

**Diurnal Cortisol Rhythms:
Social Determinants and Role as a Risk,
State or Scar Marker for Major
Depressive Disorder in Youth**

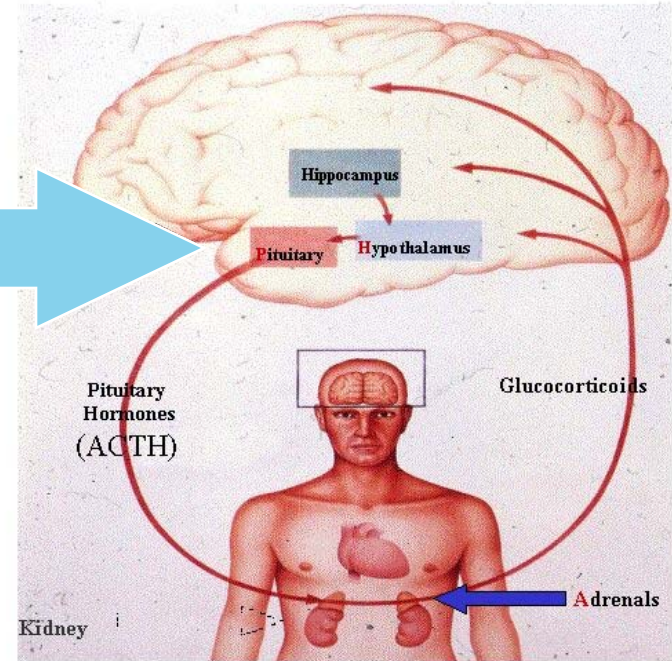
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&

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Northwestern University**

General Research Question



How everyday social and emotional experiences “get under the skin” to influence biology, health and developmental outcomes?

Socioeconomic and Policy Environment

Chronic Social and Emotional Stress:
Social Isolation, Interpersonal Conflict,
Loss, Violence Exposure, Discrimination

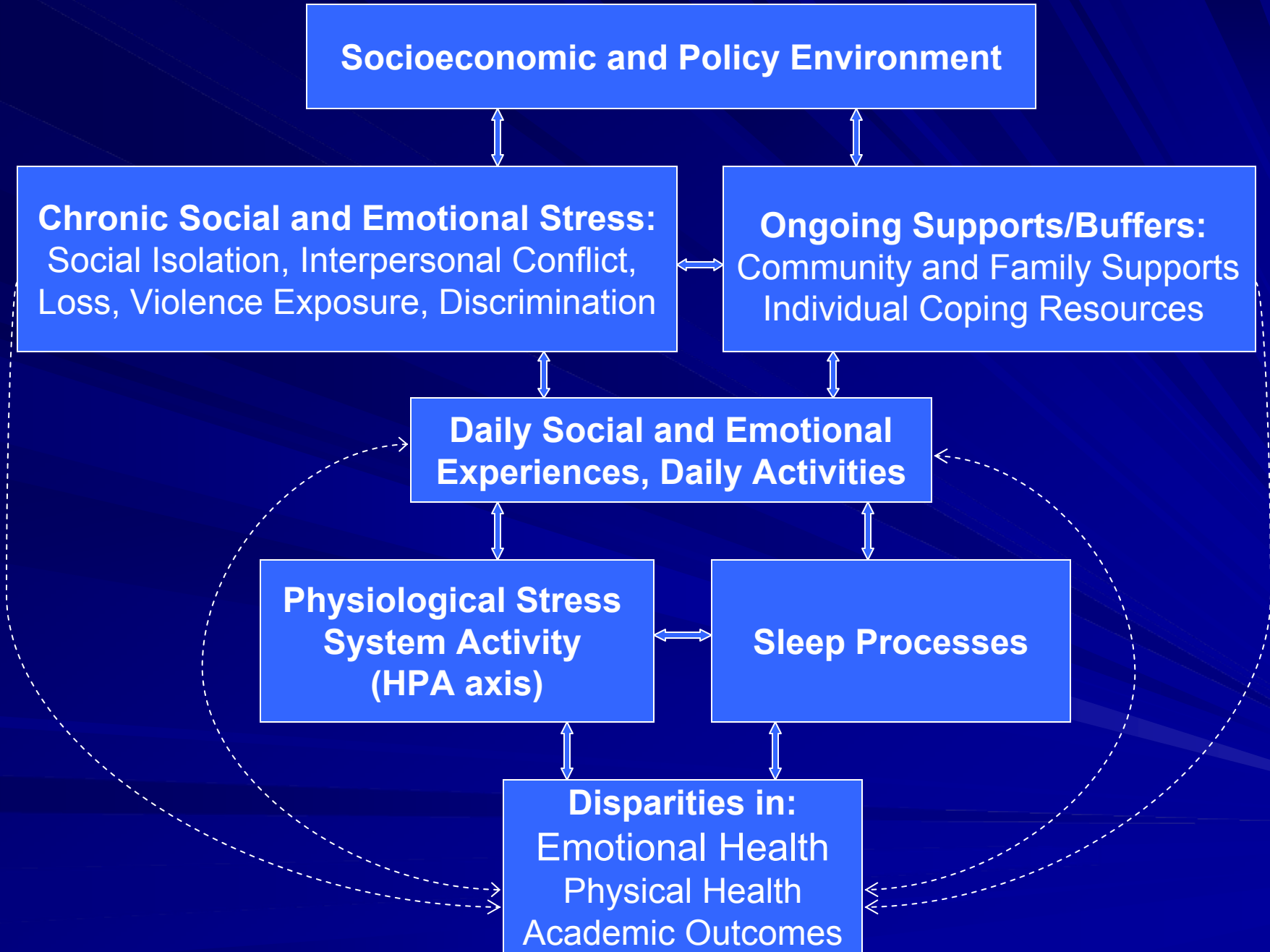
Ongoing Supports/Buffers:
Community and Family Supports
Individual Coping Resources

**Daily Social and Emotional
Experiences, Daily Activities**

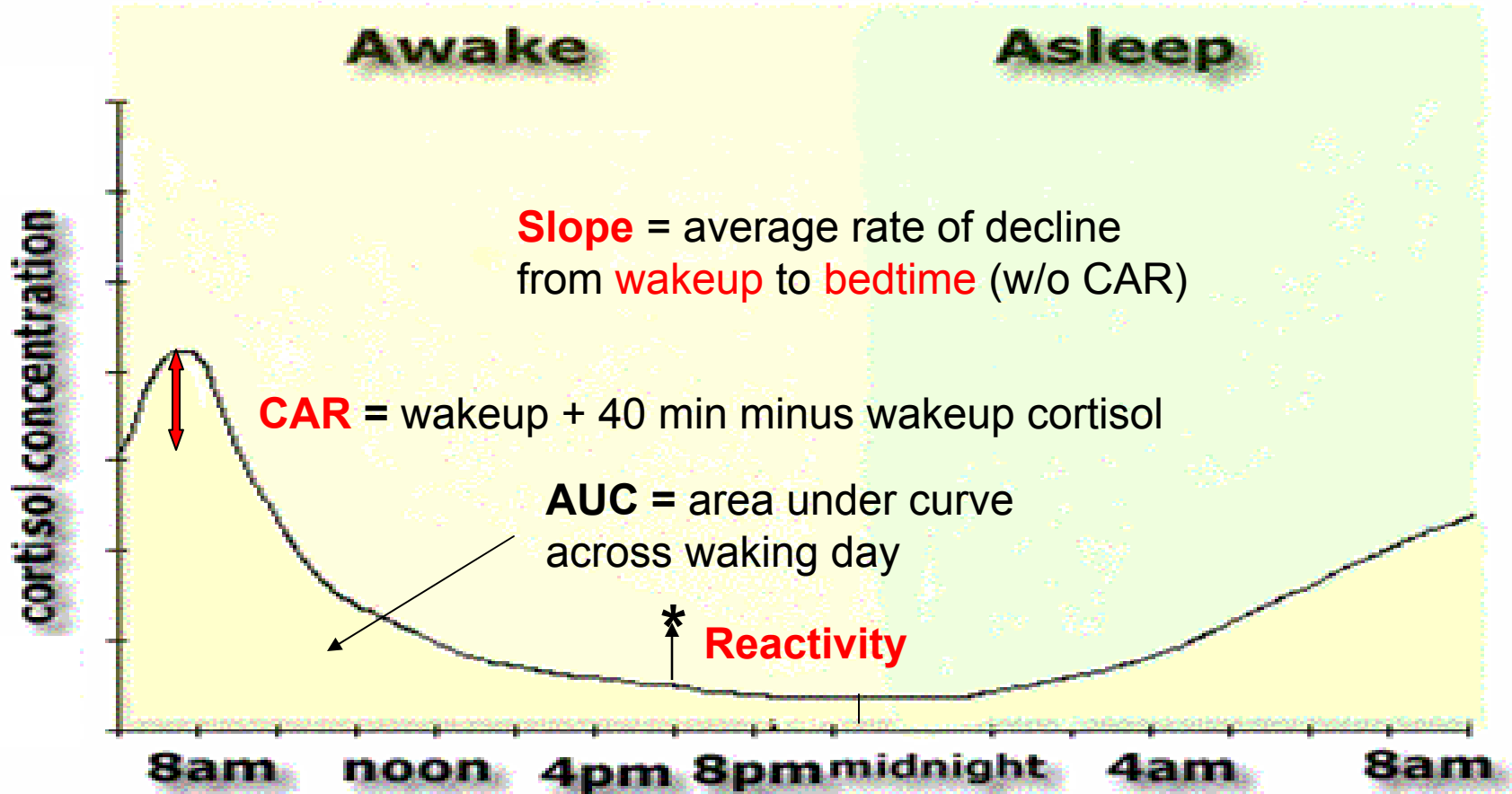
**Physiological Stress
System Activity
(HPA axis)**

Sleep Processes

Disparities in:
Emotional Health
Physical Health
Academic Outcomes



Cortisol Diurnal Rhythm and its “Markers”



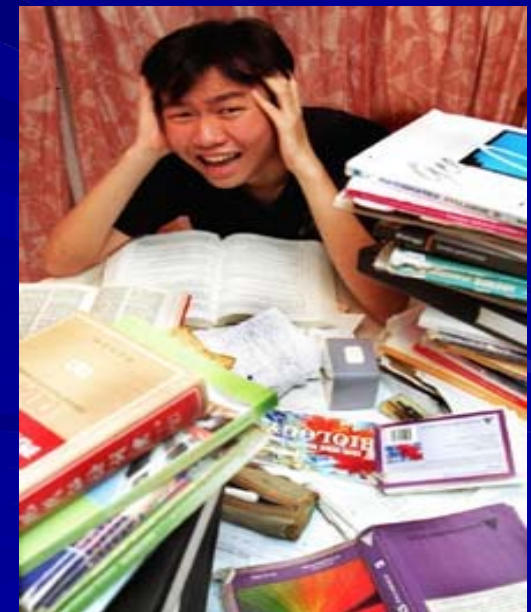
Reactivity = cortisol higher than expected for that time of day for that person

Different Cortisol Parameters:

- **Measure distinct aspect of cortisol activity**
- **Are differentially influenced by psychosocial events**
- **Are differentially related to developmental and health outcomes**
- **Are potentially regulated by different neurobiological pathways and have different neurobiological impacts**
- **May change over differing time scales**
- **Will illustrate with examples from my study of the development of major depressive disorder in youth**

Youth Emotion Project

- Longitudinal study of factors contributing to the emergence of emotional disorders over the transition to adulthood
- Youth oversampled for risk for emotional disorder based on high levels of neuroticism
- Diverse sample recruited age 17, followed for 4 + years
- Full study: N=627
- Cortisol study: N=300

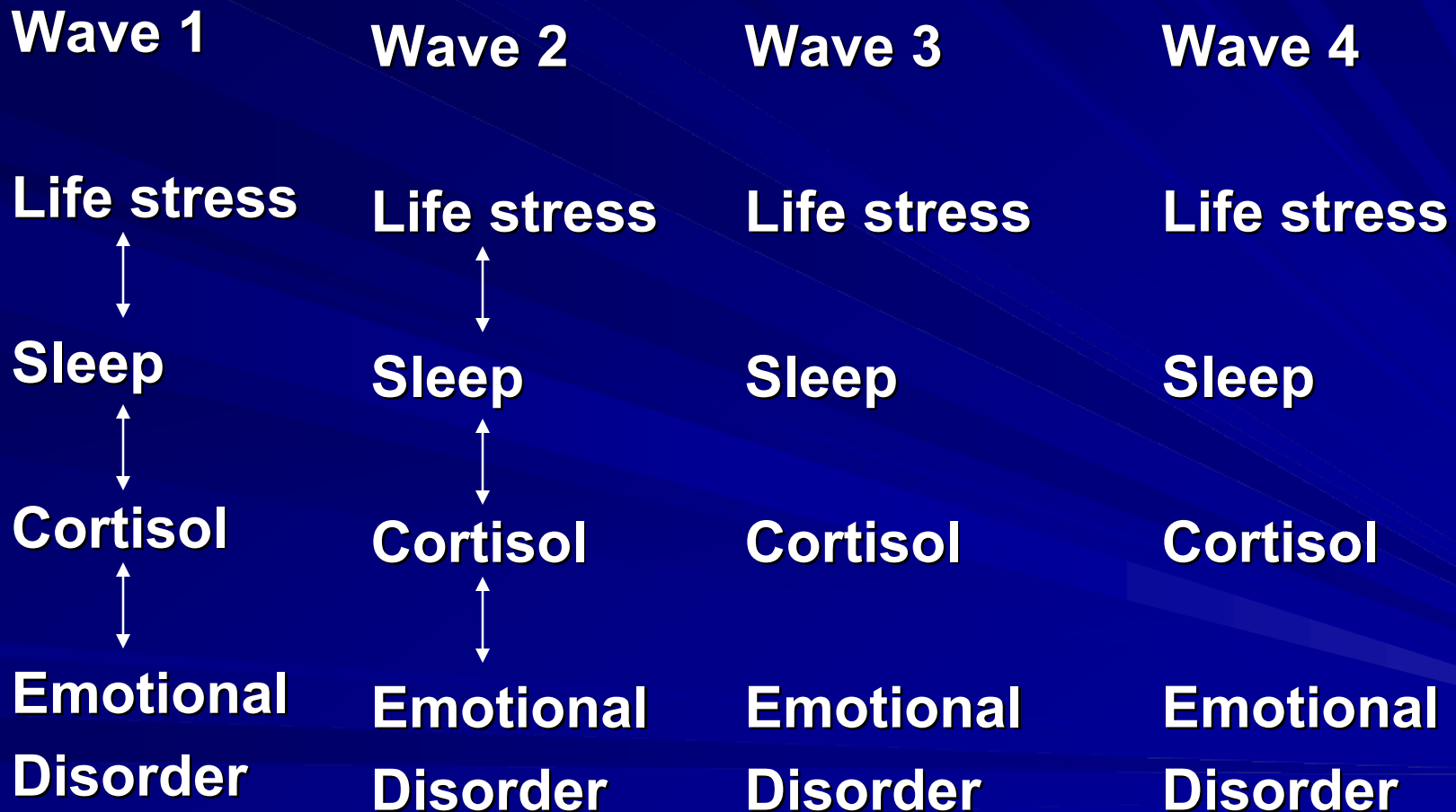


Measures (repeated yearly)

- **HPA axis activity / cortisol**
 - Salivary cortisol, 6x per day for 3 days
- **Momentary and daily stress**
 - ESM diary method, 6x per day for 3 days
- **Chronic and Episodic Life Stress**
 - Hammen's Life Stress Interview
- **Psychopathology**
 - SCID diagnostic interview
 - DSM IV diagnoses of Mood and Anxiety Disorders and Comorbid Mood and Anxiety
- **Sleep Timing and Quality via Actigraphy**

Data Overview

(Cross-sectional Models)

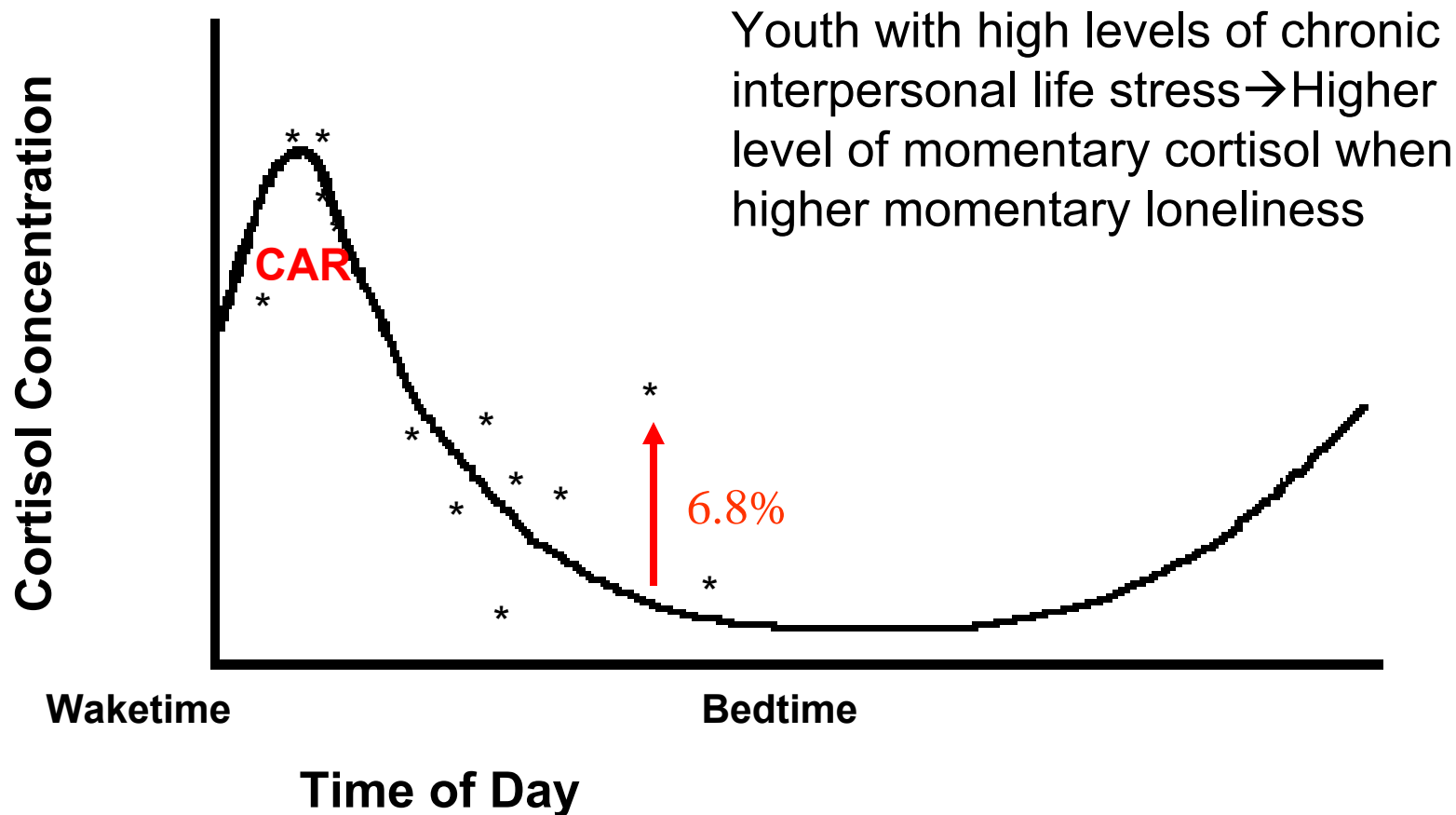


Loneliness and Cortisol

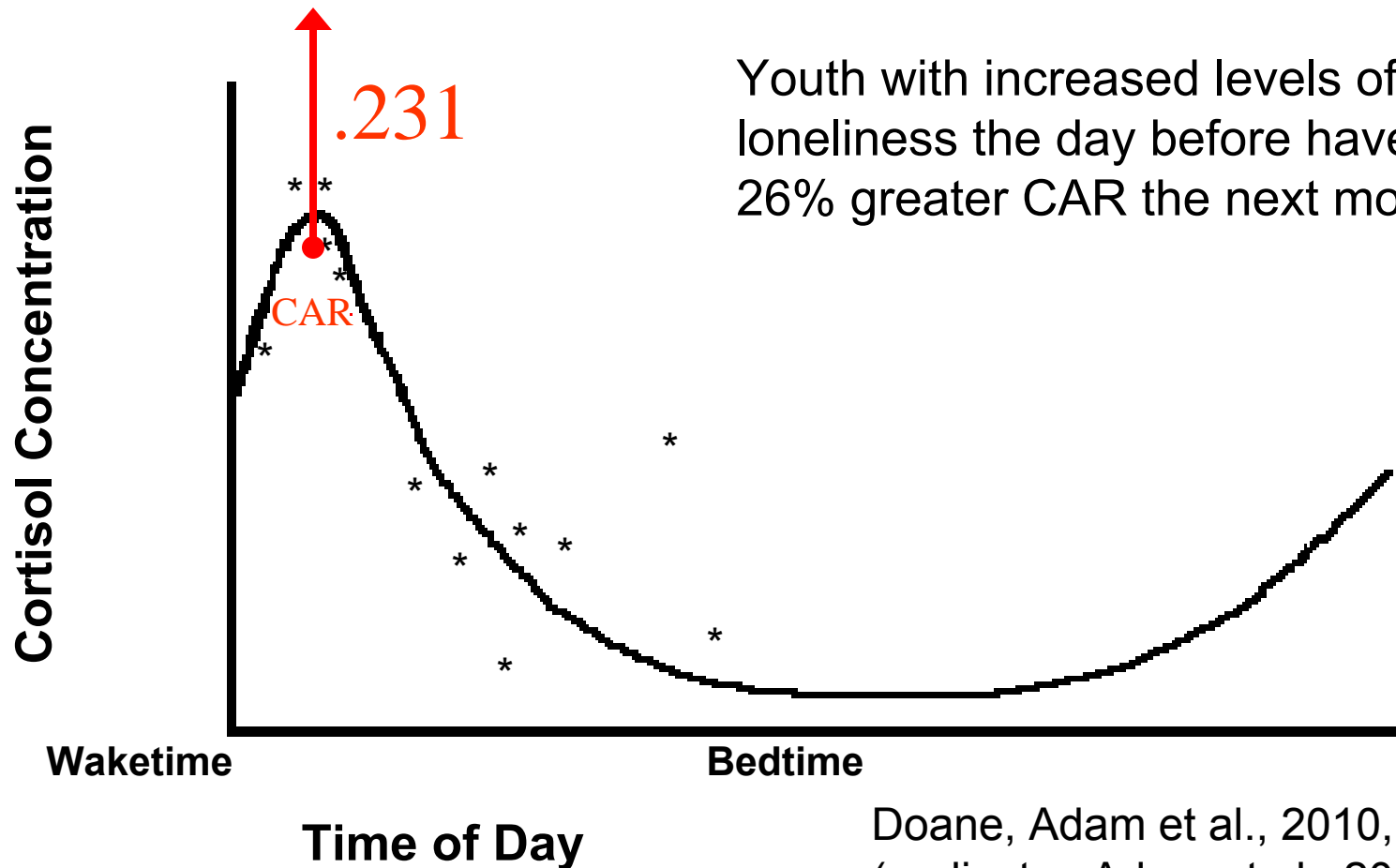
(Doane & Adam, 2010, PNEC, 35, 430-441)

- To what degree are state (momentary and daily) and trait (typical) experiences of loneliness related to cortisol levels?
- Three Level Hierarchical Linear Growth Models
 - Level 1: Momentary Cortisol and Emotions
 - Level 2: Day Level Predictors
 - Level 3: Person Level Predictors and Covariates

Dependent variable: momentary cortisol



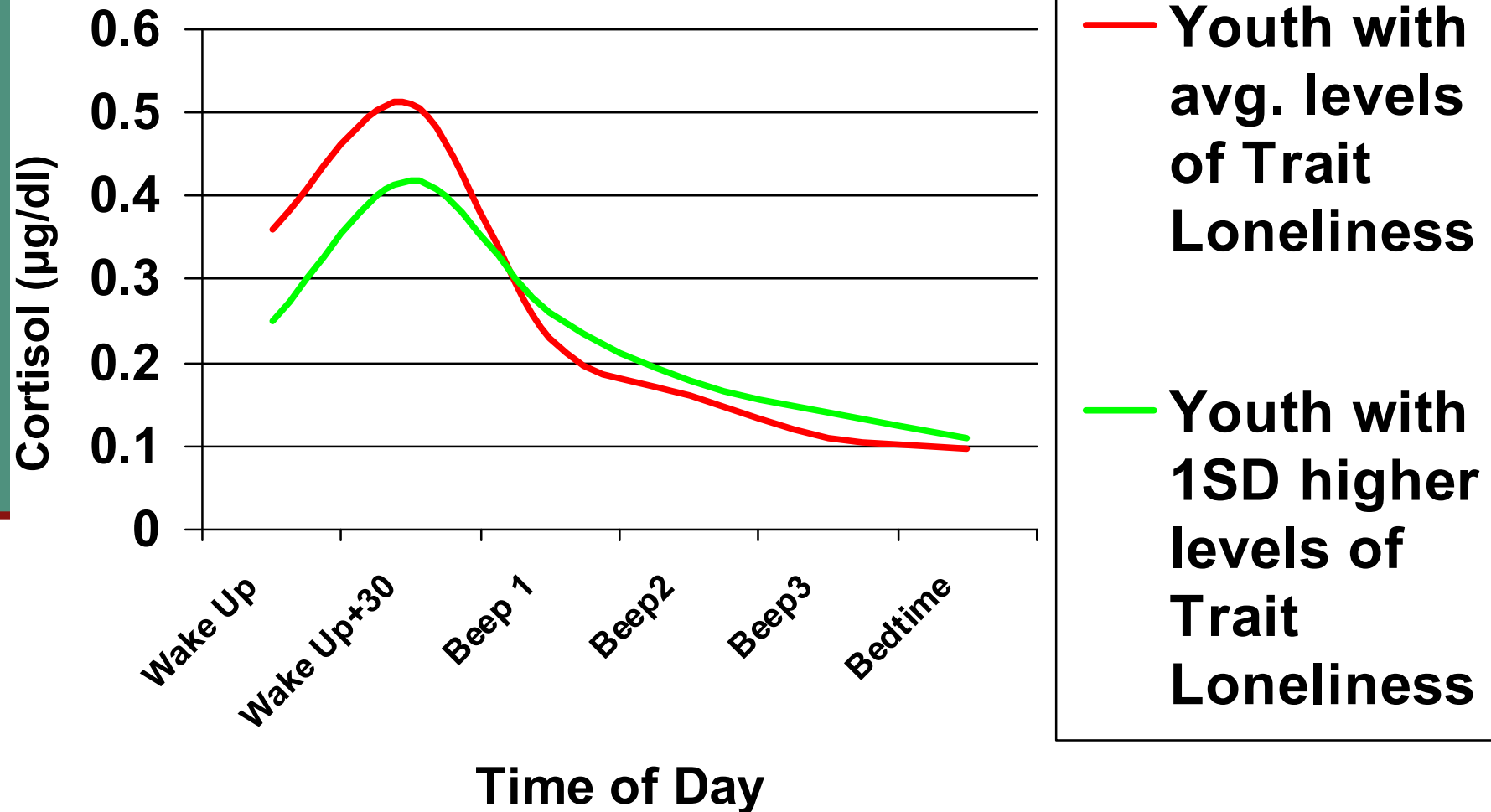
Higher Levels of Loneliness the day before...



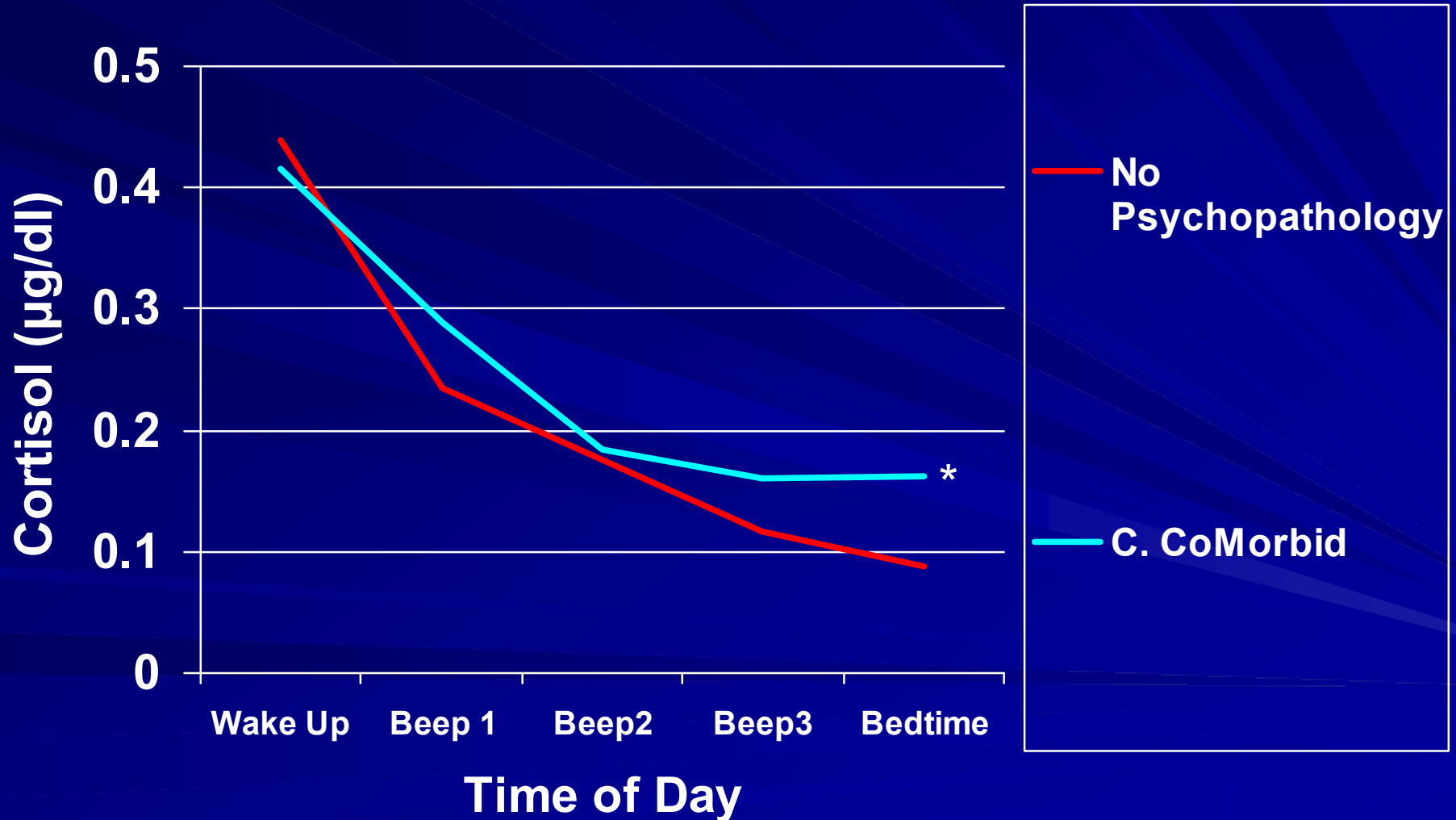
Youth with increased levels of loneliness the day before have 26% greater CAR the next morning

Doane, Adam et al., 2010, PNEC
(replicates Adam et al., 2007, PNAS)

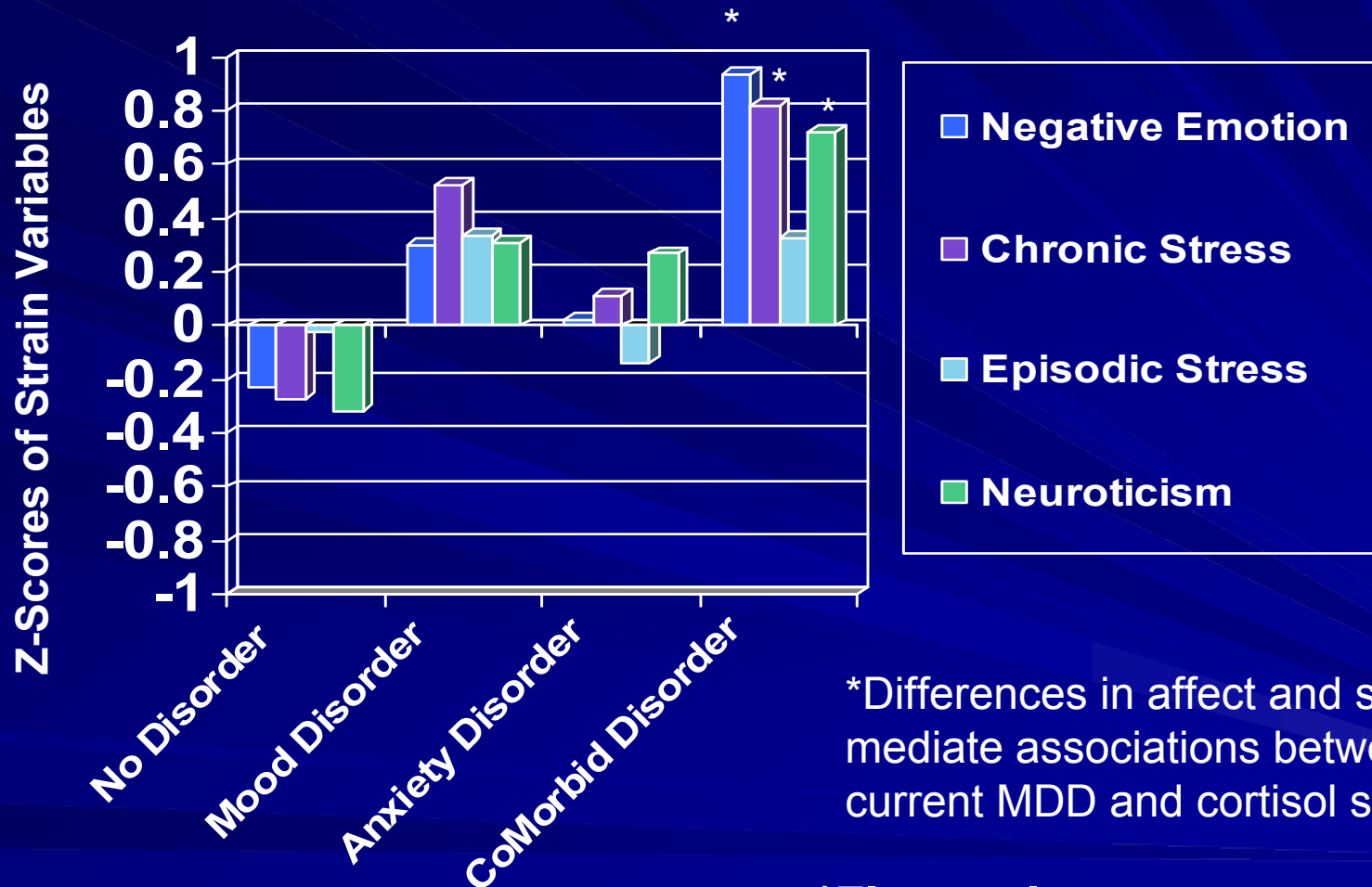
Flatter diurnal rhythm for youth with high levels of trait loneliness



Diurnal Rhythm by Psychopathology



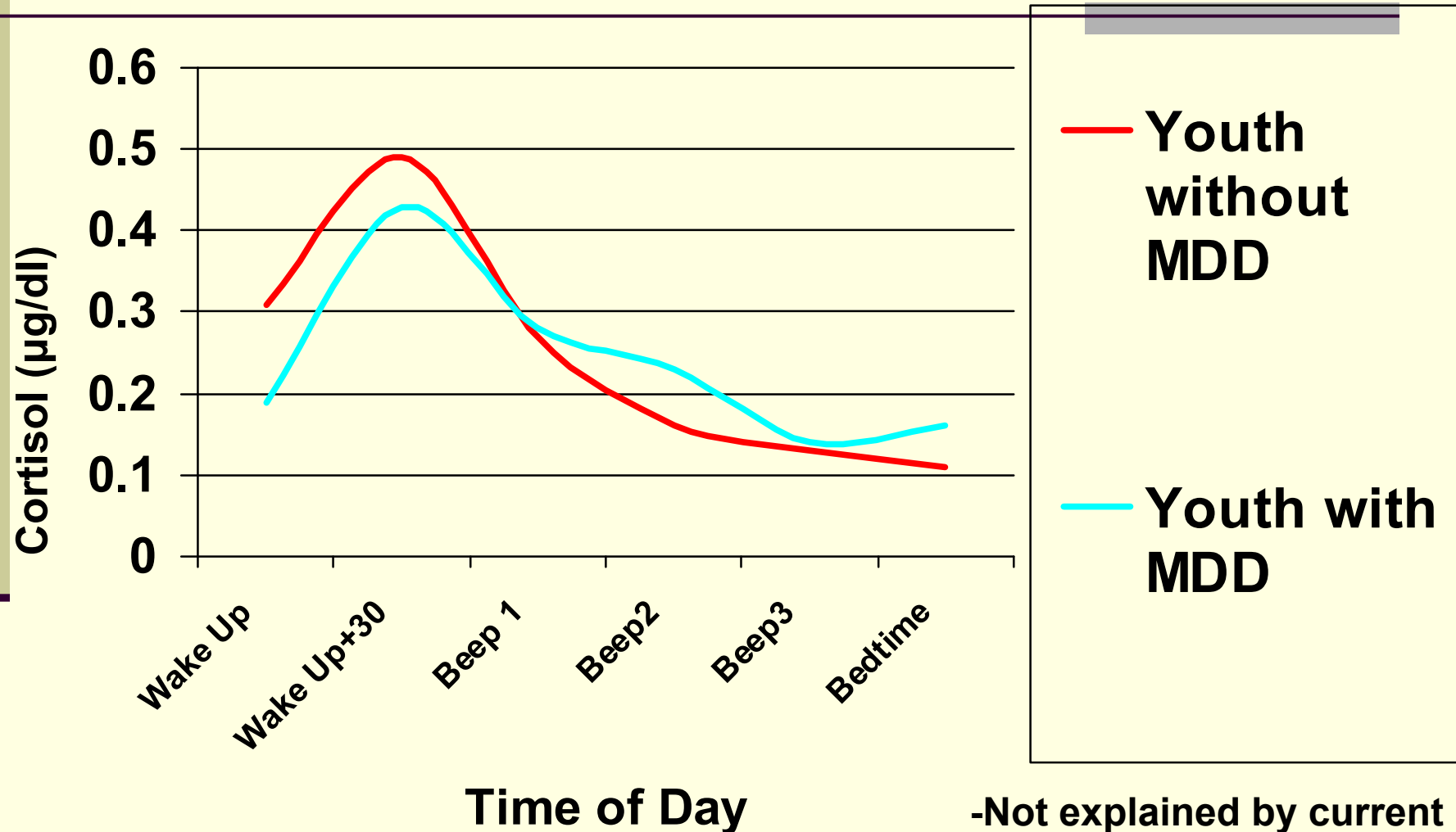
Psychopathology and Affective Experiences



*Differences in affect and stress mediate associations between current MDD and cortisol slopes

***Flatter slope = state marker?**

Diurnal Rhythm by Past MDD



-Not explained by current affective experience
=SCAR MARKER?

Data Overview (Longitudinal Models)



Wave 1

Wave 2

Wave 3

Wave 4

Life stress

Life stress

Life stress

Life stress

Sleep

Sleep

Sleep

Sleep

Cortisol

Cortisol

Cortisol

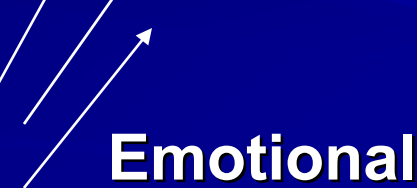
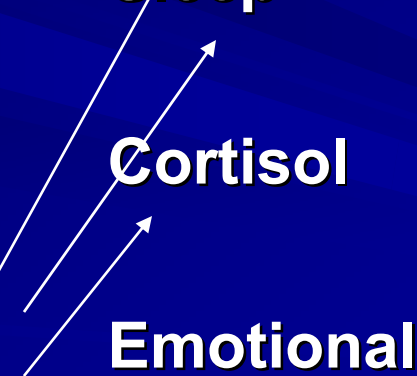
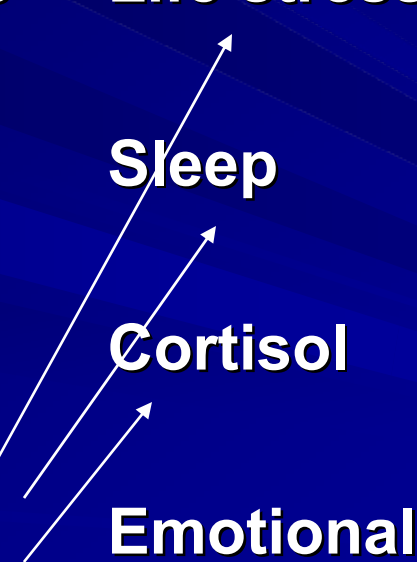
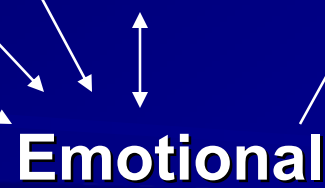
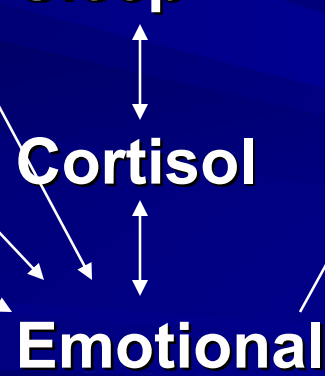
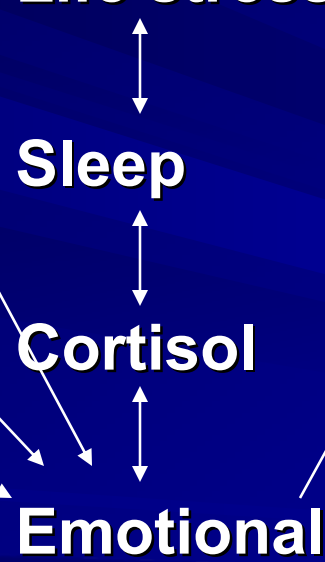
Cortisol

**Emotional
Disorder**

**Emotional
Disorder**

**Emotional
Disorder**

**Emotional
Disorder**



Longitudinal Prediction of New Cases of Mood Disorders

	β	<i>p</i> -value	Exp(β)
Negative Emotion on Days of Cortisol Testing	.675	.053	1.965
Chronic Relationship Stress	.198	n.s.	1.219
Episodic Stress	.910	.011	2.485
Neuroticism	.740	n.s.	2.097
CAR	1.217	.041	3.378
Cortisol AUC	.478	n.s.	1.612
Cortisol Slope	-.700	n.s.	.497

Independent predictors of new onset of mood disorders 1.5 years later:

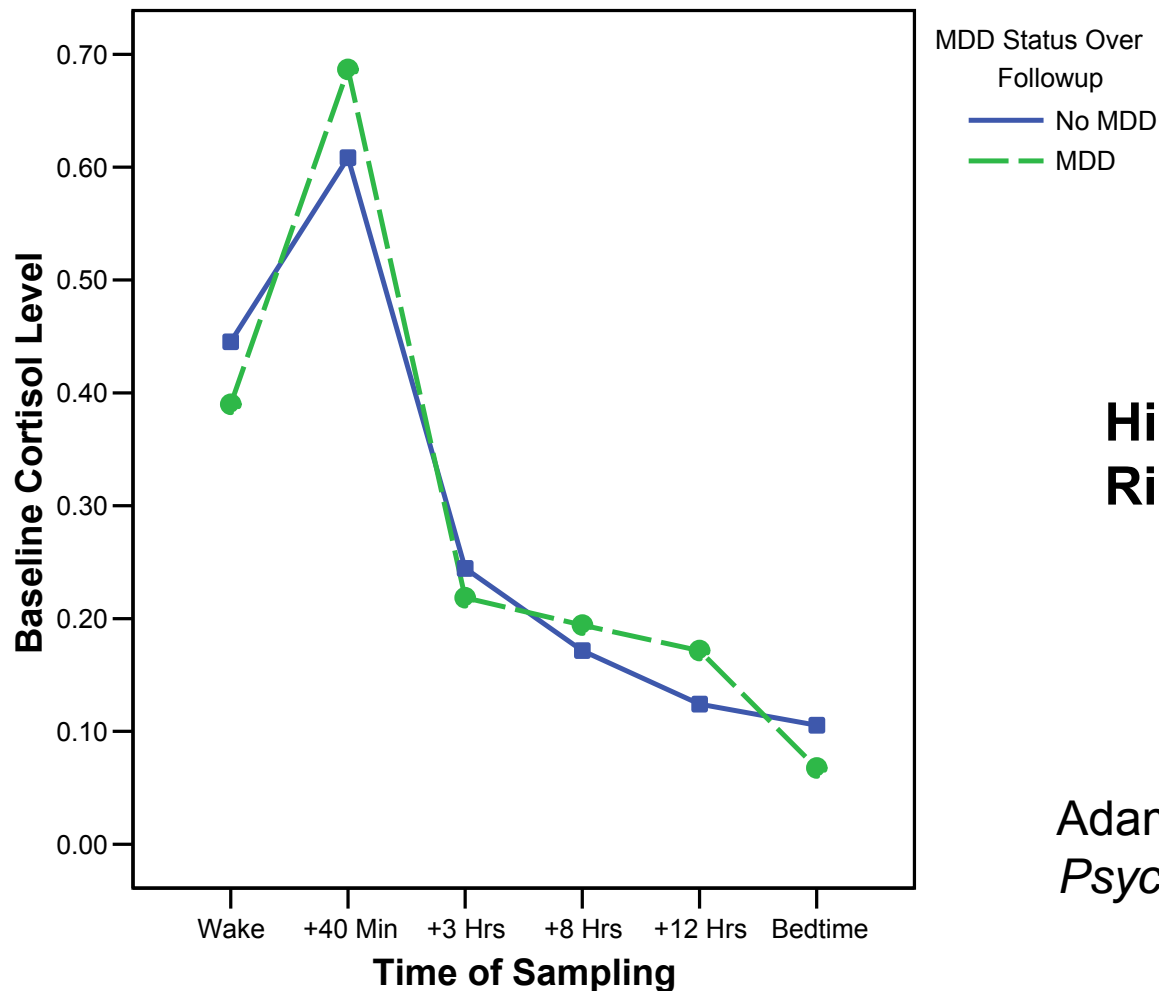
T1 Negative Emotion on Days of Cortisol Testing (<.10)

T1 Episodic Stress (Life Events) (<.05)

T1 Cortisol Awakening Response (<.05)

Also controlling for caffeine, nicotine, birth control use, race/ethnicity, SES, age, gender, % of time alone

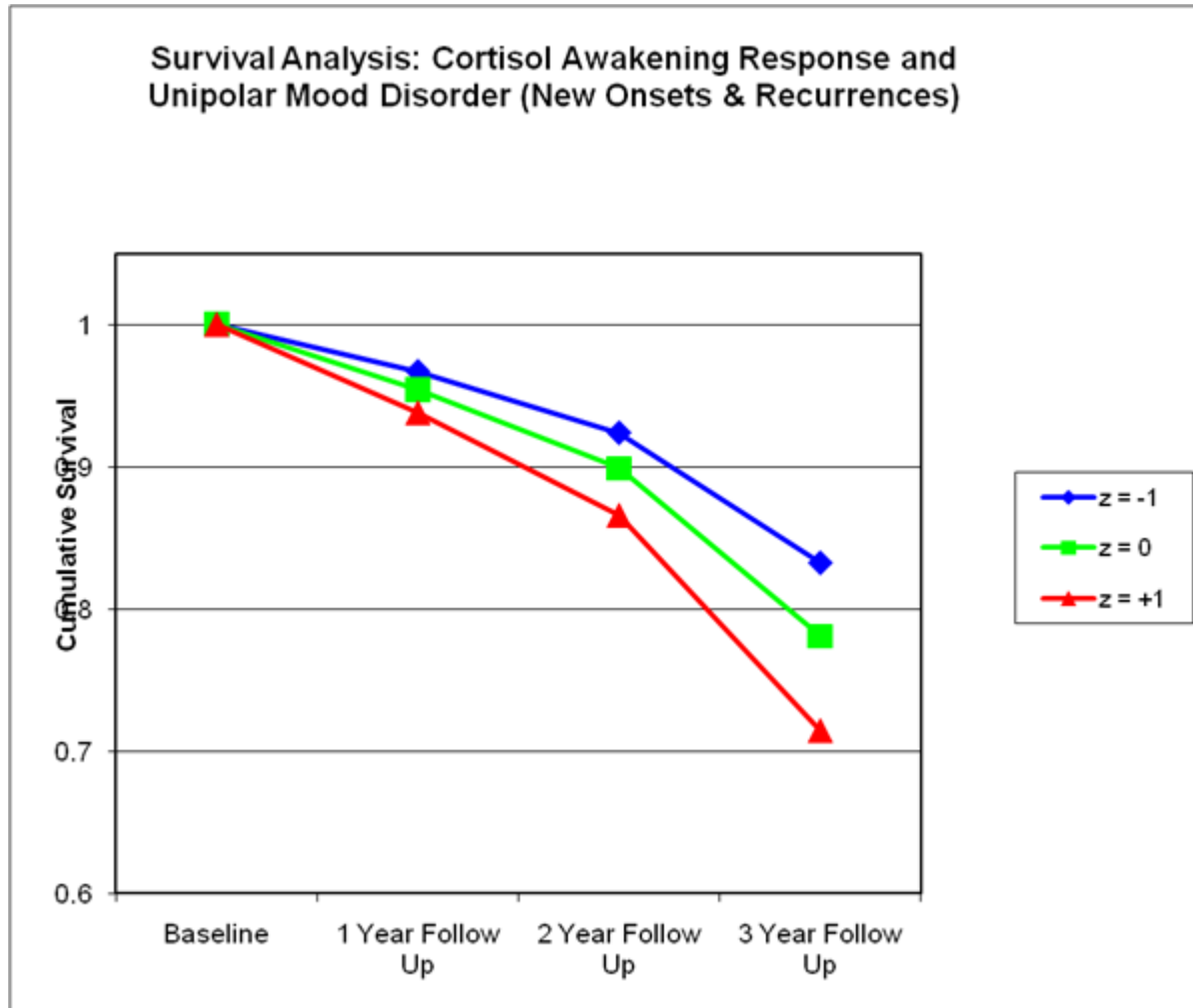
Figure 1. Baseline diurnal cortisol profiles of participants who do (dashed line) and do not (solid line) go on to develop an episode MDD over the following year.



**High CAR=
Risk Marker?**

Adam et al. (In press),
Psychoneuroendocrinology.

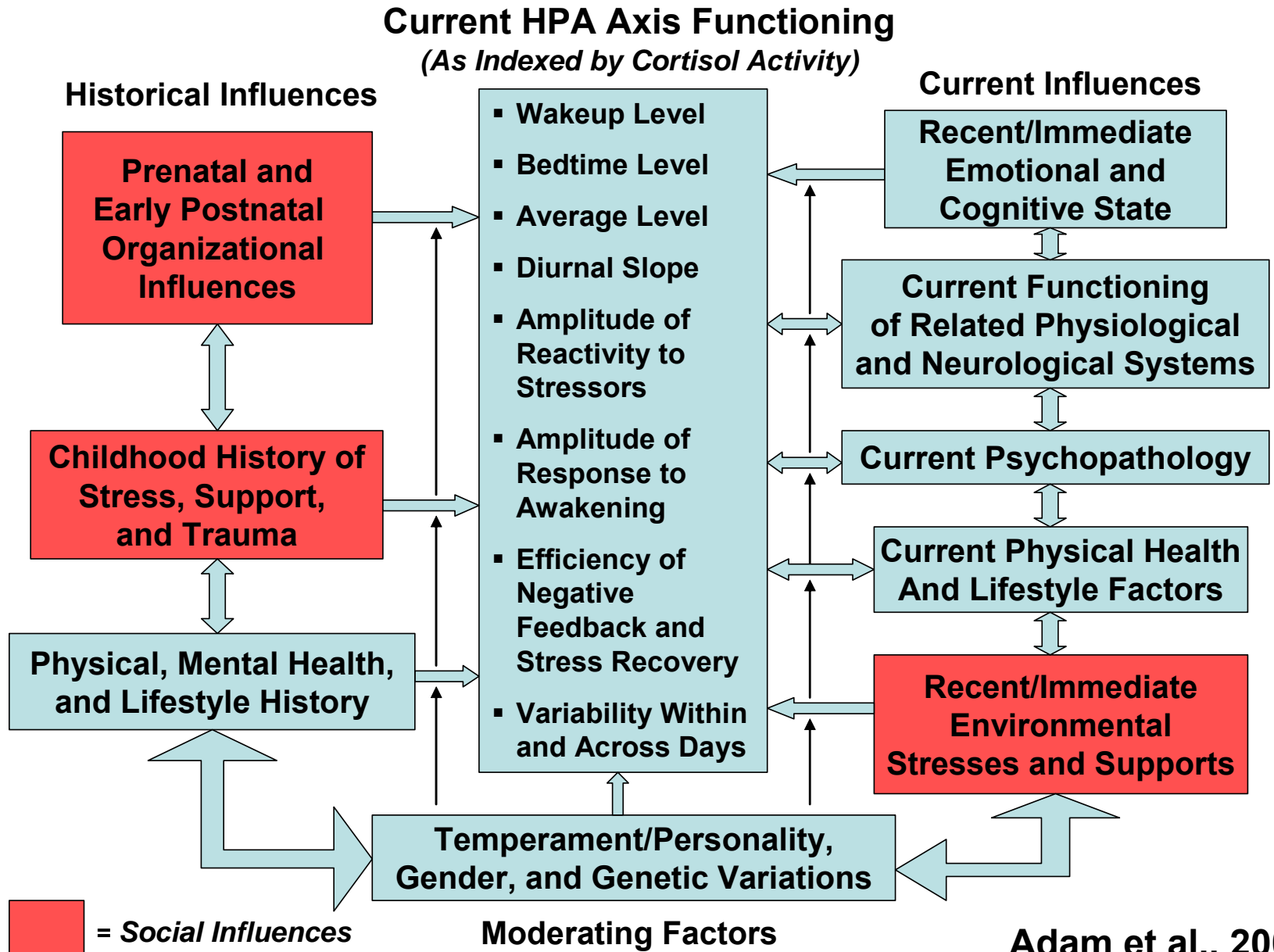
Survival Analysis



Key Points

- Multiple markers/indices of cortisol exist, defined by variations in the diurnal pattern
- Different cortisol markers mean different things
- In relation to MDD, my research suggests:
 - Flatter diurnal cortisol slope = **state and scar**
 - Higher cortisol awakening responses = **risk**
- HPA axis function **dynamically changes** with age, current stress, and illness stage
- **Need longitudinal, developmental data** and a nuanced understanding of a system in order to understand the role of a particular marker/system in the etiology of disorder

Multiple Influences on Cortisol Parameters



Thanks to...

Collaborators

- Sue Mineka, Rick Zinbarg, Michelle Craske
- Leah Doane, Amy DeSantis, Suzanne Vrshek-Schallhorn
- John Cacioppo, Louise Hawkley, Brigitte Kudielka

Participants

- Stress in the Working Family Study Participants
- Youth Emotion Project Participants
- CHASRS participants

Funders

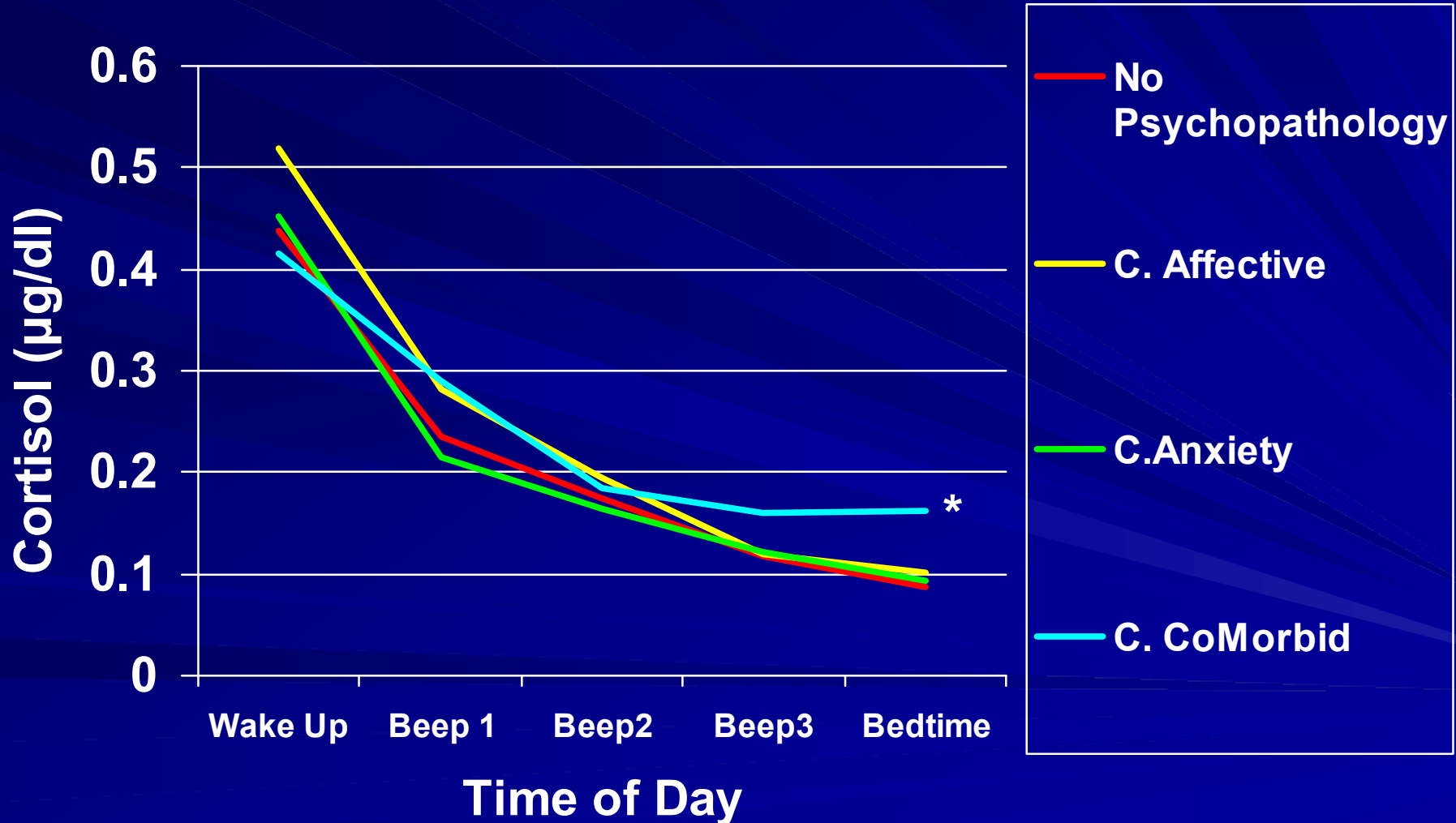
- National Institute of Mental Health
- National Institute on Aging
- National Institute of Child Health & Human Development
- National Academy of Education
- Alfred P. Sloan Foundation
- Spencer Foundation
- **W.T. Grant Foundation**

Extra Slides – For Q and A

Three Level Model

- Level 1: $\text{Cortisol} = \pi_0 + \pi_1 * \text{Time Since Waking} + \pi_2 * \text{Time Since Waking}^2 + \pi_3 * \text{CAR} + e$
- Level 2: π_0 to $\pi_3 = b_{i0} + b_{ij} * \text{Prior Day Experience} + b_{ij} * \text{Same Day Experiences} + b_{ij} * \text{Day Level Controls} + r_{ij}$
- Level 3: b_{i0} to $b_{ij} = g_{ij0} + g_{ijk} * \text{Person Level Controls} + g_{ijk} * \text{Average Experiences} + u_{ijk}$

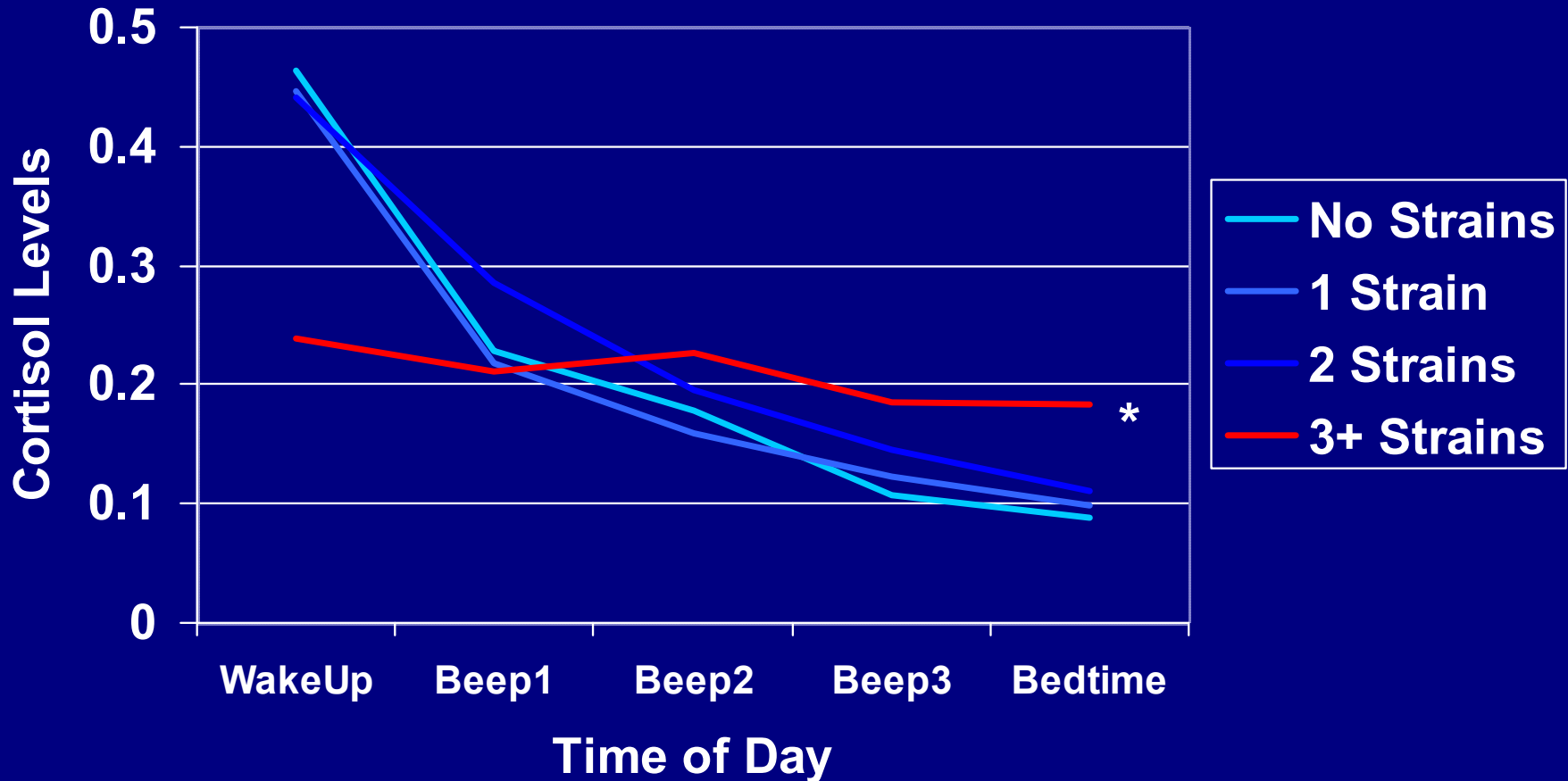
Diurnal Rhythm by Psychopathology (Wave 1, Cross-sectional)



Cortisol Slopes with Psychopathology and Emotional Strain Variables (simple correlations)

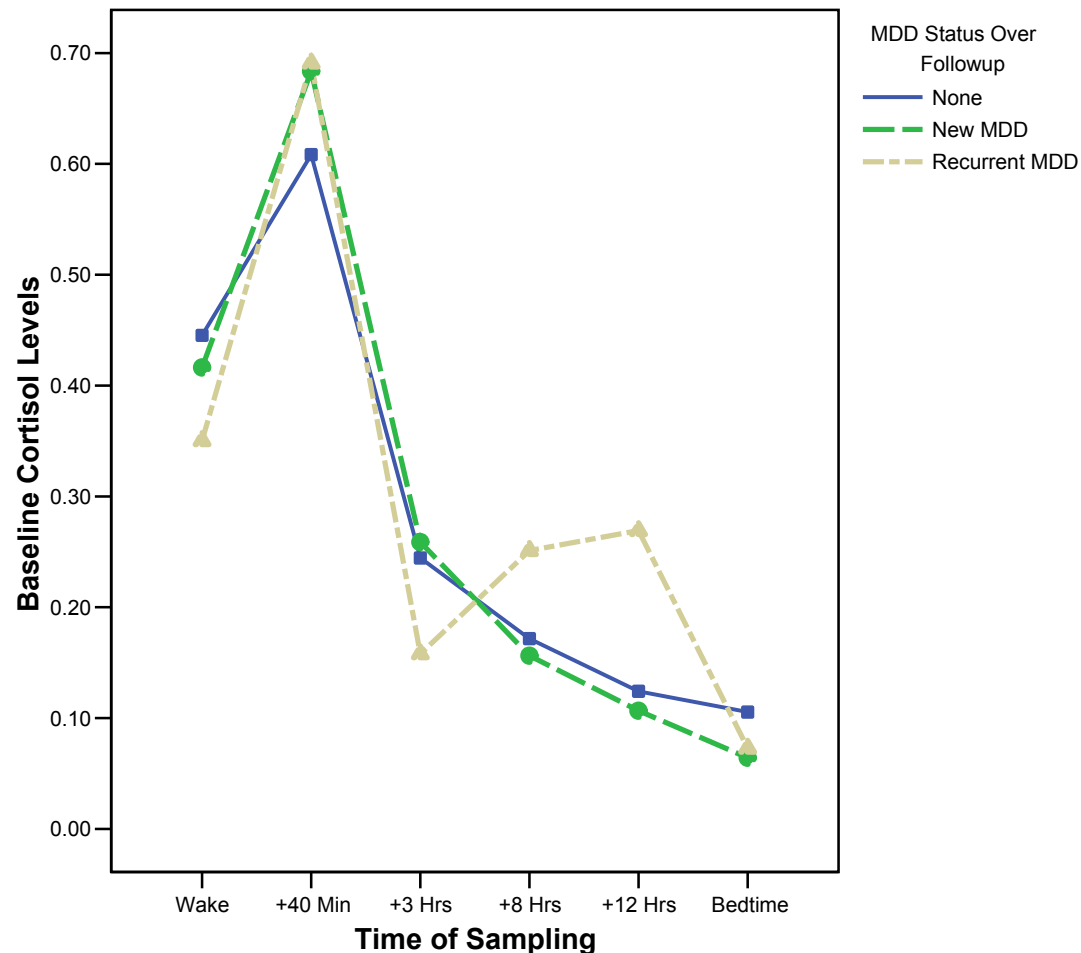
	Correlations with Slopes	
	Pearson <i>r</i>	<i>p</i> -value
Current Mood	.032	n.s.
Current Anxious	.023	n.s.
Current CoMorbid	.183	.005
ChronicRelStress	.156*	.016
Episodic Stress	.151**	.020
High Neuroticism	.174**	.008
ESM Negative Emotion	.207**	.001

Diurnal Rhythm by Cumulative Emotional Strain

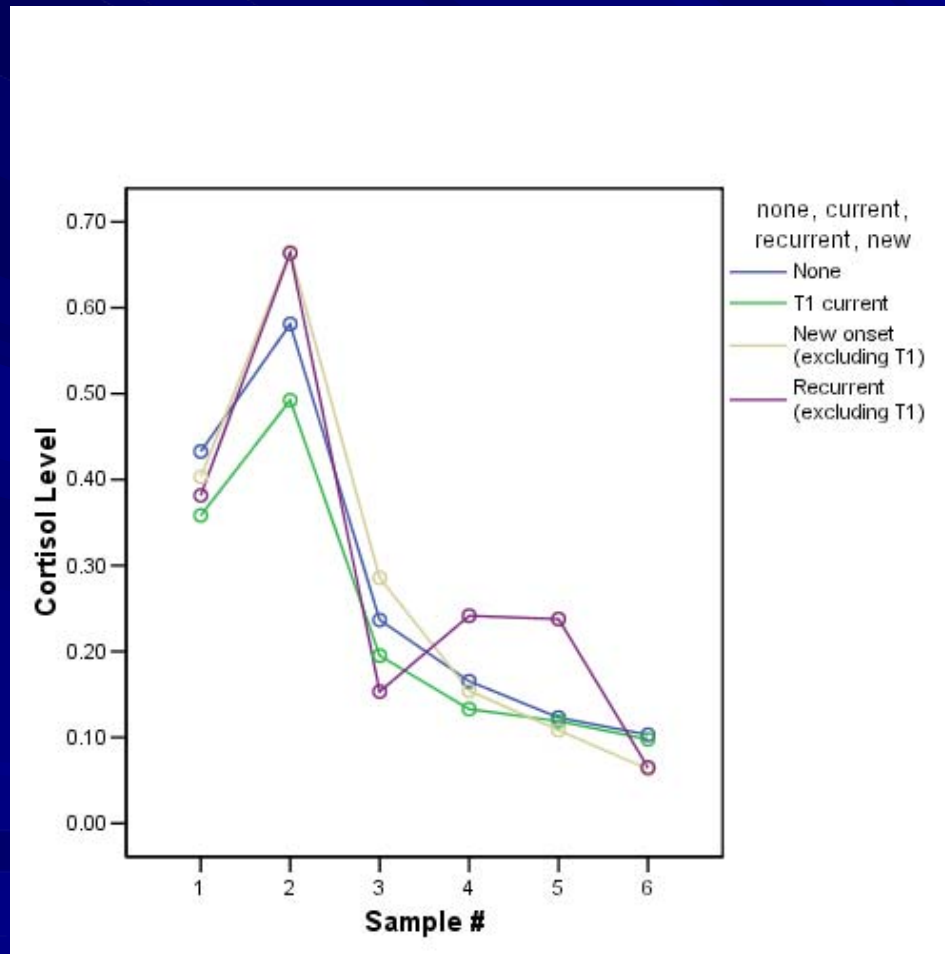


*Dramatic flattening with 3 out of 4 of: high chronic relationship strain, high recent life stress, high neuroticism, and high state negative affect

Figure 2. Baseline diurnal cortisol profiles of Ps who do (dashed lines) and do not (solid line) develop an episode MDD over the following year, differentiating *initial onsets* of MDD (dark dashed line) and *recurrences* (light dashed line).



Current Depression if anything is associated with a low CAR



Relationships among Strain and Psychopathology Variables

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Mood	1	-.011	-.091	.165*	.045	.047	.069
Anxiety		1	-.112	.127*	.052	.140*	.163*
CoMorbid			1	.299**	.126*	.342**	.154*
Chronic				1	.215**	.220*	.155*
Episodic					1	.221**	.09
ESM Negative						1	.277**
Neuroticism							1

Intercorrelations Among Cortisol Indices

	(1)	(2)	(3)
CAR	1	.298**	.280**
AUC	.298**	1	.413**
Slope	.280**	.413**	1

Cortisol Parameters and Cardiovascular Risk

	Waist/Hip Ratio	HDL Cholesterol	Total/HDL Cholesterol
> Cortisol Awakening Response	.29**	-.25*	.25*
Flatter Cortisol Slope	.28*	-.24*	.25*

Controlling for age, SES, smoking, alcohol, time of awakening

Steptoe et al., 2004

Central Adiposity and Cortisol Responses to Awakening

Cortisol Slopes and Breast Cancer Survival

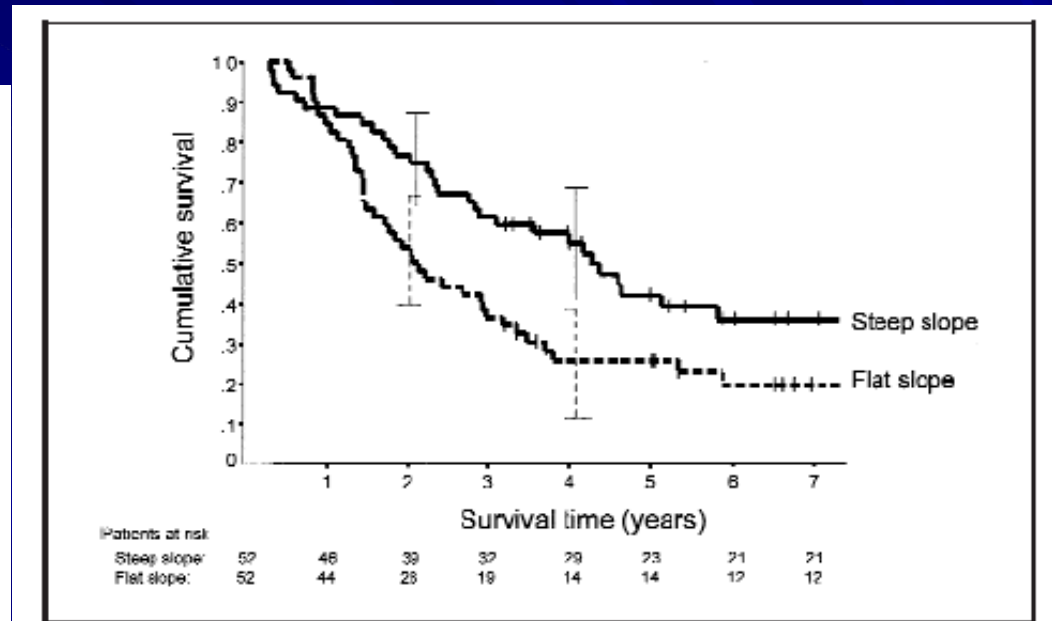
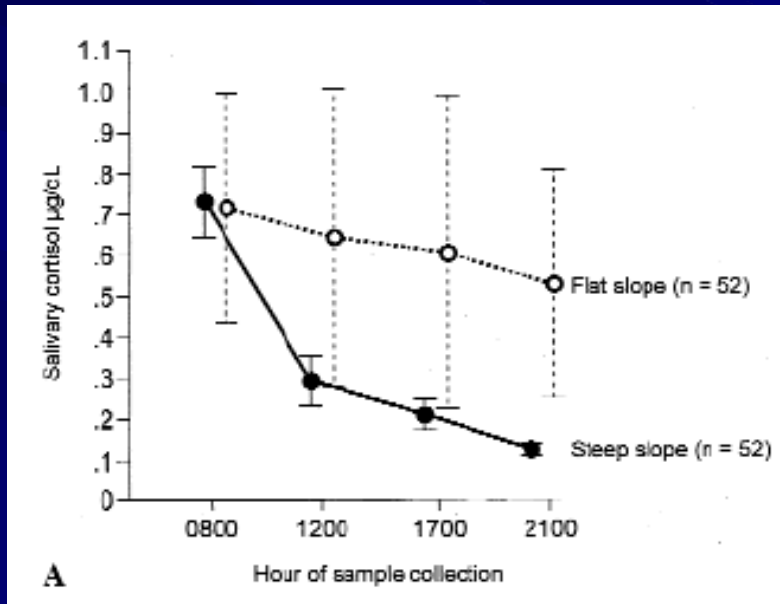


Fig. 2. Kaplan-Meier survival curves for patients split into two equal groups at the median diurnal cortisol slope ($-0.091 \log [\mu\text{g}/\text{dL}]$ per hour). This grouping was performed only to illustrate survival curves representing patients with relatively steep versus flat cortisol slopes. The definitive survival analysis was conducted on the entire sample using the continuous variables of cortisol slope and survival time in a Cox regression. Patients with relatively flat cortisol slopes experienced shorter subsequent survival (Cox proportional hazards, two-tailed $P = .0036$). Among the patients split at the median cortisol slope, 77% of those with flat rhythms died, after surviving an average of 3.2 years (broken line). In contrast, 60% of the patients with relatively steep rhythms died, but they survived more than 1 year longer on average, with an average survival of 4.5 years (solid line). Survival plots of these groups diverged significantly (log-rank, two-tailed $P = .016$). Patients still living at the time of analysis are indicated by black vertical slash marks. The numbers of living patients at each year mark are listed for the "flat-slope" and "steep-slope" groups whose survival curves are shown in the figure.

Sephton, Sapolsky, Kraemer, Spiegel, (2000) Journal of the National Cancer Institute, 92 (12), 994-1000