

**Sickness behavior in cancer:
Immune mechanisms of fatigue and
other side effects of cancer treatment**

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Cancer-related fatigue

- **Fatigue** is the most common side effect of cancer and its treatment
 - 70 - 100% of cancer patients report fatigue during treatment
 - 30% of breast cancer survivors continue to experience fatigue following treatment completion
 - Fatigue may persist for up to 10 years post-dx

Description of cancer-related fatigue

- Different than “normal” fatigue due to lack of sleep or overexertion
- More pervasive, debilitating, longer-lasting
- Not relieved by adequate sleep or rest
- Involves physical, mental, and emotional fatigue

“Not just tired” (Poulson, JCO, 2001)

“During cancer therapy I always felt the exhaustion of physical exercise without any of the positive attributes....My limbs felt heavy. The quality of my sleep was changed. The mere act of sleeping itself seemed like work sometimes....My brain felt tired and so did my spirits. I seemed to have lost my zest for life.”

Impact on quality of life

- Most distressing symptom associated with cancer, more distressing than pain or nausea
- Associated with declines in all aspects of QOL
 - 30% report that fatigue affects concerns about survival and/or hope of fighting cancer
 - 16% report that treating fatigue is as important as treating cancer itself
 - 12% report that fatigue makes them want to die

Other side effects of cancer treatment

- **Sleep disturbance**
 - Over 45% of breast cancer survivors complain of sleep problems
 - 20% fulfill diagnostic criteria for chronic insomnia

Other side effects of cancer treatment

- **Mood disturbance**

- Prevalence of depression in breast cancer patients ranges from 1.5% to 46%, depending on population and type of assessment
- 22 – 30% of breast cancer survivors have elevated depressive symptoms

Other side effects of cancer treatment

- **Cognitive alterations (“chemobrain”)**
 - Many women report cognitive problems during and after chemotherapy
 - Women treated with chemotherapy show poorer performance on several neurocognitive tasks (i.e., memory tasks, visuospatial function, information processing)

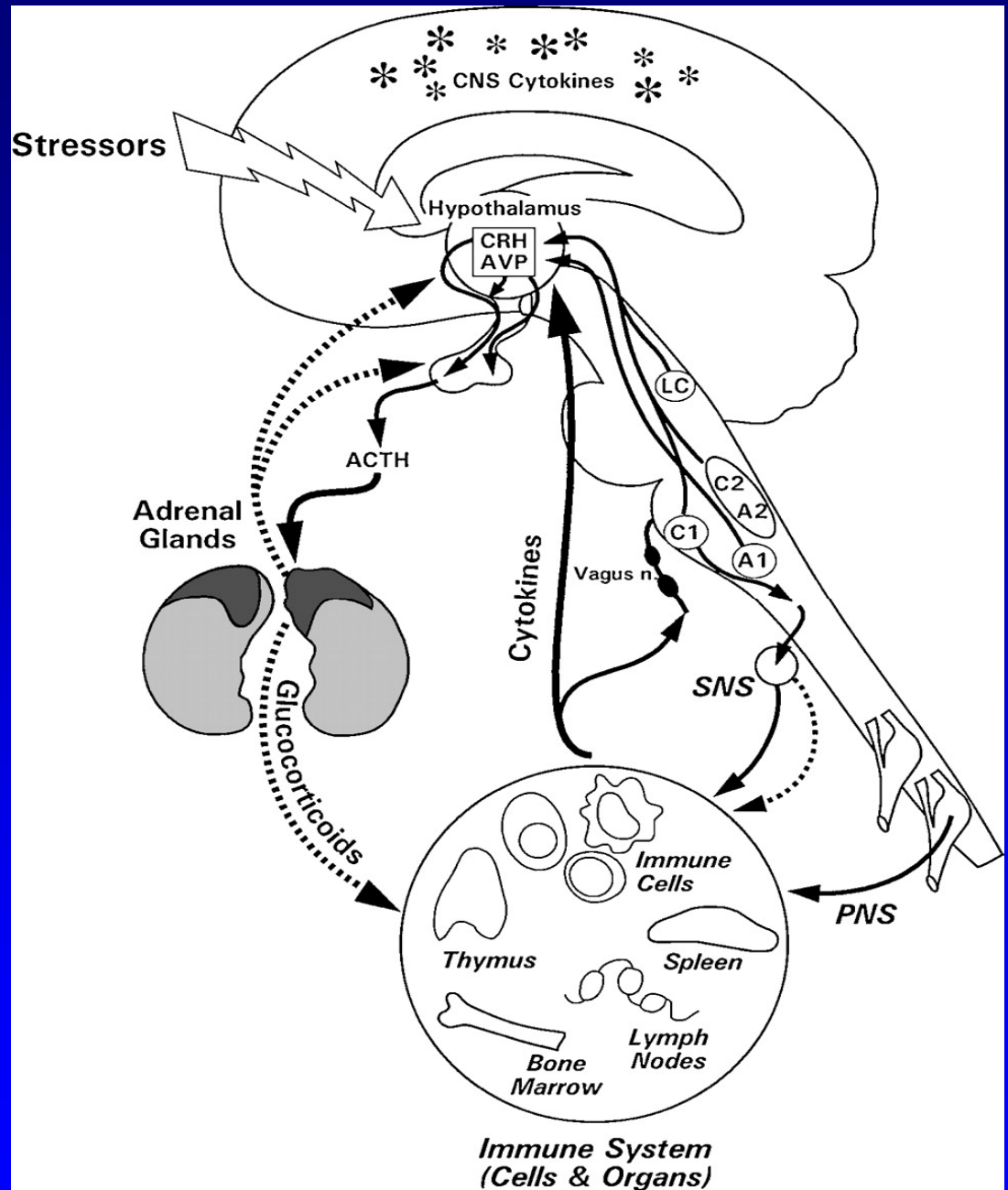
Co-occurrence of side effects

- Fatigue co-occurs with depressed mood, sleep disturbance, and subjective cognitive problems in breast cancer patients and survivors
- Each symptom may influence the development or persistence of other symptoms (e.g., sleep problems at night cause fatigue during the day, influencing mood and attention, etc.)
- Symptoms may also share a common etiology

What causes cancer-related fatigue?

- Etiology of fatigue has not been determined
- Fatigue is multi-dimensional symptom, may be influenced by multiple factors
 - Demographic: age, income, marital status
 - Symptom-related: menopausal symptoms
 - Psychological: catastrophizing coping style
 - Biological: immune alterations

Brain-immune connections



Proinflammatory cytokines

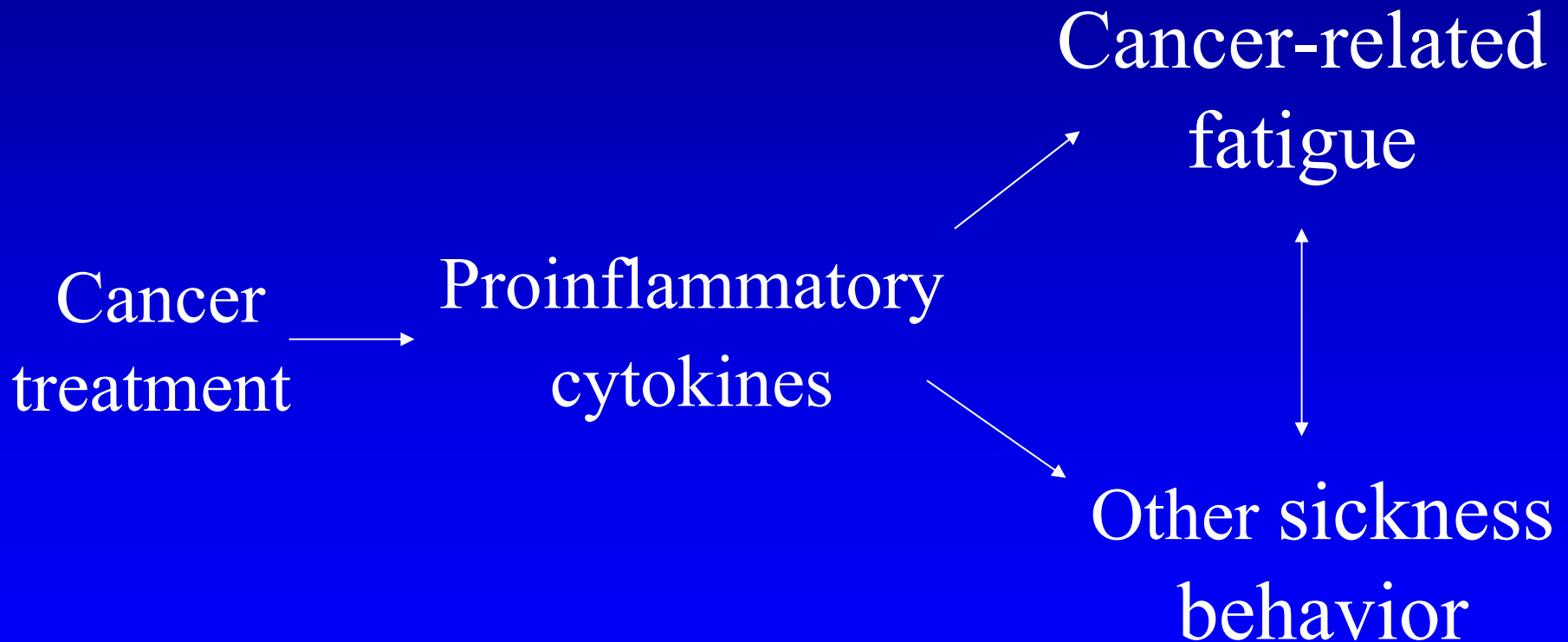
- Group of cytokines involved in inflammation:
 - IL-1
 - IL-6
 - TNF- α
- Released when immune system activated by infection or tissue injury
- Local and systemic effects, including effects on central nervous system and behavior

Cytokine effects on behavior

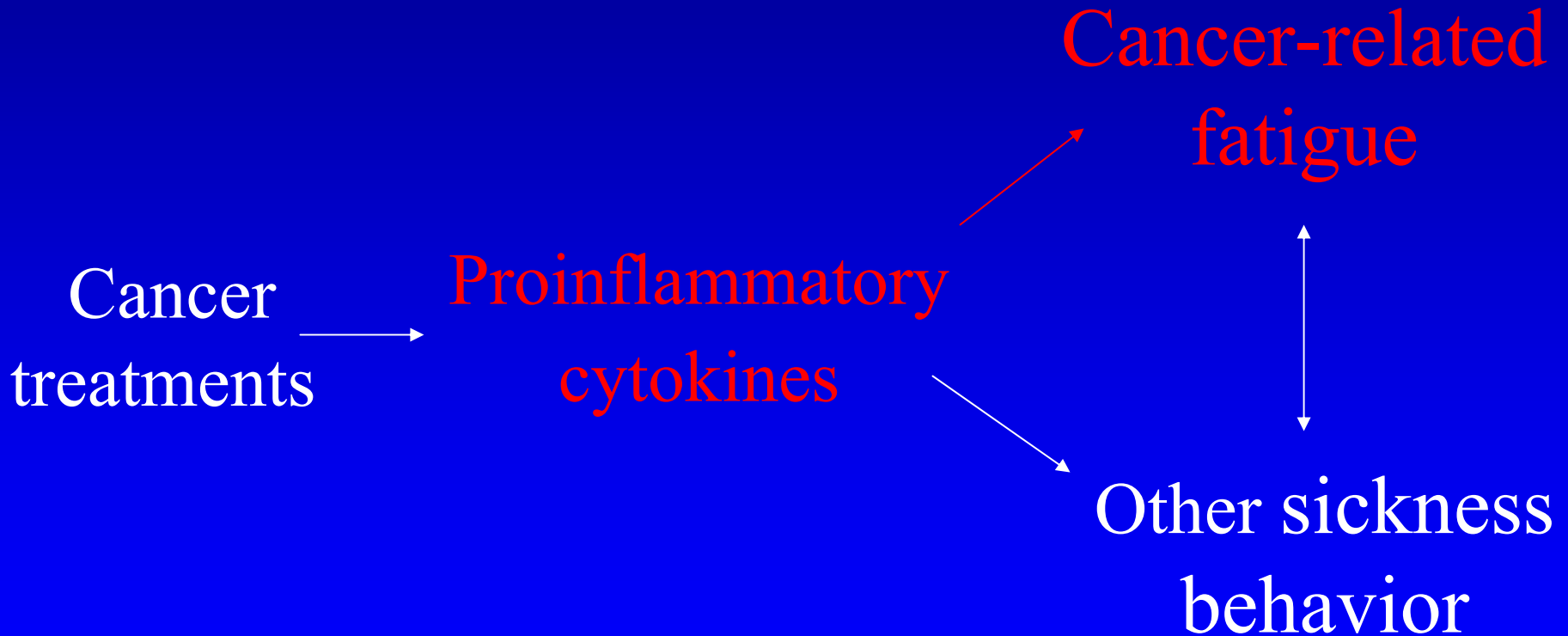
- Decreased activity/fatigue
- Decreased food and water intake
- Decreased social and sexual behavior
- Alterations in sleep and cognitive function
- Mood disturbance

“Sickness behavior”

Model of sickness behavior in cancer



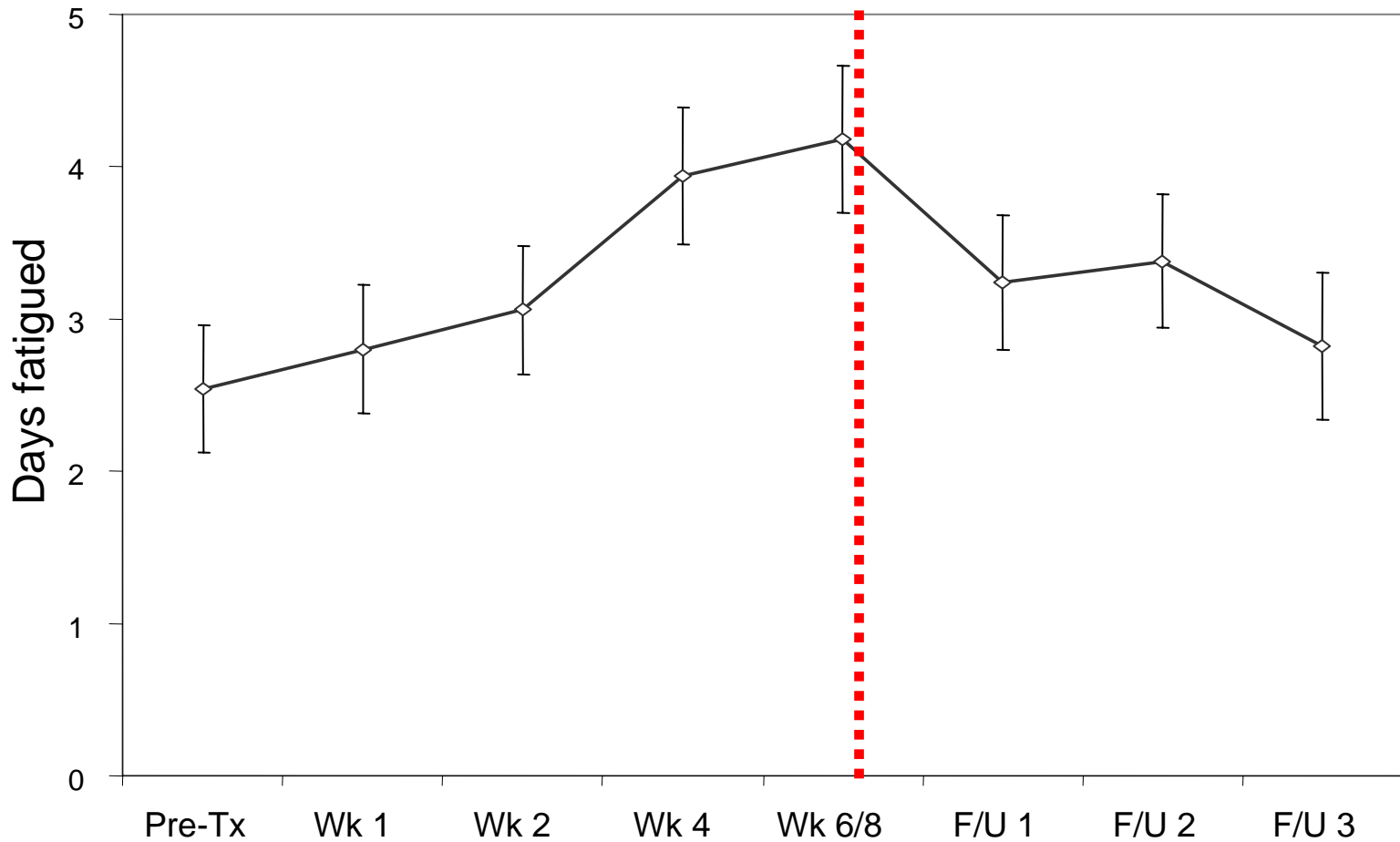
Model of sickness behavior in cancer



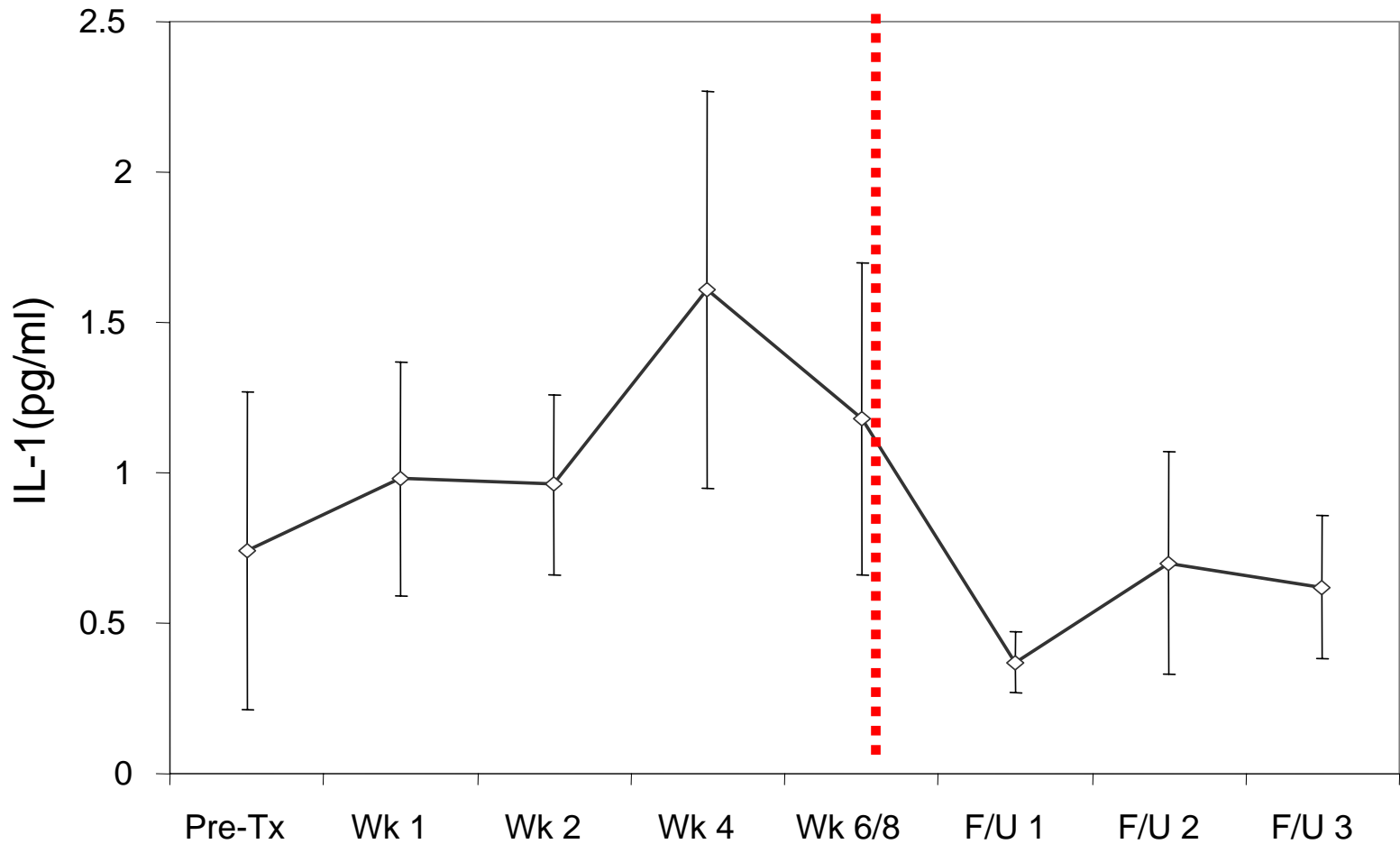
Fatigue during cancer treatment

- Participants: 28 women undergoing radiation therapy for early-stage breast cancer
- Assessed fatigue and other sickness behavior via self-report questionnaire
- Collected peripheral blood for assessment of proinflammatory cytokines (IL-1 β and IL-6)

Number of days fatigued



Serum IL-1 β (pg/ml)



Cytokines predict fatigue during tx

Number of days fatigued

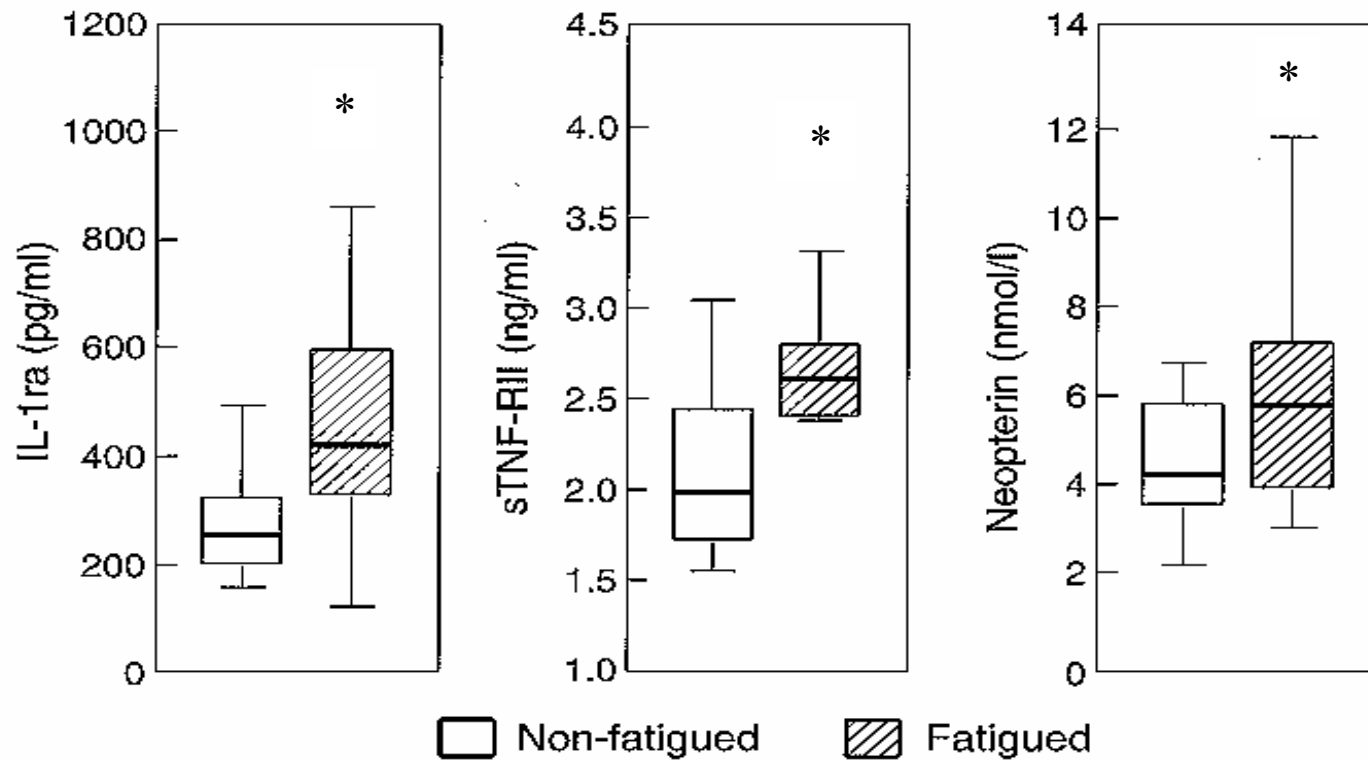
Cumulative IL-1 β B = 0.19, p < .05

Cumulative IL-6 B = 0.13, p < .01

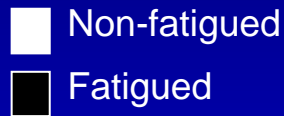
Fatigue in cancer survivors

- Participants: 40 breast cancer survivors (20 fatigued, 20 non-fatigued)
- Assessed fatigue and other sickness behavior via self-report questionnaire
- Collected peripheral blood for assessment of markers of proinflammatory cytokine activity

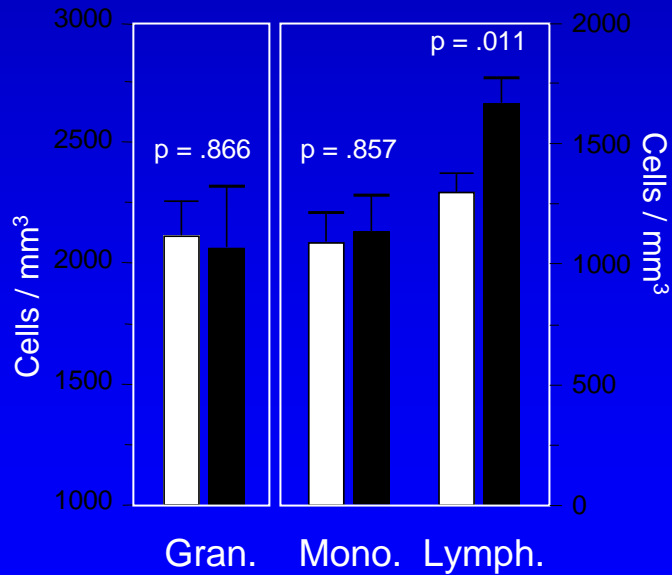
Elevated inflammatory markers



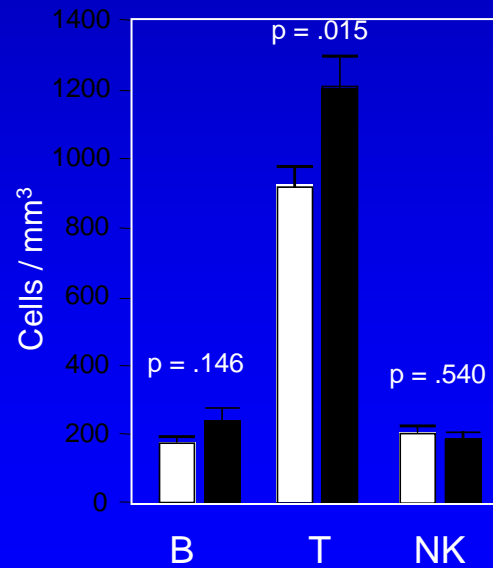
Elevated T cell subsets



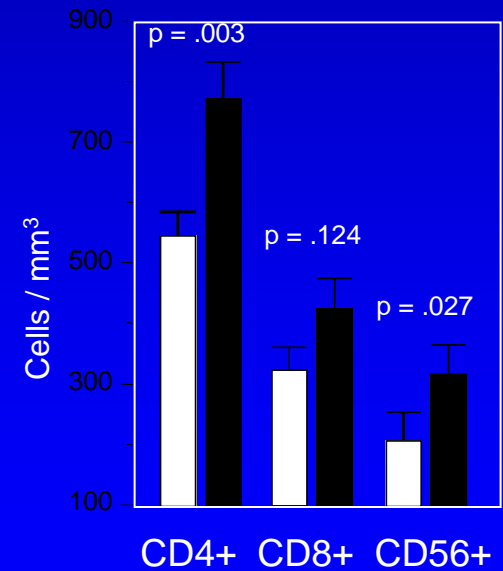
Leukocytes



Lymphocytes



T Lymphocytes

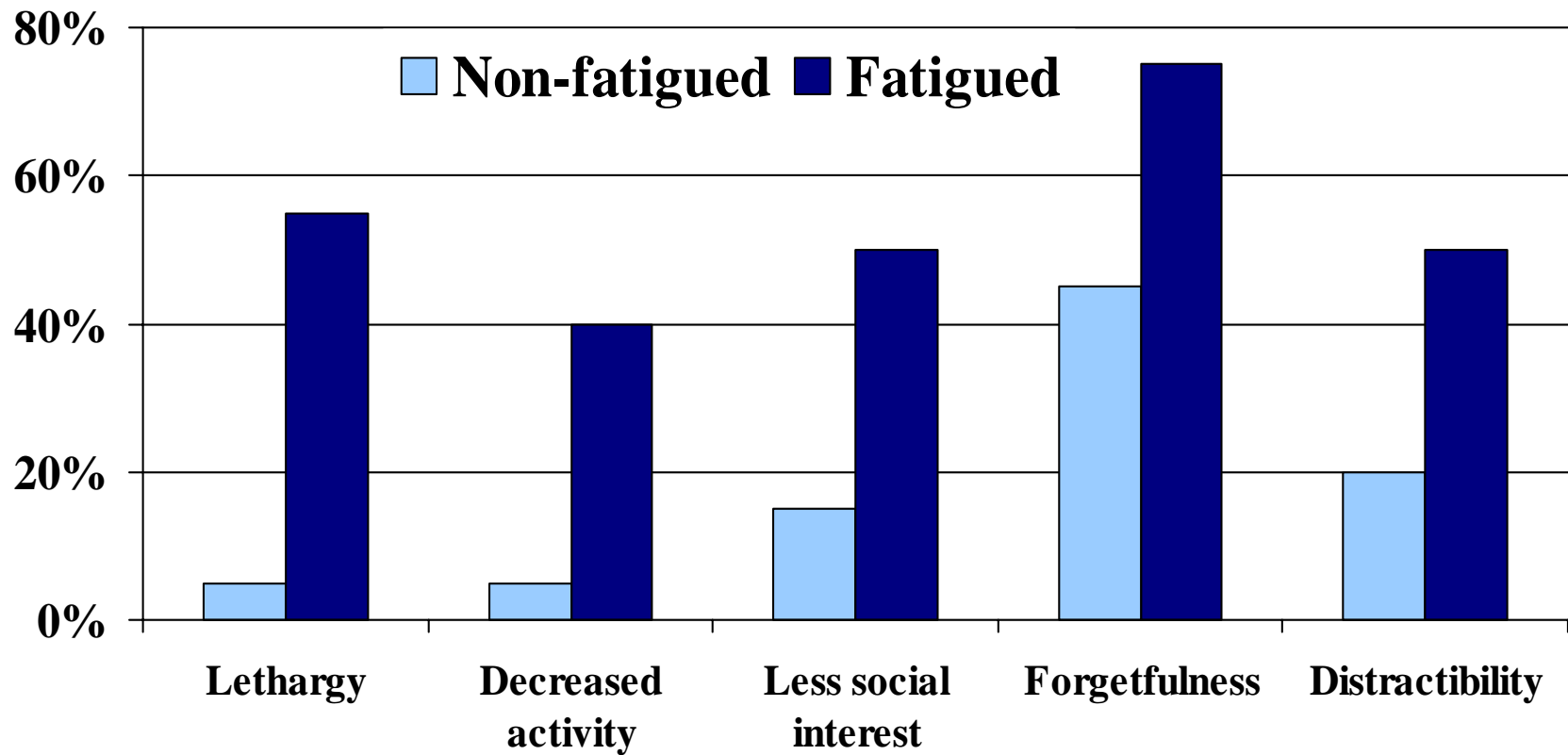


Fatigue, depression, and sleep

| | Fatigued | Non-fatigued |
|-------------------------|-----------------|---------------------|
| Vitality (SF-36) | 39.5 | 80.5 |
| Depressed mood (BDI-II) | 12.9 | 3.1 |
| Sleep disturbance (MOS) | 0.38 | -0.38 |

*all ps < or = .05

Other sickness behaviors

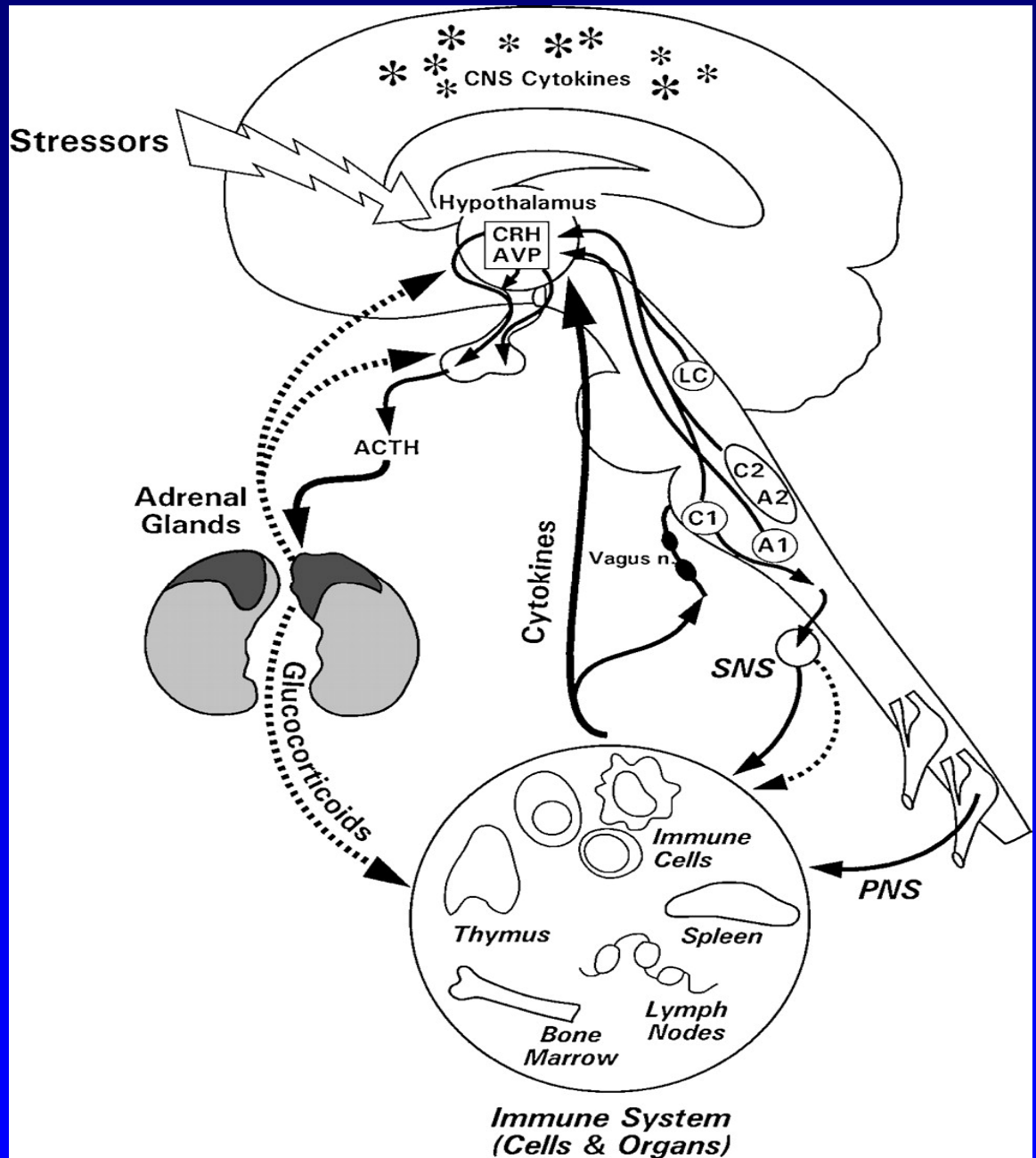


*all ps < or = .05

What causes ongoing inflammation?

- Alterations in immune regulatory systems
 - Hypothalamic-pituitary-adrenal axis

Brain-immune connections

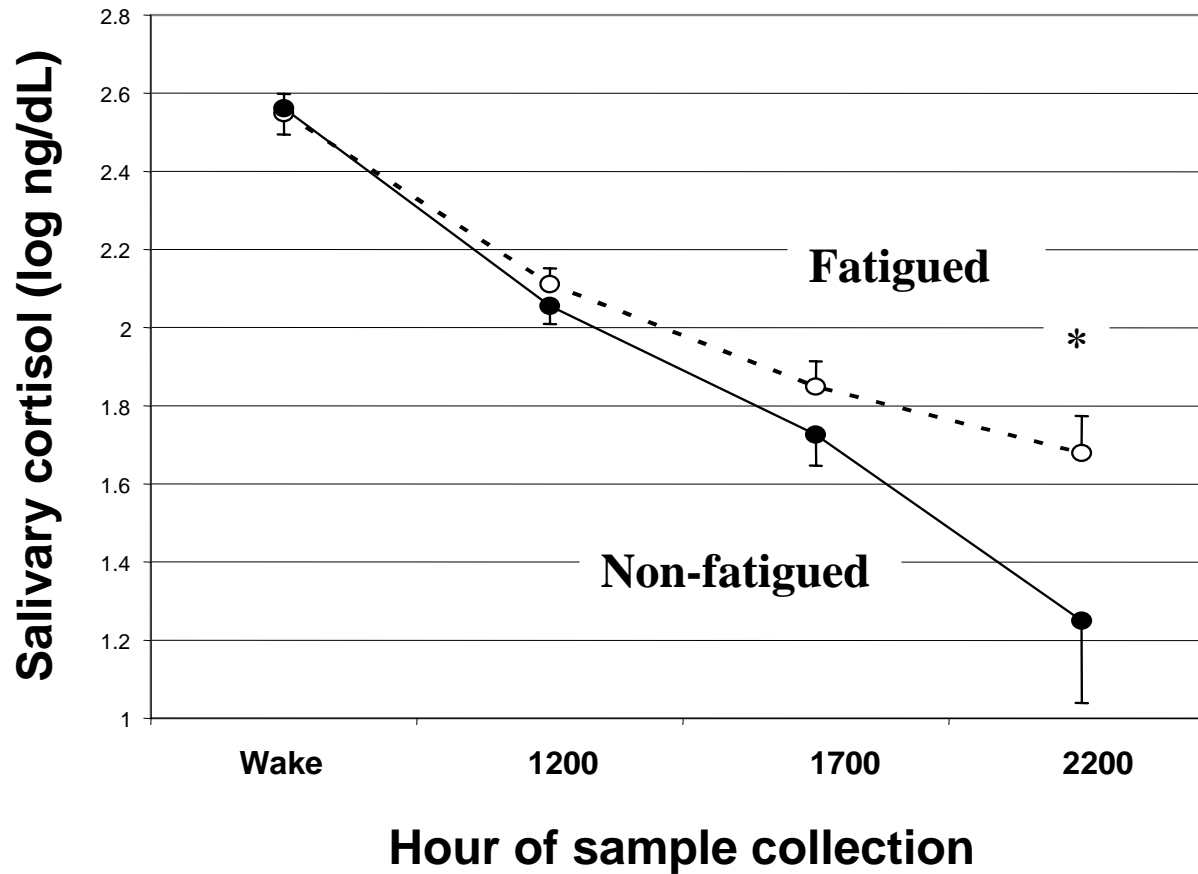


Lower morning serum cortisol

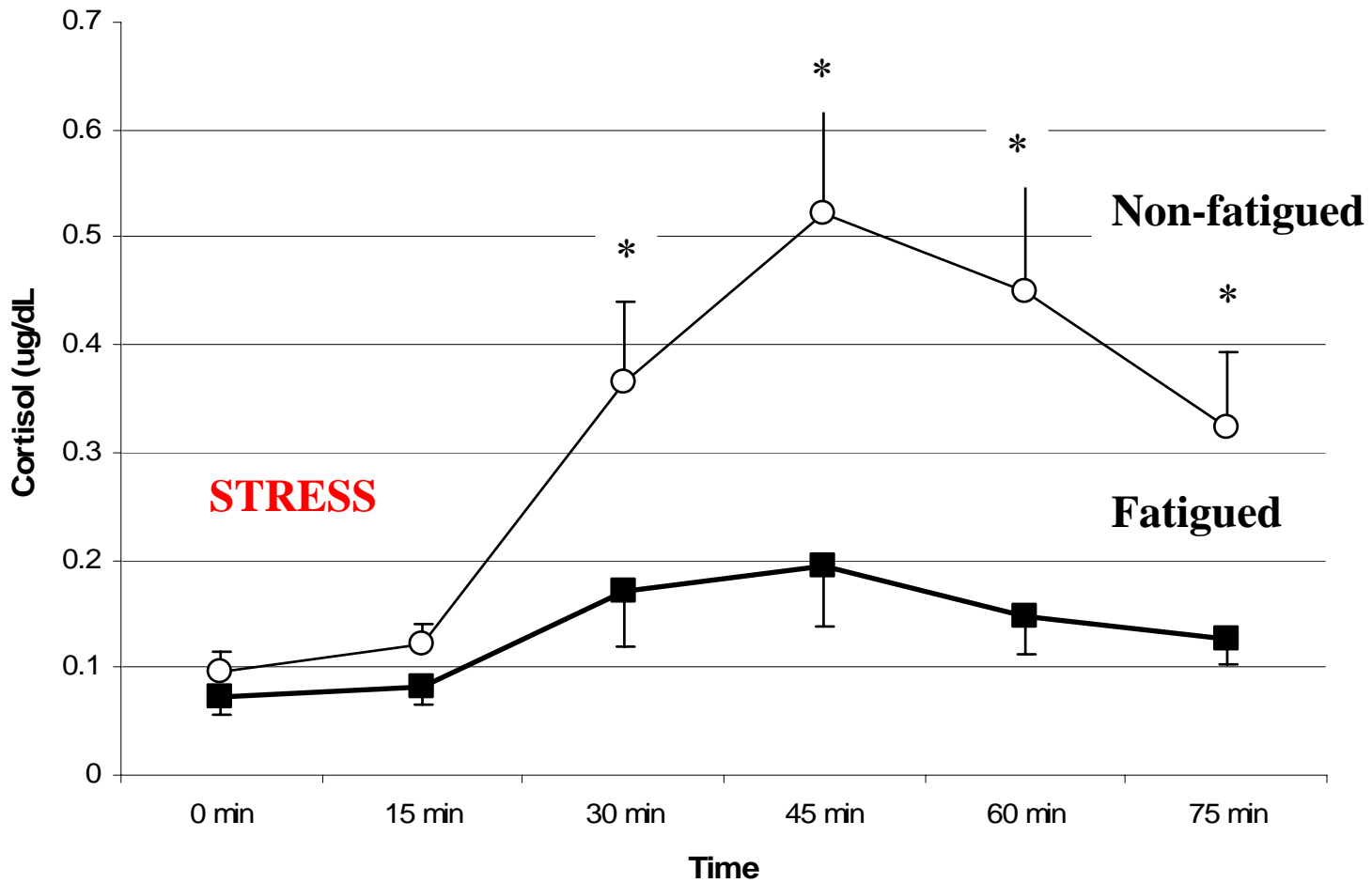
| | Fatigued | Non-fatigued |
|--------------------------------------|-----------------|---------------------|
| Cortisol ($\mu\text{g}/\text{dl}$) | 11.9 (3.7) | 14.0 (3.2)* |

* $p < .05$

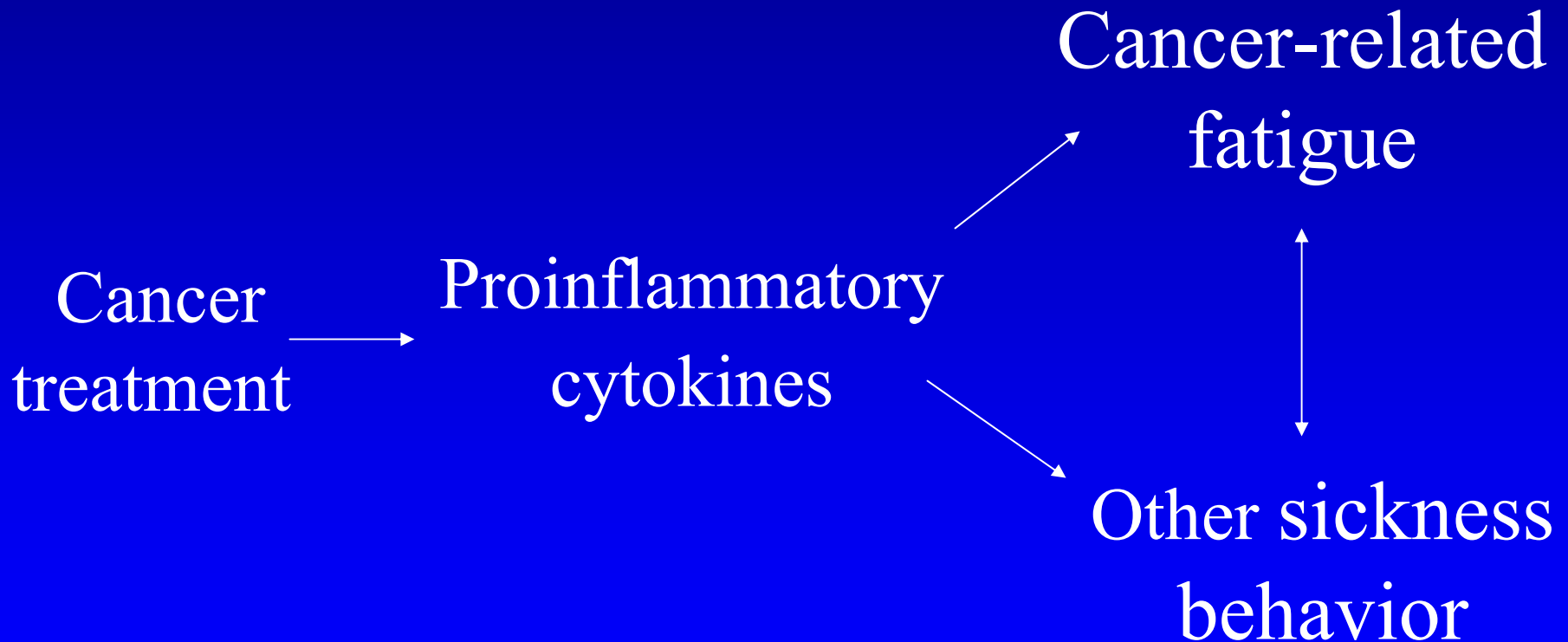
Flattened diurnal cortisol slope



Blunted cortisol response to stress



Model of sickness behavior in cancer



Other sickness behavior

- Injection or induction of proinflammatory cytokines leads to fatigue, depressed mood, cognitive disturbance, and sleep alterations
 - Healthy individuals
 - Cancer patients undergoing immunotherapy
- Cancer patients with depression show elevations in proinflammatory cytokines
- Common underlying mechanism?

Why is this important?

- Understanding mechanisms guides development of targeted therapies for cancer-related fatigue and other symptoms
- Two current trials for cancer-related fatigue
 - Pharmacological: blocking proinflammatory cytokines
 - Behavioral: targeting physiological systems associated with fatigue using yoga

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