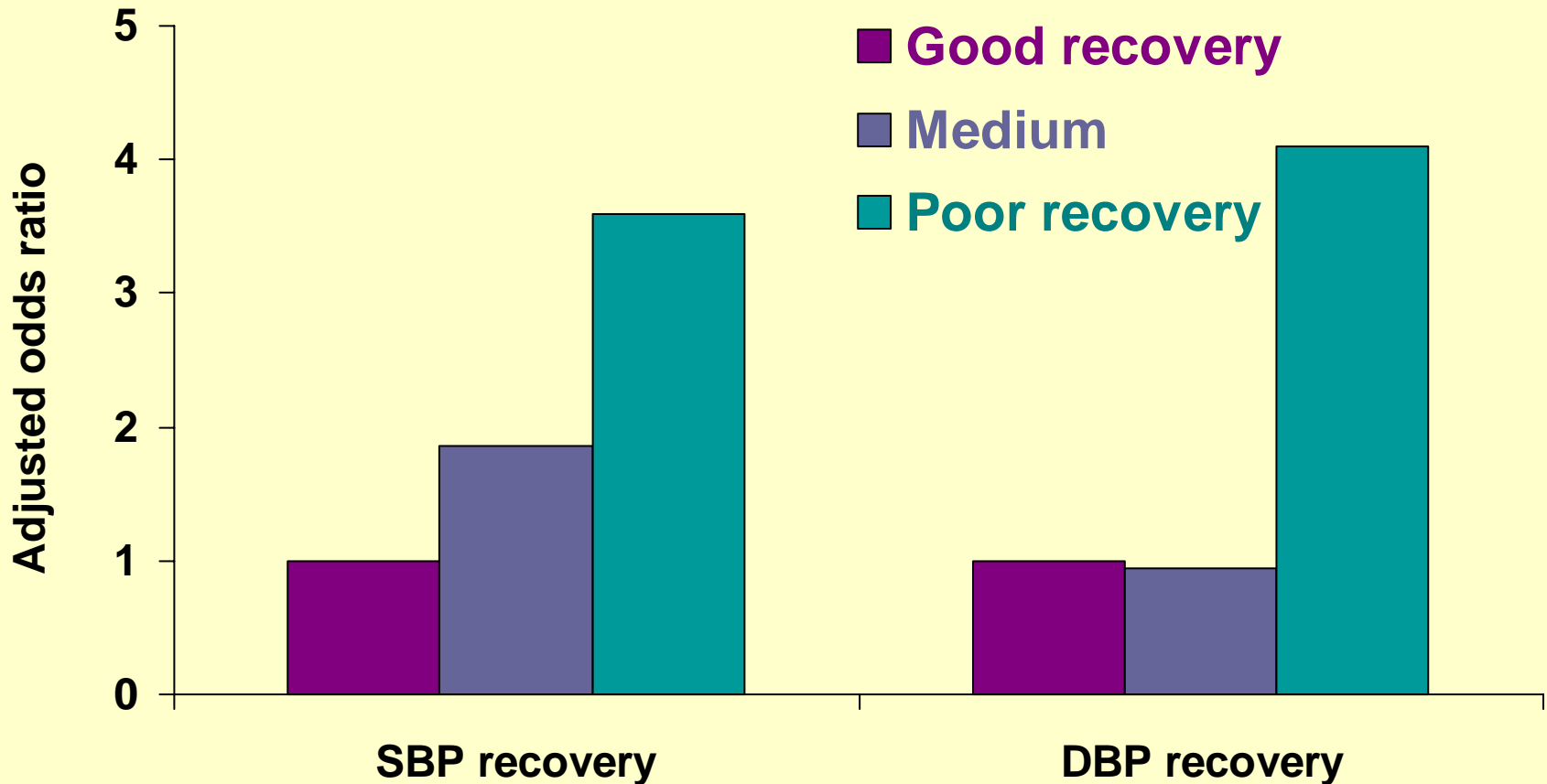
*Standardized β values.

Jennings et al
2004
Circulation

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)

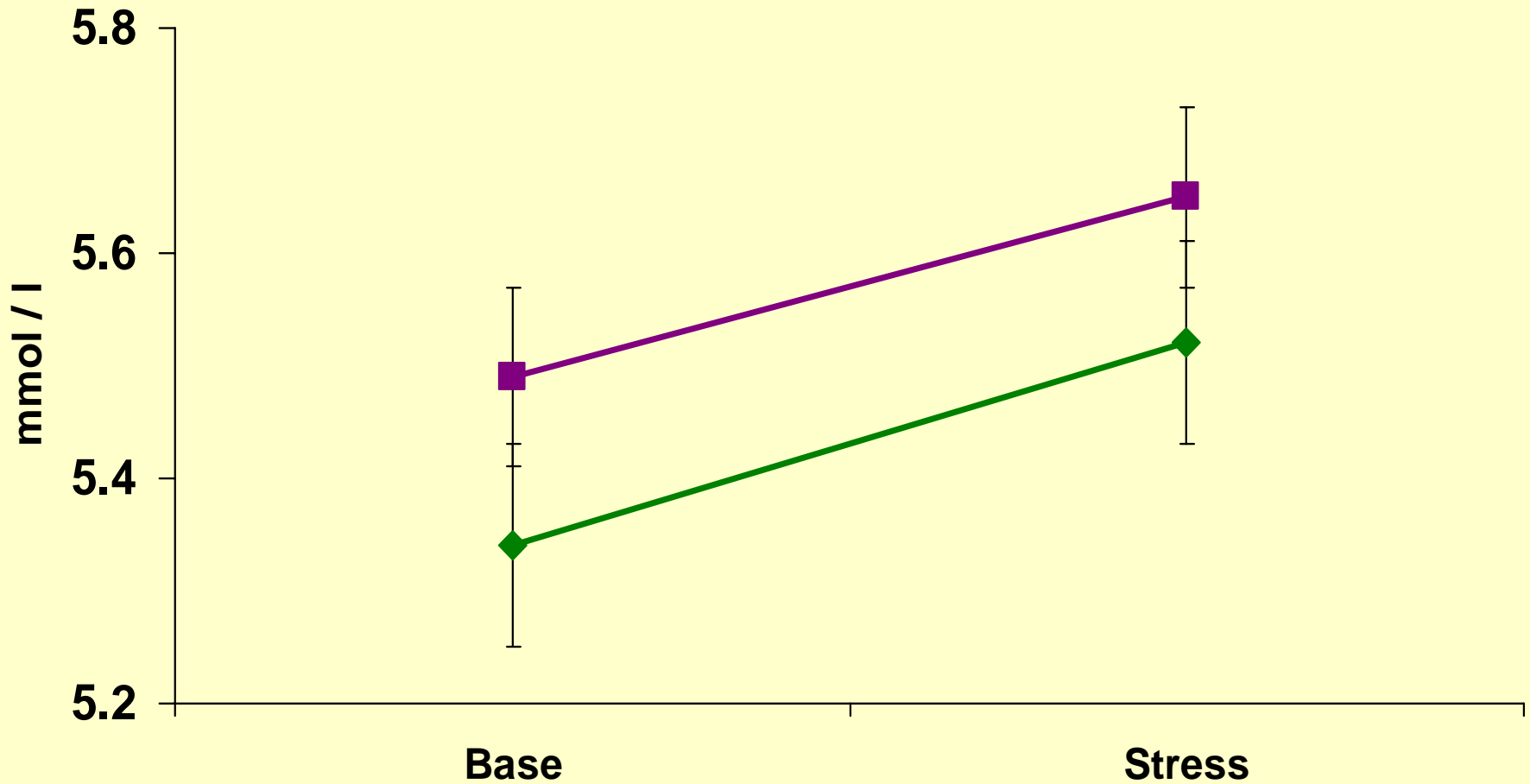
3 year systolic BP increase ≥ 5 mmHg



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

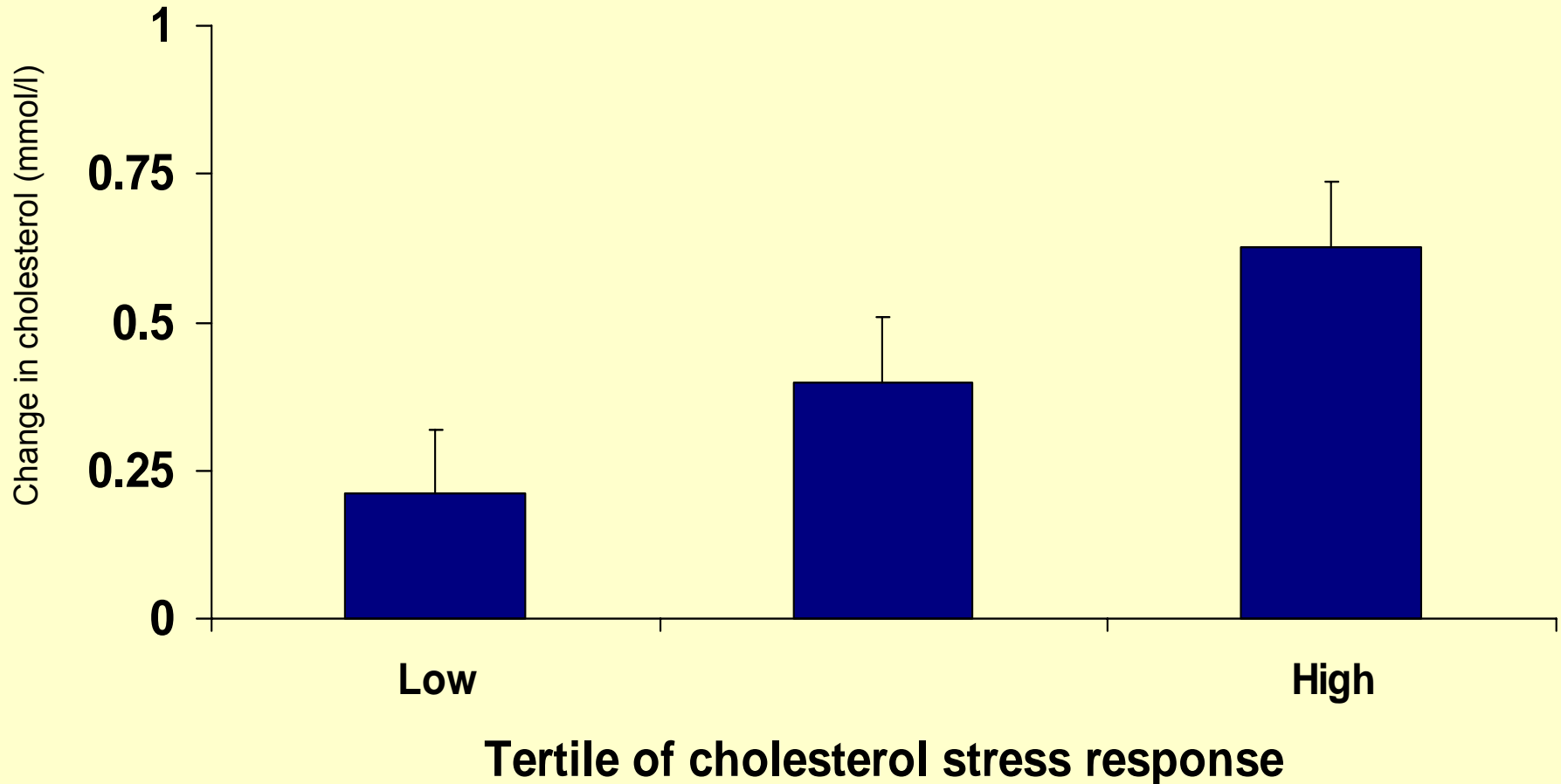
Steptoe & Marmot
J Hypertension, 2005

Cholesterol response to acute stress



Adjusted for socioeconomic status, age, body weight, smoking, alcohol, and haematocrit

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

Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies

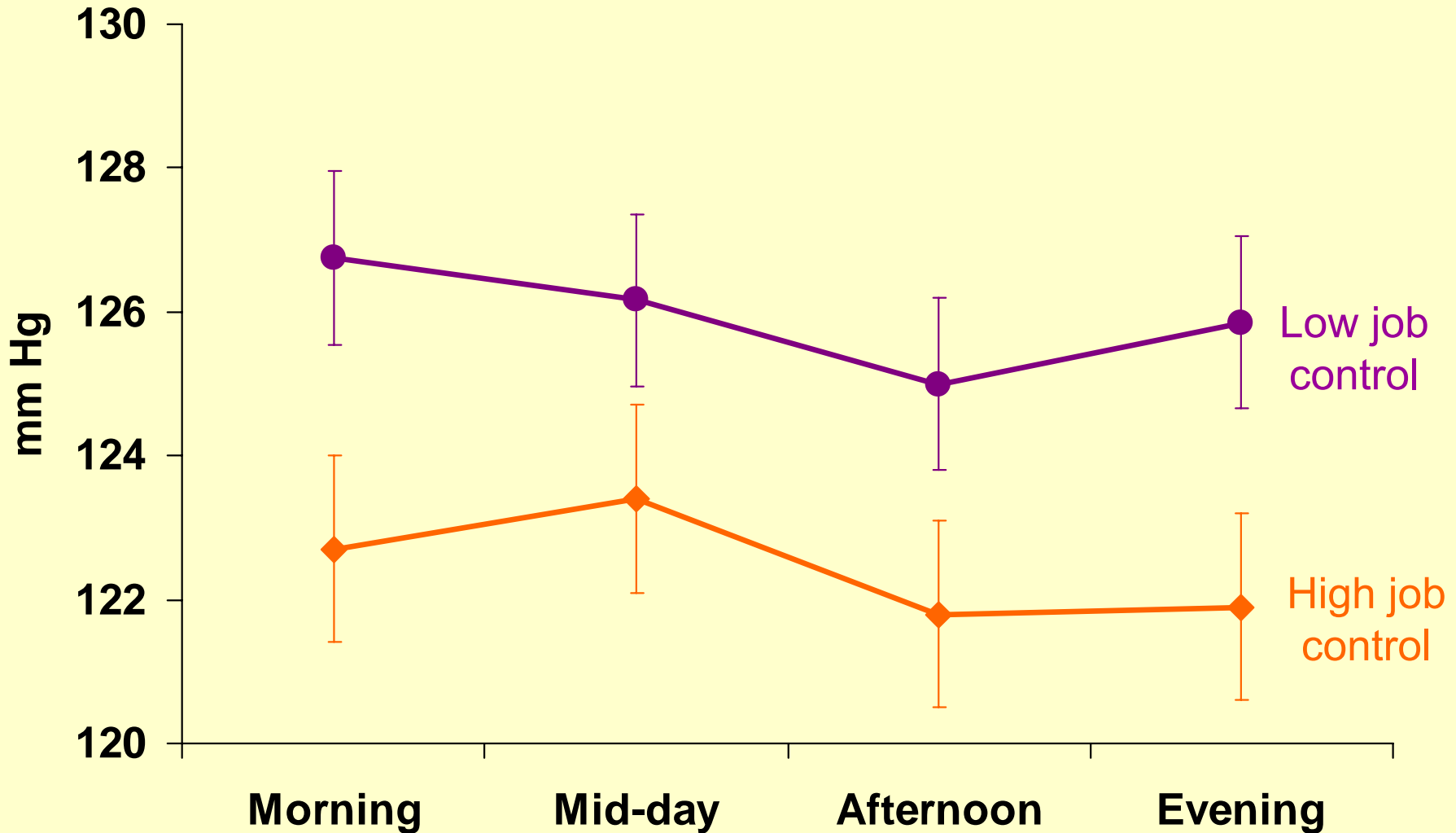
Naturalistic / ambulatory monitoring studies

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

Ambulatory blood pressure

Salivary cortisol

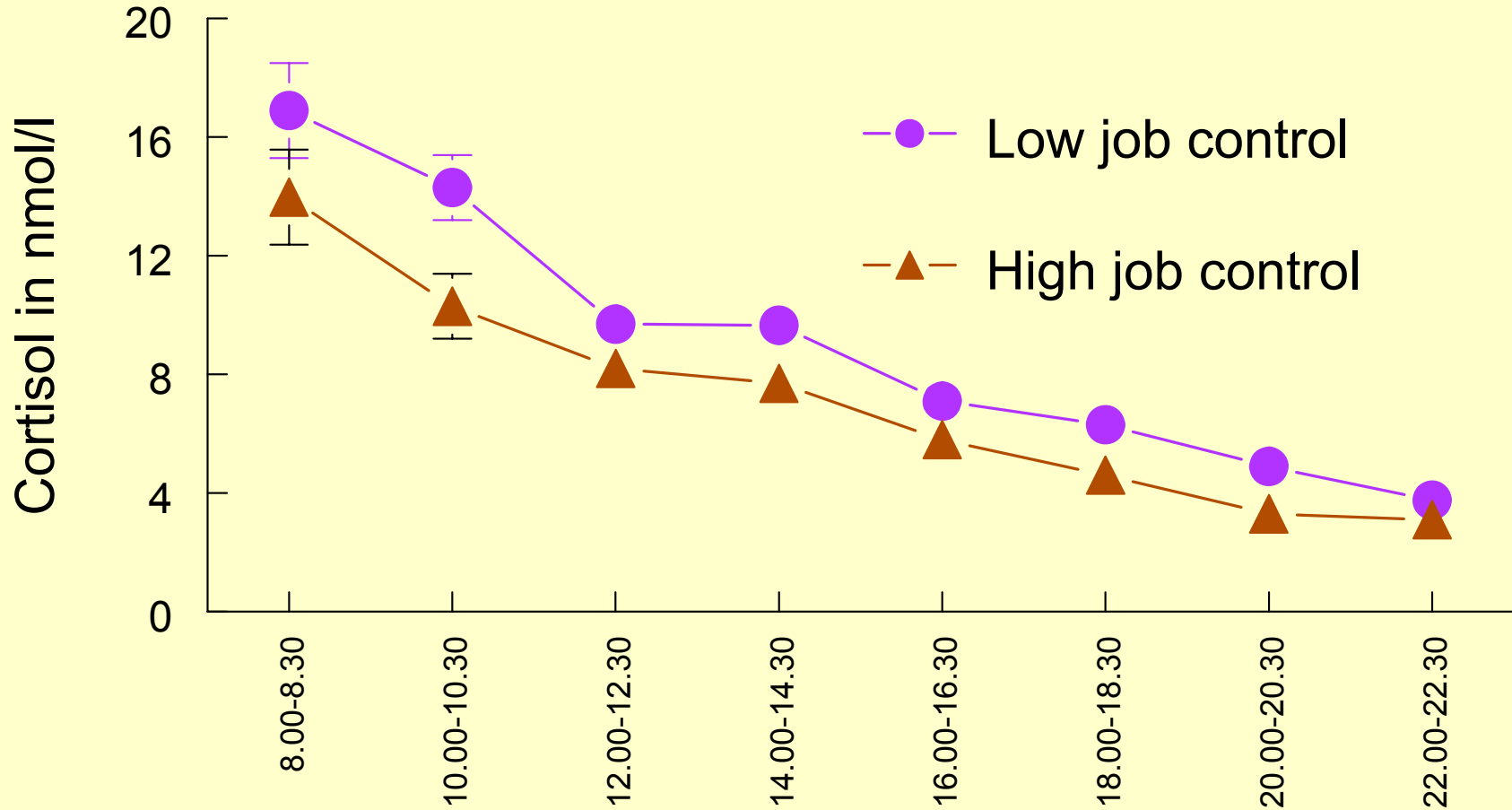
Ambulatory systolic pressure: working day



Adjusted for gender, age, occupational grade, smoking, bmi, and physical activity

Steptoe & Willemssen
J Hypertension, 2004

Cortisol and job control



Men, age-adjusted

Kunz-Ebrecht et al
Soc Sci Med, 2004

Naturalistic / ambulatory monitoring studies

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

Limited range of biological measures

Control for confounders

6 year risk of stroke in older men and women

Variable	Relative risk / <i>p</i>
• Positive affect	0.74 (0.62-0.88)
• Negative affect	1.01 (0.97-1.05)
• Age	0.004
• Education	0.08
• Smoking	0.008
• Previous heart attack	0.002
• Diabetes	0.001
• Blood pressure	0.001

10 year mortality in older men and women

Variable	Conditional hazard ratio
• Age \geq 75	1.78 (1.61-1.96)
• Male	2.12 (1.91-2.36)
• Unmarried	1.30 (1.17-1.50)
• Low education	1.22 (1.10-1.35)
• Cognitive impairment	1.64 (1.45-1.87)
• Functional impairment	2.07 (1.87-1.28)
• Low positive affect	1.12 (1.05-1.18)

Blazer & Hybels, *JAGS*, 2004

Psychobiology and Happiness

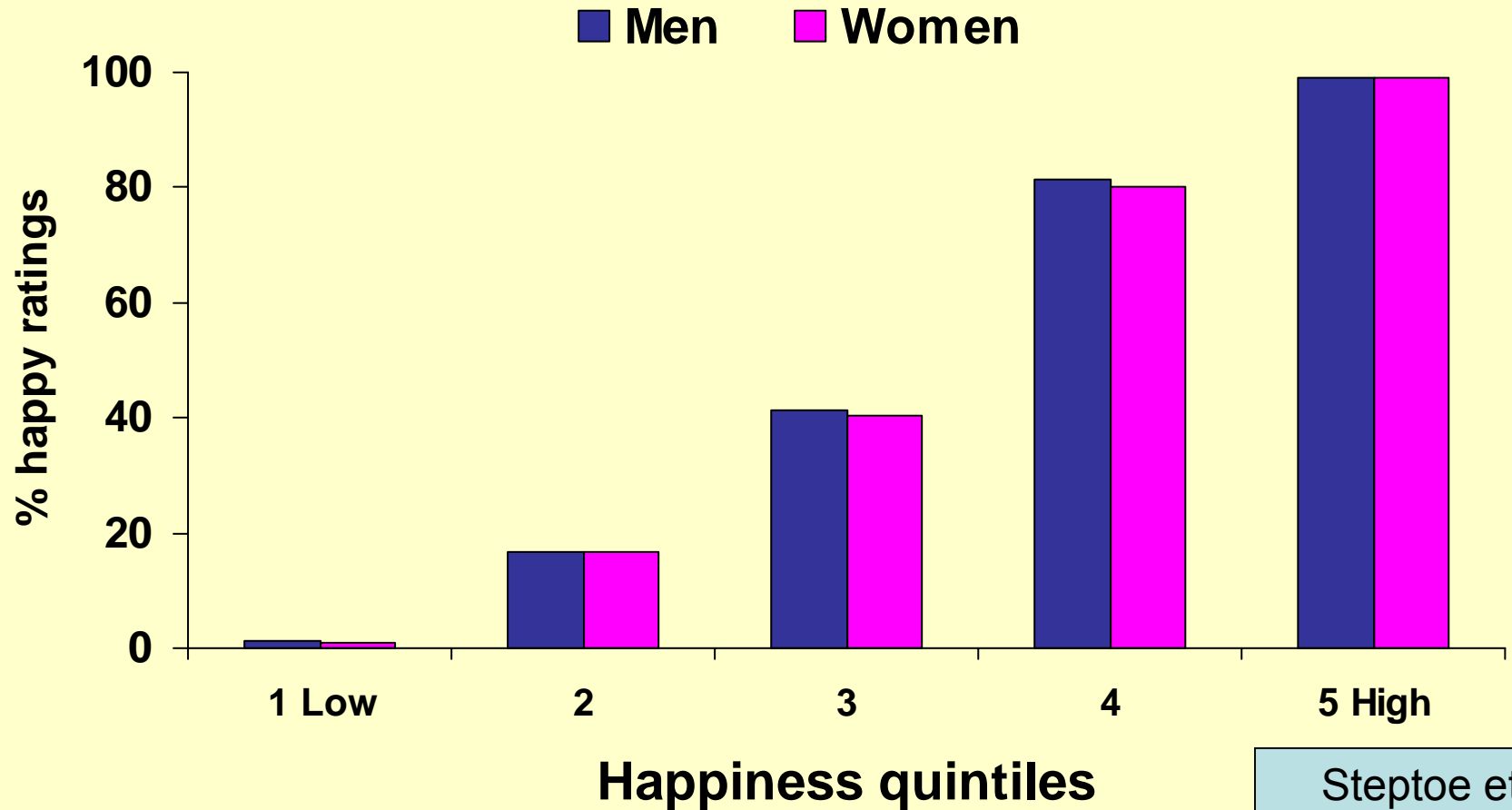
Aims

- To assess associations between happiness and psychobiological responses relevant to health and disease risk
- To determine whether associations of psychobiological responses and happiness are independent of negative emotional states

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)

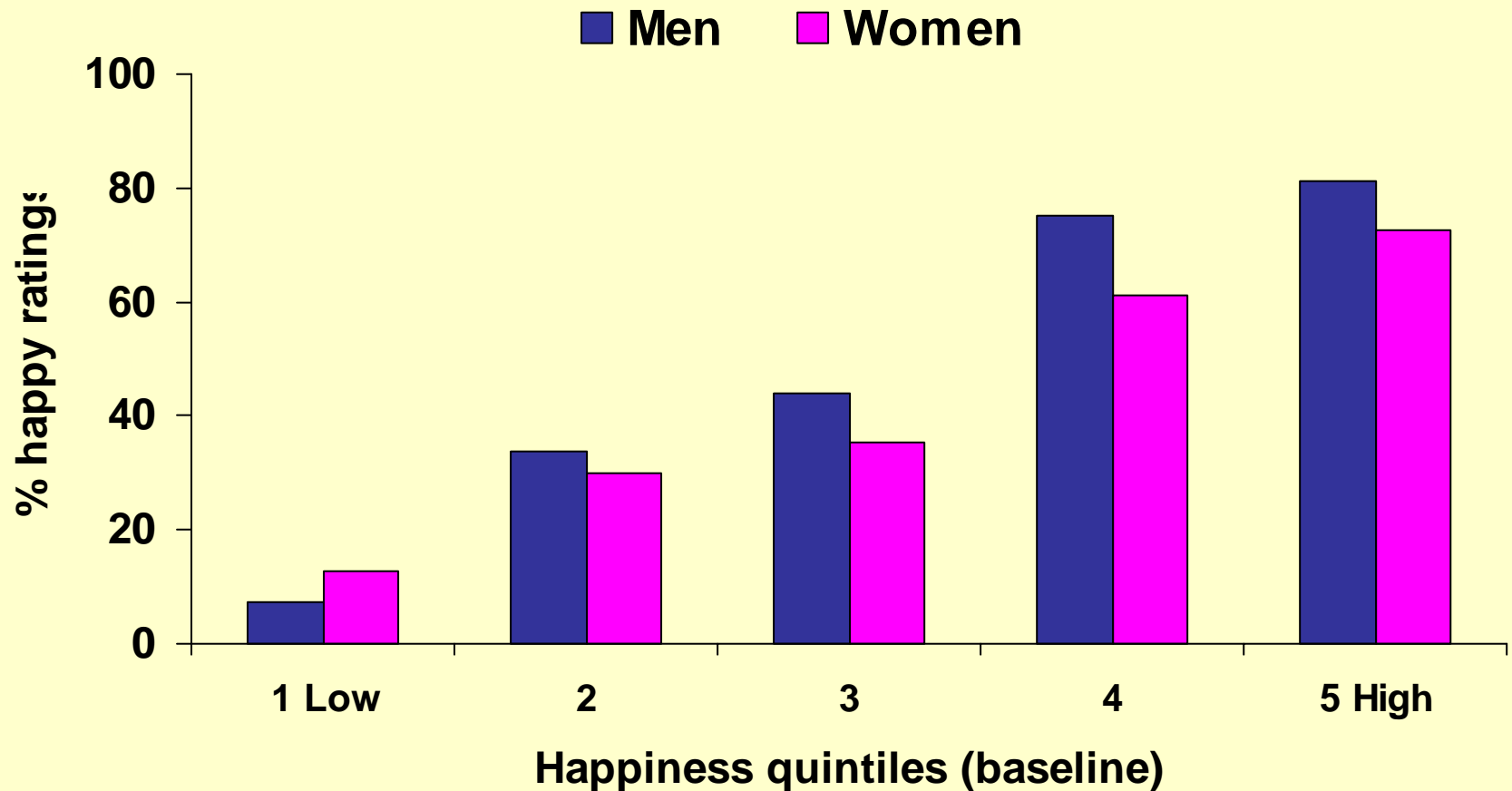
Adjusted for gender, age, occupational grade, smoking, bmi, and GHQ

Fibrinogen stress responses



Adjusted for gender, age, occupational grade, smoking, bmi, haematocrit, baseline fibrinogen, and GHQ

Happiness ratings - 3 years



Cortisol and happiness – 3 year



N = 144

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

Systolic BP and happiness – 3 year



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

Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies

Psychobiological measures:

- Cortisol
- Inflammatory markers: IL-6
- Heart rate variability

Cortisol:

- General marker of activation and associated with health outcomes
- Related to physical health outcomes, mental health (depression) and cognitive function (memory)
- Influenced by current and earlier life psychosocial factors
- Easy to measure in saliva, urine or blood

Cortisol and cognition:

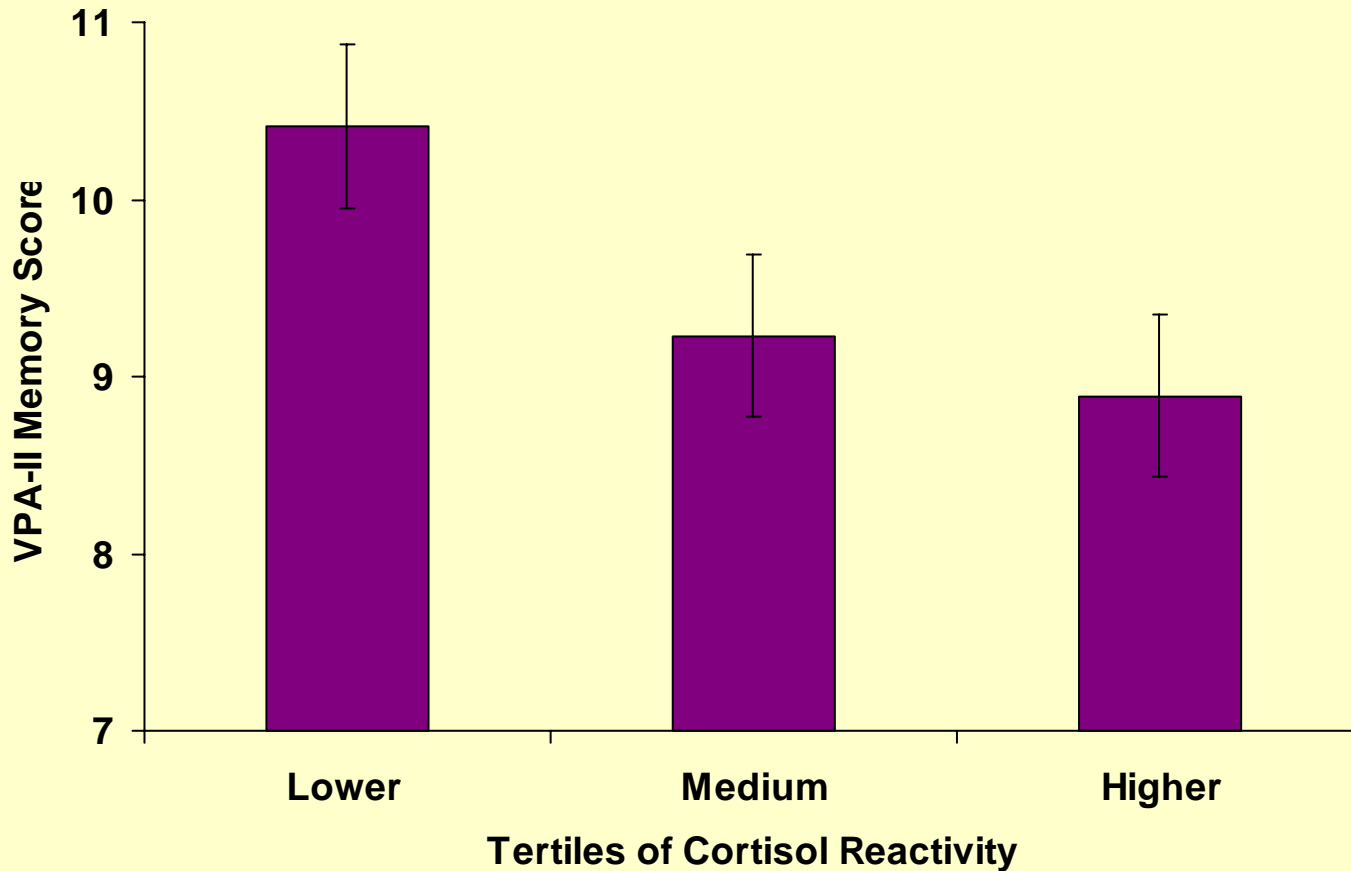
- Wide variation in natural cortisol levels
- In aging, some increase, others decrease cortisol levels
- High increases in natural levels with aging associated with impaired memory, smaller hippocampal volume

Lupien, PNEC, 2005

- General cognitive function associated with higher cortisol in older men

MacLulich, PNEC, 2005

Acute cortisol reactivity and memory in old age



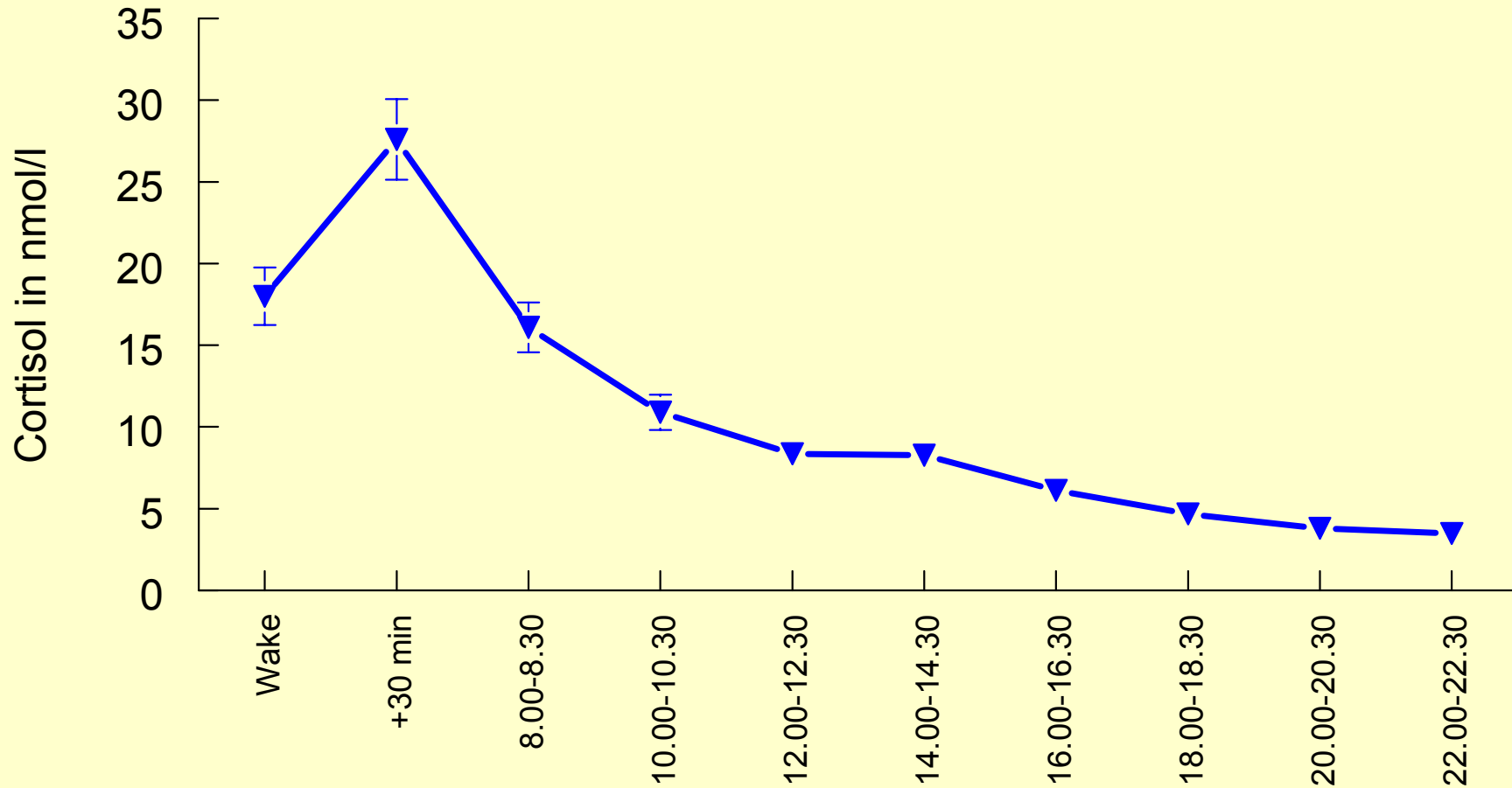
Adjusted for age, gender, education, chronic illness, medication, baseline cortisol and time of day

Wright et al,
PNEC, 2005

Problems of interpretation of cortisol data:

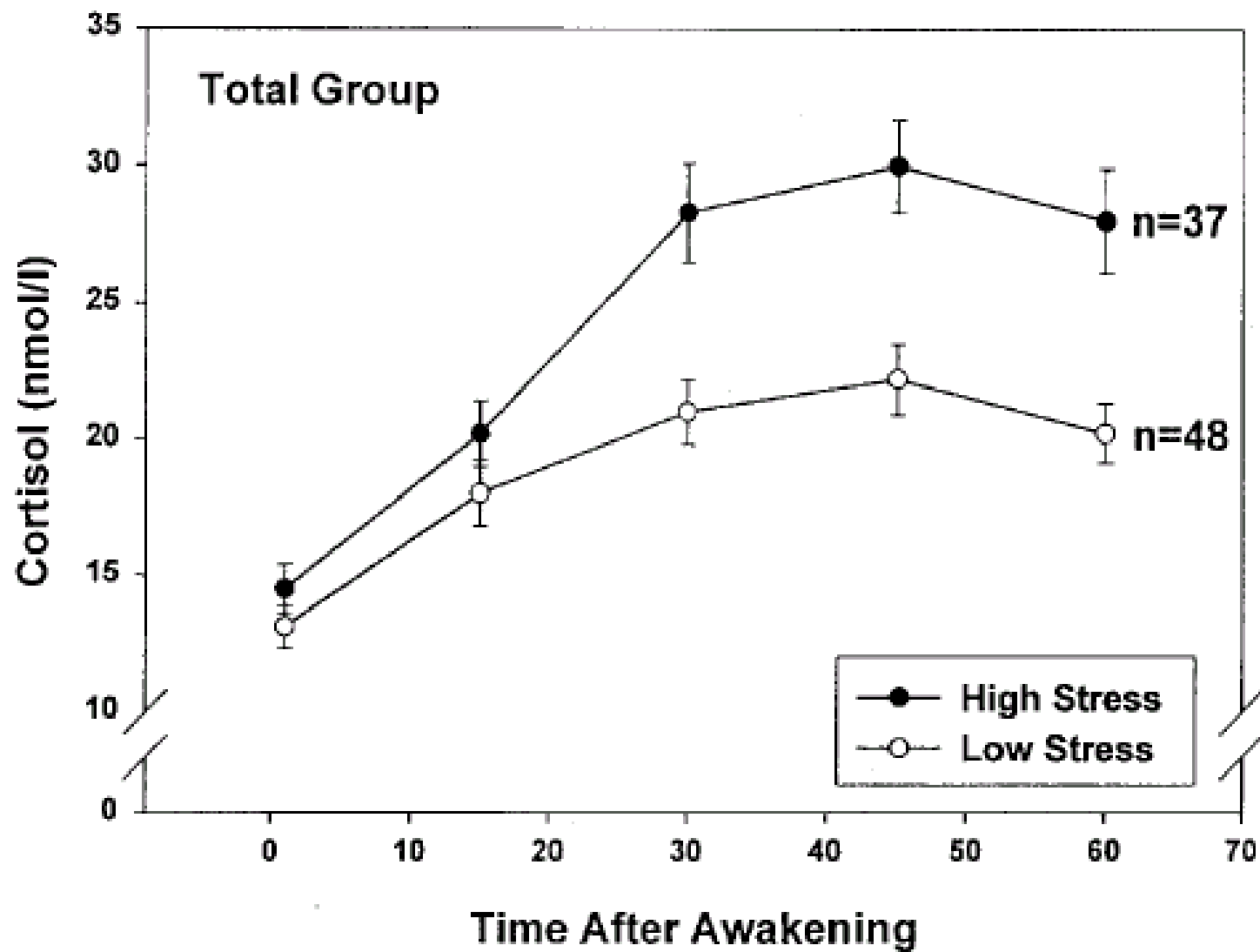
- Variation over the day; single readings of limited value

Cortisol profile over working day

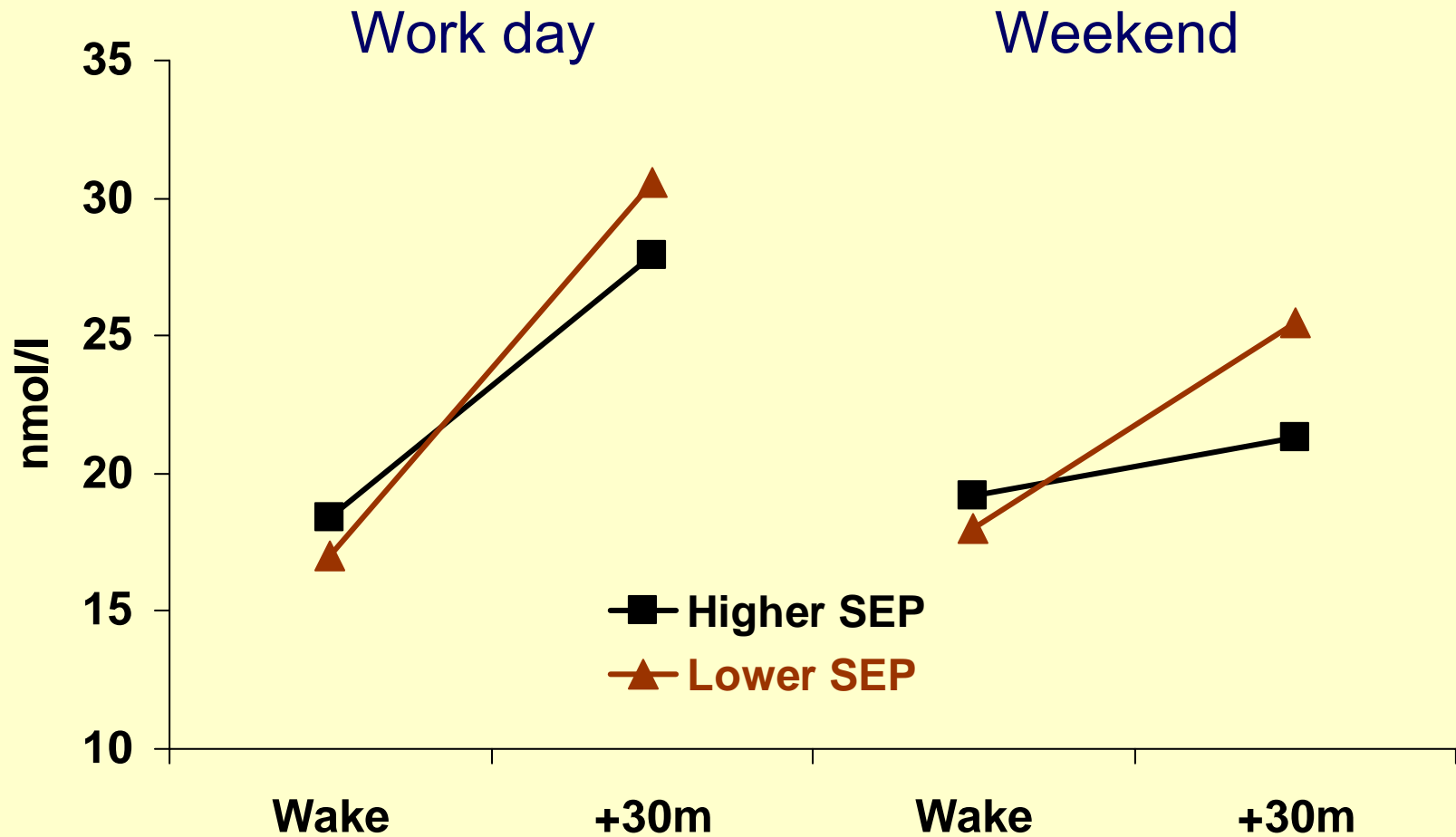


Problems of interpretation of cortisol data:

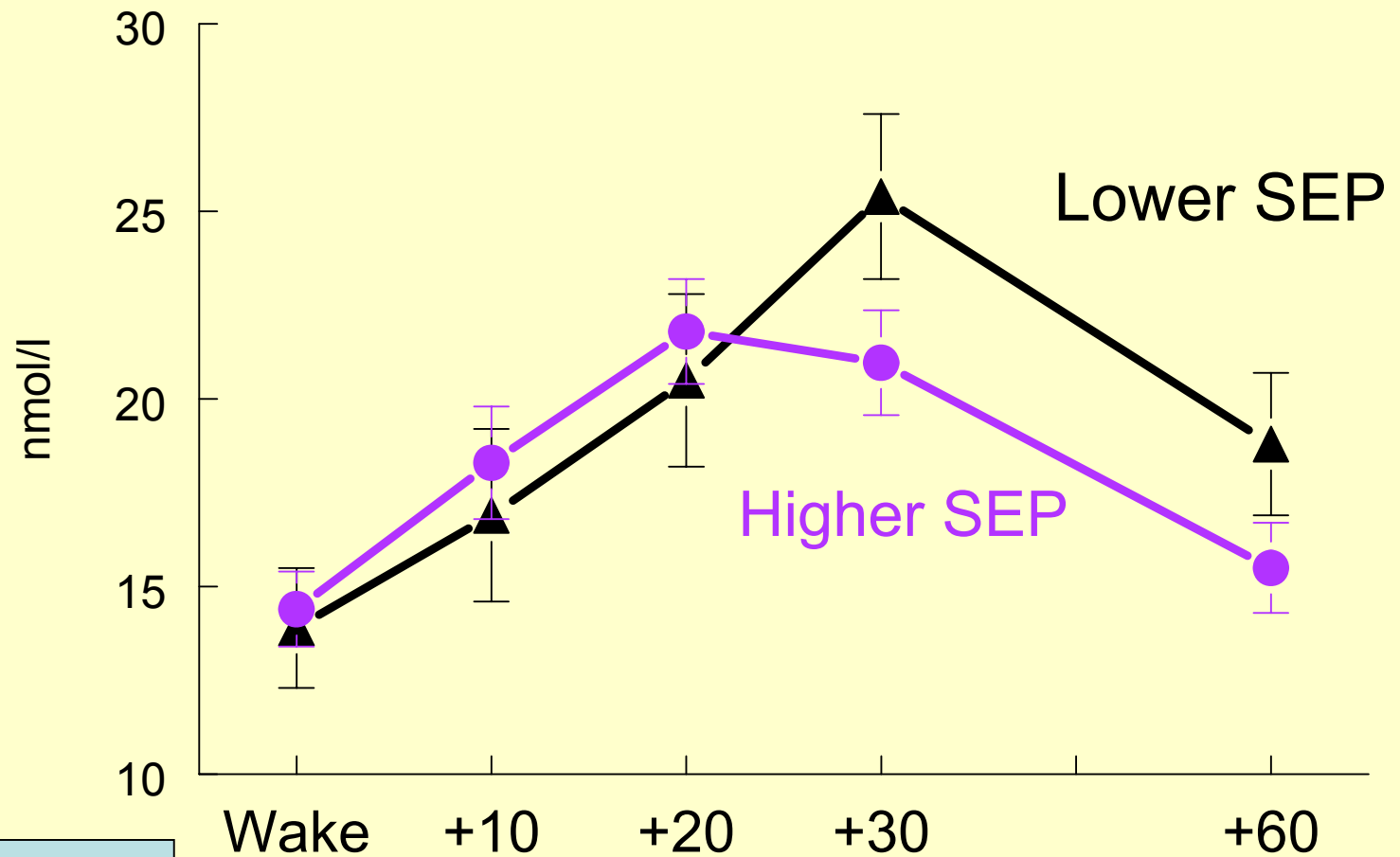
- Variation over the day; single readings of limited value
 - Cortisol awakening response
 - Levels over the day, slope



Cortisol waking response



Cortisol waking response



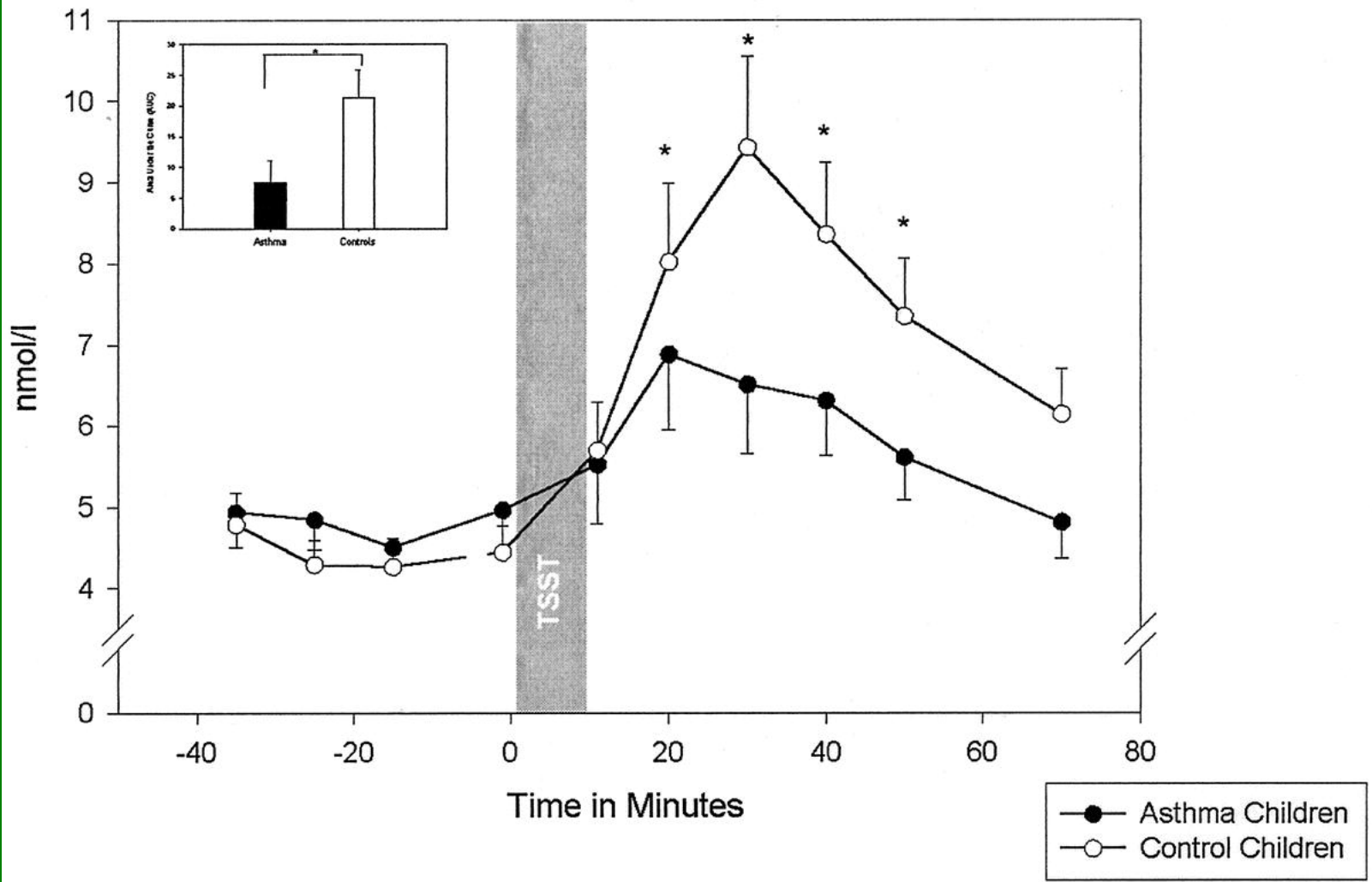
Cortisol waking response

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)

Problems of interpretation of cortisol data:

- Variation over the day; single readings of limited value
- Which is bad – high or low level?



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)

Cortisol and recent trauma:

- 190 low income women from urban Michigan
- Samples in clinic, on waking, 30 min after waking, and before bed
- 12 month exposure to trauma (assault, rape, car crash, sudden death of close friend etc)

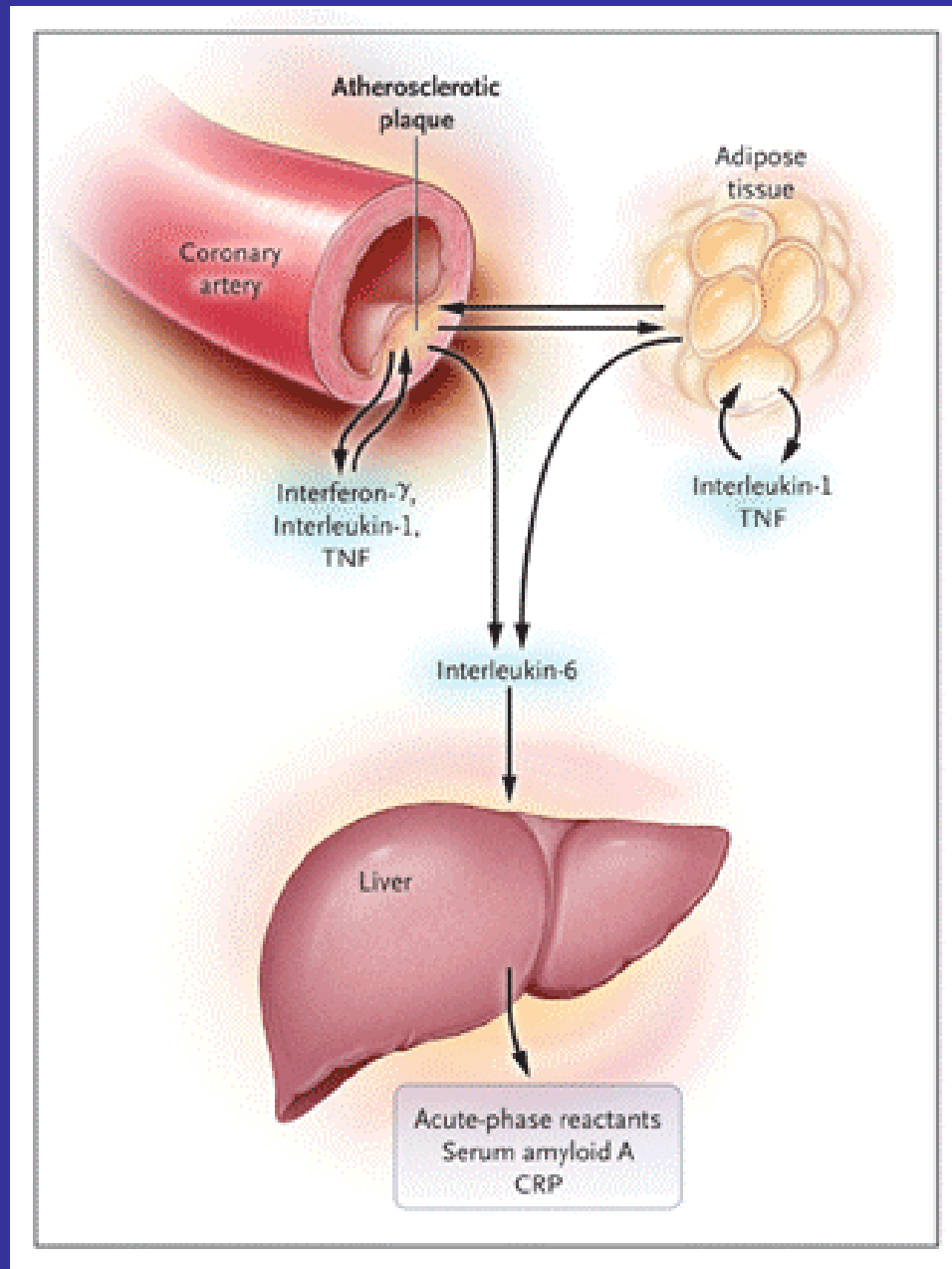
Young et al, Biol Psychiatry, 2004

Cortisol and recent trauma:

- 163/190 clinic
- 170/190 waking
- 173/190 second morning
- 166/190 bedtime samples
- Second morning sample very late in more than a third
- Pooled data used

Inflammatory markers

- C-reactive protein
- Interleukin 6 (IL-6)
- Fibrinogen
- Tumor necrosis factor alpha

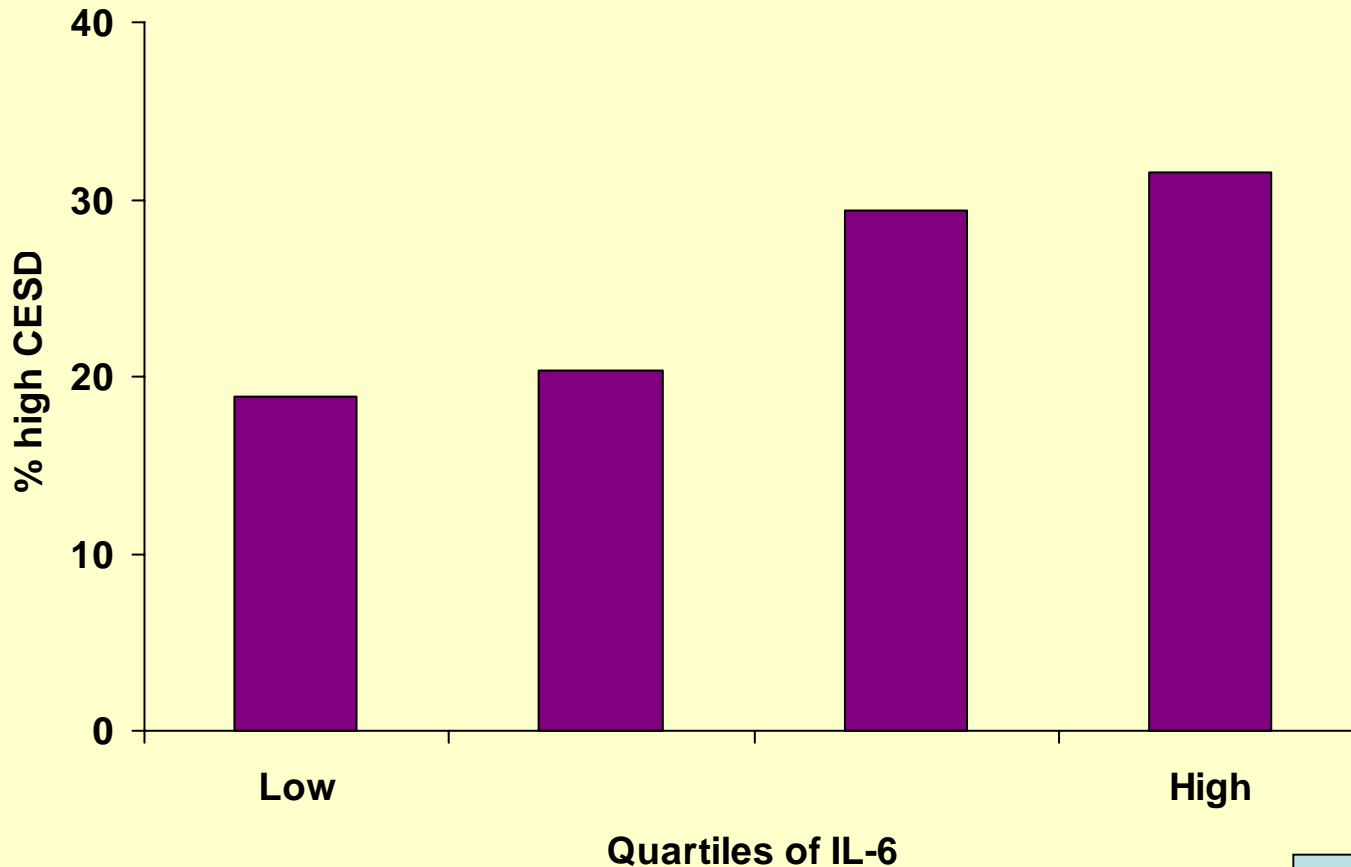


Interleukin 6

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

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

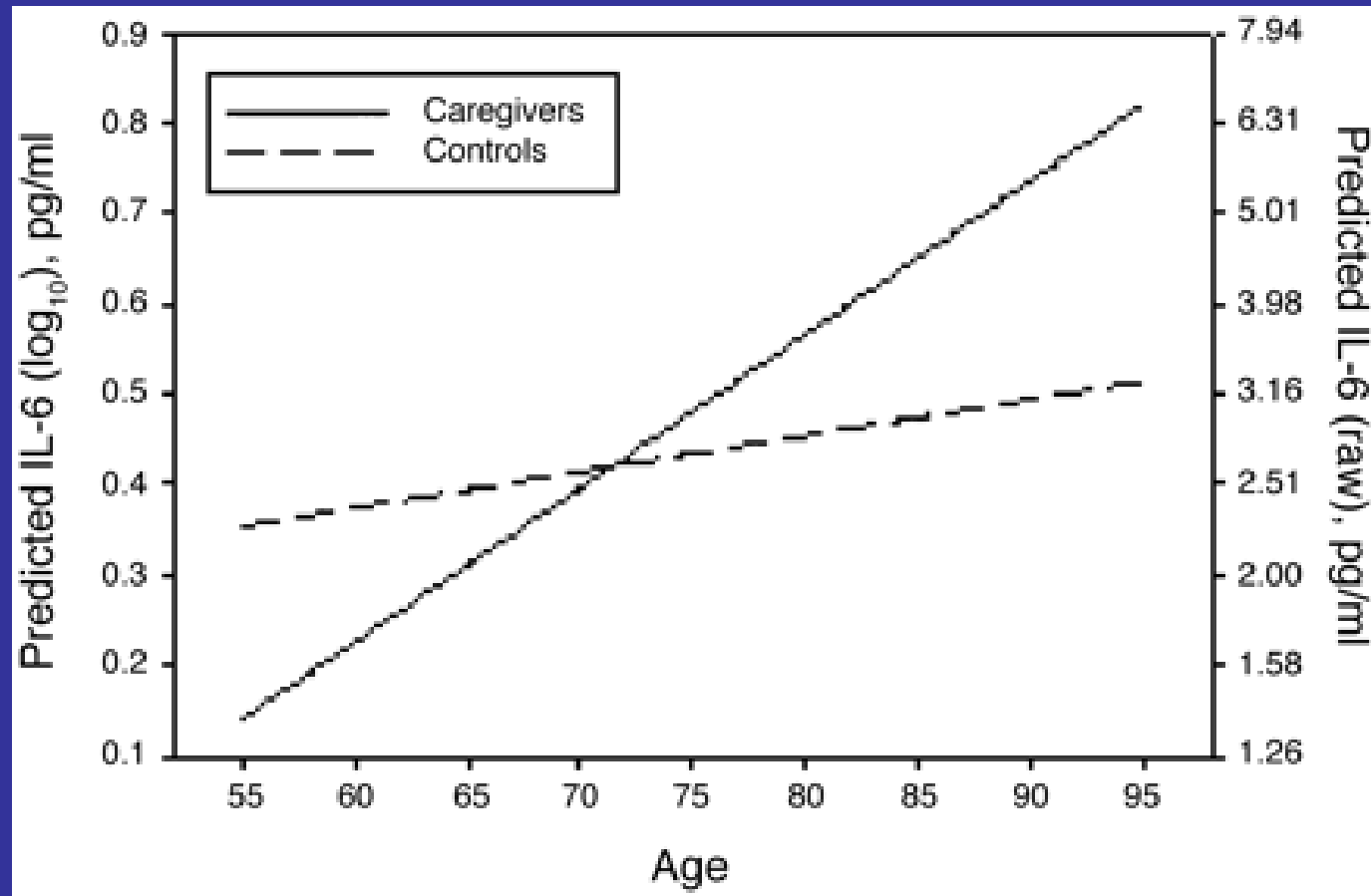
Interleukin 6

An 'endocrine' cytokine associated with

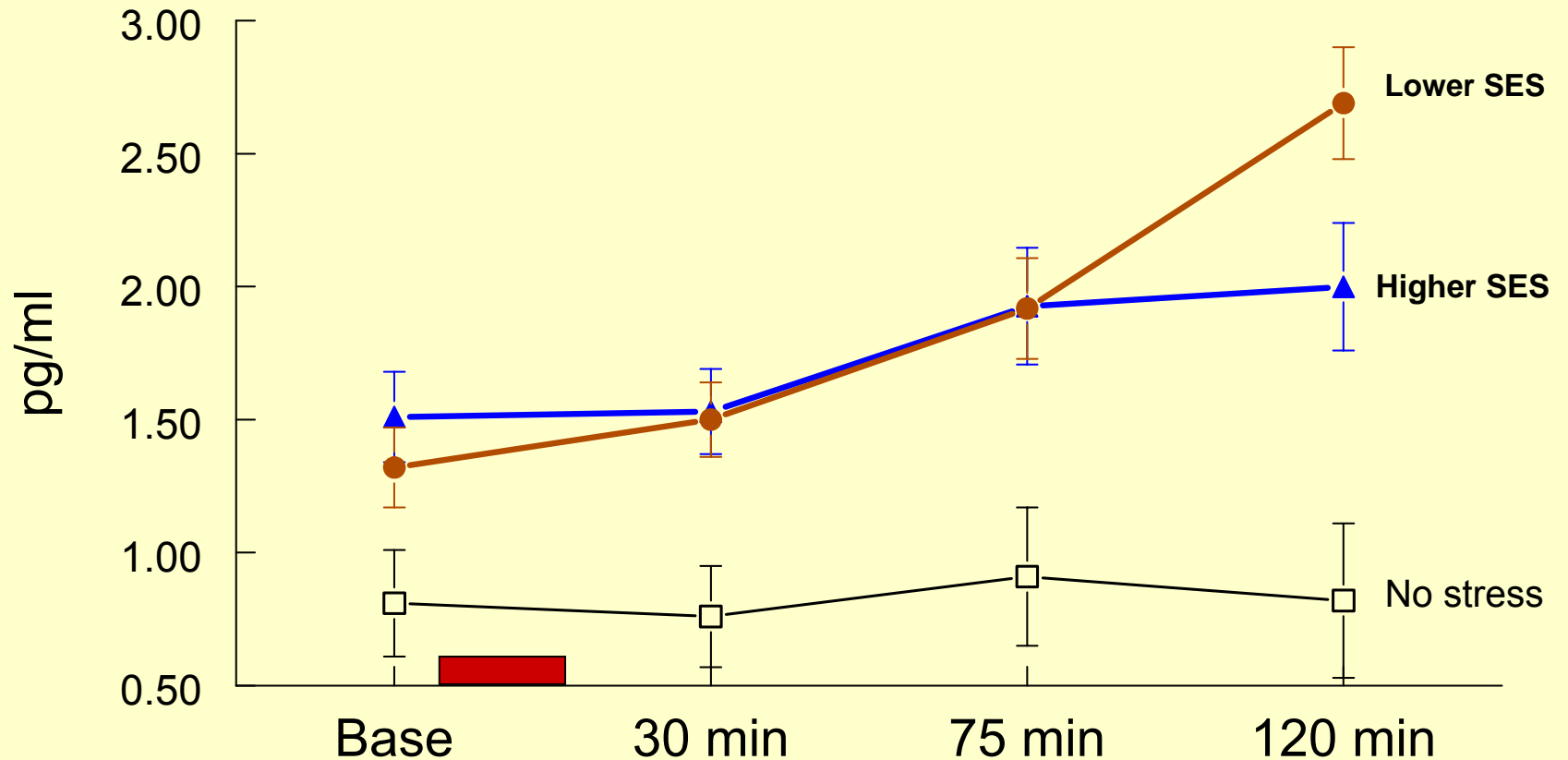
- Coronary heart disease
- Type 2 diabetes, insulin resistance
- Depression
- Disability

- Sensitive to acute and chronic stress

Caregiver stress and plasma interleukin-6



Stress and plasma interleukin-6



Brydon et al
Brain, Behav Immun, 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:

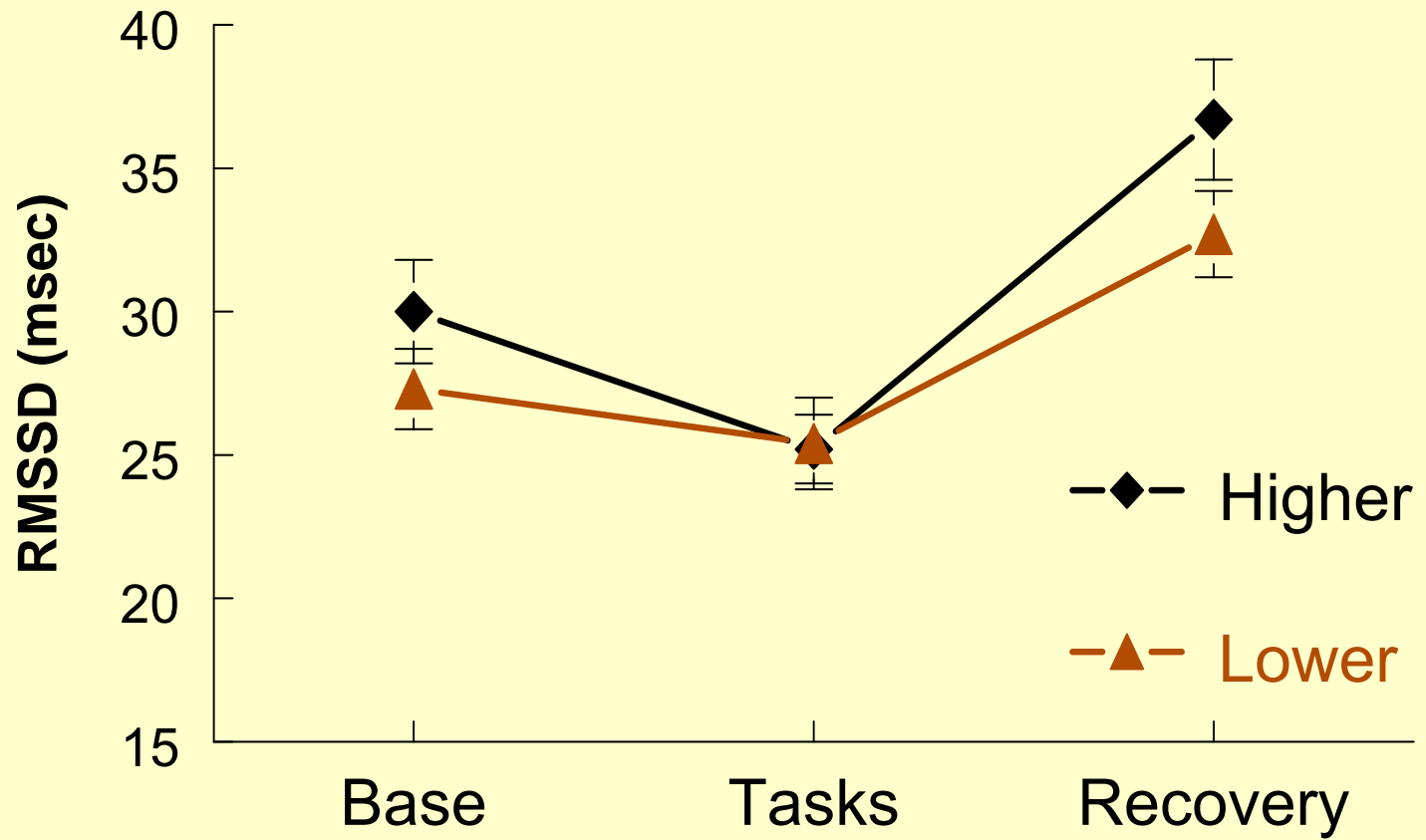
- Low employment grade
- Lower job control
- Smoking, inactivity, high alcohol intake
- Metabolic syndrome

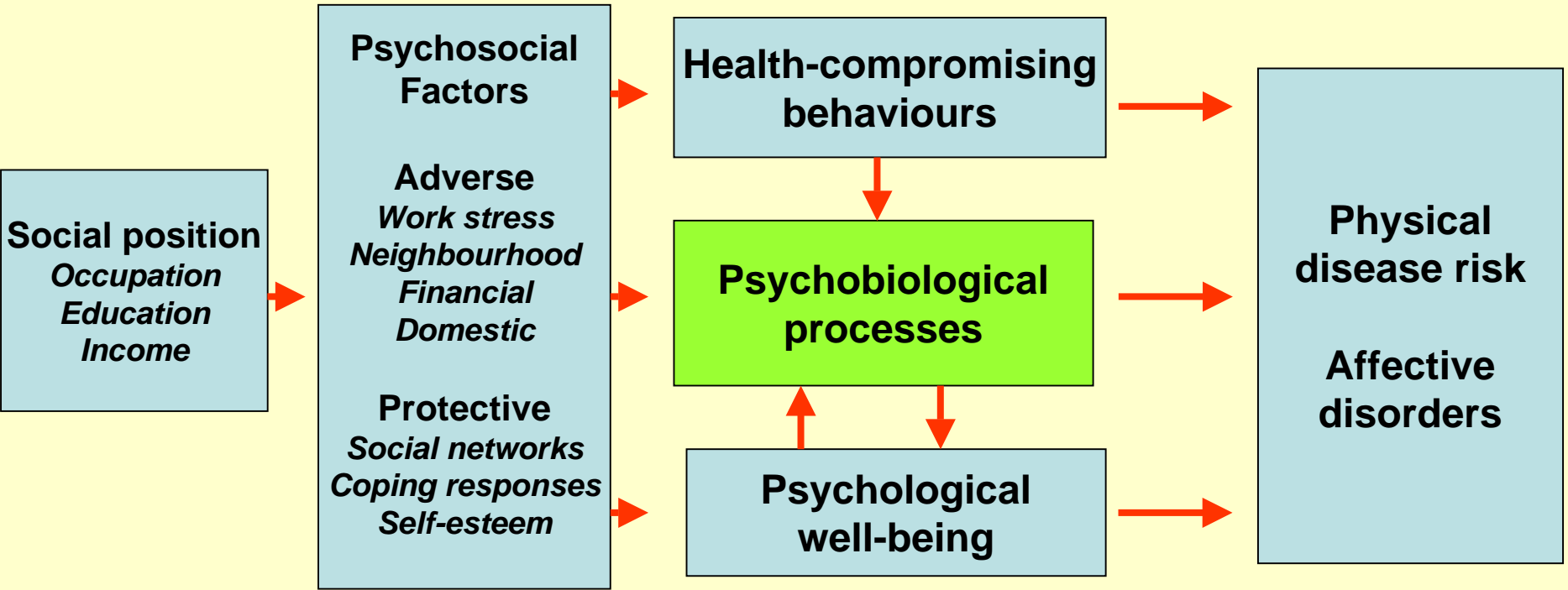
Hemingway et al
Circulation, 2005

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





Conclusions

- Psychobiological processes are plausible mediators of social influences on disease development
- The involvement of psychobiological responses is determined by the interplay between individual differences in responsivity and exposure to positive and negative life experiences
- Some psychobiological responses appear to be relevant across a range of health outcomes

What we need to know

- The precise pathological significance of some psychobiological responses is poorly understood
- The full sequence from social factor to biological response to disease has seldom been documented
- Whether interventions along this sequence will block health effects and demonstrate causality

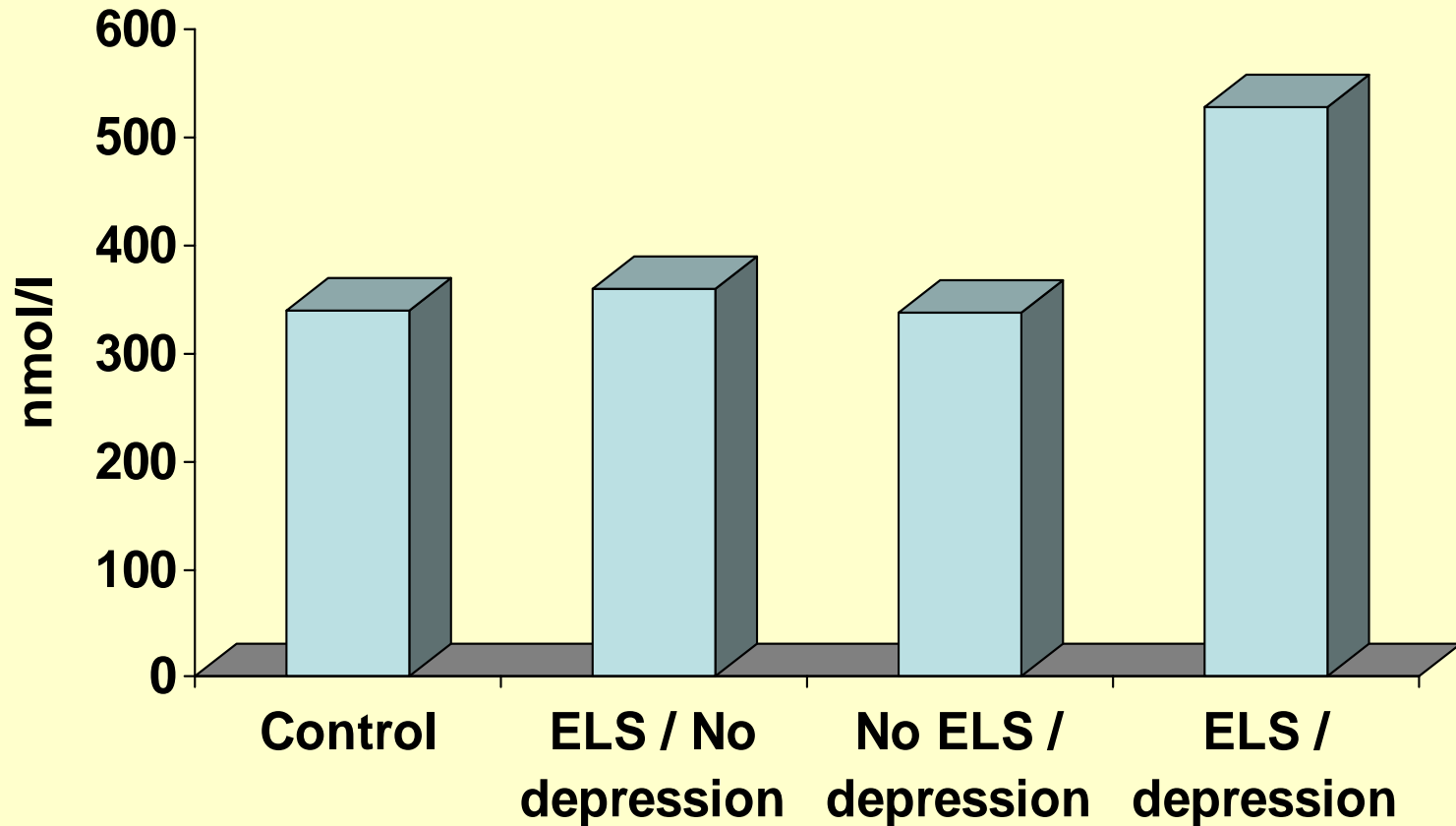
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British Heart Foundation

Early life stress and adult cortisol stress responses



Heim et al,
JAMA, 2000

ELS – history of childhood physical or sexual abuse
Depression – current major depressive disorder