

Families and Health: Inflammation as a Central Pathway



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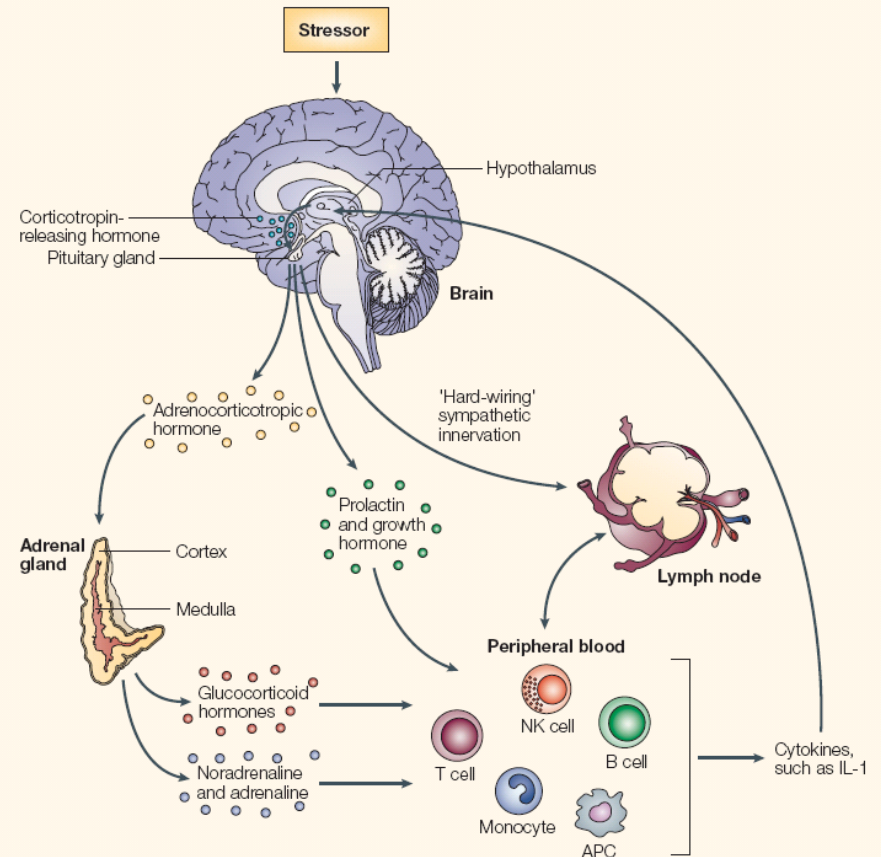


Figure 1 | Stress-associated modulation of the hormone response by the central nervous system. Experiencing a stressful situation, as perceived by the brain, results in the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) axis. The production of adrenocorticotropic hormone by the pituitary gland results in the production of glucocorticoid hormones. The SAM axis can be activated by stimulation of the adrenal medulla to produce the catecholamines adrenaline and noradrenaline, as well as by ‘hard-wiring’, through sympathetic–nervous–system innervation of lymphoid organs. Leukocytes have receptors for stress hormones that are produced by the pituitary and adrenal glands and can be modulated by the binding of these hormones to their respective receptors. In addition, noradrenaline produced at nerve endings can also modulate immune-cell function by binding its receptor at the surface of cells within lymphoid organs. These interactions are bidirectional in that cytokines produced by immune cells can modulate the activity of the hypothalamus. APC, antigen-presenting cell; IL-1, interleukin-1; NK, natural killer.

Proinflammatory cytokines

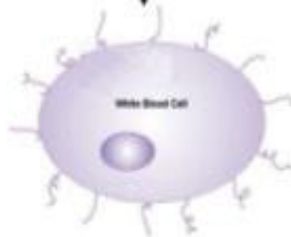
- Tumor necrosis factor- α (TNF- α)
- Interleukin 1 (IL-1)
- Interleukin 6 (IL-6)

- IL-6 directly promotes production of C-reactive protein (CRP), an important risk factor for cardiovascular disease

Infection and Trauma Trigger the Inflammatory Response

- Inflammatory mechanisms are critical to resolving infections and repairing tissue damage
- Proinflammatory cytokines attract immune cells to sites of infection or injury, and activate the cells to respond to the insult

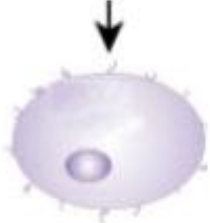
Virus Infection



Proinflammatory cytokines, such as IL-1, IL-6 and TNF-alpha are produced

No stress

Virus Infection Cleared



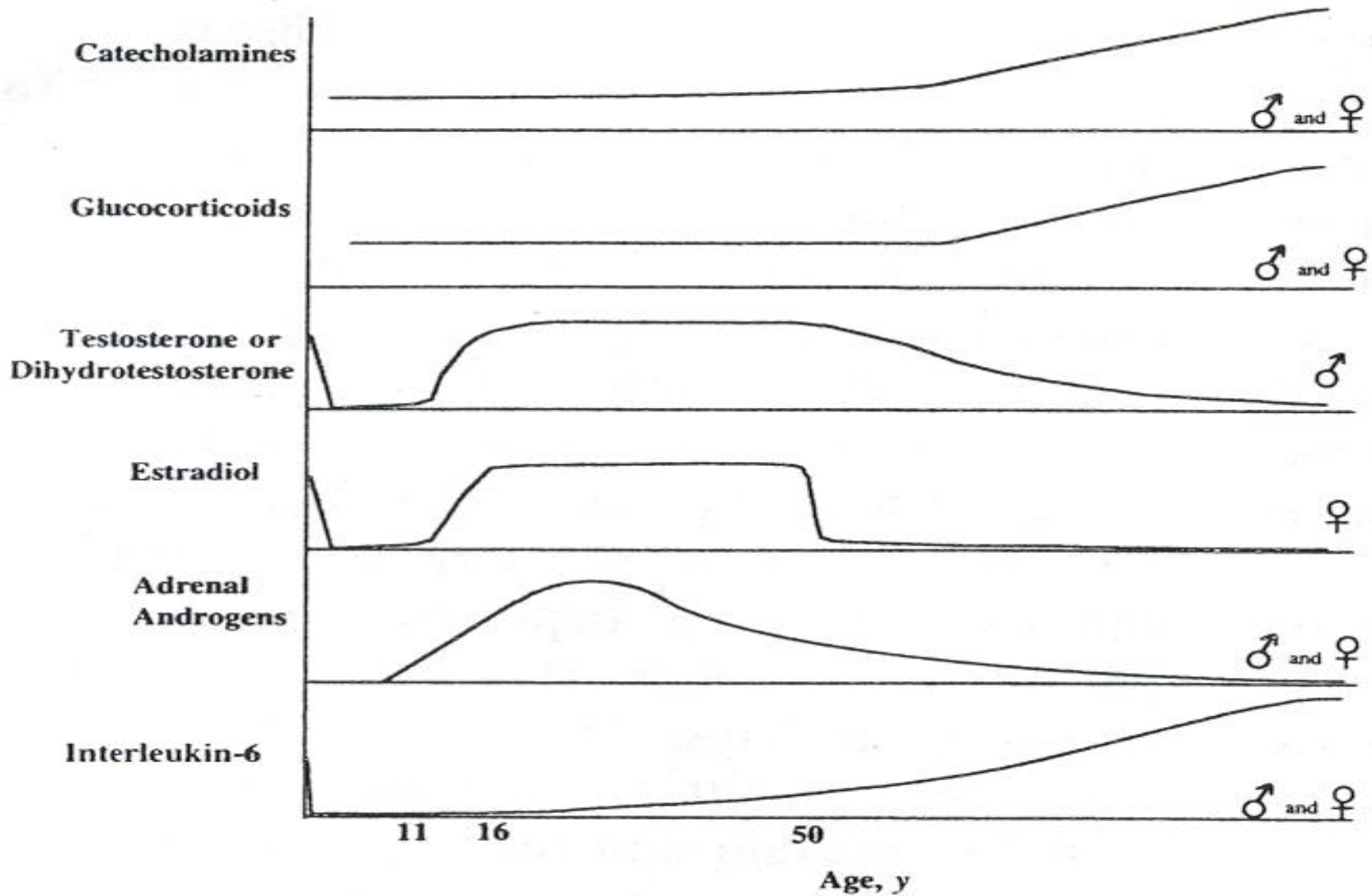
Return to baseline levels of cytokines

Chronic Stress: Stress hormones will stimulate white blood cells to continue to make high levels of proinflammatory cytokines, such as IL-6



Chronic or Recurring Infections Can Provoke Pathological Changes

Low levels of persistent inflammation (higher levels of proinflammatory cytokines) may be provoked by chronic infectious processes



Changes in circulating hormones and IL-6 with aging

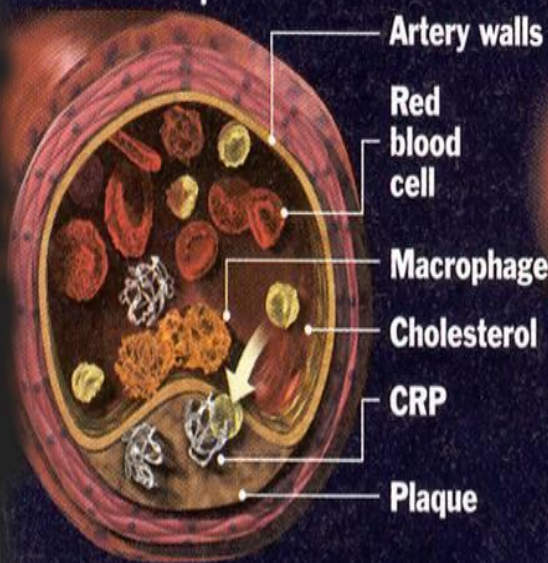
Papanicolaou et al. Annals of Internal Medicine 1998

AGE-ASSOCIATED DISEASES LINKED TO PROINFLAMMATORY CYTOKINES

- Cardiovascular disease
- Osteoporosis
- Arthritis
- Type 2 diabetes
- Certain cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia)
- Periodontal disease
- Frailty and functional decline

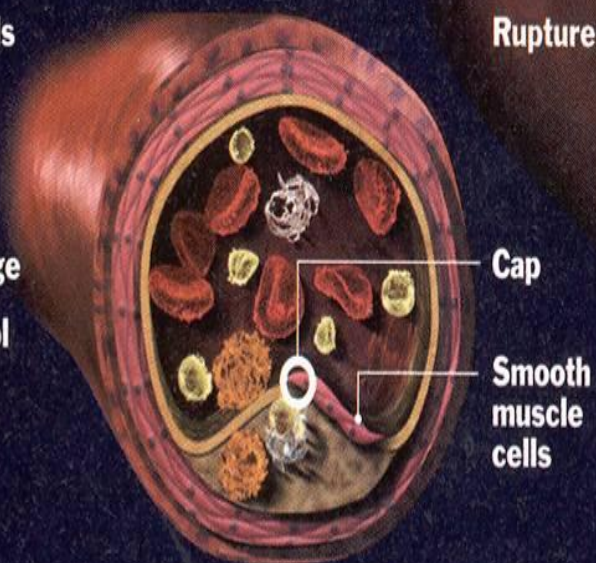
THE NEW PARADIGM

Scientists now believe that cholesterol and the immune system work together to clog arteries and cause heart attacks or strokes



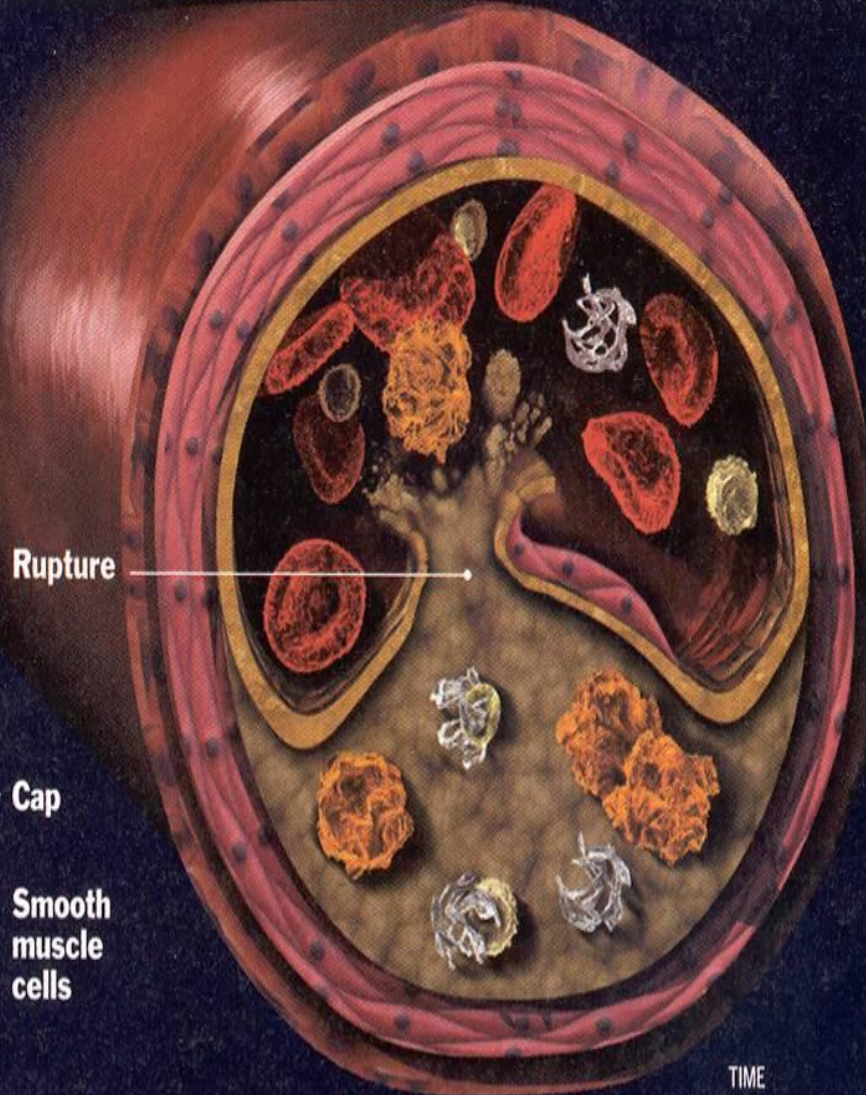
1 A PLAQUE FORMS

CRP (C-reactive protein) actively pulls **macrophages** and **cholesterol** from the blood into artery walls, forming **plaque**. **Macrophage immune cells** begin attacking the plaque



2 THE ARTERY RESPONDS

As the plaque grows, **smooth muscle cells** migrate to the site, creating a **cap** to stabilize the plaque

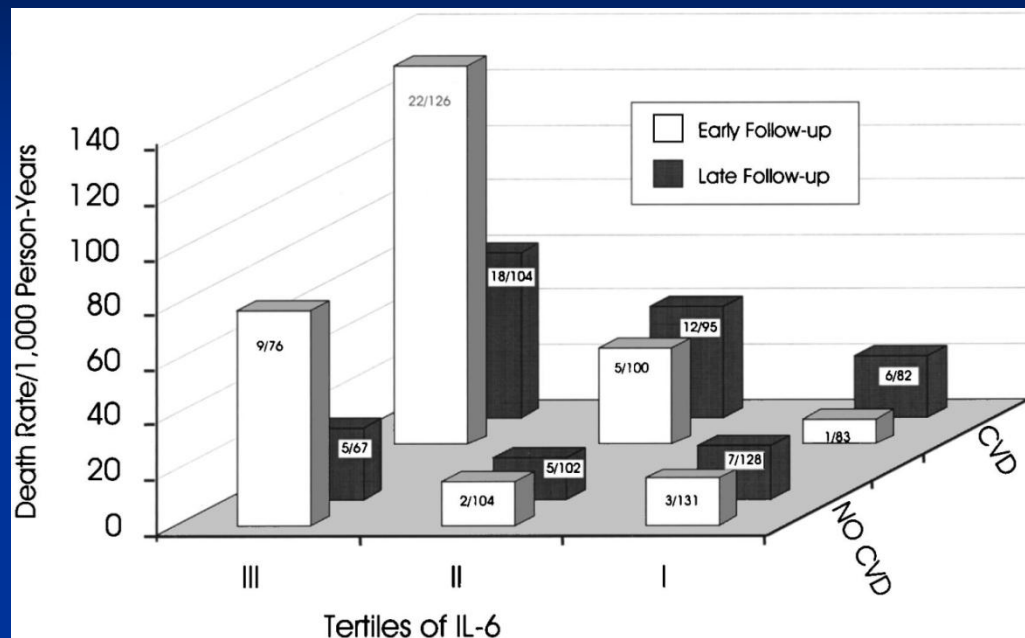


3 THE CAP BURSTS

Among patients with high levels of **CRP**, the inflamed plaque and its cap **rupture**, spewing out fat and creating a blood clot in the artery, causing a heart attack or a stroke

TIME
Graphic by
Ed Gabel

IL-6 is prospectively associated with both all-cause and cardiovascular disease mortality over 3 years



620 women, ≥ 65 community-dwelling, difficulty with ≥ 1 task in ≥ 2 of 4 domains of functioning (mobility/exercise tolerance, upper extremity activities, basic self-care, and higher functioning tasks of independent living)

Age-adjusted all-cause mortality rates/1000 person-years by IL-6 levels, history of CVD, and follow-up period. Figures on bars are numbers of deaths and subjects at risk.

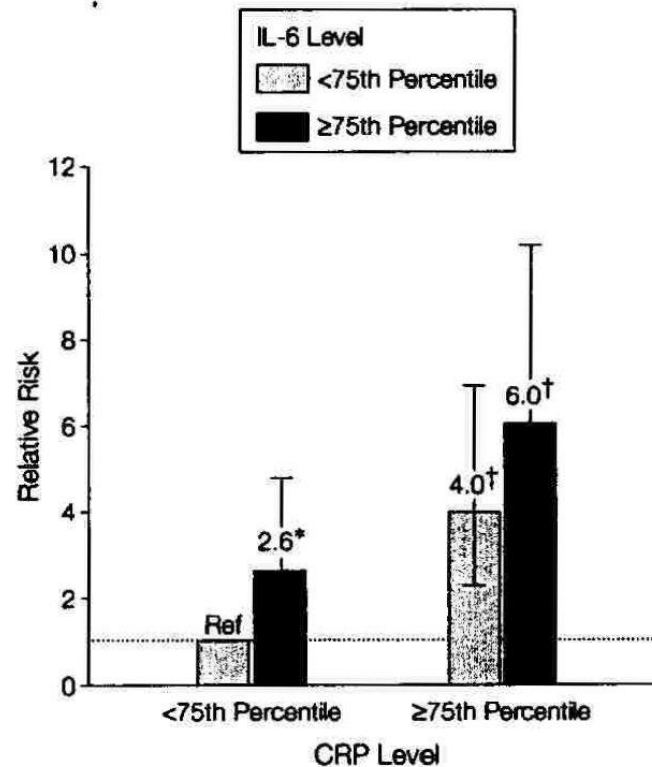
High IL-6 enhances mortality, prevalent CVD with high IL-6 > 4-fold risk of death. Adjustment for all chronic diseases and disease severity measures, including ankle-brachial index, forced expiratory volume, and exercise tolerance, did not change the results

Volpato et al., 2001, *Circulation*

- Elevated levels of CRP and IL-6 predicted the development of type 2 diabetes over 4 years after adjustments for BMI, family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy.

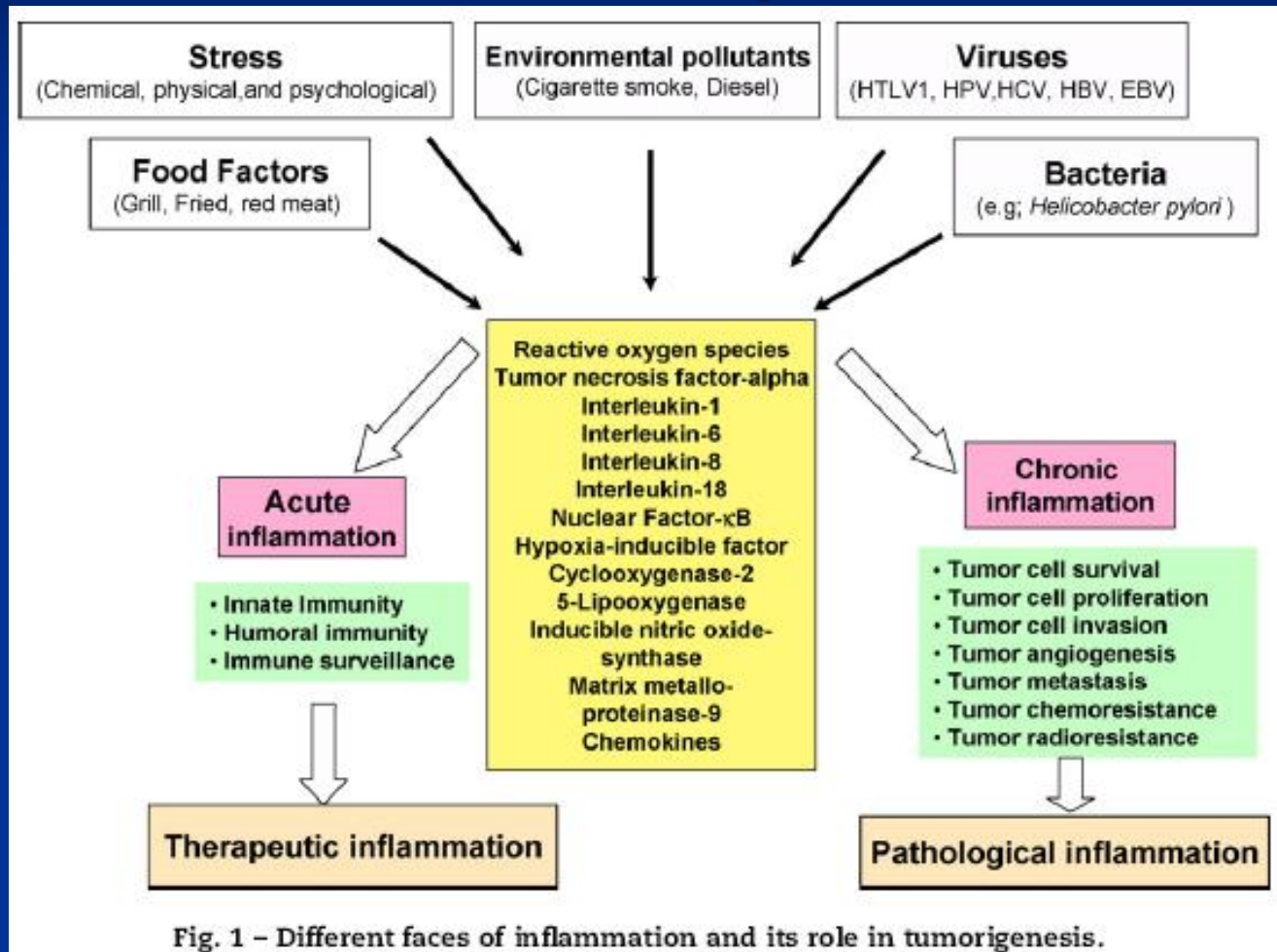
- Pradhan *et al.* *JAMA* 2001

Figure 1. Relative Risk of Type 2 Diabetes Mellitus in Women According to Baseline Levels of Interleukin 6 and C-Reactive Protein



IL-6 indicates interleukin 6; CRP, C-reactive protein. Groups were formed based on the 75th percentile cut-point value of each biomarker (>0.61 mg/dL for CRP and >2.05 pg/mL for IL-6) using the distributions among control subjects in the study population. Risk estimates were matched on age and fasting status. Error bars indicate 95% confidence intervals. Asterisk indicates $P = .002$ and dagger, $P < .001$ for comparisons with the reference group (Ref).

Inflammation Impacts Cancer: Pathways





- Stress/depression



- Immune dysregulation




- Enhanced risk of infection/prolonged infections/delayed wound healing

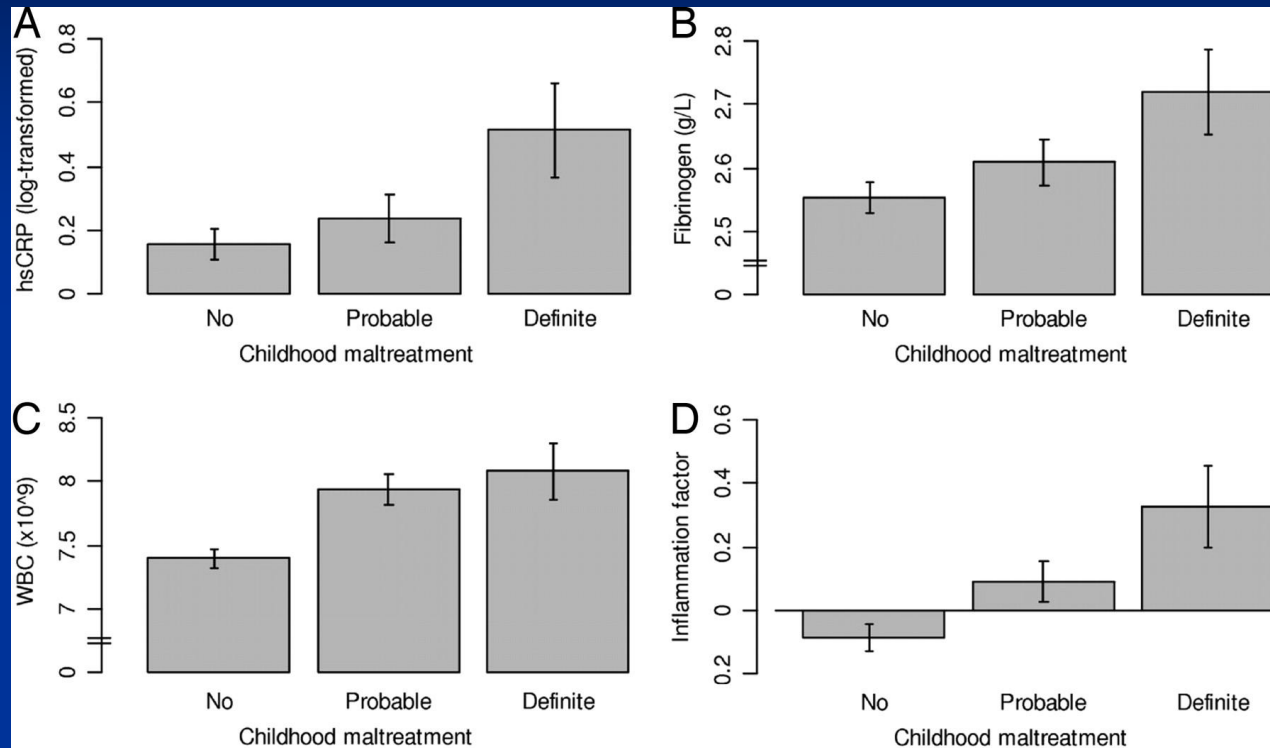


- Increased proinflammatory cytokine production

STRESS/DEPRESSION ENHANCE PROINFLAMMATORY CYTOKINE PRODUCTION

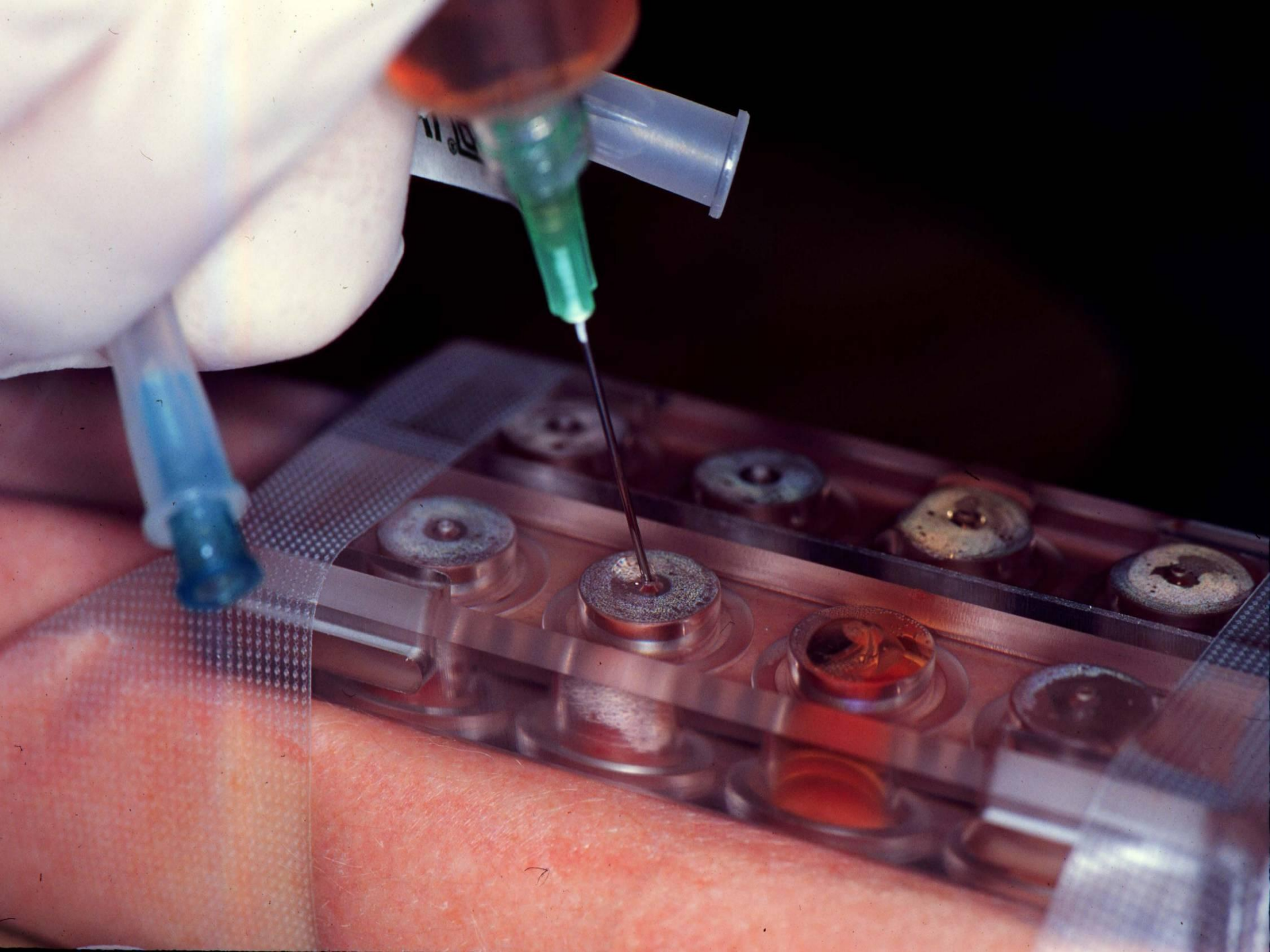
- Major depression  increased secretion of proinflammatory cytokines; treatment with antidepressants decreases secretion (Maes; Irwin; Miller)
- Depressive symptoms were linked to increased IL-6 in community samples of older adults (Dentino et al., 1999)
- Depressed mood was associated with higher levels of serum IL-6, TNF- α , and CRP among older adults ages 70-79 (Penninx et al., 2003)
- Chronic stressors like caregiving have been associated with heightened IL-6 compared to noncaregiving controls (Lutgendorf et al.; Kiecolt-Glaser et al.; Glaser et al.)
- Acute stressors enhance production of proinflammatory cytokines (Goebel et al., 2000; Steptoe et al., 2001)
- Lower SES is associated with great inflammation (Koster et al. 2006)

Childhood maltreatment predicts adult inflammation in a life-course study



Danese et al. PNAS 2007;104:1319-1324

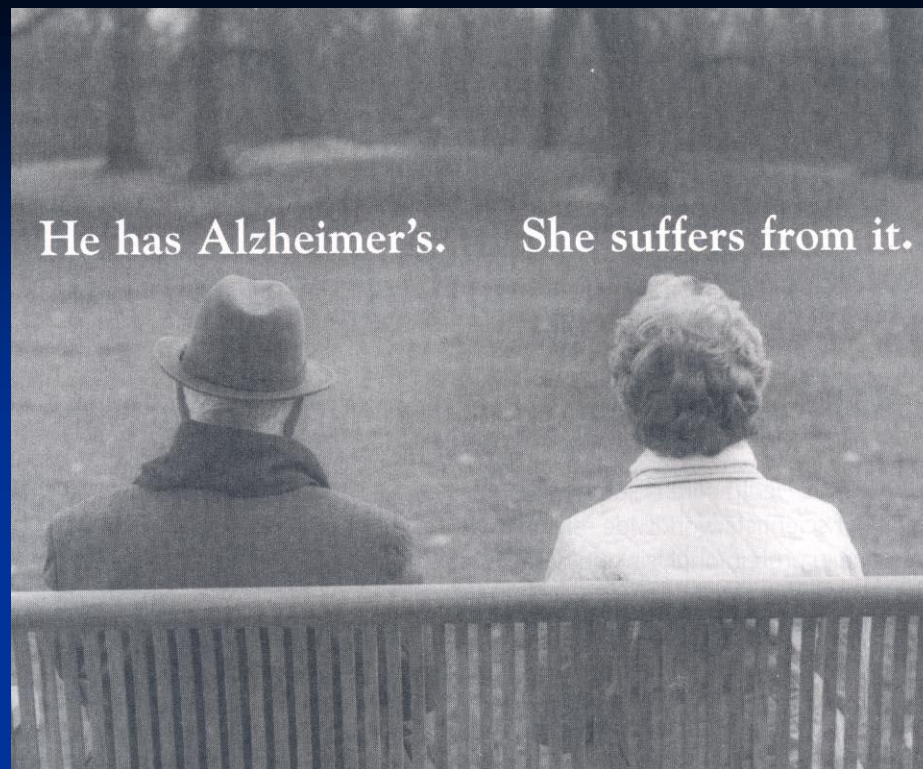
PNAS



Acute stress enhances systemic proinflammatory cytokine production while inhibiting local production at wound sites

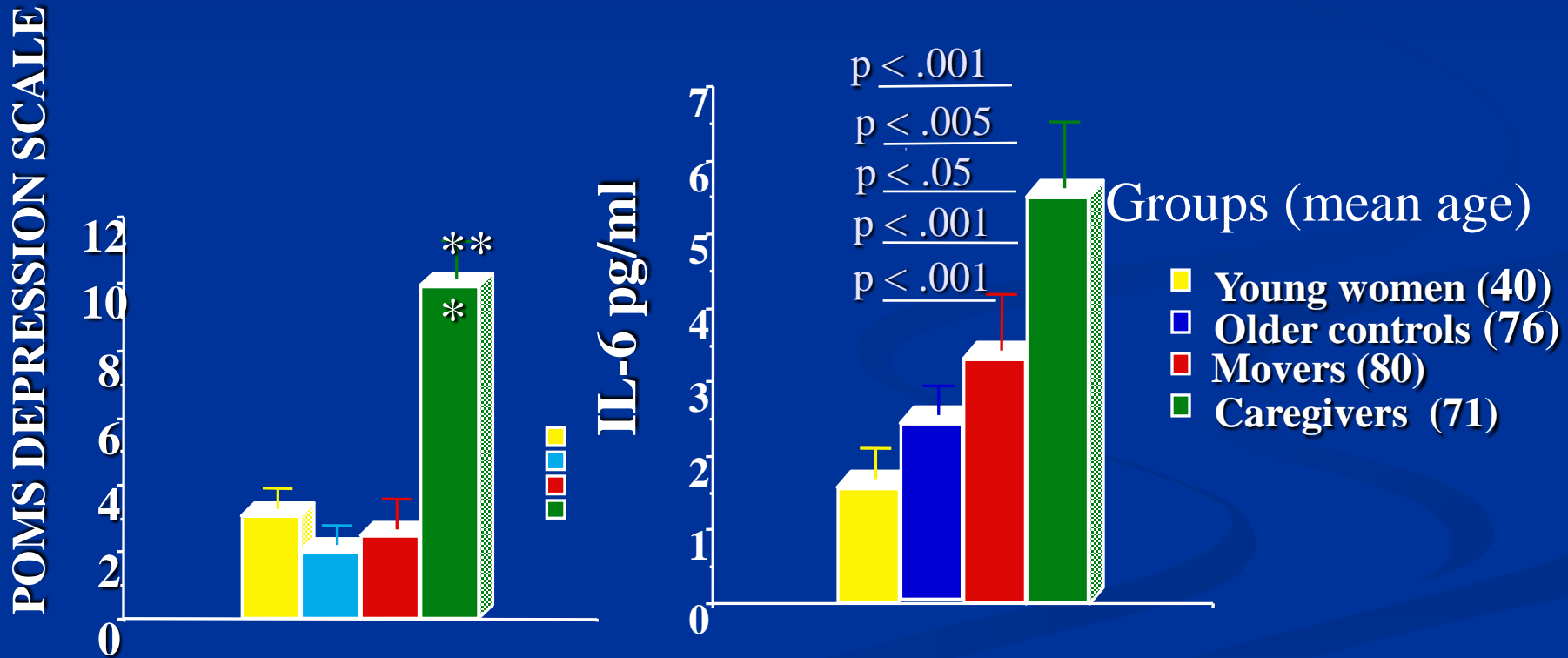
- Couples were admitted twice to the GCRC (hospital research unit), 24 hours each admission (mean age=37, range=22-77)
- First admission: Structured social support interaction
- Second admission: Structured conflict (marital disagreement)
- Both admissions: blister wounds before the interaction, wore wound chambers 22 hours, assessed proinflammatory cytokine secretion at wound sites and plasma
- Couples' blister wounds healed more slowly, and local cytokine production (IL-6, TNF- α , IL-1 β) was also lower at wound sites following marital conflicts than after social support interactions.
- Hostile couples showed larger increases in plasma IL-6 and TNF- α the morning after a conflict than after a social support interaction compared to less hostile couples, and hostile couples took an average of two days longer to heal wounds.
 - Kiecolt-Glaser, Loving, Stowell, Malarkey, Lemeshow, Dickinson & Glaser (2005). *Archives of General Psychiatry*.

Dementia family caregiving as a chronic stressor



“The 88-year old former airline pilot had been ill for five years, during which time his cognitive abilities had steadily deteriorated. At times he did not recognize his wife and accused her of being a stranger. He could only follow the most simple of commands. His moods were extremely labile, with frequent crying spells and occasional outbursts of anger. He often followed his wife around the house, interrupting her activity with questions and demands. Urinary incontinence and night time agitation were bothersome problems. He often paced at night, occasionally leaving the house and becoming lost... His wife of forty years now devoted her time to looking after her husband. She rarely left home except to do necessary shopping or bill paying, and rarely invited neighbors or friends to her home because of embarrassment about her husband’s behavior.”

Interleukin-6 in 4 Groups of Community Women



Longitudinal community study spanning 6 years:

119 caregivers

106 noncaregivers

(mean age at study entry, 71)

Key Measures:

IL-6 in frozen plasma samples, 2x/year

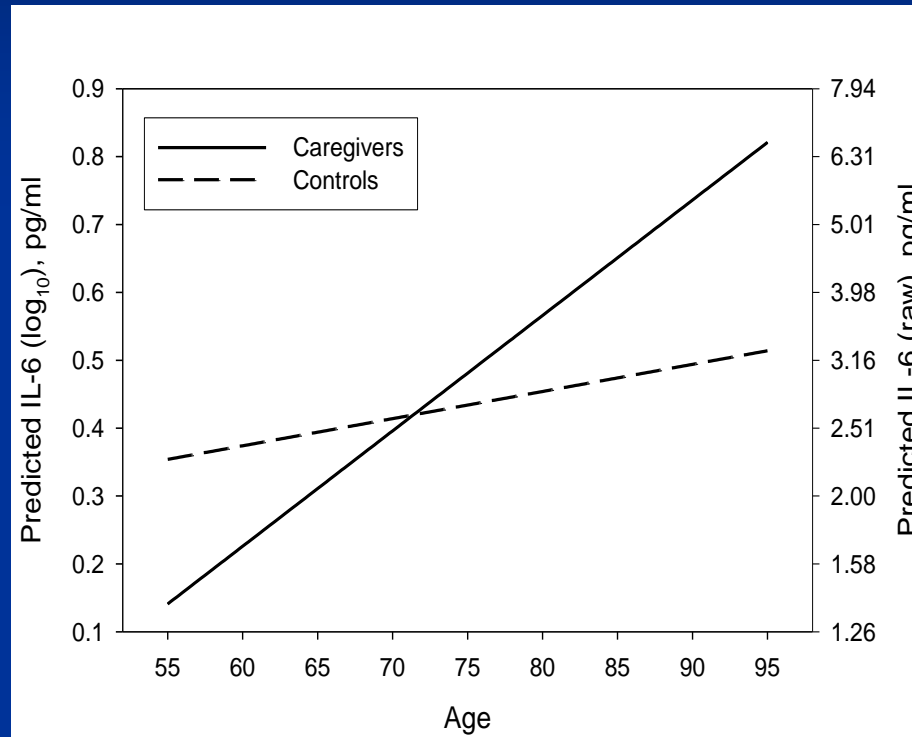
Health behaviors associated with IL-6

Depressive symptoms

Kiecolt-Glaser, Preacher, MacCallum, Atkinson, Malarkey, & Glaser
(2003). *Proceedings of the National Academy of Sciences, USA*

MODELED CHANGE IN IL-6 IN CAREGIVERS VS. NONCAREGIVERS

IL-6 is represented as a linear function of age; each individual's pattern of change is represented by a straight line defined by an intercept (predicted level of IL-6 at age 55) and slope (predicted change in IL-6 per year).



➤ **3.19 = upper quartile, epidemiologic studies**

Caregivers' average rate of increase in IL-6 was about ***four times as large*** as that of noncaregivers, and the two slopes were significantly different from one another, $p = .01$.

Compared to noncaregivers, men and women who provide care to a spouse with a stroke or a dementia are at greater risk for

- developing diabetes
- becoming hypertensive
- coronary heart disease (CHD)

Lee et al., 2003; Shaw et al., 1999;
Vitaliano et al., 1996, 2002

A large population-based study of the elderly drawn from a random, stratified sample: relative risk for all-cause mortality among strained caregivers was 63% higher than noncaregiving controls. These data represent the “best case” scenario, with caregiving defined very broadly (Schulz & Beach, JAMA, 1999)

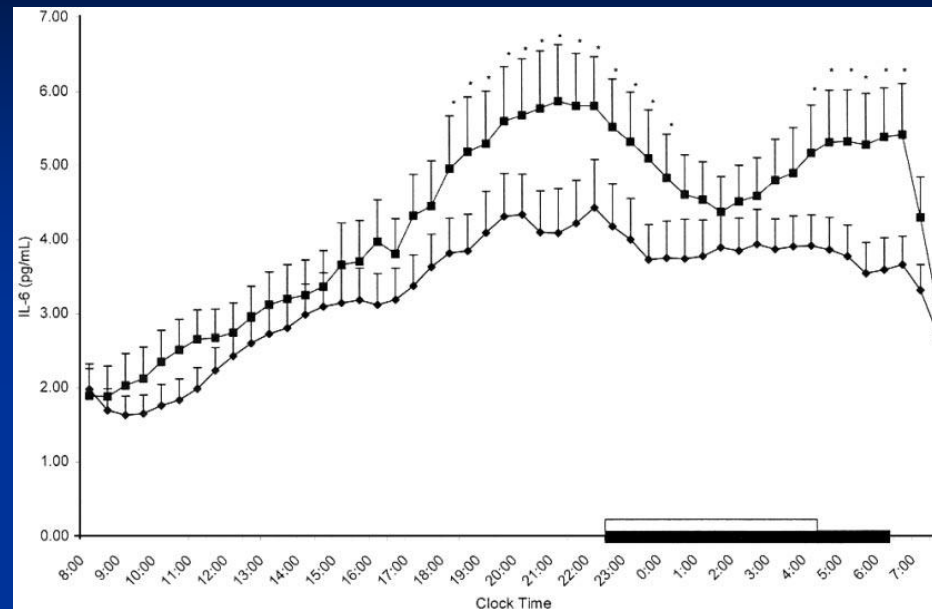
Advantages of Inflammatory Markers

- Well-documented ties to health outcomes
- Responsive to both chronic and acute stressors
- Small quantities of blood
- Common assays performed by many labs; CTSA/CRC labs are a good resource
 - BUT FOR INTERPRETABLE/PUBLISHABLE DATA—be sure to consider
- Health behaviors/health status
- Methodological issues

STRESS PROMOTES POOR HEALTH BEHAVIORS THAT ENHANCE PROINFLAMMATORY CYTOKINE PRODUCTION

- High fat diet
- Less exercise
- Poorer sleep
- Smoking

Modest sleep deprivation enhances IL-6 production



Twenty-four-hour IL-6 circadian secretory pattern before (bottom) and after (top) sleep restriction (2 hours/night for 1 week) in 25 young healthy men and women, ages 19-34.

The thick black bar on the abscissa represents the sleep recording period during baseline. The open bar on the abscissa represents the sleep recording period during partial sleep restriction. Vgontzas et al., 2004, *J Clin Endo Metab*

NOTE DIURNAL VARIATION: DRAW SAMPLES WITHIN THE SAME WINDOW
Exclude night or swing shift workers

“Adipose tissue is the largest organ in the body...” Matsuzawa, 2005, *Best Practice Res Clin Endo Metab*



Electron microscopic features of adipose tissue (Matsuzawa, 2005)

Up to 30% of IL-6 may be produced by adipose tissue

Mohamed-Ali 1997, *J Clin Endo Metab*

Abdominal adipose tissue may secrete up to three times as much IL-6 as other subcutaneous fat tissues

Browning; *Proc Nutri Soc* 2003

WEIGHTY MATTERS

Individuals with a higher body mass index have higher levels of IL-6, TNF- α and CRP

Central adiposity may be associated with larger stress-induced cytokine responses

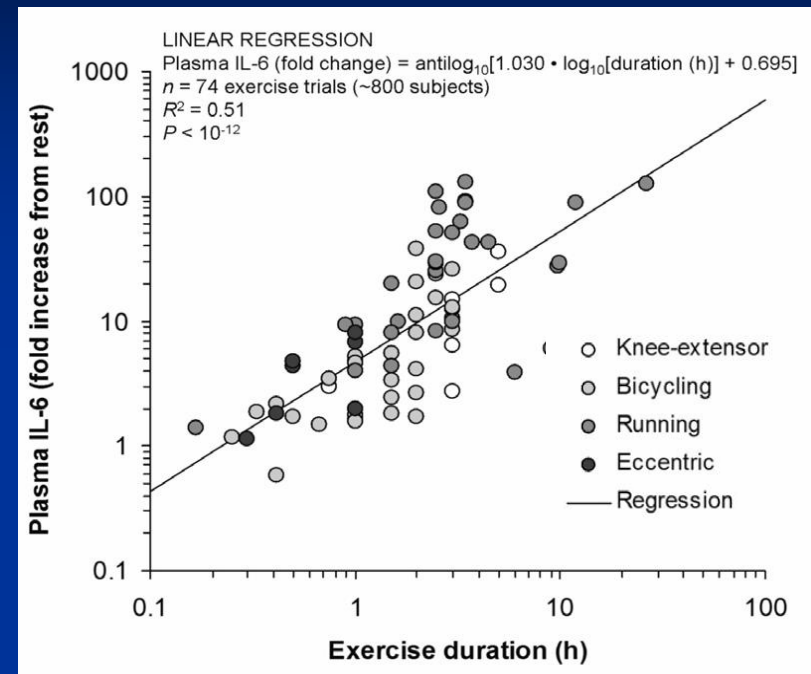
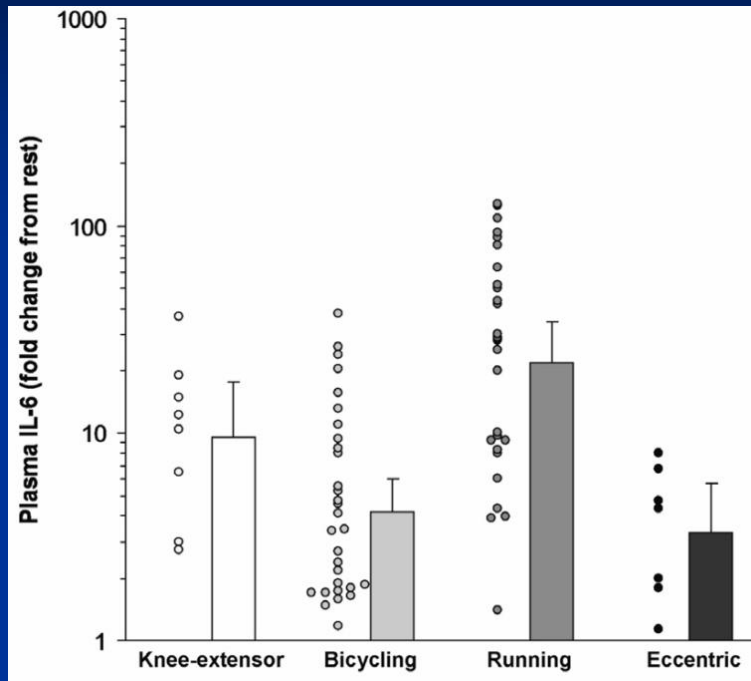
Brydon et al., *Int J Obes* 2007

Important to measure adiposity (body mass index [BMI], waist/hip ratio, sagittal abdominal diameter, DEXA, CT)

Moderate Physical Activity Reduces Chronic Inflammation

- When assessed rigorously and objectively by maximal exercise testing, fitness is inversely associated with inflammation
(Kasapis, *J Am Coll Cardiol* 2005)
- 35% reduction in CRP after 6 months of supervised moderate exercise in men and women at risk for future heart attack
(Smith et al. *JAMA* 1999)
- Elite athletes: basal IL-6 was 30% higher in the off-season compared to in-season in members of the Norwegian national cross country ski team
(Ronson et al., *Scandinavian J Med Sci in Sports*, 2001)

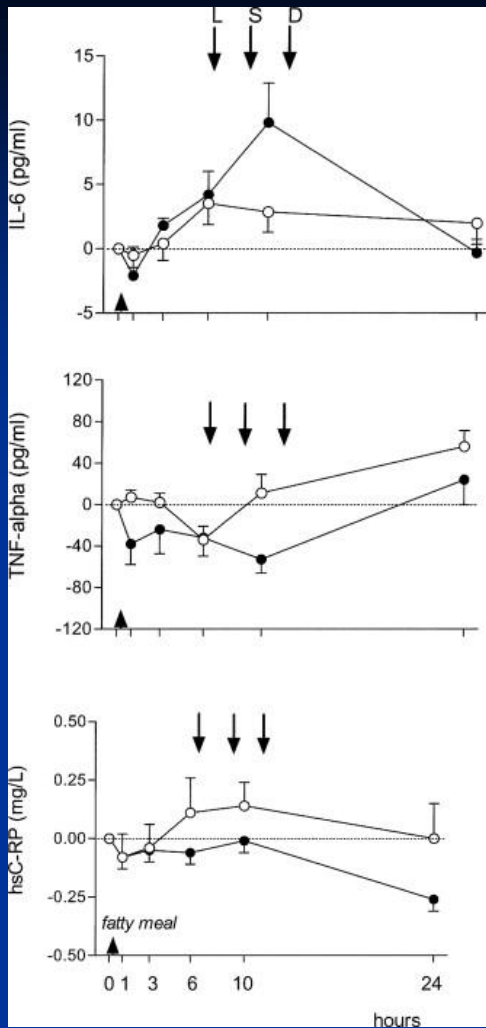
Exercise acutely increases IL-6



Effect of exercise mode and duration on post-exercise plasma IL-6.

Fischer, *Exercise Immunology Review*, 2006

Tell participants not to exercise before the visit on a day blood samples will be collected



When and what subjects eat before a blood draws matters: meals high in saturated fat provoke postprandial inflammatory responses

Fasting morning blood draws avoid meal-related variance

Postprandial changes in circulating IL-6, TNF- α , and hs-CRP after a high-fat breakfast containing a high (71:29, black circles) or low (55:45, white circles) saturated:unsaturated fatty acid profile.

D, dinner; L, lunch; S, snack. Poppitt et al. *Nutrition*, 2008

Medications with anti-inflammatory effects

- Statins
- Antidepressants
- Systemic and respiratory steroids
- Nonsteroidal anti-inflammatories
- Estrogens
- Immunomodulators, immunosuppressants
- Antirheumatic medications
- Chemotherapy, other anti-cancer meds

*Interdisciplinary teams that
assess psychological and
biological outcomes are
essential*

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