

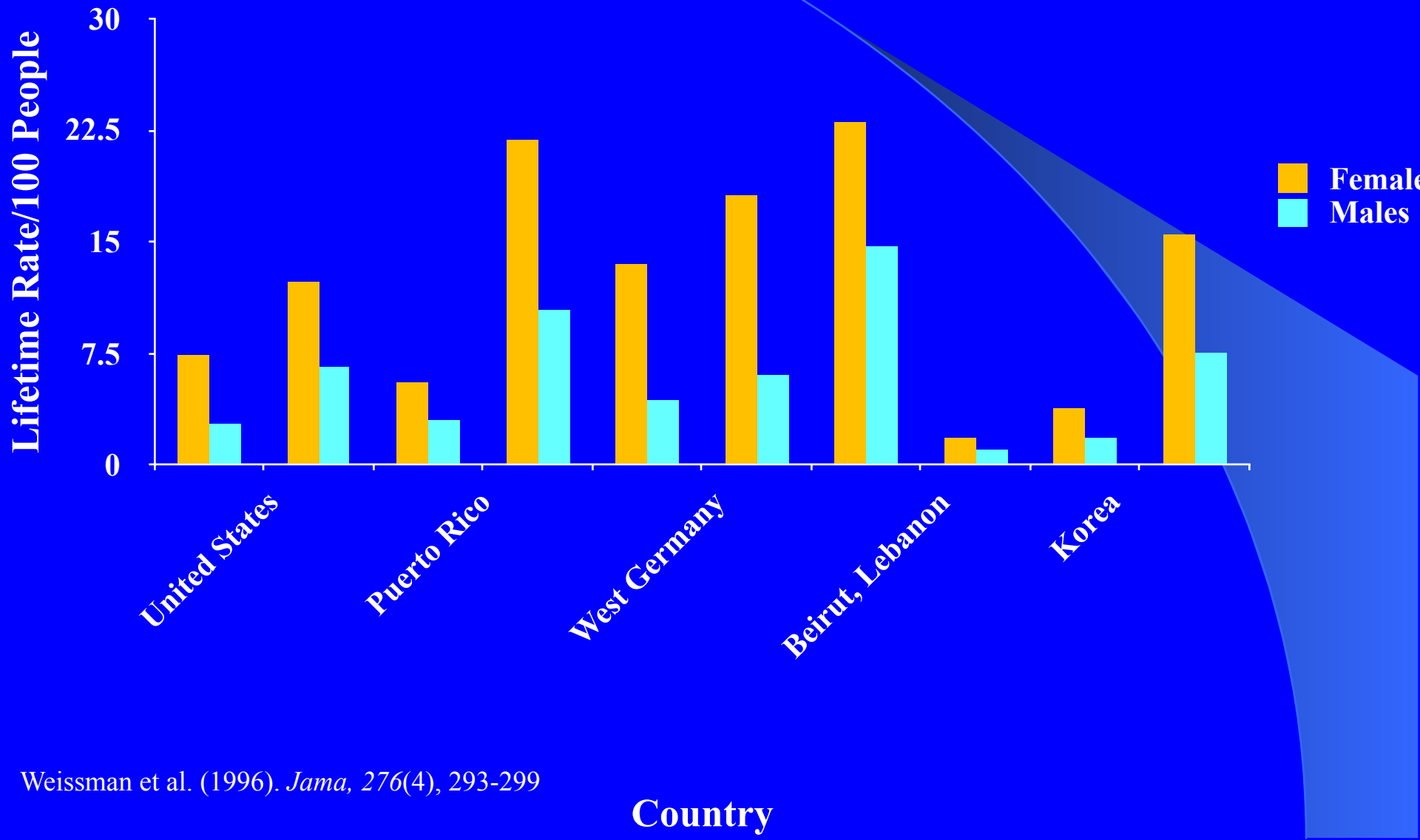
**REPRODUCTIVE MOOD DISORDERS:
From Menarche to Menopause**

The role of stress and steroid hormone sensitivity

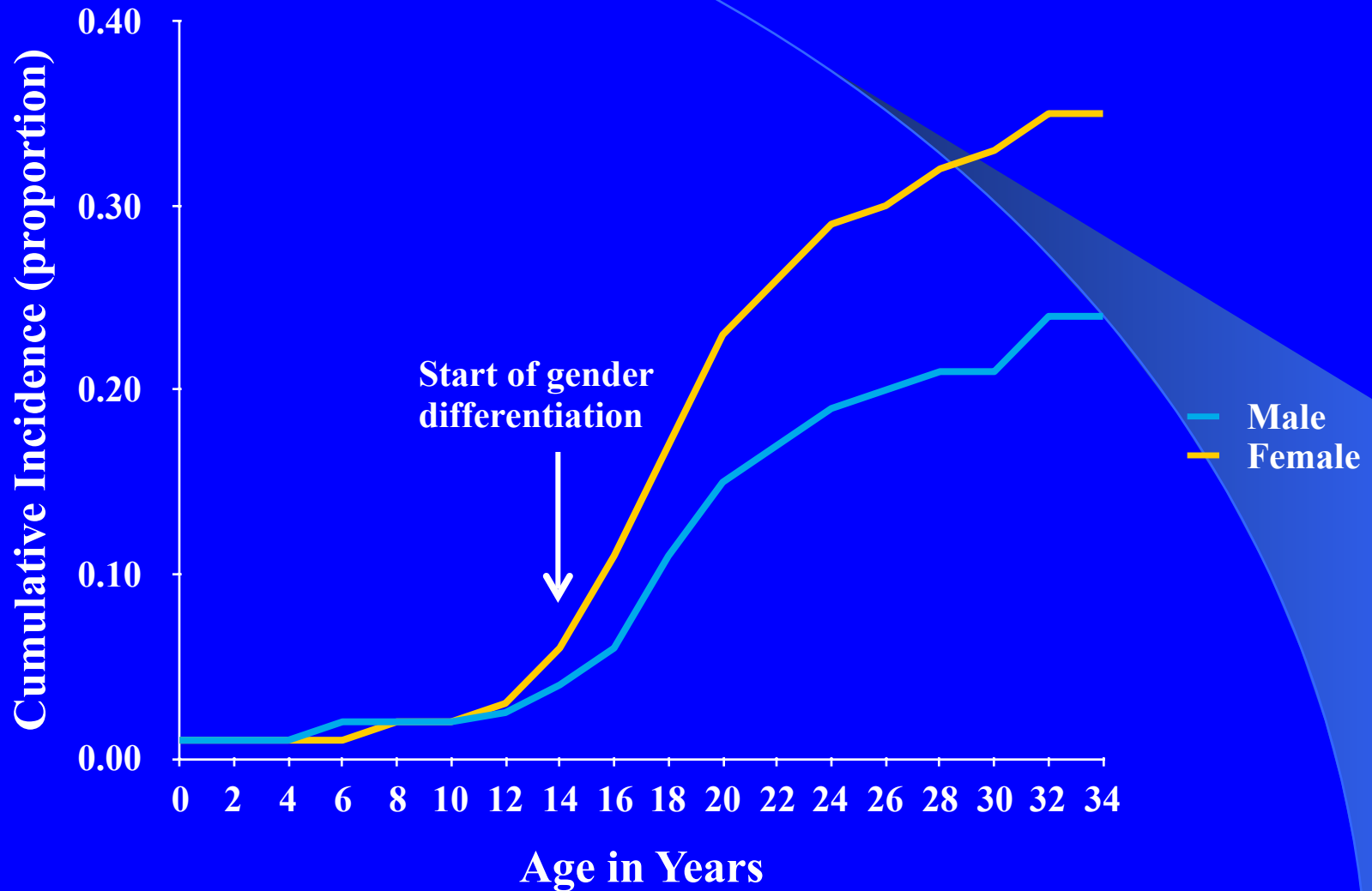


Susan S. Girdler, Ph.D., FABMR
Department of Psychiatry
University of North Carolina at Chapel Hill

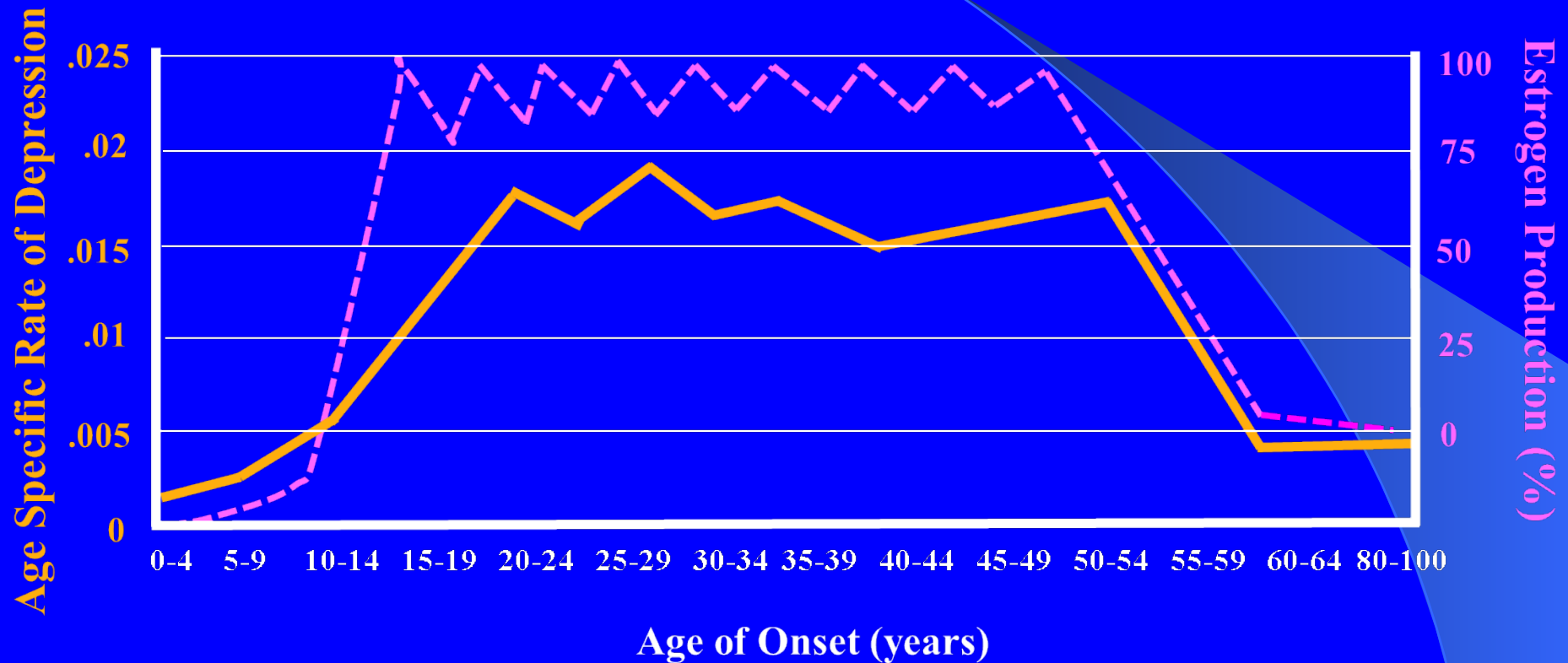
Gender Differences in Lifetime Rate for Major Depression



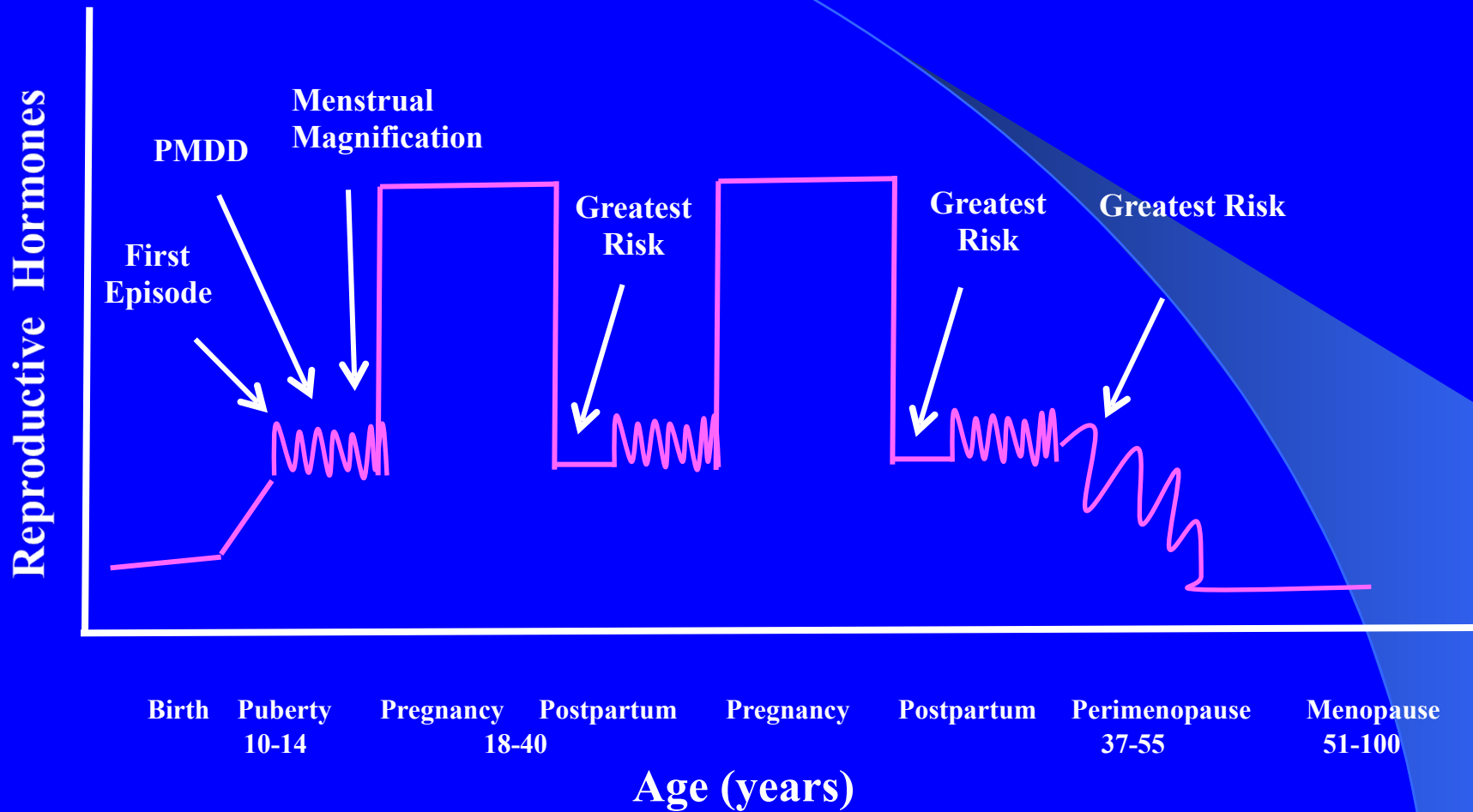
Incidence of Major Depression in Males and Females



Incidence of Depression in Women Across the Lifecycle



The Risk of Depressive Symptoms in Women Associated with Reproductive Events



Stahl, S.M., (2000). *Essential Psychopharmacology*, (2).

Wise, D. D., Felker, A., & Stahl, S. M. (2008). *CNS Spectr*, 13(8).

Objectives

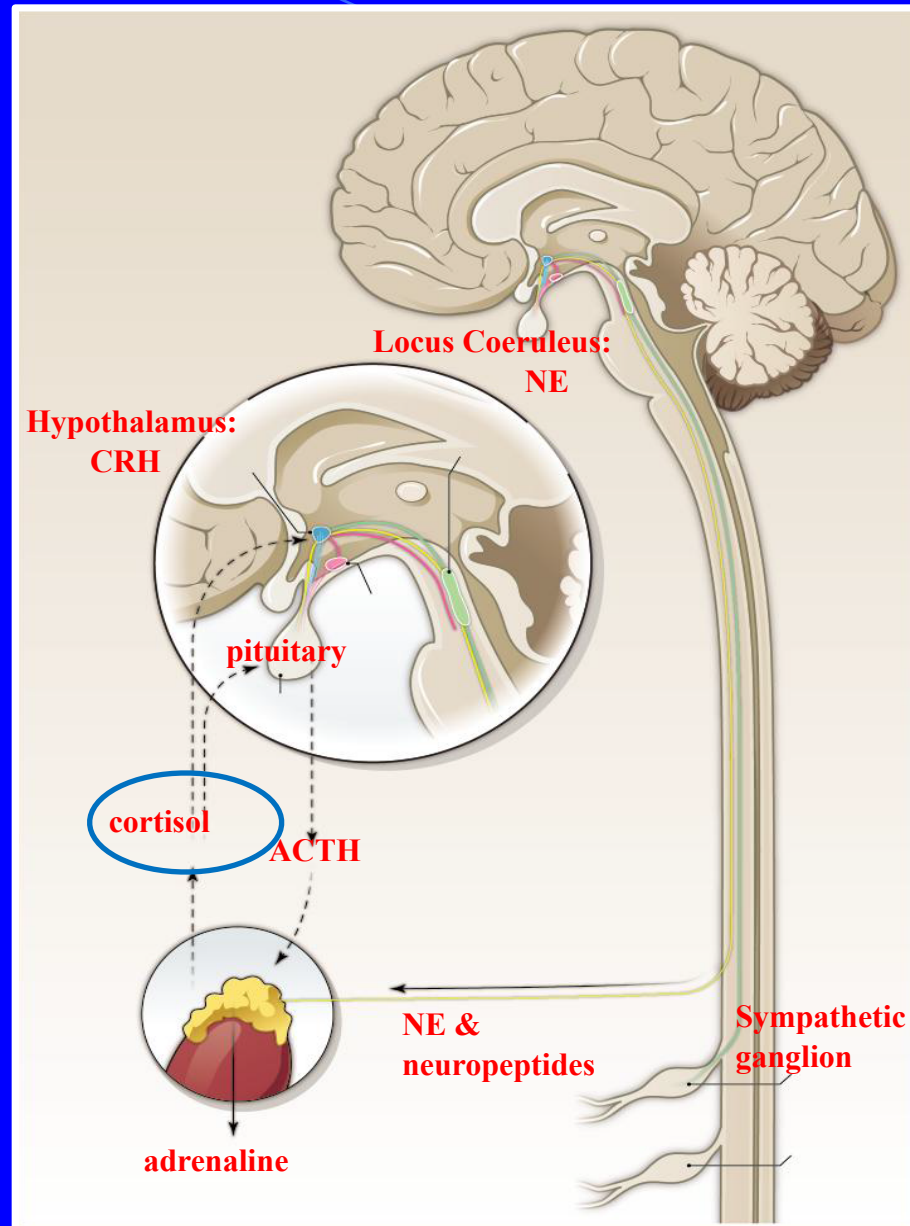
- Clinical Phenomenology of Reproductive Mood Disorders (RMDs):
 - Premenstrual Dysphoric Disorder
 - Postpartum Depression
 - Perimenopausal Depression
- Vulnerability to ‘normal’ hormonal *CHANGE* as etiologically relevant
 - a hormone sensitive “phenotype”
- **STRESS** and stress response dysregulation in the pathogenesis of RMDs

STRESS AXES

Hypothalamic-pituitary-adrenal (HPA) axis

Regulates:

- Metabolism of glucose
- Immune activation



Sympathetic Nervous System
or
“Flight or Fight”

Regulates:

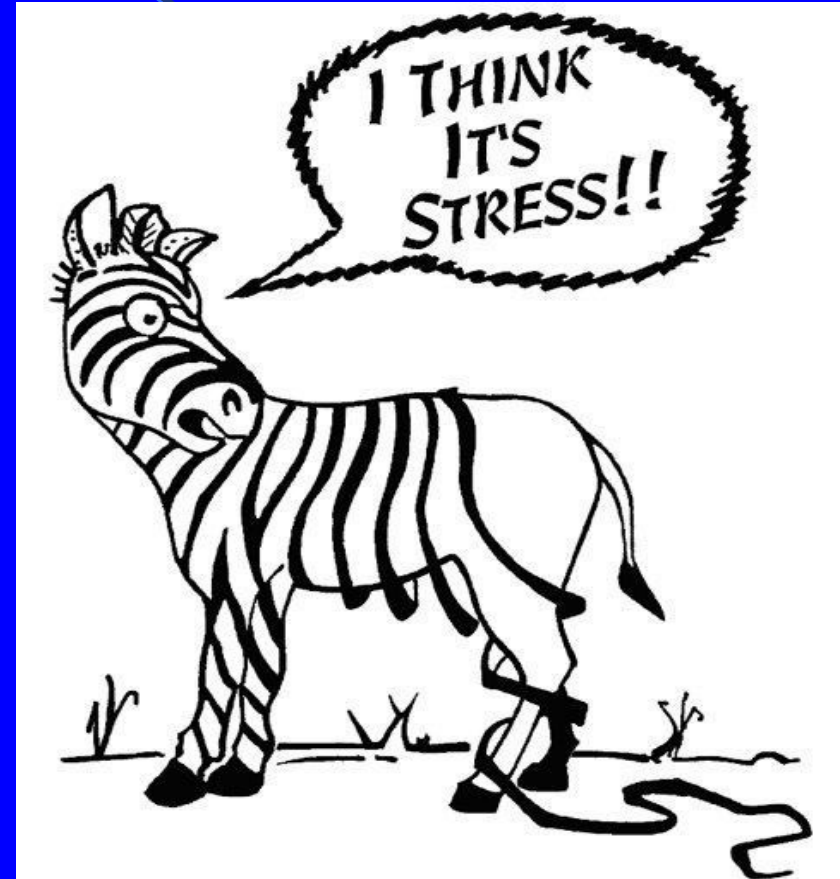
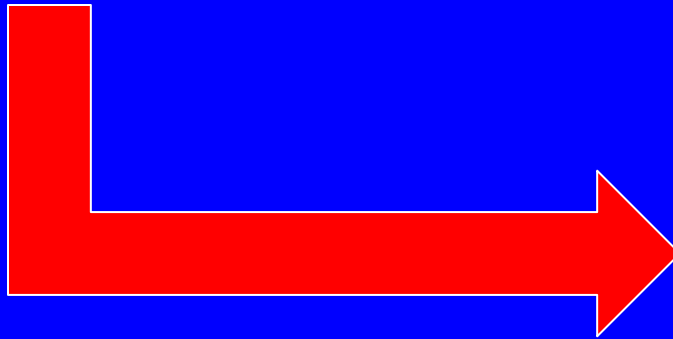
- Heart rate
- Blood Pressure



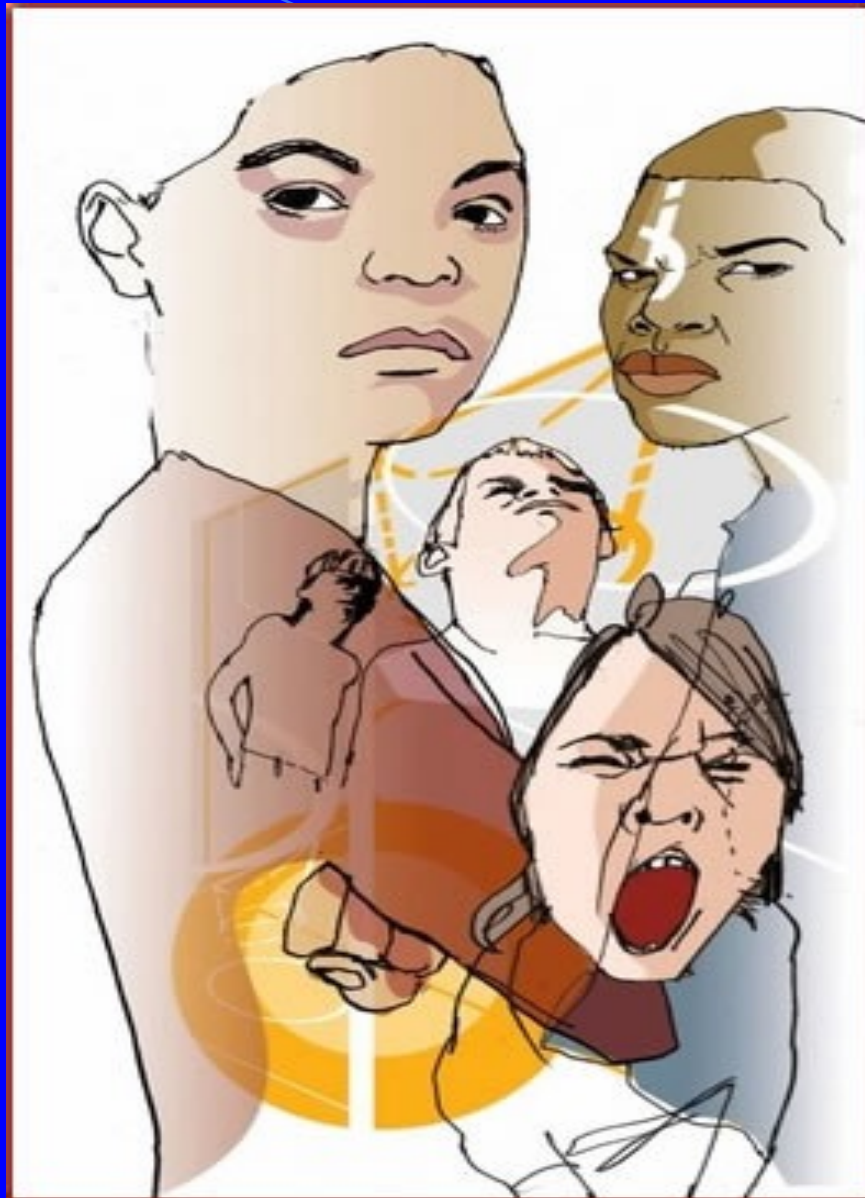


How Stress Gets “Under the Skin” to Promote Illness

WHEN PHYSIOLOGIC RESPONSES TO
STRESS ARE IN EXCESS OF OUR
METABOLIC NEEDS



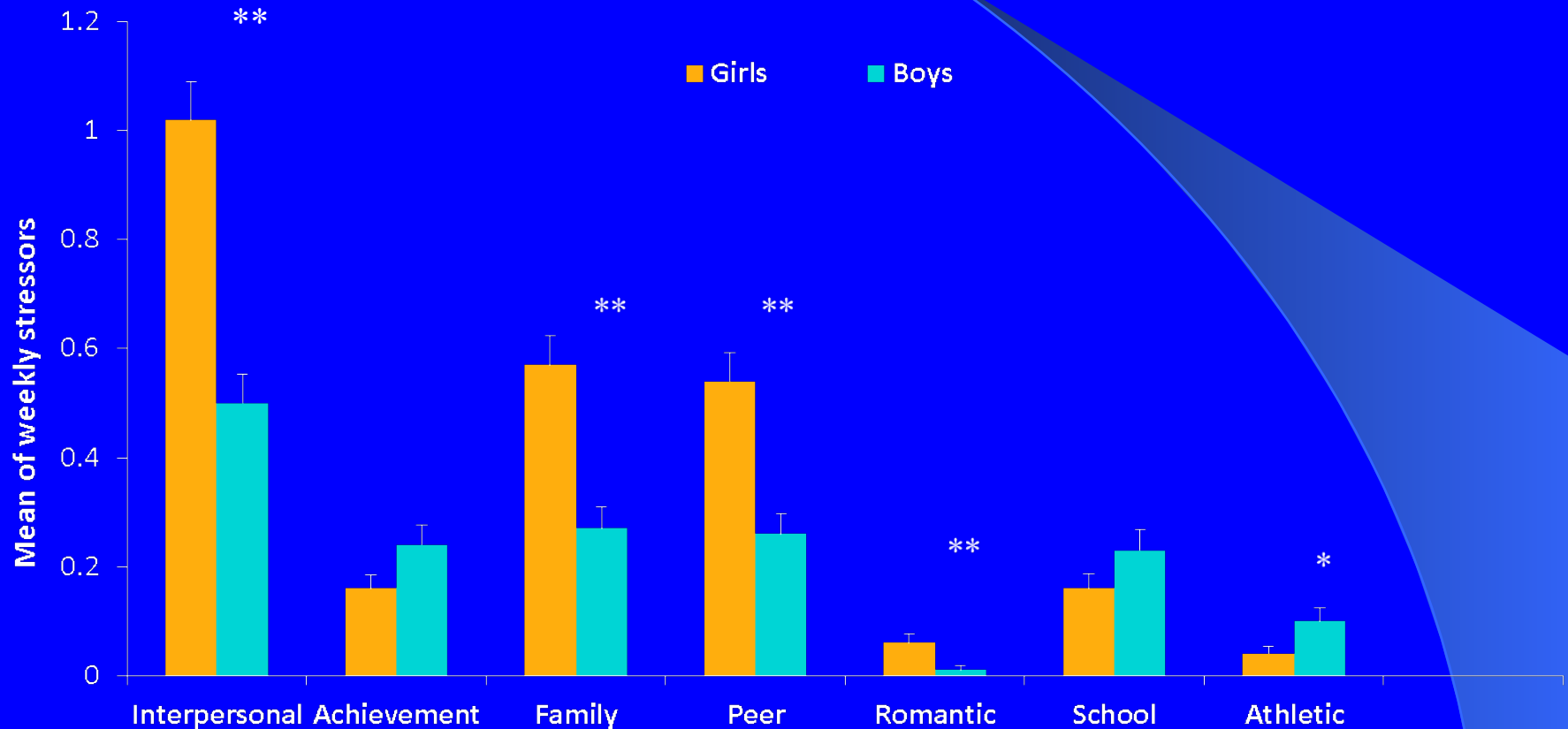
PUBERTY!





B.Ed. 2009-2010

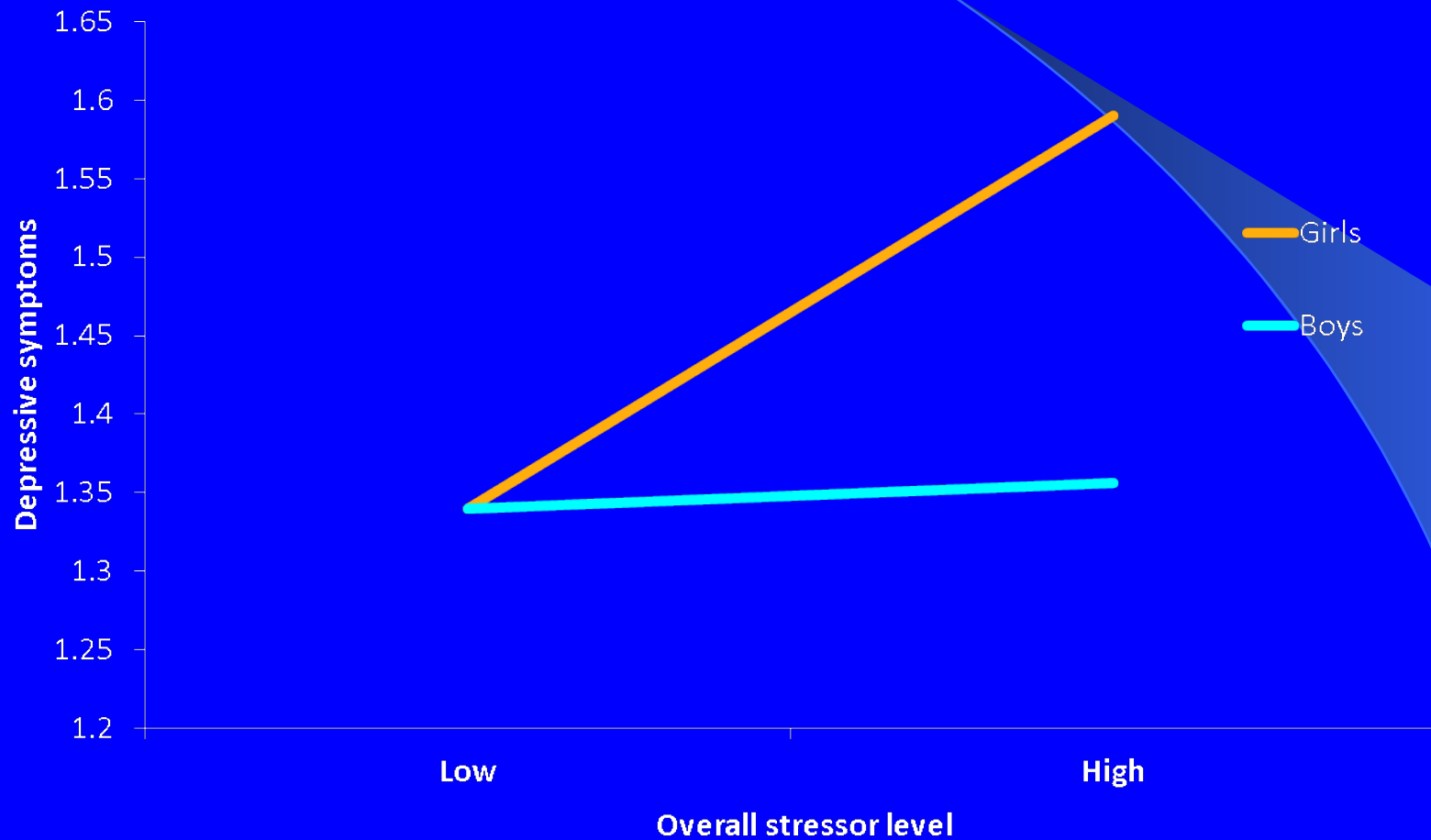
Adolescent sex differences in the nature of stressors



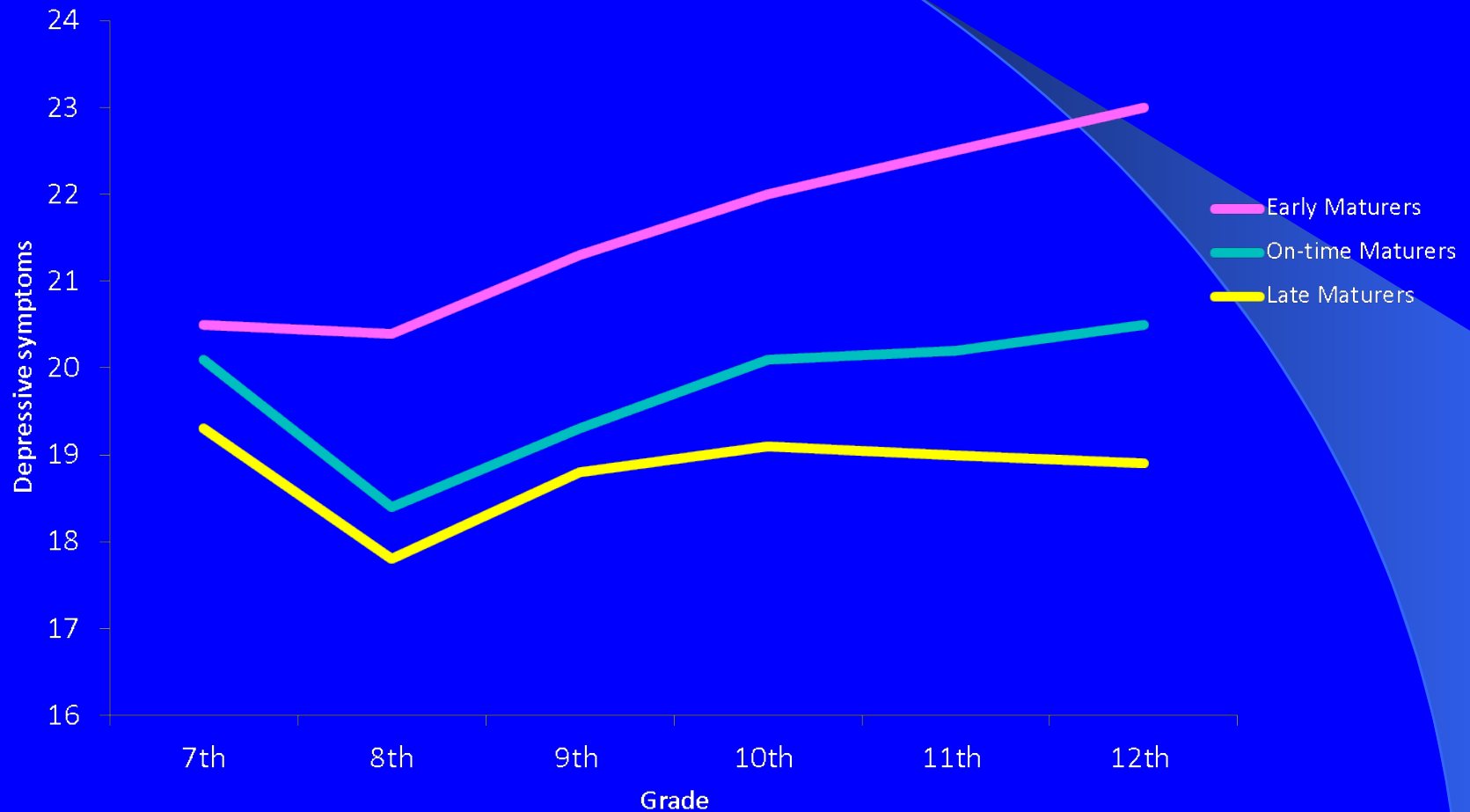
* <0.01 , ** <0.001

Hankin, B. L., Mermelstein, R., & Roesch, L. (2007). *Child development*, 78(1), 279-295.

Adolescent girls show greater depressive symptoms under stress than do boys

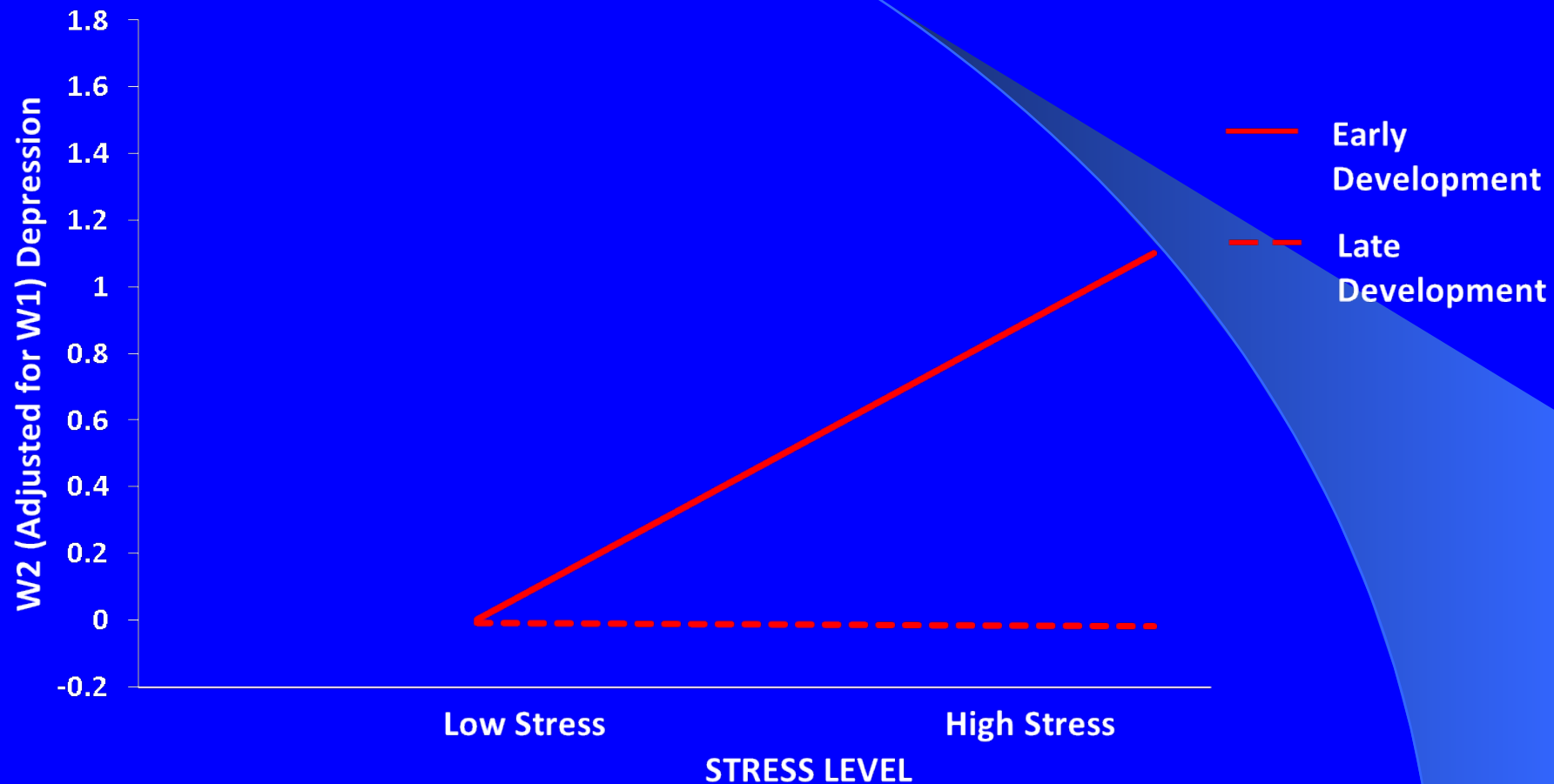


Girls' depressive symptoms by grade and pubertal timing



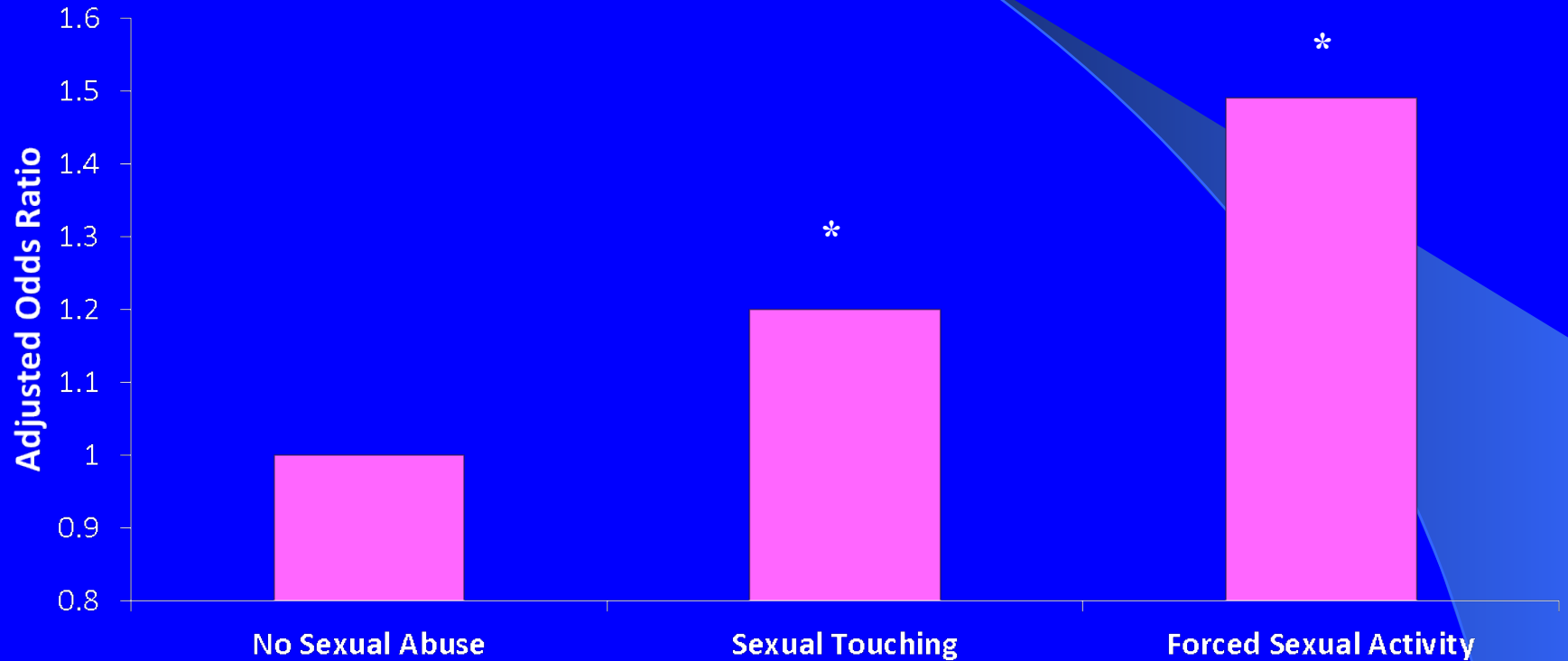
Adapted from: Ge, X., Conger, R.D., & Elder, G.R. (2001). *Developmental Psychology*, 37(3), 404-417.

Pubertal timing and peer stress predict longitudinal depression in adolescent girls



Adapted from: Conley, C. S., & Rudolph, K. D. (2009). *Development and psychopathology*, 21(02), 593-620.

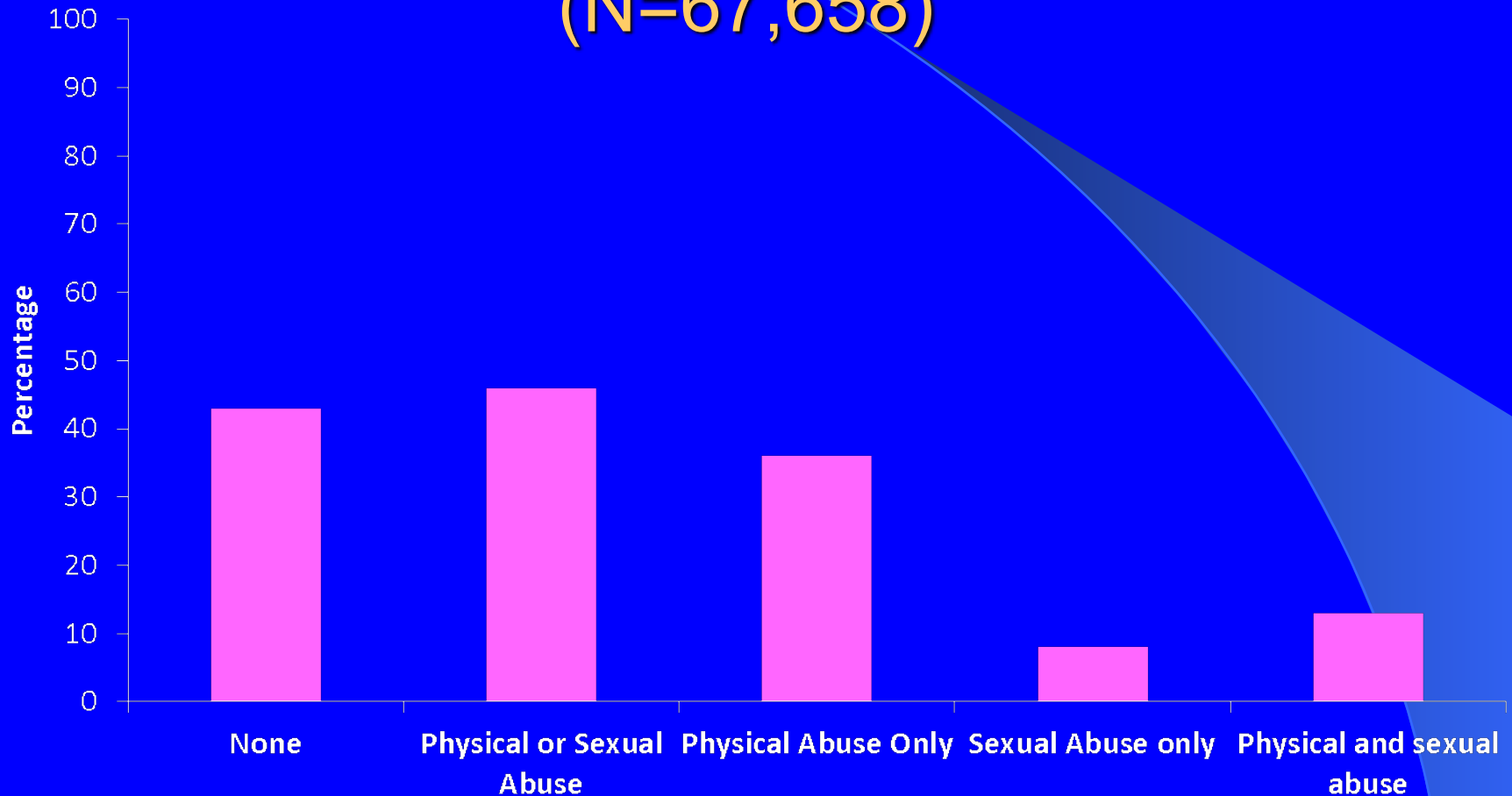
Child abuse and early timing of menarche (< 11 yrs)



* $p < 0.01$

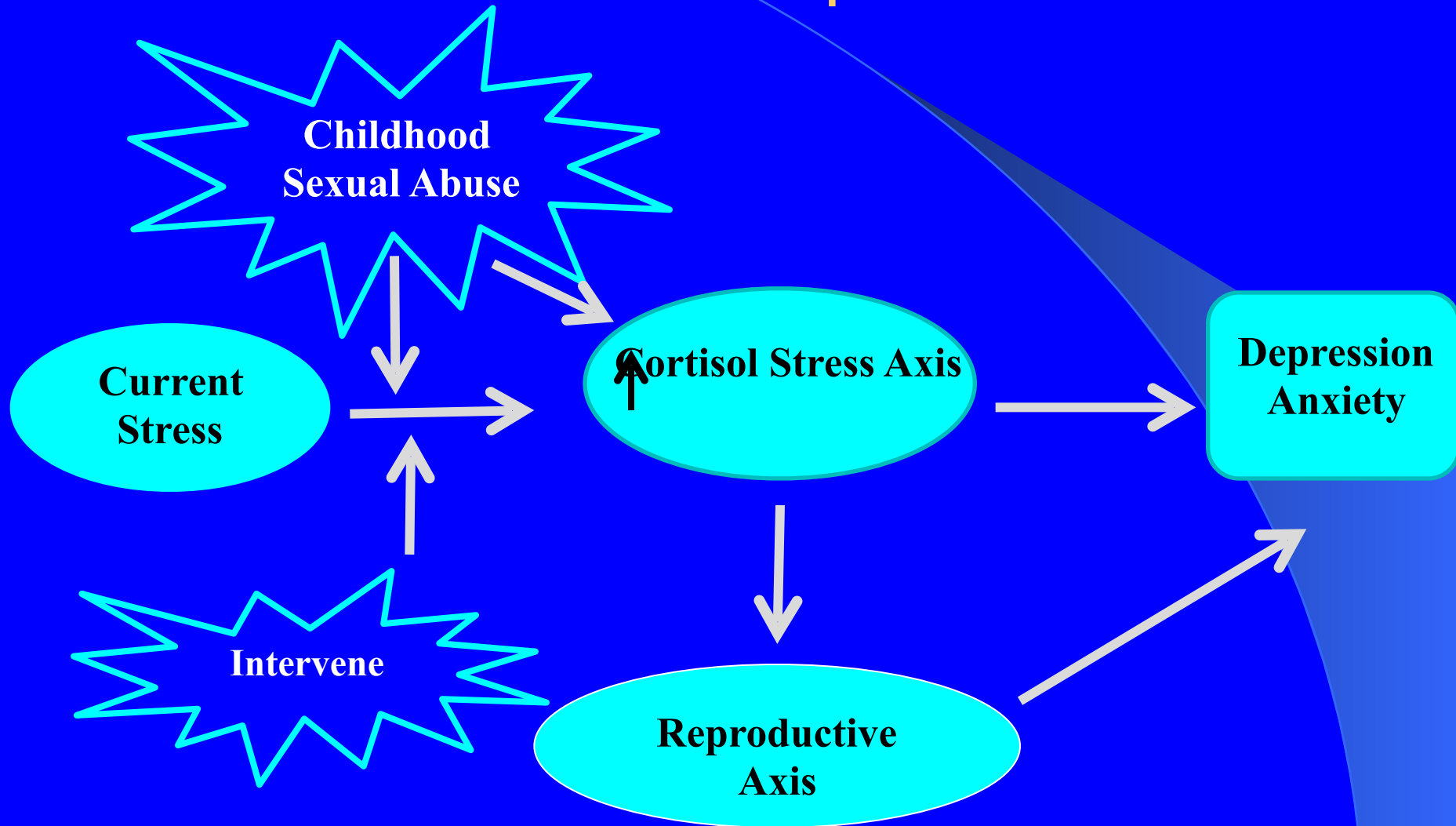
Boynton-Jarrett et al. (2013). *The Journal of adolescent health: official publication of the Society for Adolescent Medicine*, 52(2), 241.

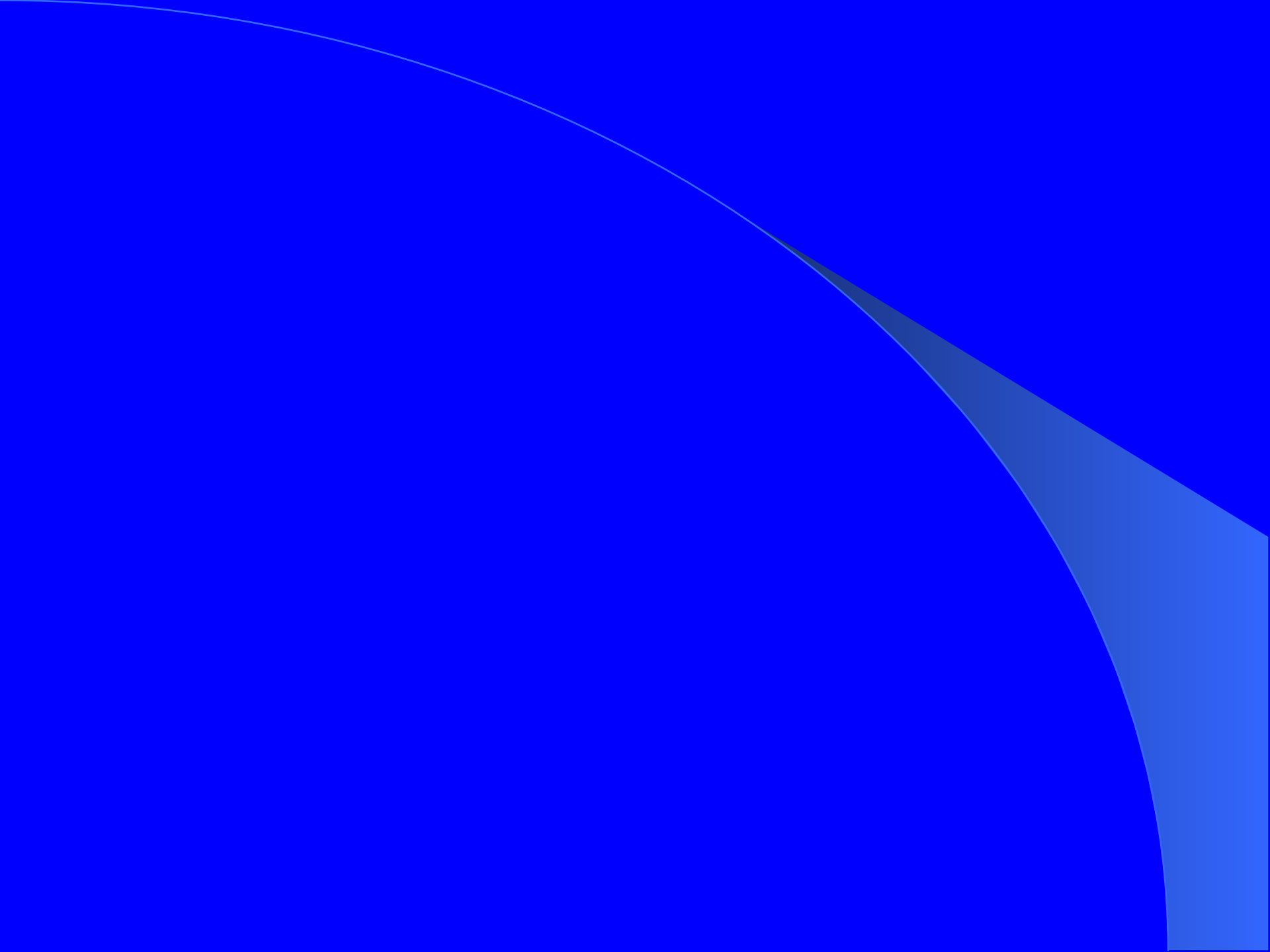
Report of physical and/or sexual abuse in childhood (< 12 yrs) (N=67,658)



Boynton-Jarrett et al. (2013). *The Journal of adolescent health: official publication of the Society for Adolescent Medicine*, 52(2), 241.

Biobehavioral model of female adolescent depression

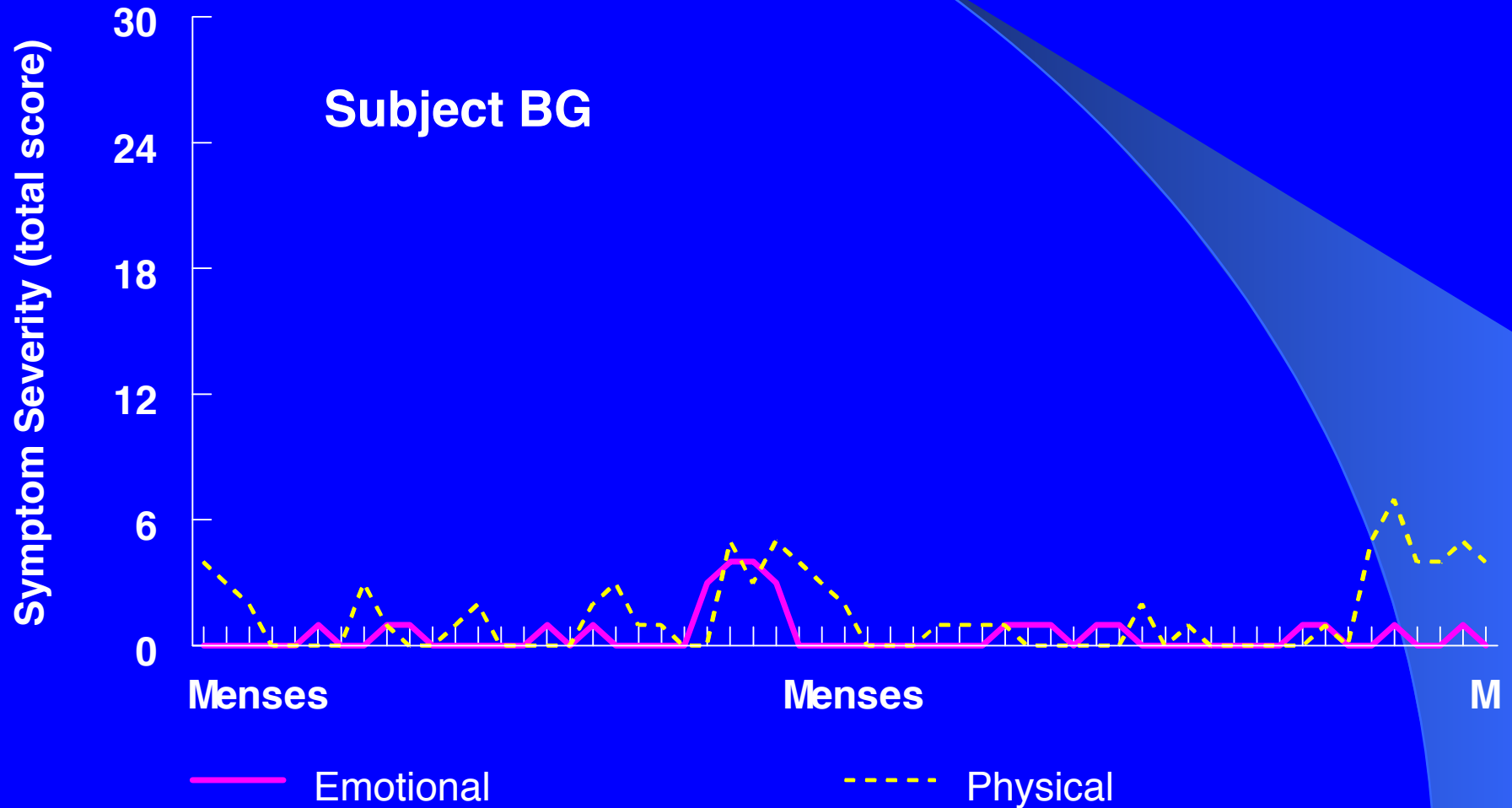




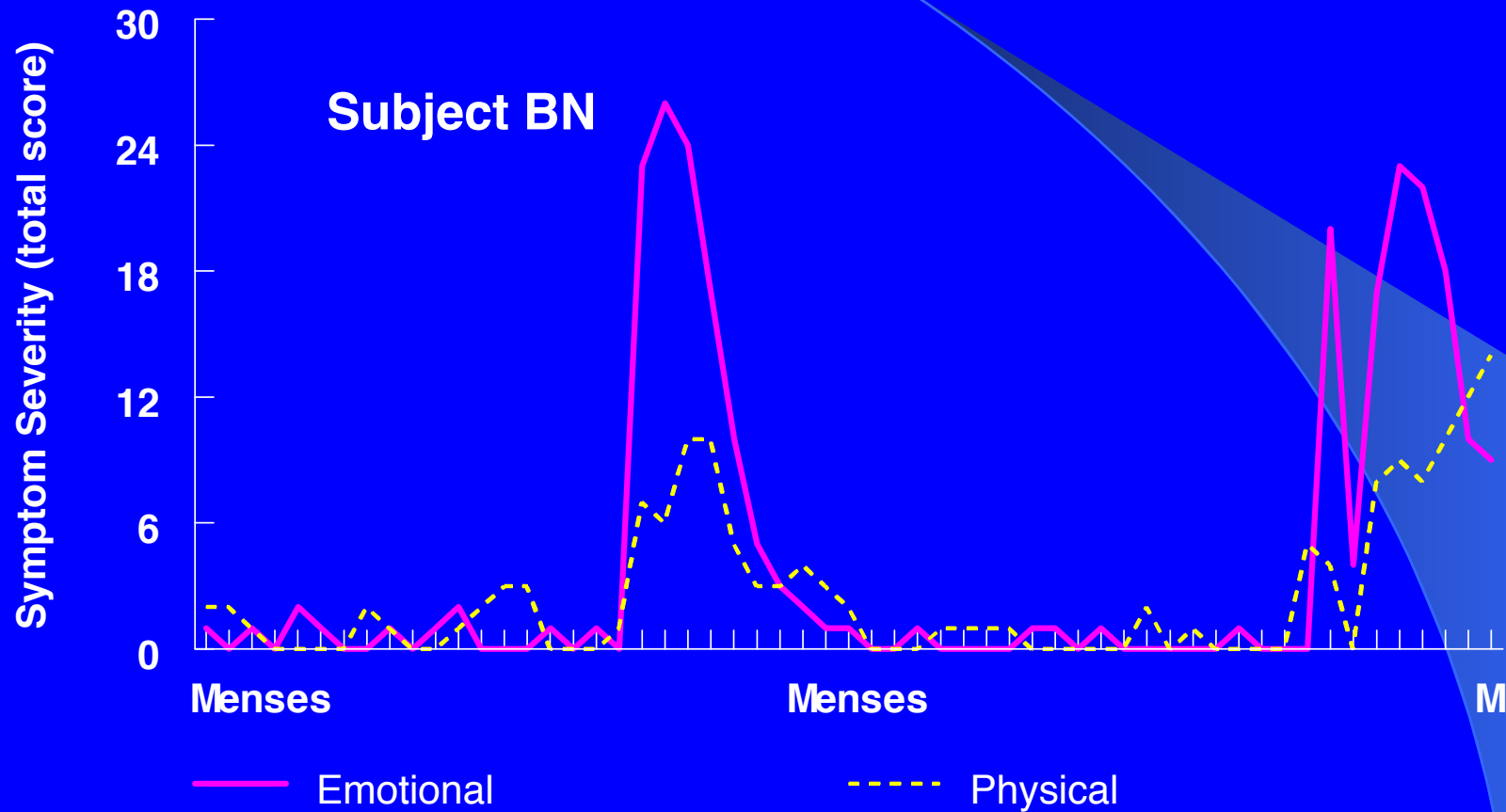
Cases of Premenstrual Tension

	Age	Regular Menses	Parity		Complaints	Relief with Onset of Menses	Treatment
			Chil- dren	Abor- tions			
R. P.	35	+	2	1	Severest tension; double oophorectomy advised elsewhere	Immediate	X-ray "toning"
B. H.	32	+	2	1	Severest tension; suicidal desire	Immediate	X-ray "toning"
F. B.	41	+	3	0	Severest tension; unbearable, shrew	Gradual	
L. H.	47	+	2	0	Severest tension; husband to be pitied	Immediate	Elimination
M. M.	28	+	0	0	Severest tension; suicidal desire	After 1 day	
A. B.	38	+	4	3	Severest tension; "almost crazy"	Immediate	X-rays advised
H. C.	35	+	1	1	Severest tension; psychoneurotic	Immediate	
B. M.	38	+	Unmarried		Severe tension; incapacitated mentally	Immediate	Elimination
K. R.	43	+	2	1	Severe tension; sexual tension also	Toward end of period	
M. L.	33	+	1	0	Severe tension; cardiac irregularity	Gradual	Elimination
A. W.	41	+	2	1	Severe tension; "impossible to live with"	Immediate	
B. N.	32	+	1	0	Moderate tension; despondent	Immediate	
E. M.	35	+	3	0	Moderate tension	Immediate	
O. R.	33	+	2	0	Moderate tension	Immediate	
S. S.	24	+	0	0	Moderate tension	Immediate	

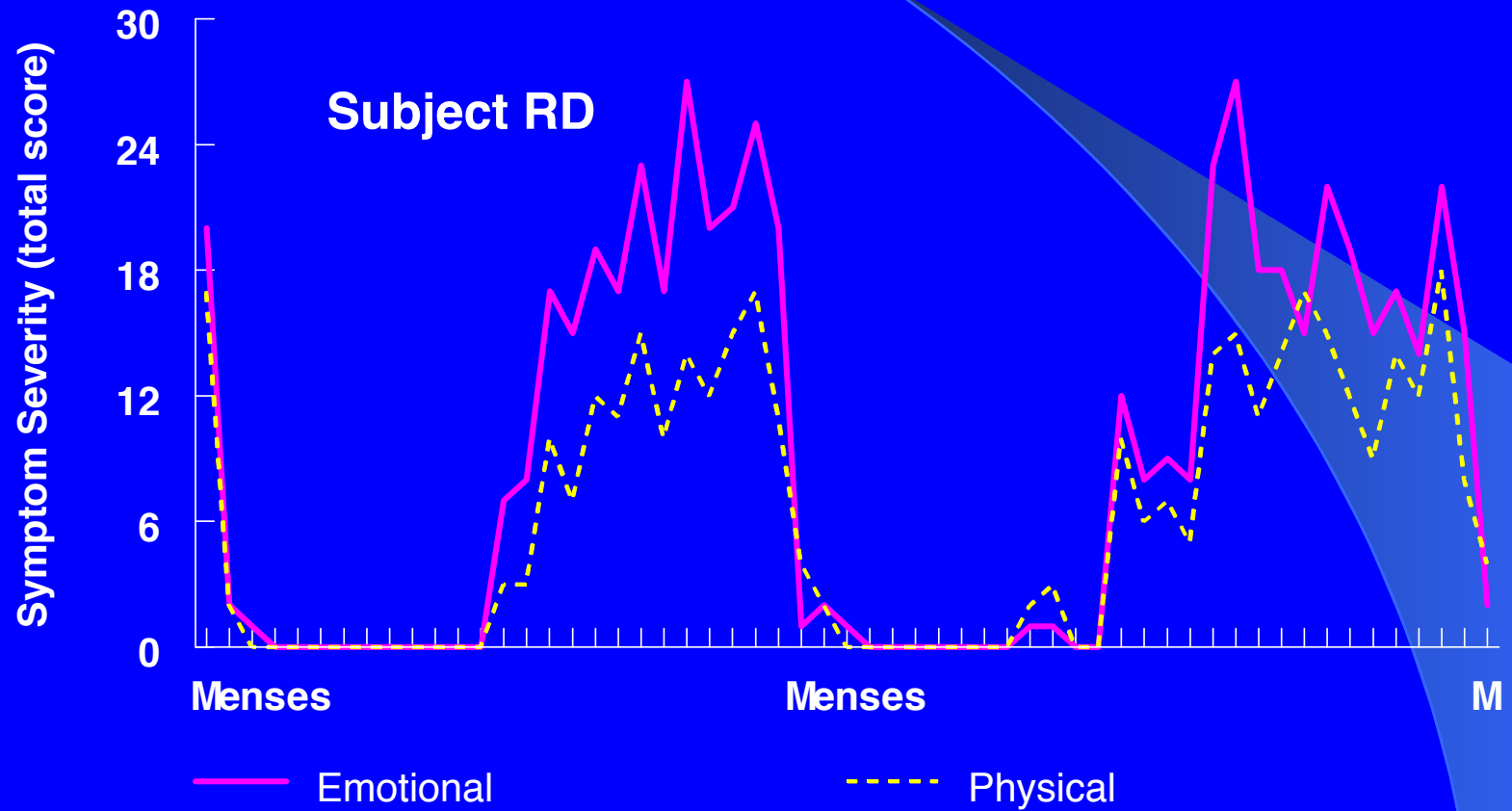
Daily Symptom Severity in a non-PMDD control woman



Daily Symptom Severity in PMDD



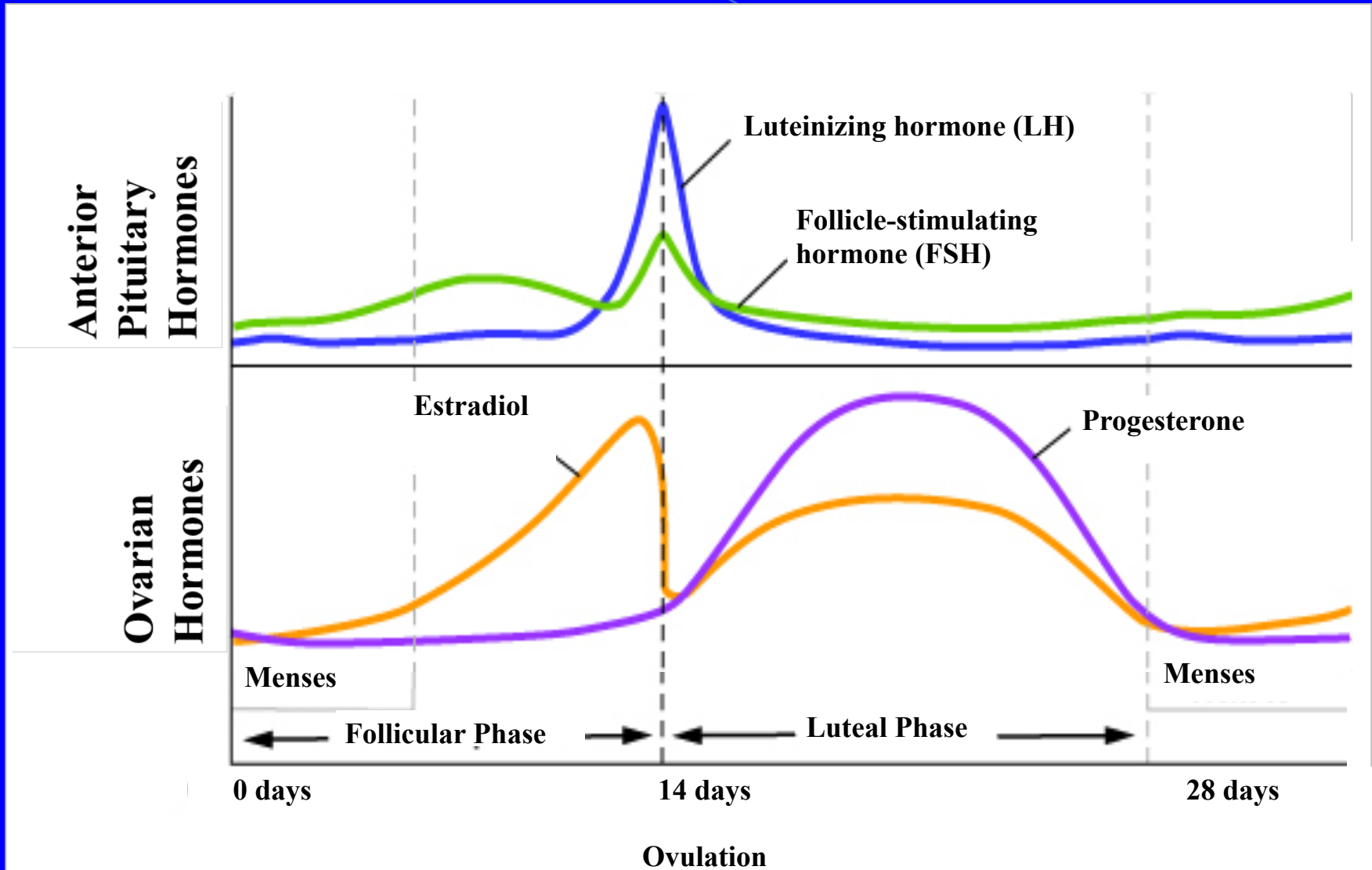
Daily Symptom Severity in PMDD



Estrogen and Progesterone Beneficially Modulate Systems Implicated in Depression and Anxiety

- Regulates the synthesis, metabolism, and receptor concentration of **neurotransmitters** implicated in depression (i.e., serotonin, dopamine, norepinephrine) (Rubinow et al., Biol Psychiatry 44, 1998; Malyala et al., Steroids 70, 2005).
- Physiologic **responses to stress**, including the Hypothalamic-Pituitary-Adrenal (HPA) axis (Peiffer et al, Endocrinology 129, 1991).
- Modulates **neuroprotection** in brain (Sato et al., Brain Res 1150, 2007; Scharfman et al., Headache 48, 2008; McEwen BS Endocr Rev 20, 1999)
- Prevents or **counteracts the pro-inflammatory processes** described as contributing to depression (Leonard, BE. Prog Neuropsychopharmacol Biol Psychiatry 15, 2001)

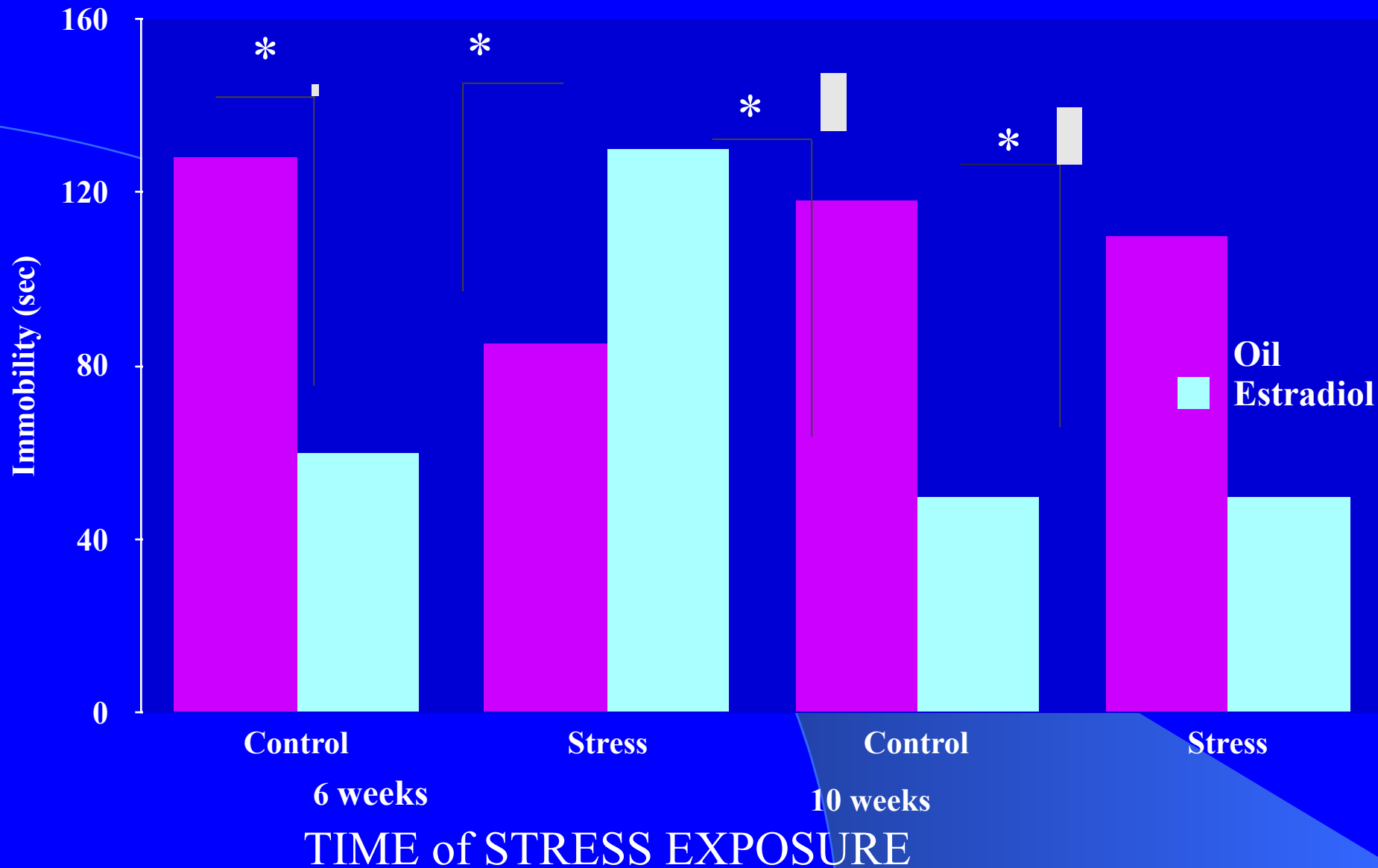
FEMALE REPRODUCTIVE HORMONAL FLUX ACROSS THE MENSTRUAL CYCLE



Duration of immobility during the tail suspension test is measure of 'depression' in female mice



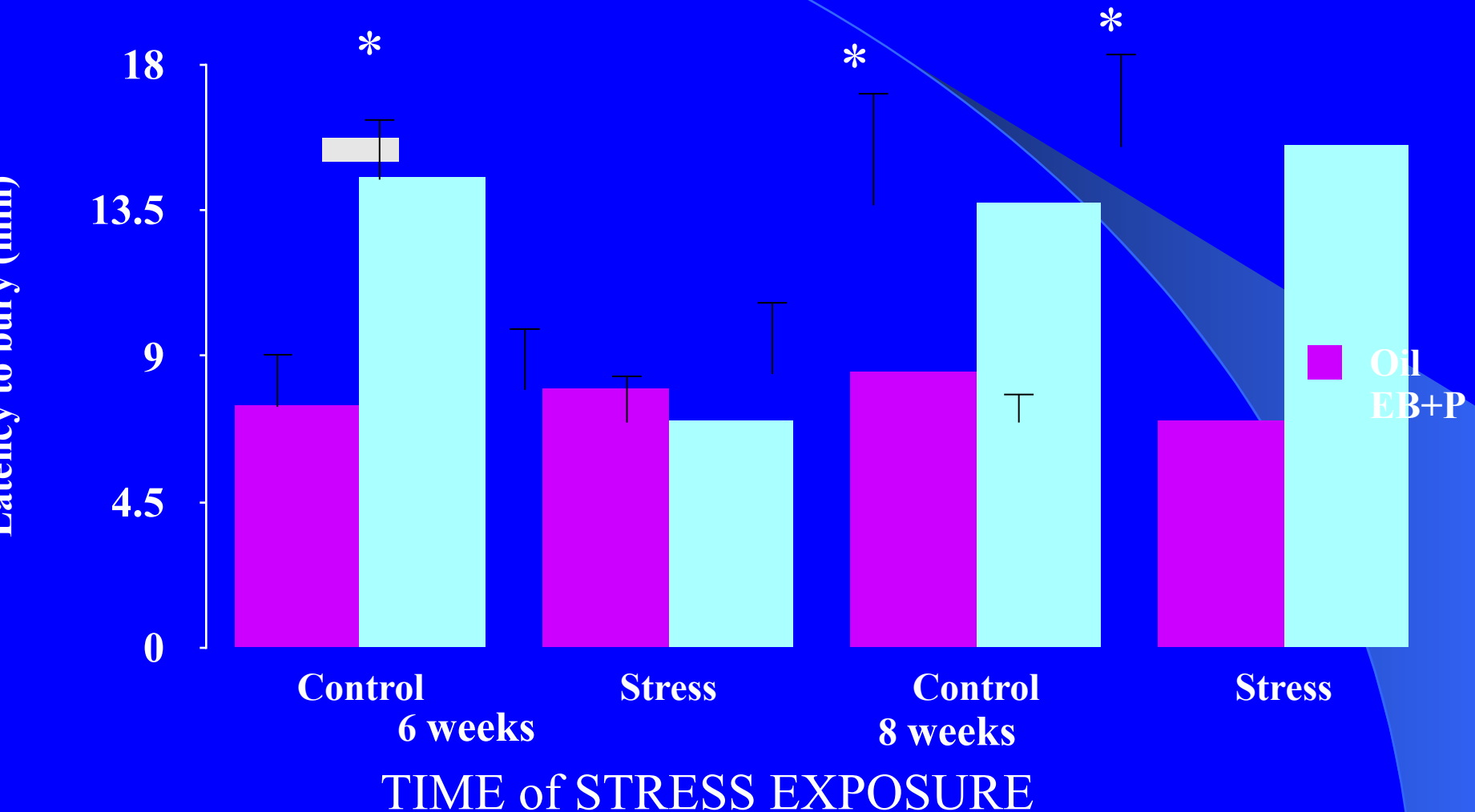
Female mice stressed during puberty (6 weeks) show a depressogenic effect when exposed to estrogen in adulthood



Time (latency) to bury marbles is an index of anxiety in female mice



Female mice stressed during puberty (6 weeks) fail to experience the anxiolytic effect of estrogen and progesterone in adulthood



Blaustein et al., *Hormones and Behavior*, Volume 64, Issue 2, 2013.

Biological Systems Implicated in the Pathogenesis of PMDD

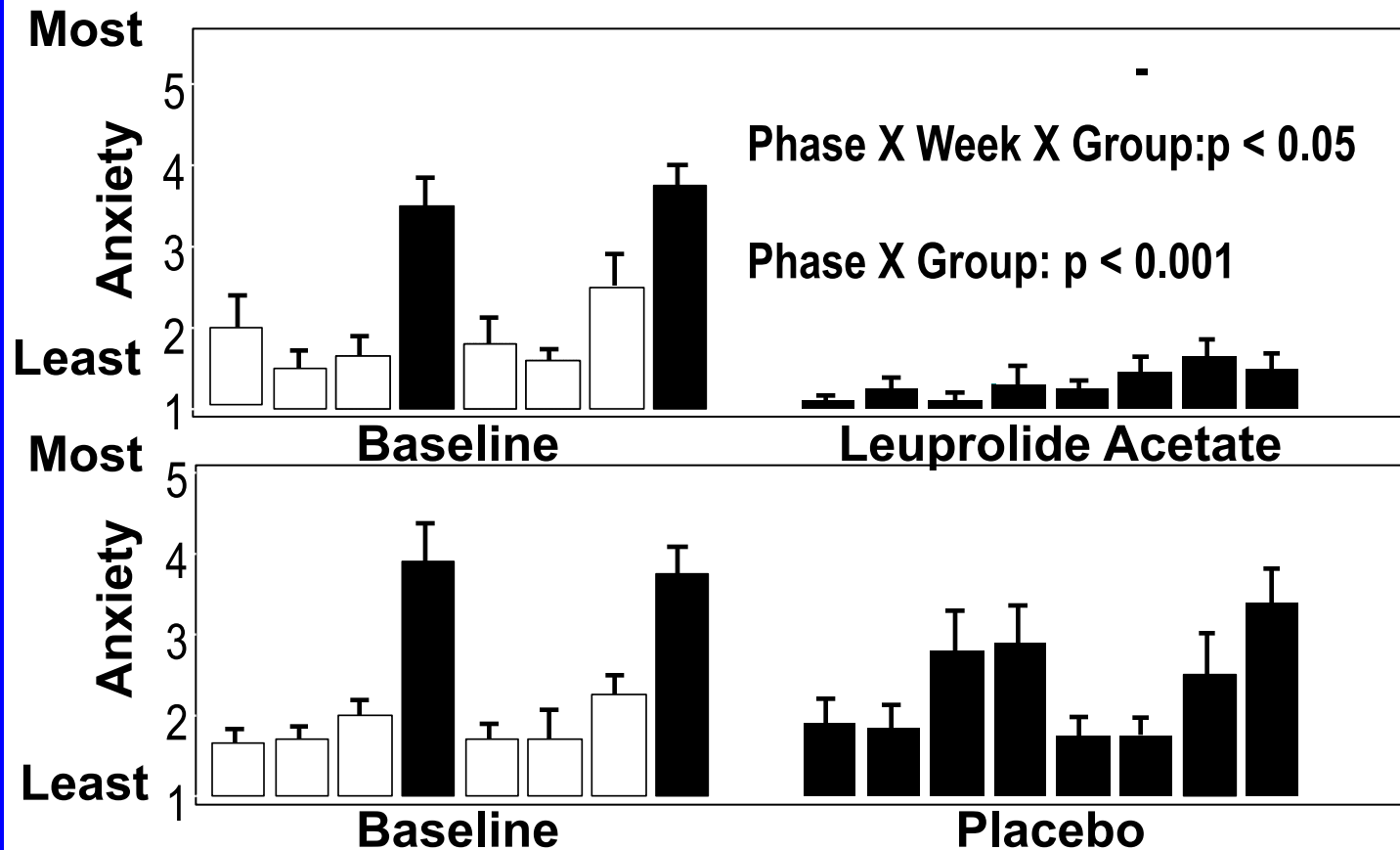
- Differential sensitivity to mood effects of gonadal steroid fluctuations
- Serotonergic dysfunction
- Adrenergic dysregulation
- GABAergic neurosteroids
- Thyroid hormones

PMDD as a Stress - Related Disorder

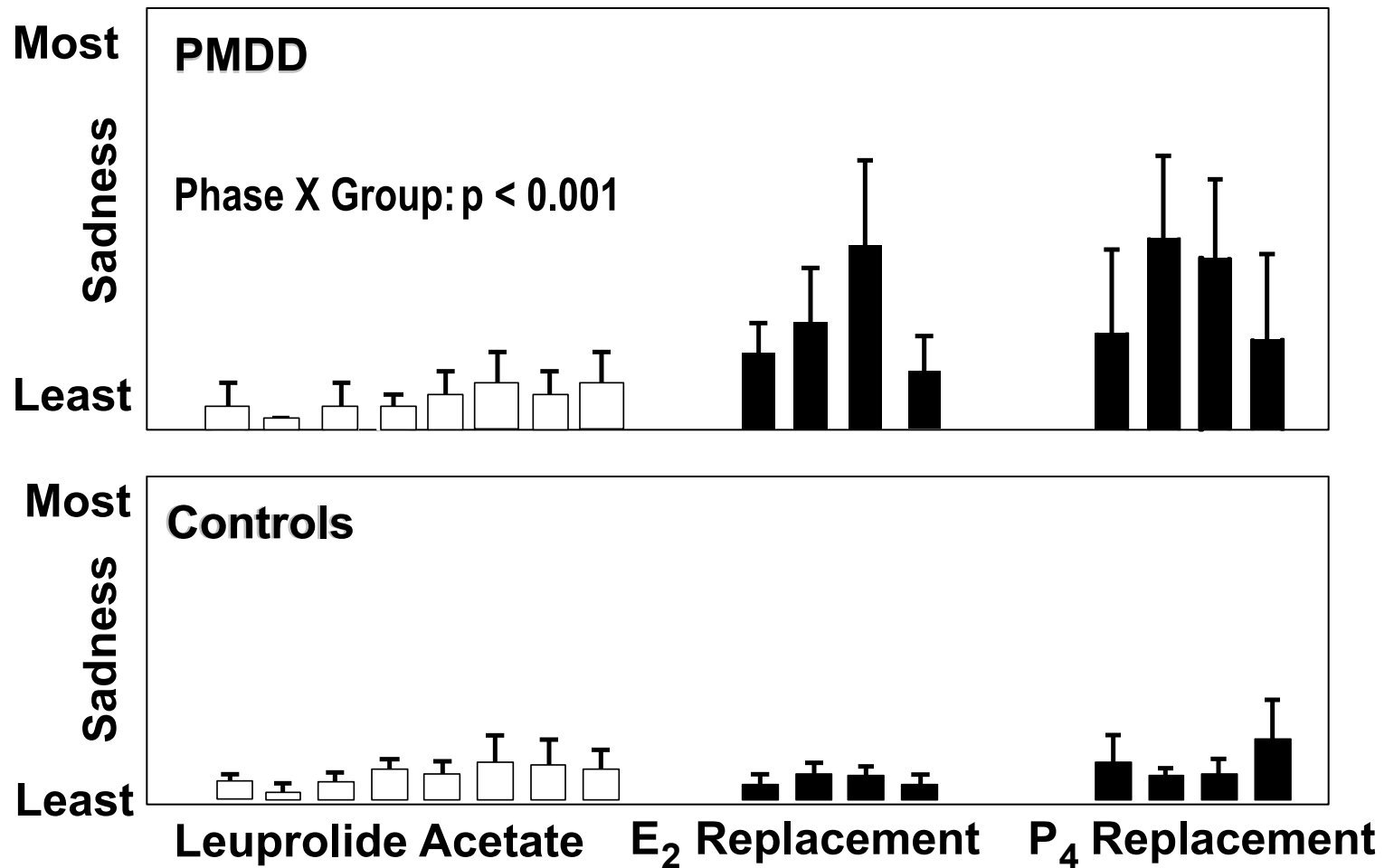
- Clinically distinct subgroups of PMDD women for whom *historical factors* provide a context of vulnerability for stress response dysregulation and perhaps for the development of the disorder

Hormone Sensitive Phenotype in PMDD

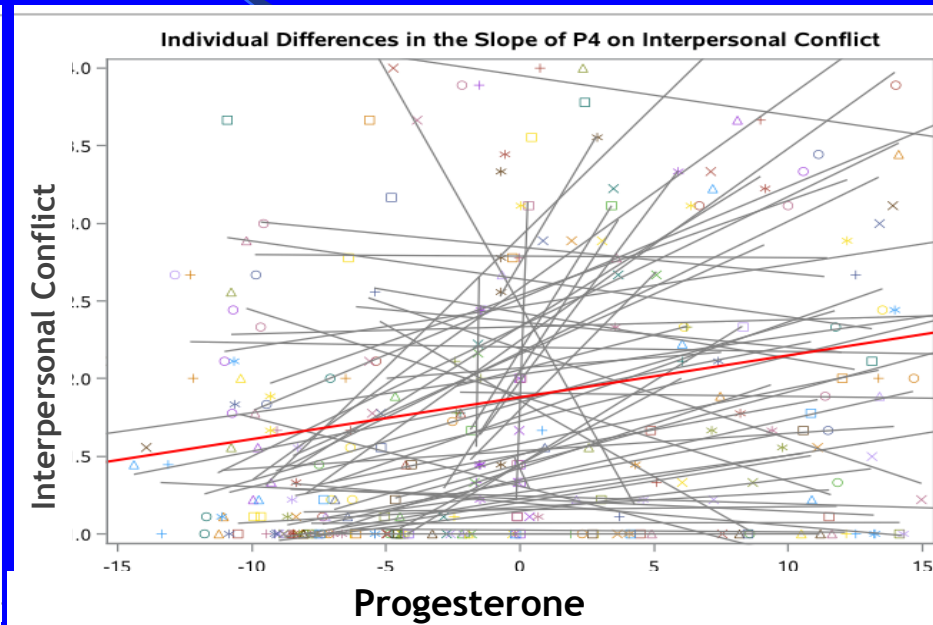
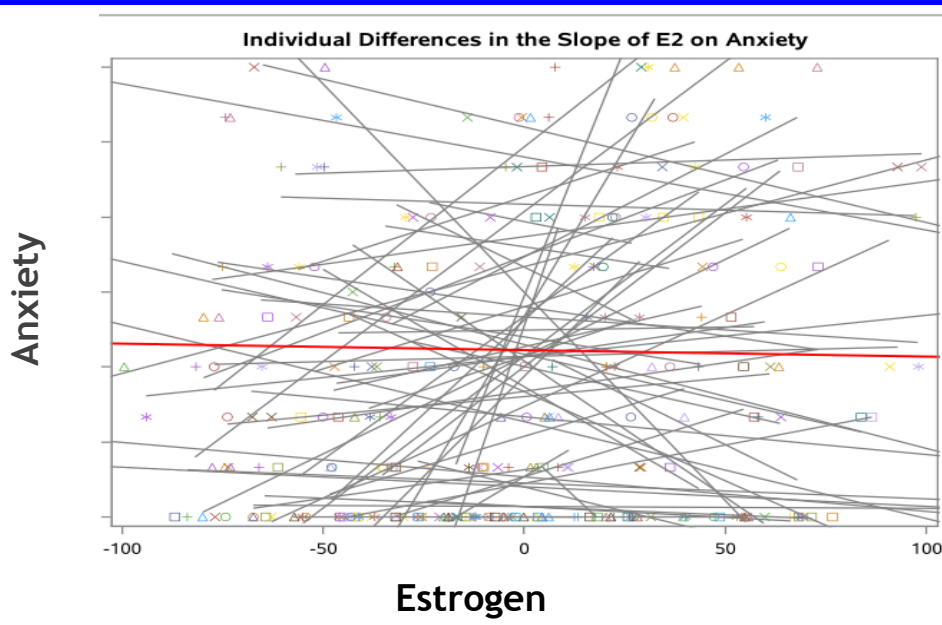
Efficacy of GnRH-A in the Sxs of PMDD (Weekly Means + SEM)



Steroid Precipitation of PMDD Sxs



Relationship between changing estrogen and progesterone levels and symptom severity in 66 women with PMDD



Abuse Interview

(Leserman et al., Psychosom Med 1996;58:4-15)

- Sexual Abuse (SA):

Adult: Clear threat of harm or force

Child (<14 yrs): threat or force not required if implied by age differential

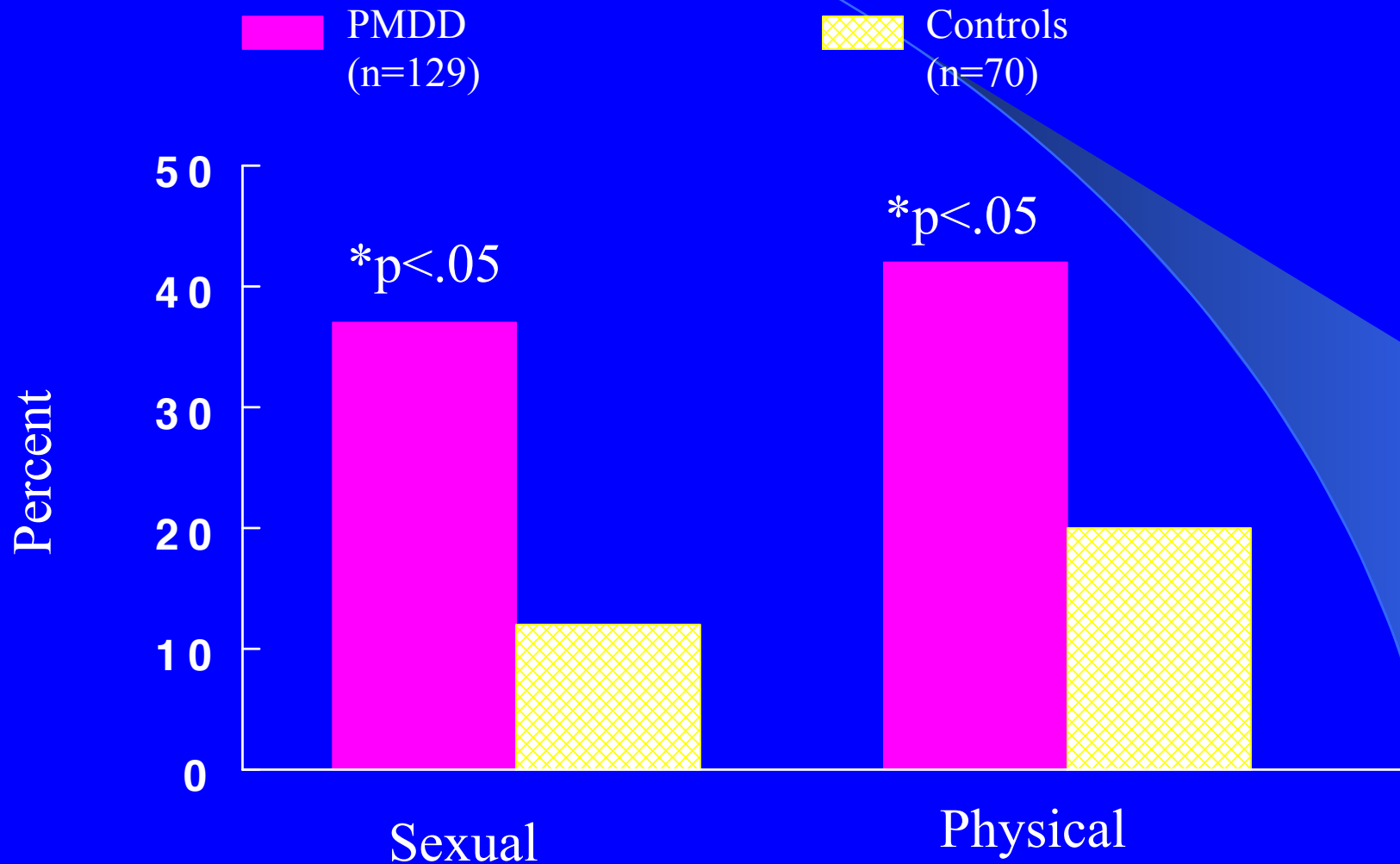
2 Types: 1) forced sexual touching
2) intercourse (rape)

Abuse Interview (cont.)

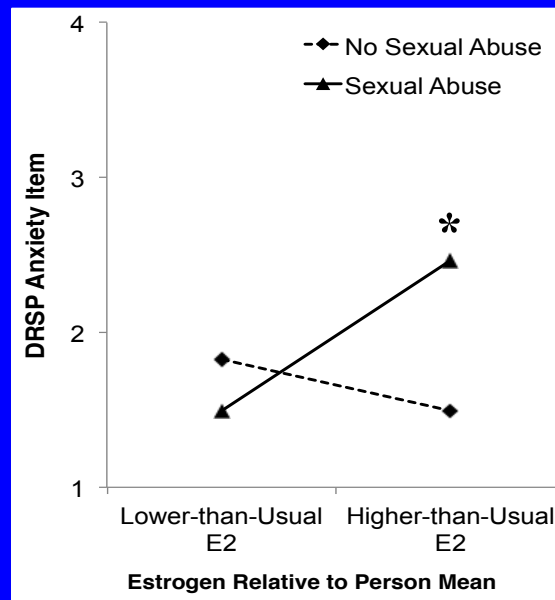
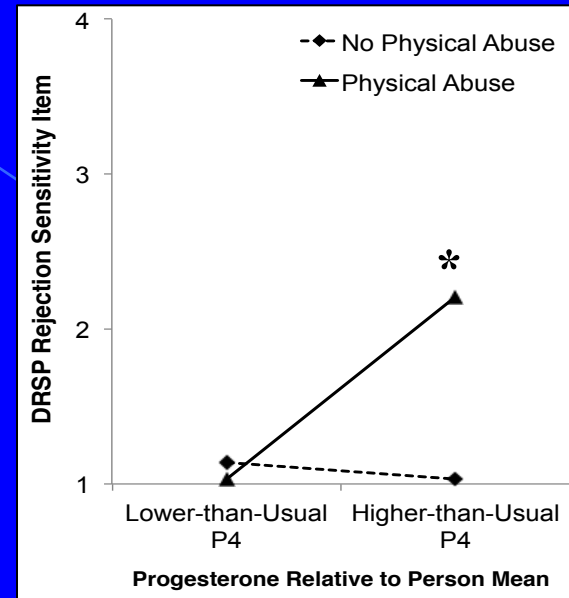
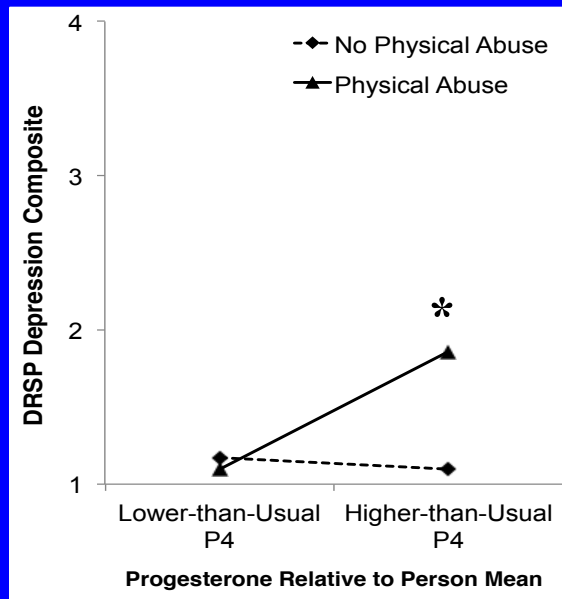
- Physical Abuse (PA):
 - 2 Types: 1) beat, hit or kicked
 - 2) life threat (intent to kill or seriously injure)

Only counted if the incident(s) occurred separately from any SA incident

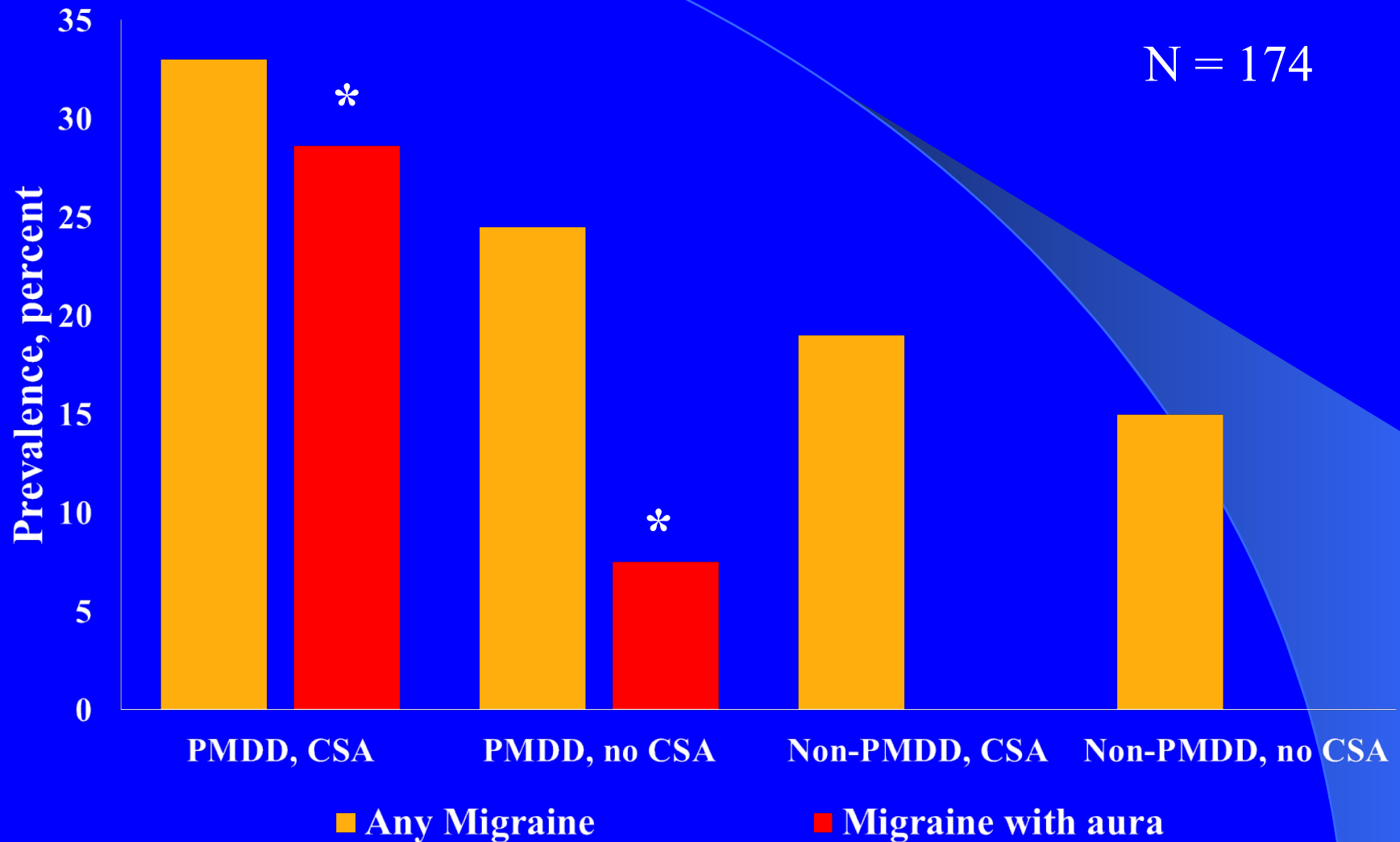
Greater Rates of Sexual and Physical Abuse in PMDD



Histories of Abuse predict a hormone sensitive phenotype in women with PMDD

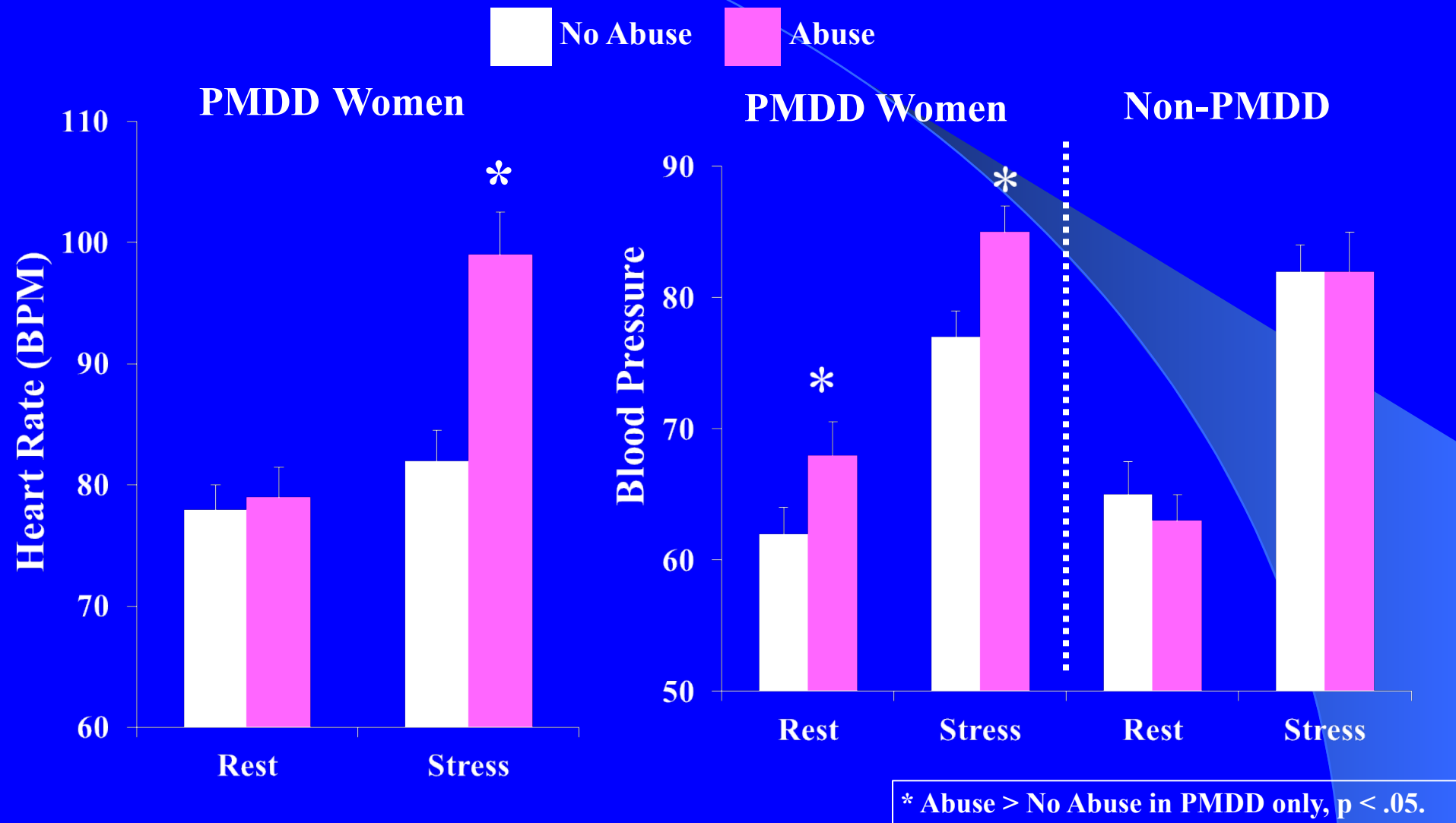


Childhood Sexual Abuse predicts Migraine with Aura (ICHD-II criteria) in Women with PMDD

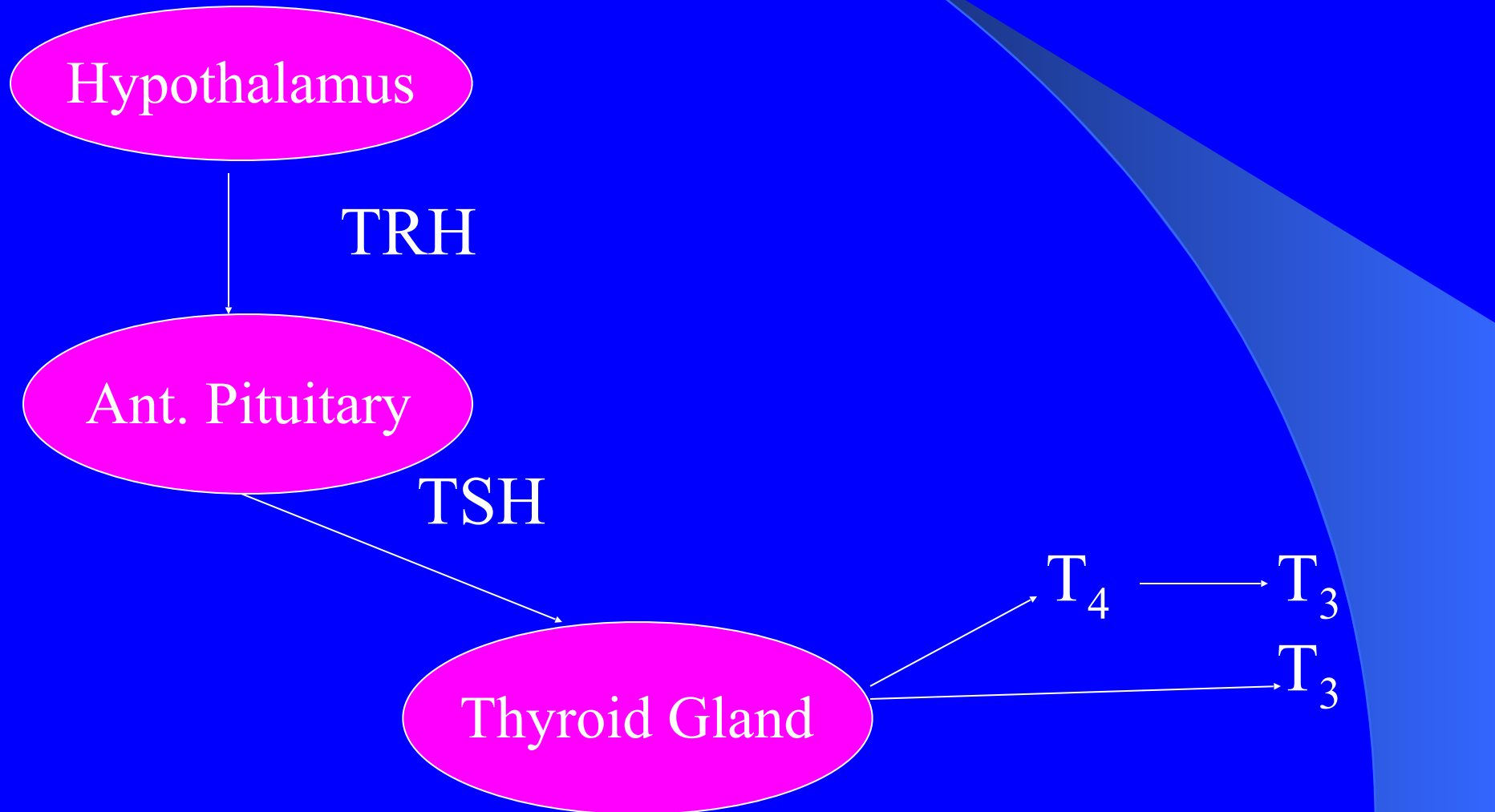


*Fisher exact test, $p = 0.019$.

PMDD Women with a History of Abuse Have Greater Sympathetic Responses to Mental Stress



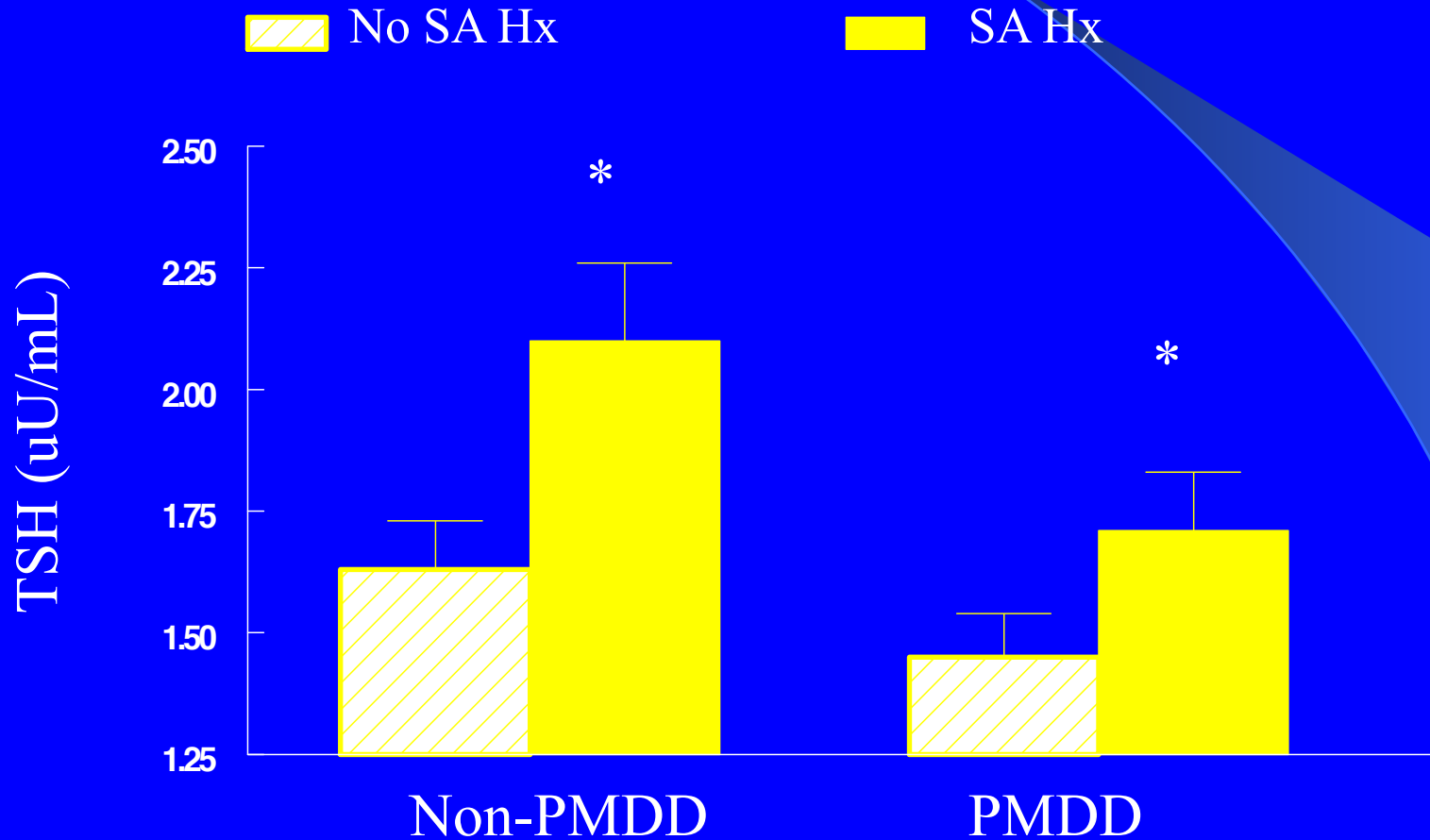
The Hypothalamic-Pituitary Thyroid Axis



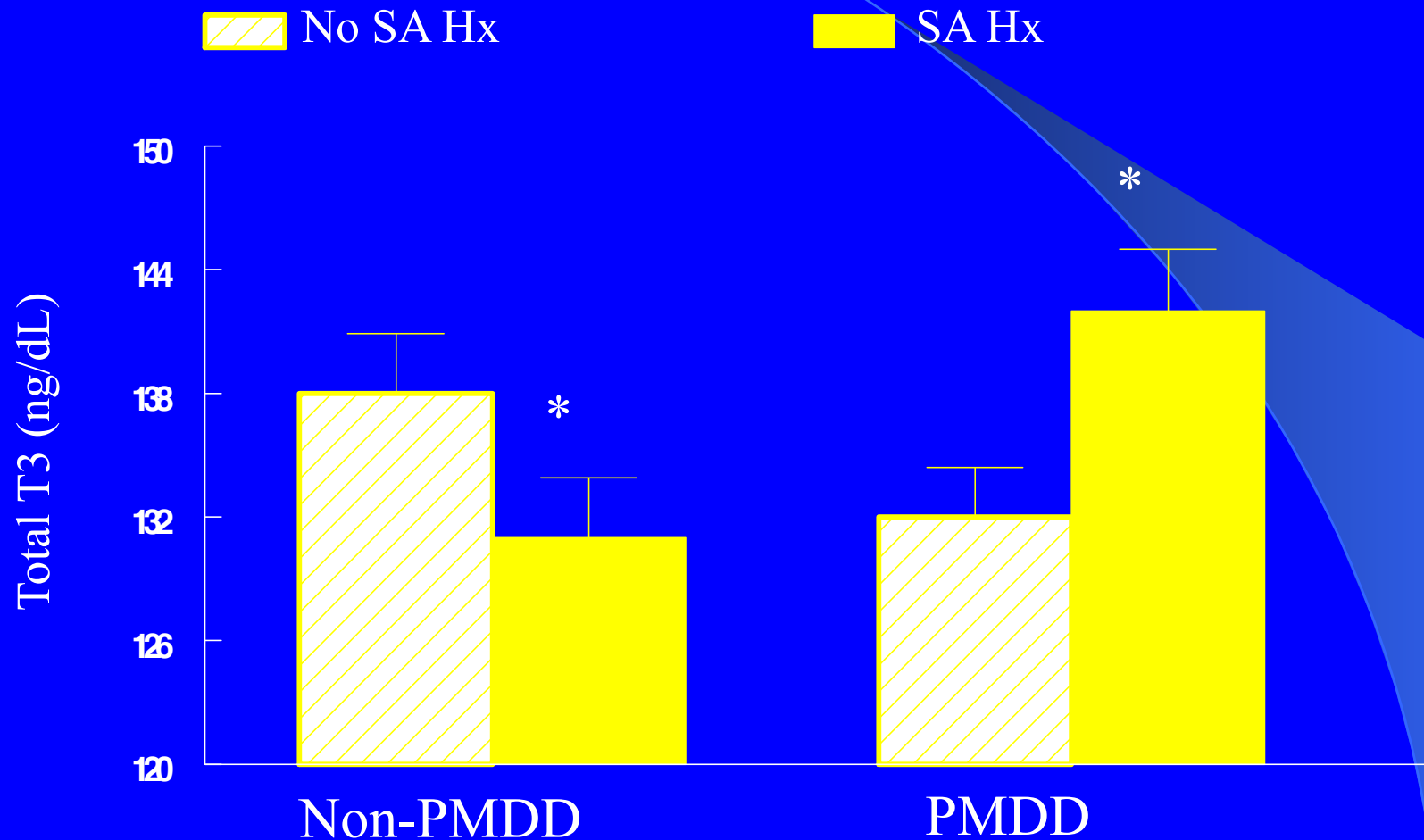
HPT-Axis Facts

- T_3 is 4x more biologically active than T_4
- Tissues use T_3 in preference to T_4
- Like other tissues, brain makes T_3 from T_4
- T_3 and T_4 penetrate the BBB

A History of Sexual Abuse (SA) is associated with Elevated TSH concentrations



A History of Sexual Abuse (SA) differentially Impacts T3 concentrations in PMDD vs. non-PMDD women



Conclusions

- A History of Abuse May Identify a Clinically Distinct Subgroup of Women with PMDD

Predictors of New-Onset (Incident) PMDD in a Sample of 1251 Women

Baseline Predictors	Incidence Threshold PMDD versus no PMDD	
	OR	95% CI
Age at final follow-up	0.8	0.7 to 0.9
Subthreshold PMDD	11.0	4.7 to 25.9
Any qualifying trauma	4.2	1.2 to 12.0
Diagnosis of PTSD at baseline	0.7	0.1 to 2.8
Low self-competence	1.1	0.7 to 1.8
No. of negative life events	0.9	0.7 to 1.3
Increased daily hassles	1.6	1.1 to 2.3
Substance use disorder	0.4	0.1 to 1.6
Nicotine dependence	1.7	0.6 to 4.5
Any anxiety disorder	2.5	1.1 to 5.5
Any mood disorder	1.1	0.4 to 3.2
Any somatoform disorder/syndrome	0.8	0.3 to 2.1
Any eating disorder	2.2	0.8 to 6.9

Postpartum Depression



➤ COMMON

- **10-15% prevalence**
- 4 million women give birth annually in U.S.; ½ million with PPD
- Most common, unrecognized complication of perinatal period

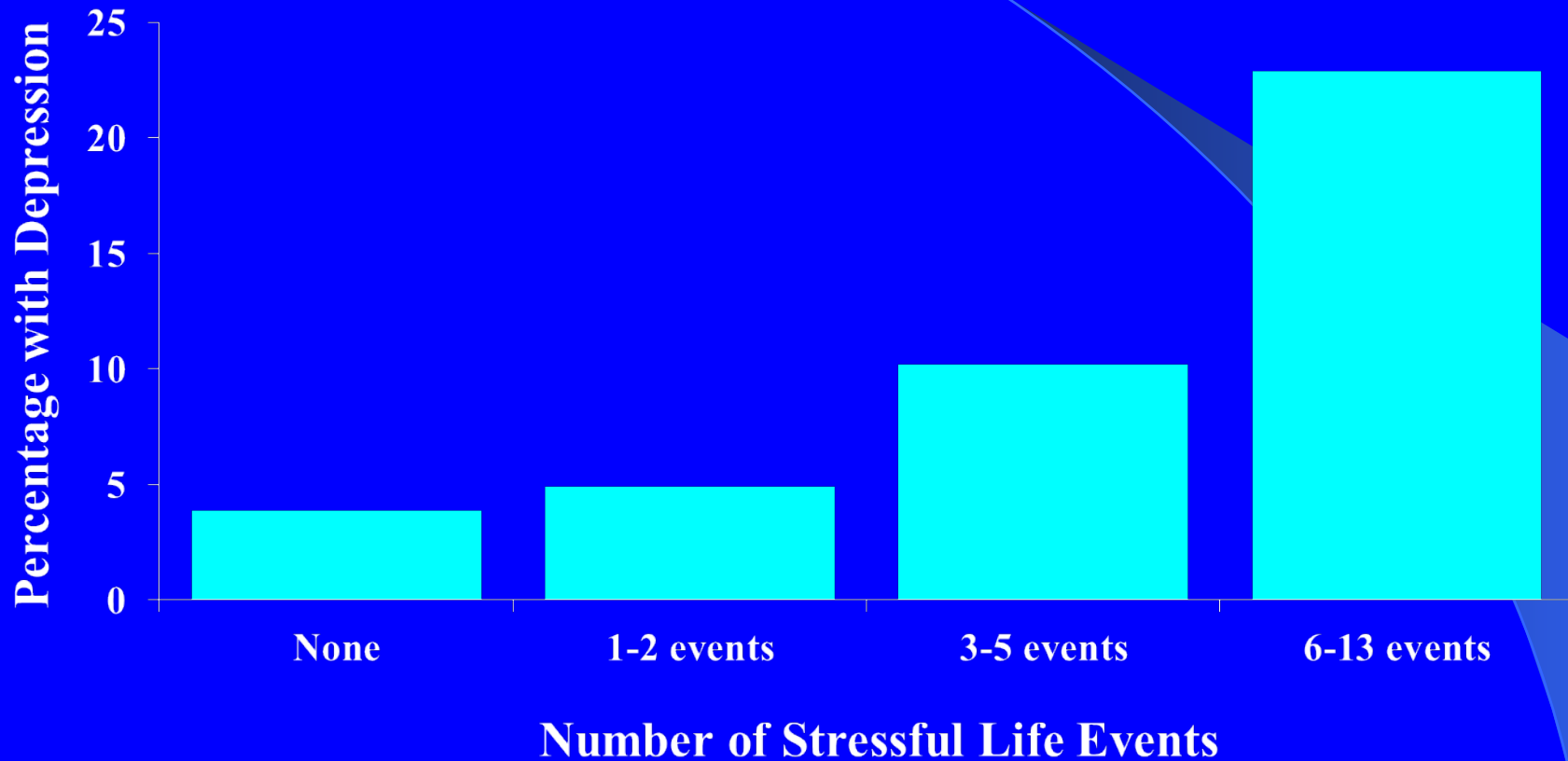
➤ MORBIDITY AND MORTALITY

- Devastating consequences for patient and family
 - Impaired bonding between mother and infant
 - **Leading cause of maternal mortality in the postpartum period**

➤ PREDICTORS

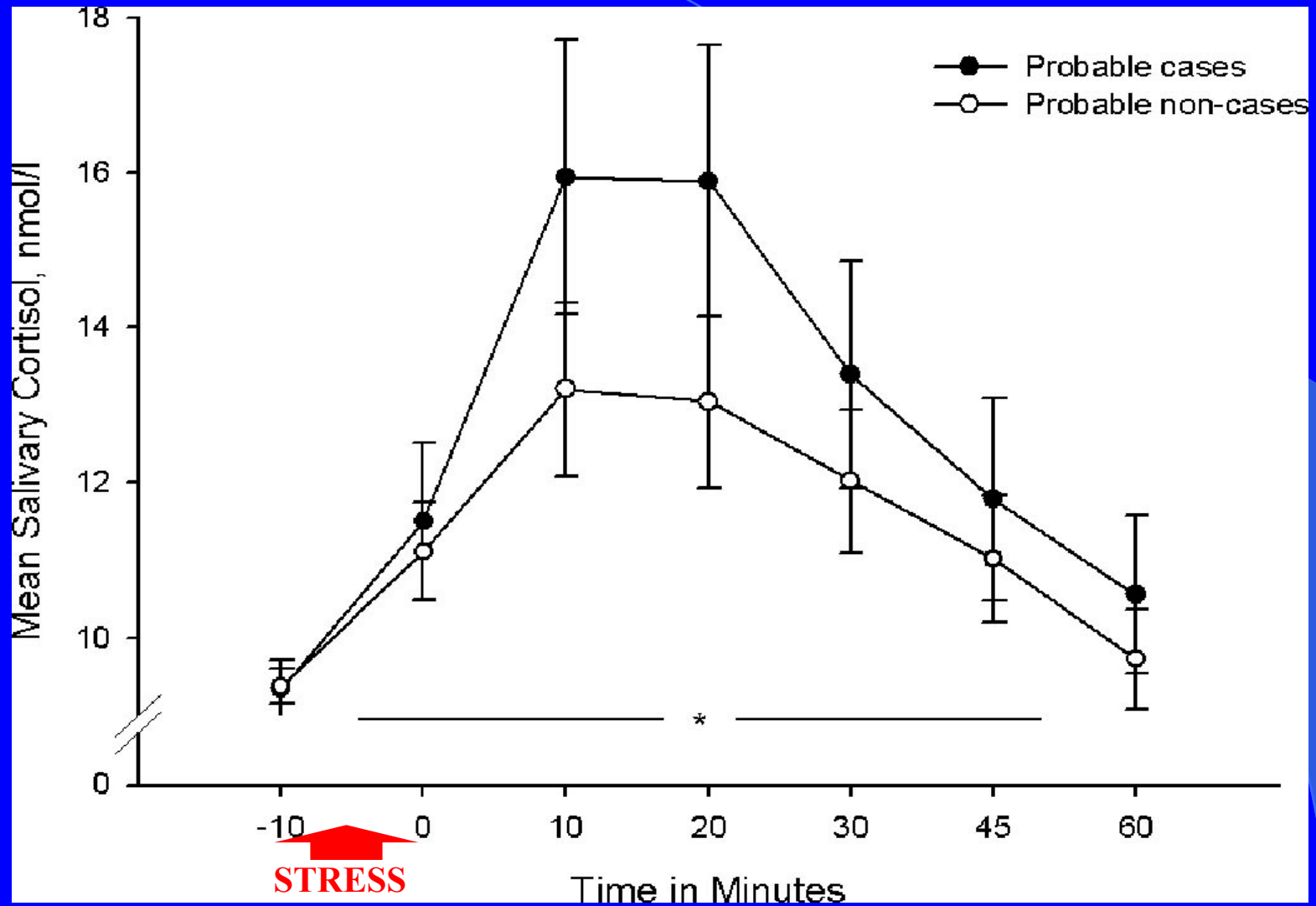
- History of depression
- Depression or anxiety during pregnancy
- **Stressful life events**
- Poor social support

Percentage of Mothers with Postpartum Depression by Total Number of Stressful Life Events

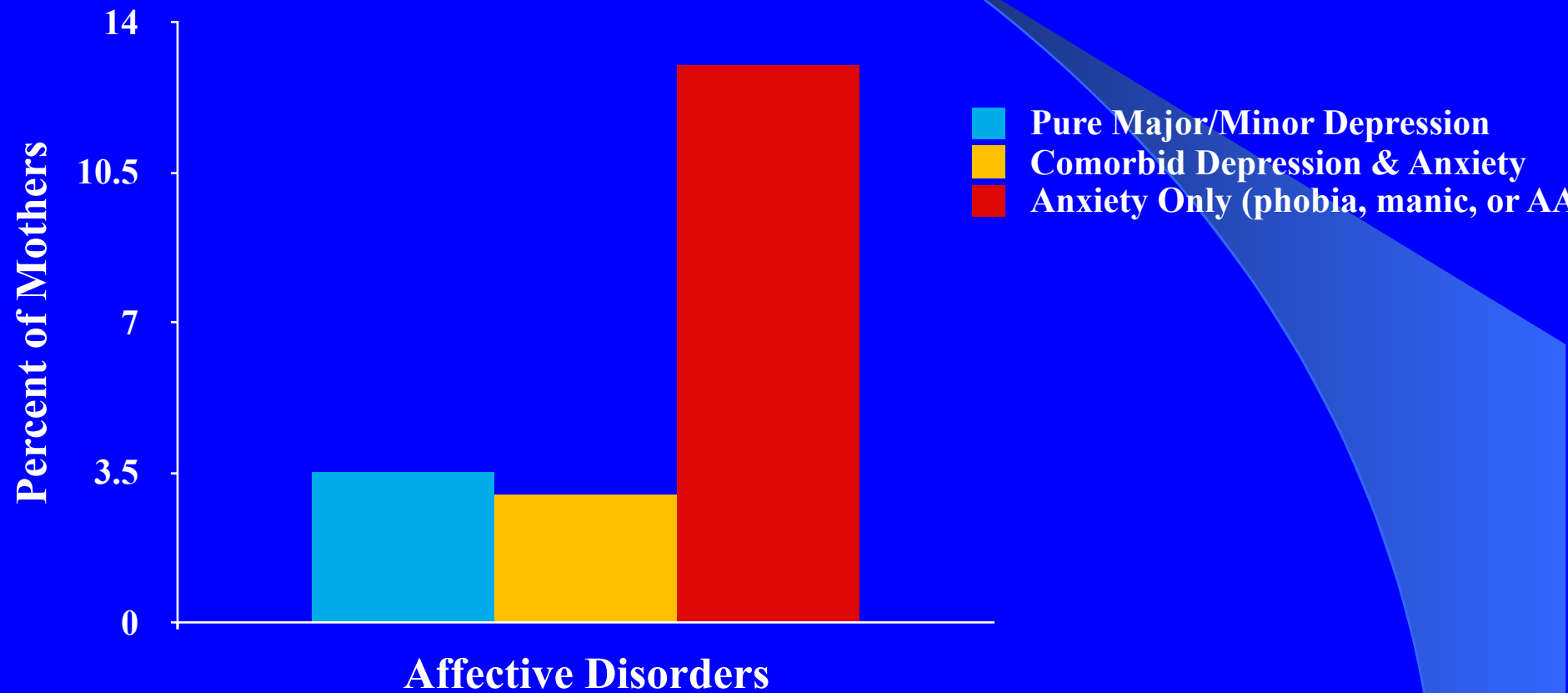


Herrick, H. W. (2000). The Effect of Stressful Life Events on Postpartum Depression Results from the 1997-1998 North Carolina Pregnancy Risk Assessment Monitoring System (PRAMS)

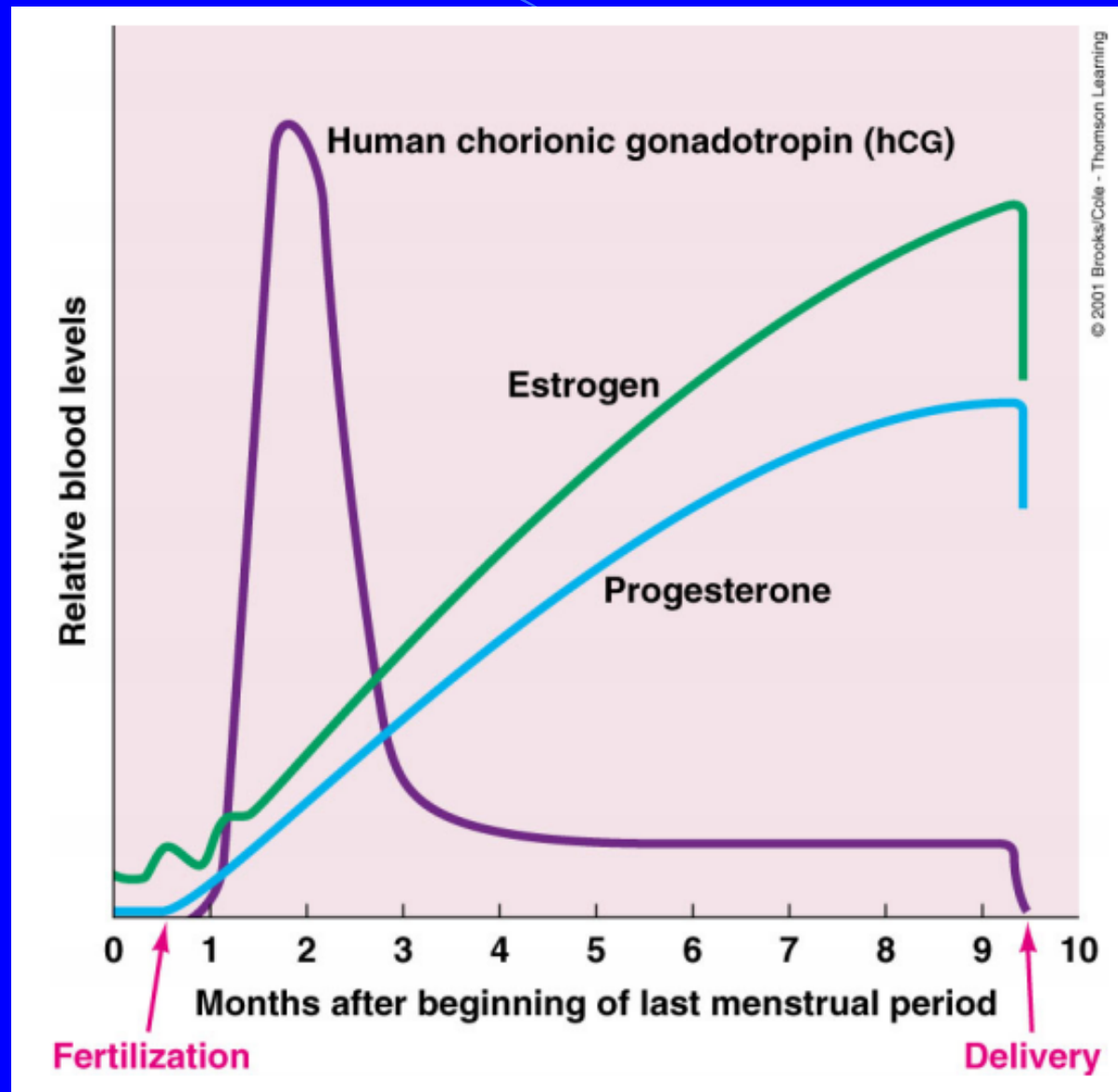
Greater HPA Axis Response to Stress During Pregnancy Predicts Post Partum Depression within One Month of Delivery



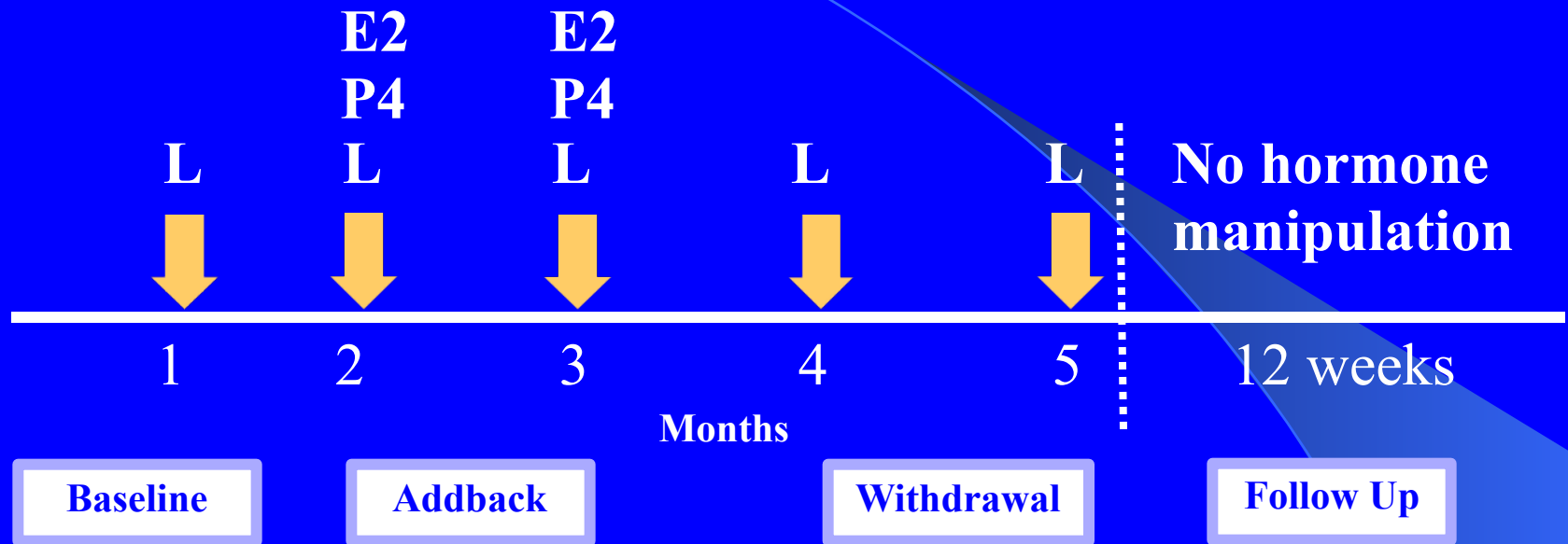
Rates of Affective Disorders for Mothers at 6 weeks Postpartum



Reproductive Steroid Hormone Profile in Pregnancy and the Immediate Postpartum Period

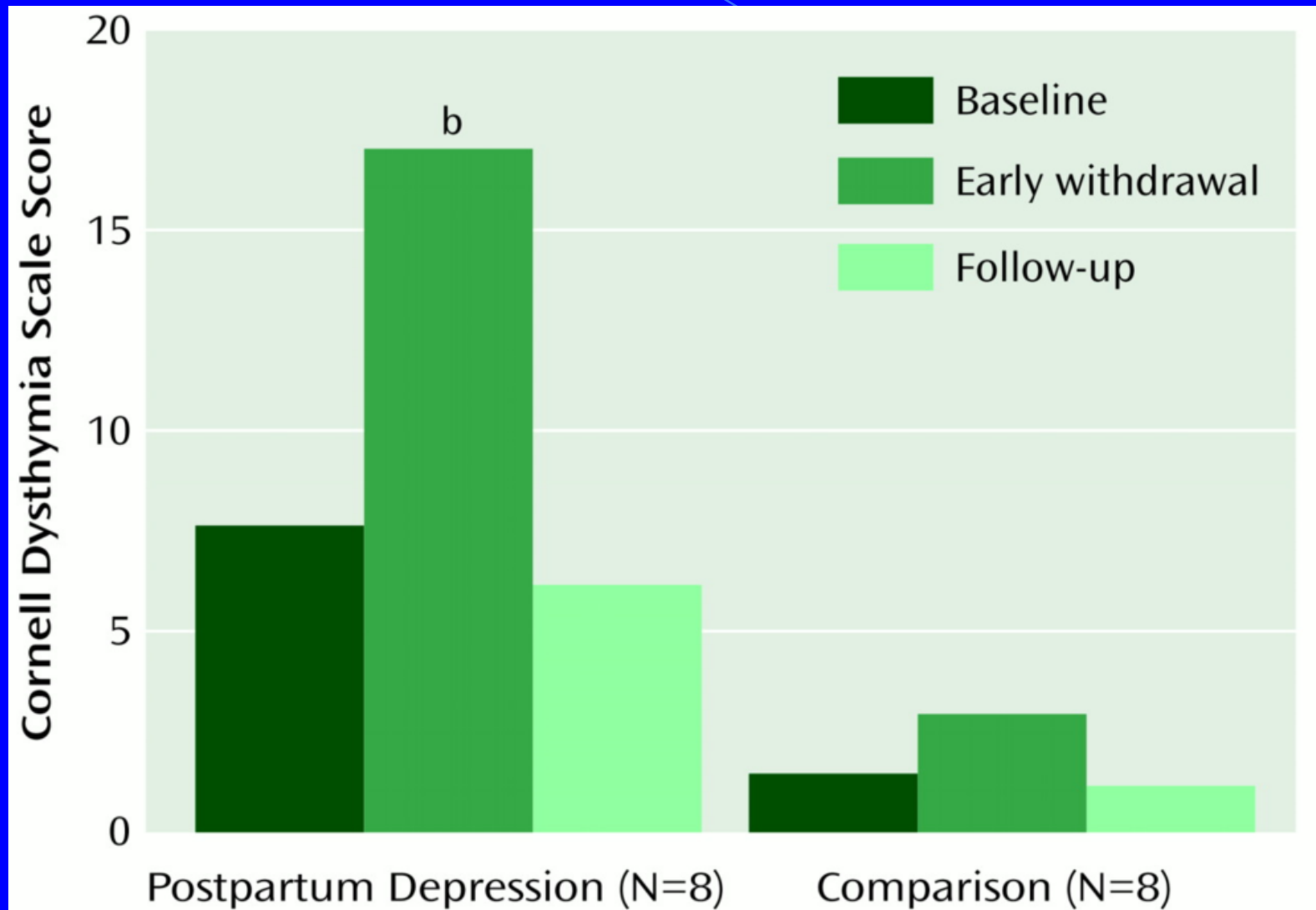


Euthymic Women with a History of PPD vs. No History of PPD

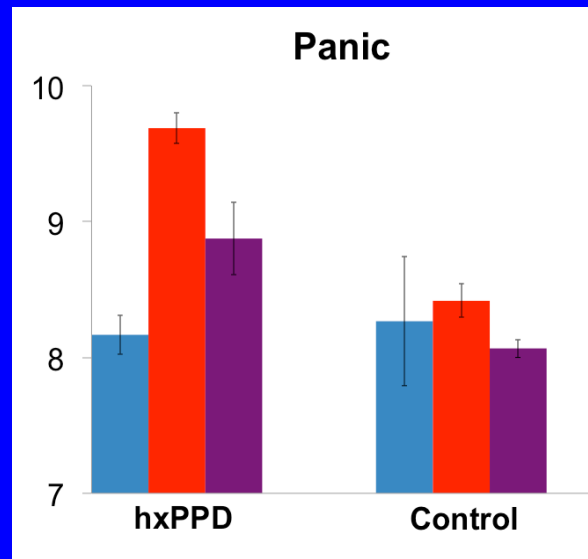
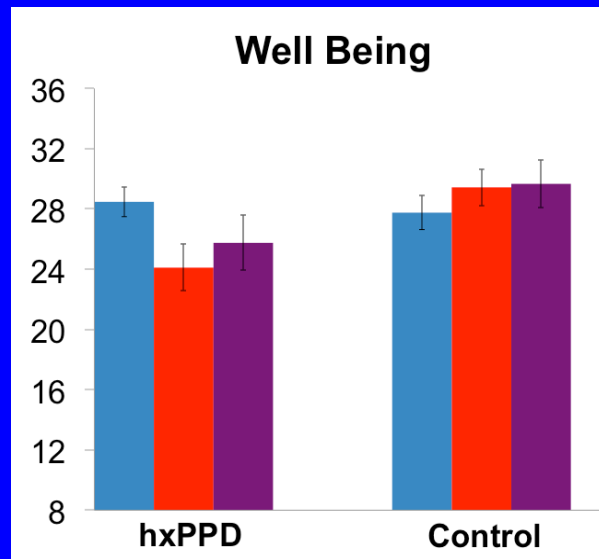
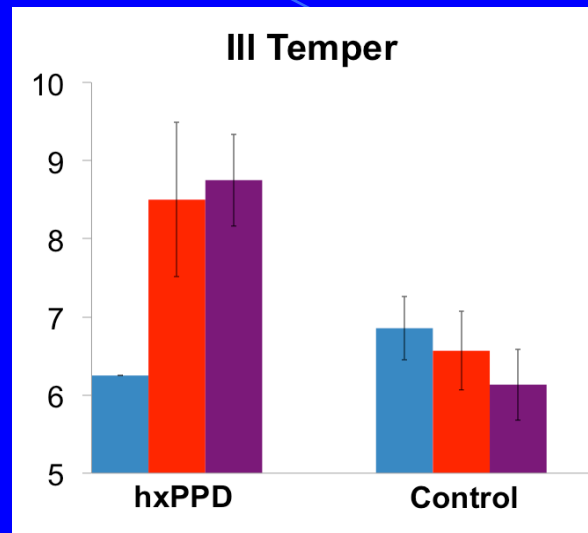
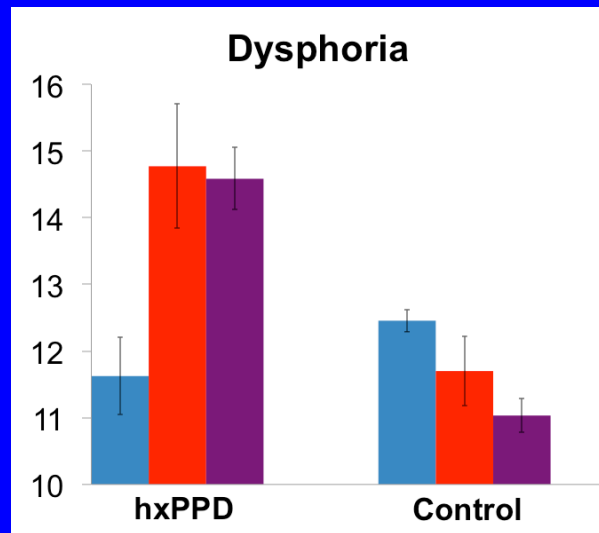


L Leuprolide acetate (3.75 mg/month)
E2 Micronized estradiol (10mg/day)
P4 Micronized progesterone
(target level = 50 ng/ml; 400-900 mg/day)

Women with a History of PPD are Differentially Sensitive to Hormone Withdrawal



Effects of Hormones on Mood in women with a history of Postpartum Depression



Hx PPD $n = 12$
Control $n = 15$

The painting is a reproduction of J.M.W. Turner's 'Rain, Steam, and Great Bridge' (1844). It depicts a woman in a long, flowing white dress and a large green umbrella standing in a field of tall grass. The sky is filled with soft, white clouds, and the overall atmosphere is one of a rainy day. The brushwork is visible and expressive, characteristic of the Impressionist style.

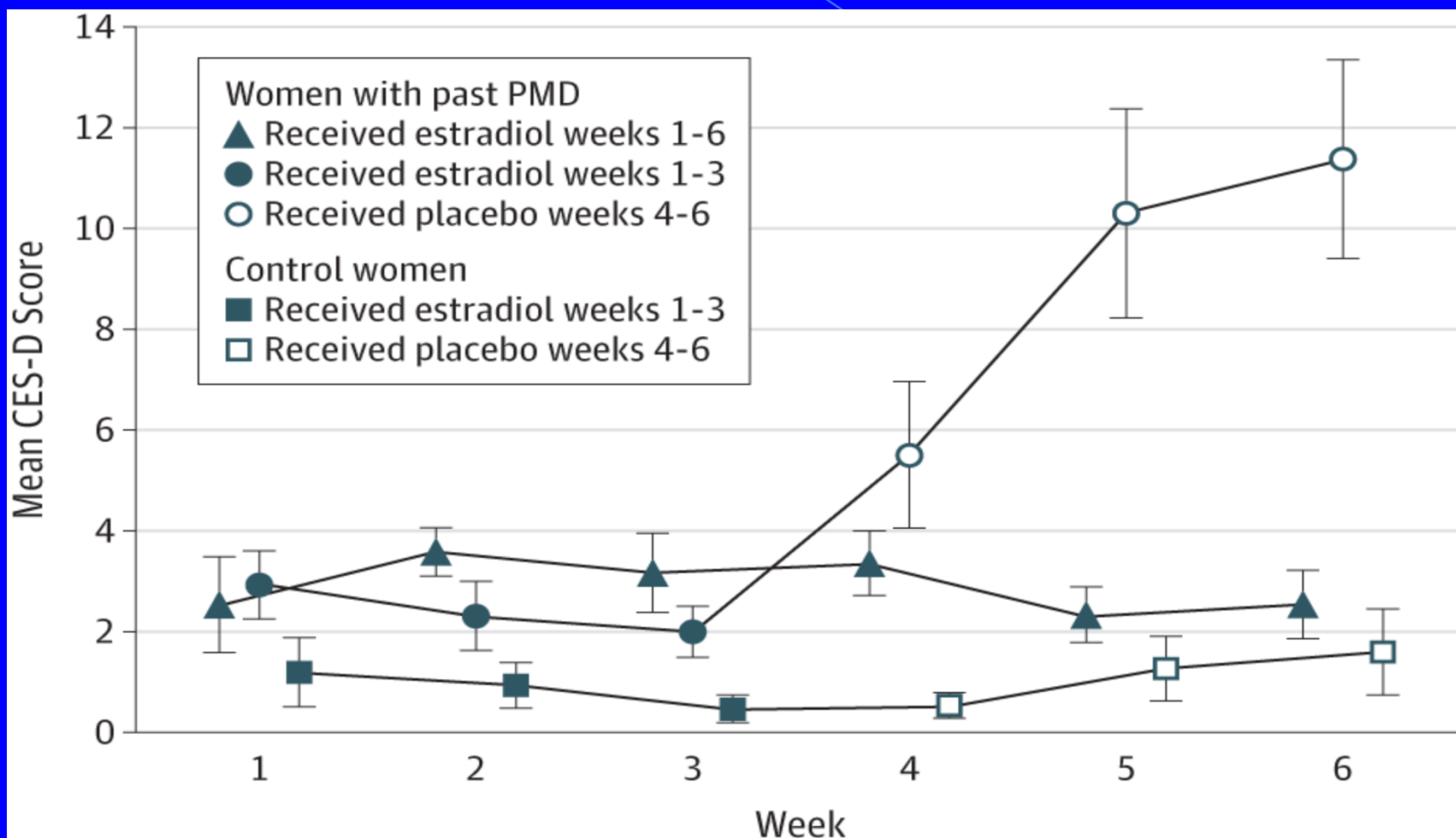
The Menopause Transition

Depression in the Menopause Transition

- The risk of first-onset depression increases 2 fold
- A history of depression increases risk 4 fold
 - Major Depression: 9-17%^{1,2}
 - Clinically significant depressive symptoms: 24-33%^{1,3}



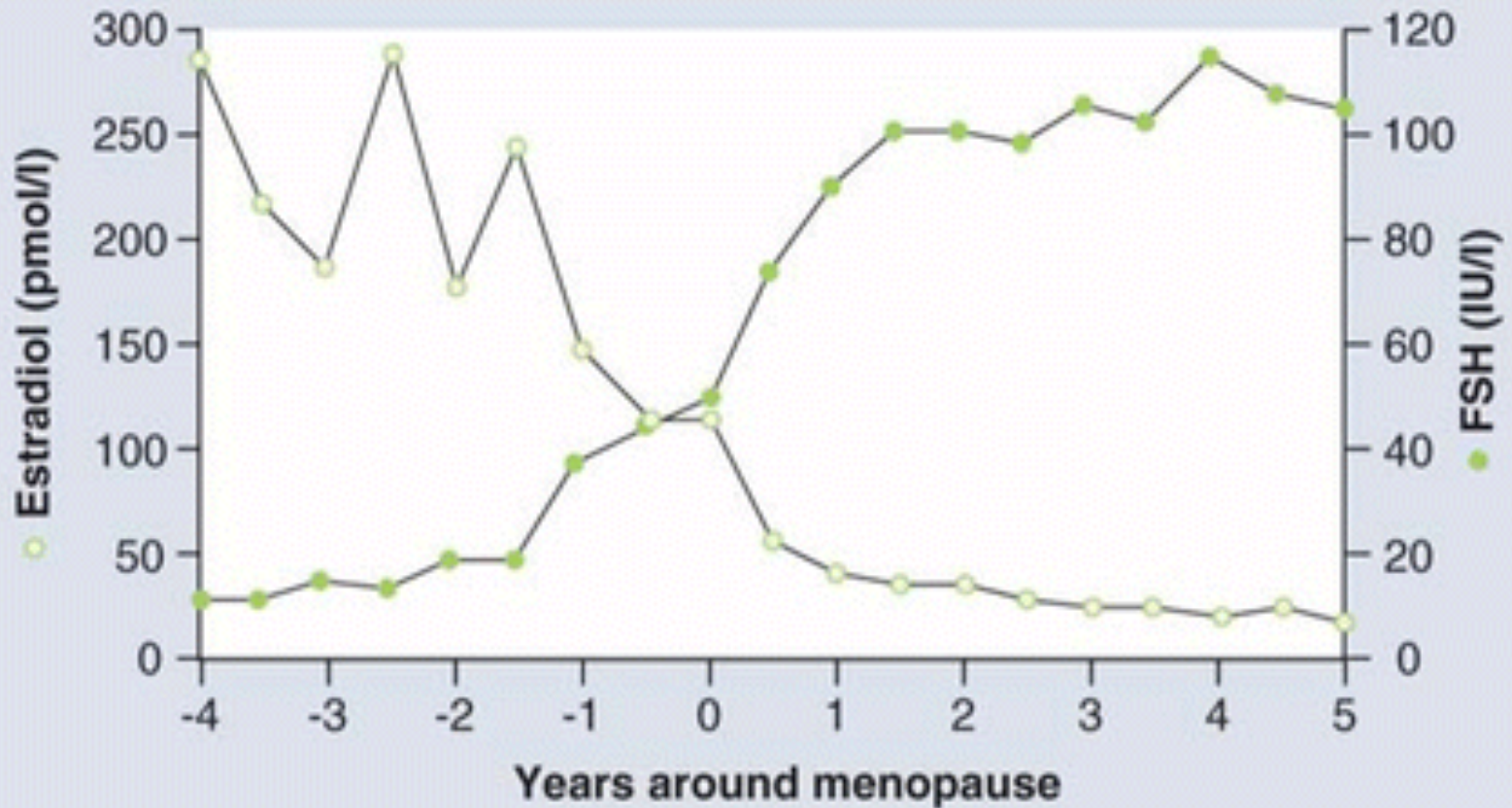
Hormone sensitive depressive phenotype in women with a past history of perimenopausal depression



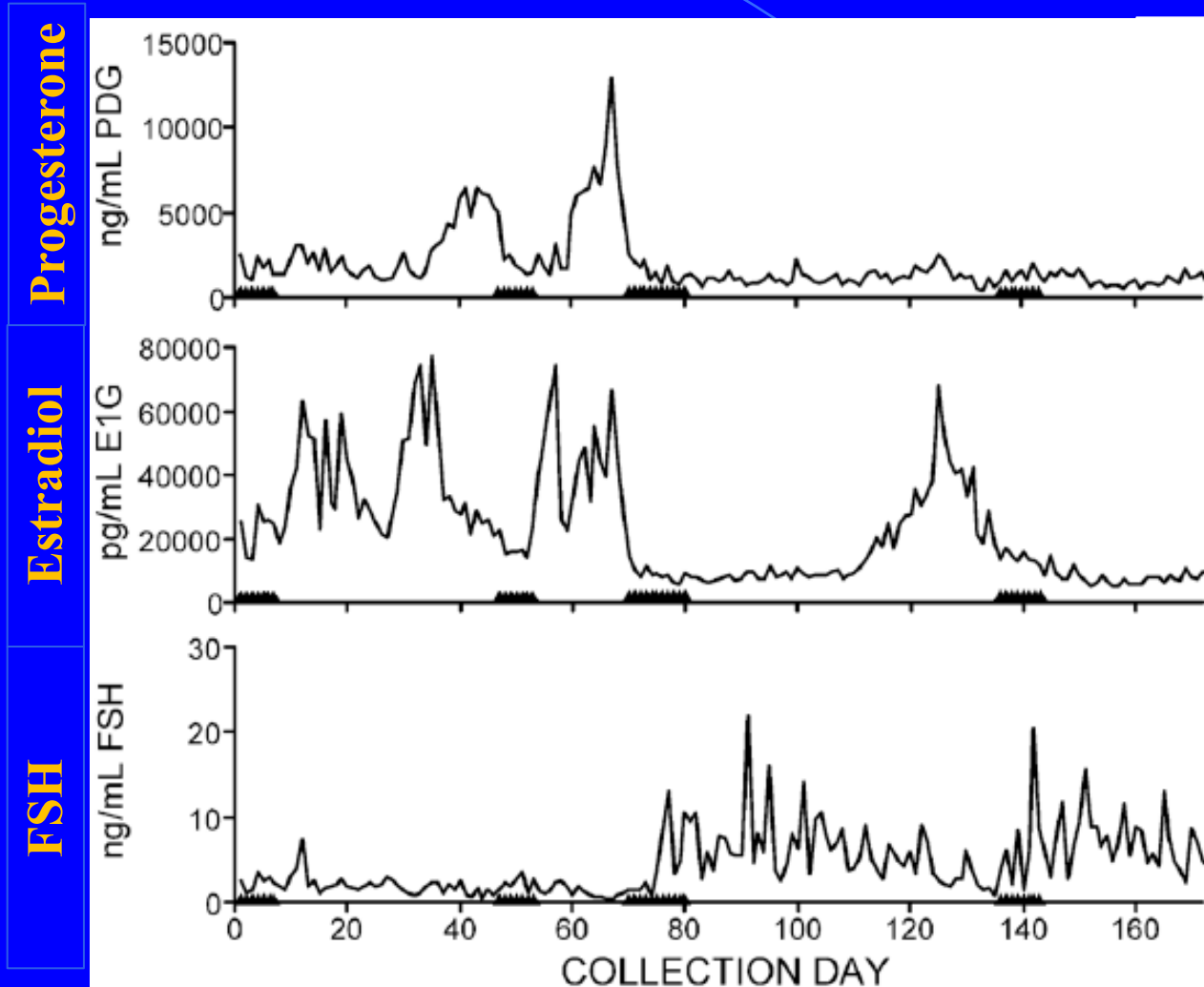


"I was on hormone replacement for two years before I realized that what I really needed was Steve replacement."

Endocrine Changes Around Menopause



Hormone Fluctuations in the Late Menopause Transition



Depression During the Menopause Transition: Association with Mean Hormone Levels and Hormone Variability

Hormone	Odds Ratio	CI	P Value
Estradiol (pg/ml)			
Mean	1.06	(0.63 – 1.78)	.83
Variability (SD)	1.36	(1.02 – 1.80)	.03
FSH (pg/ml)			
Mean	4.58	(2.03 – 10.35)	.001
Variability (SD)	2.09	(1.70 – 3.41)	.001



PERIT

Perimenopausal Estrogen Replacement Therapy Study

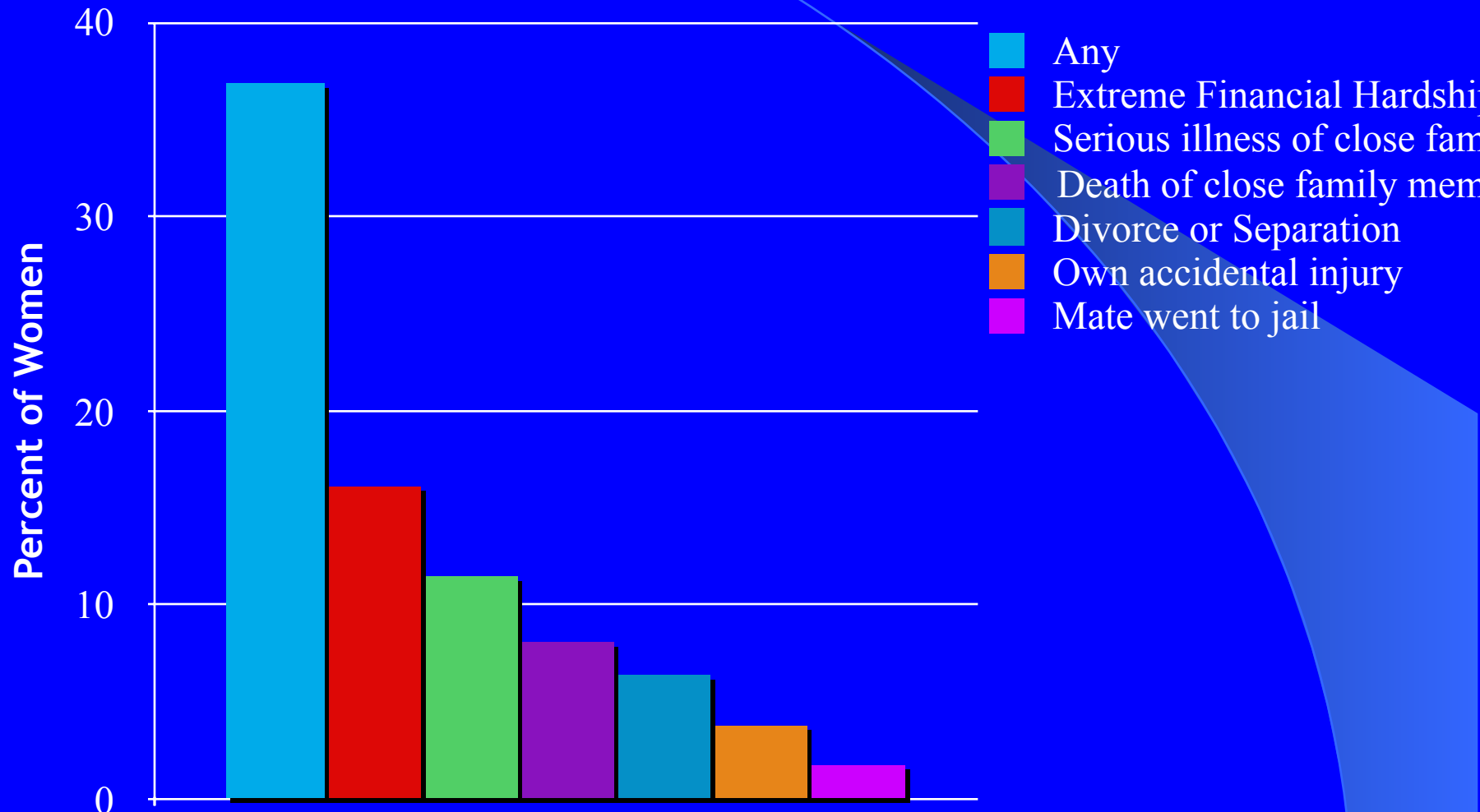
Funded by the National Institutes of Health:
NIH RO1 MH087619

Principal Investigators:
Susan Girdler, Ph.D. and David Rubinow, M.D.
Center for Women's Mood Disorders
University of North Carolina at Chapel Hill

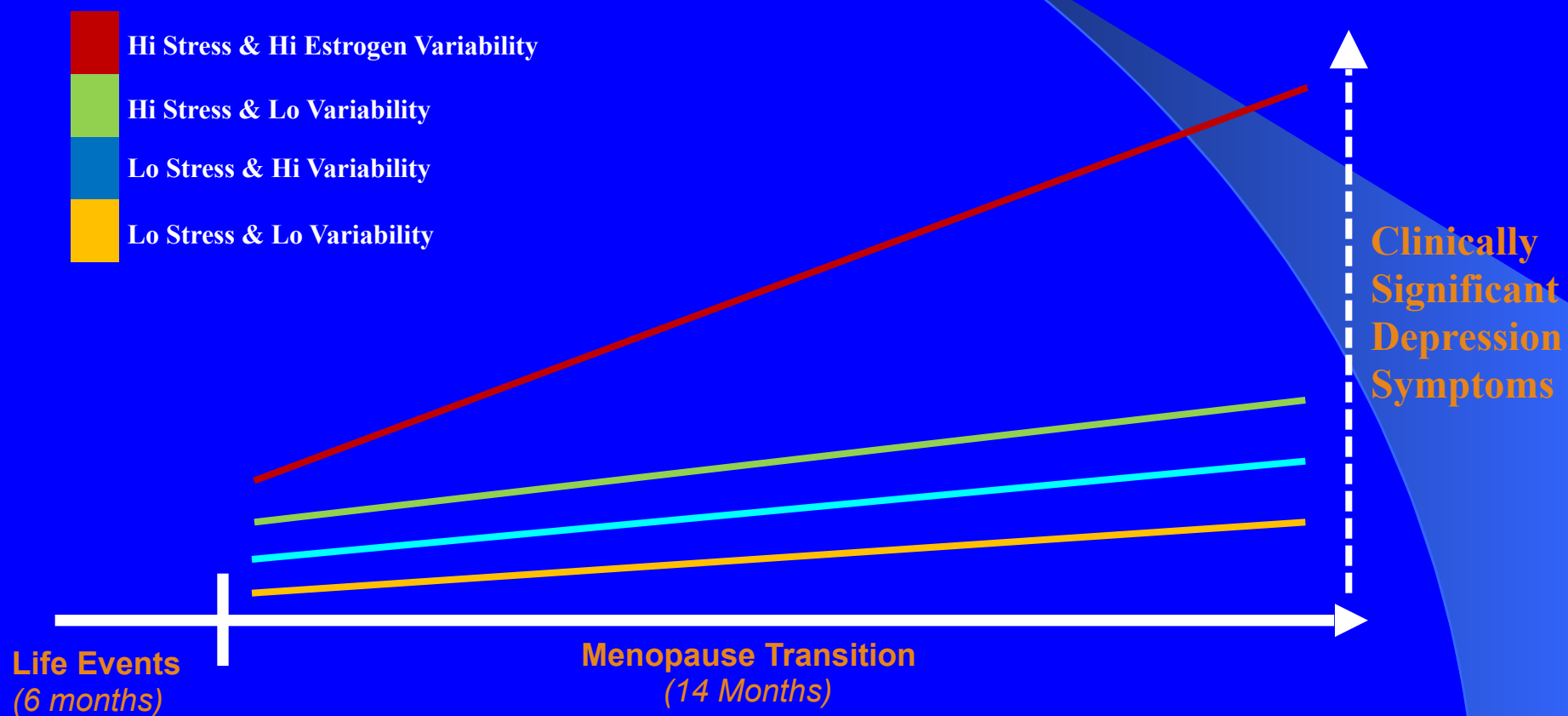
Cohort: Medically healthy, non-depressed women, 45 – 60 years of age in the menopause transition (STRAW -1 or -2)

Mid-Life Women Are at High Risk for Very Stressful Life Events

(past 6 months)



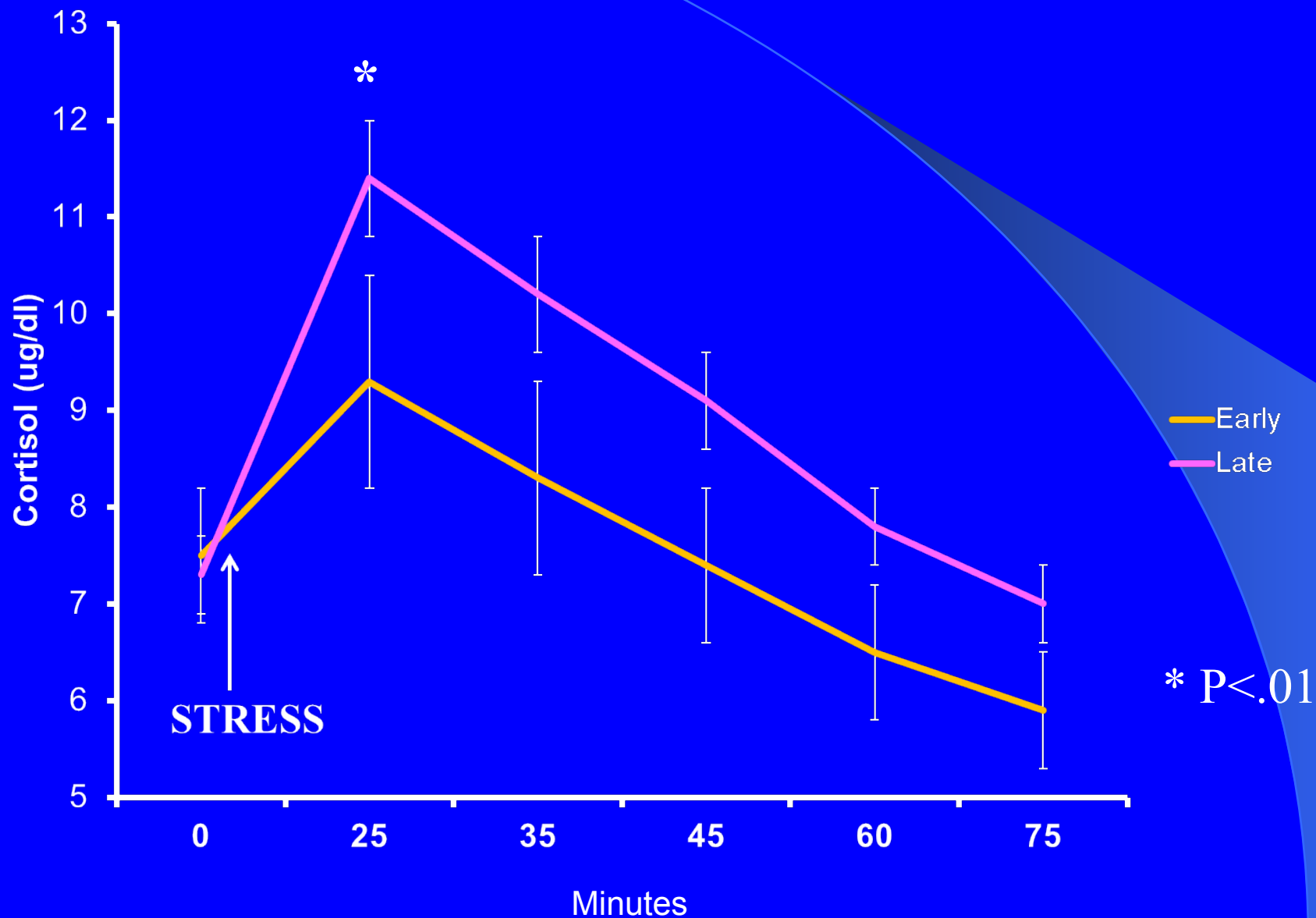
Mid-life Women with both high levels of stress and high estrogen variability *DEVELOP* depression in the menopause transition



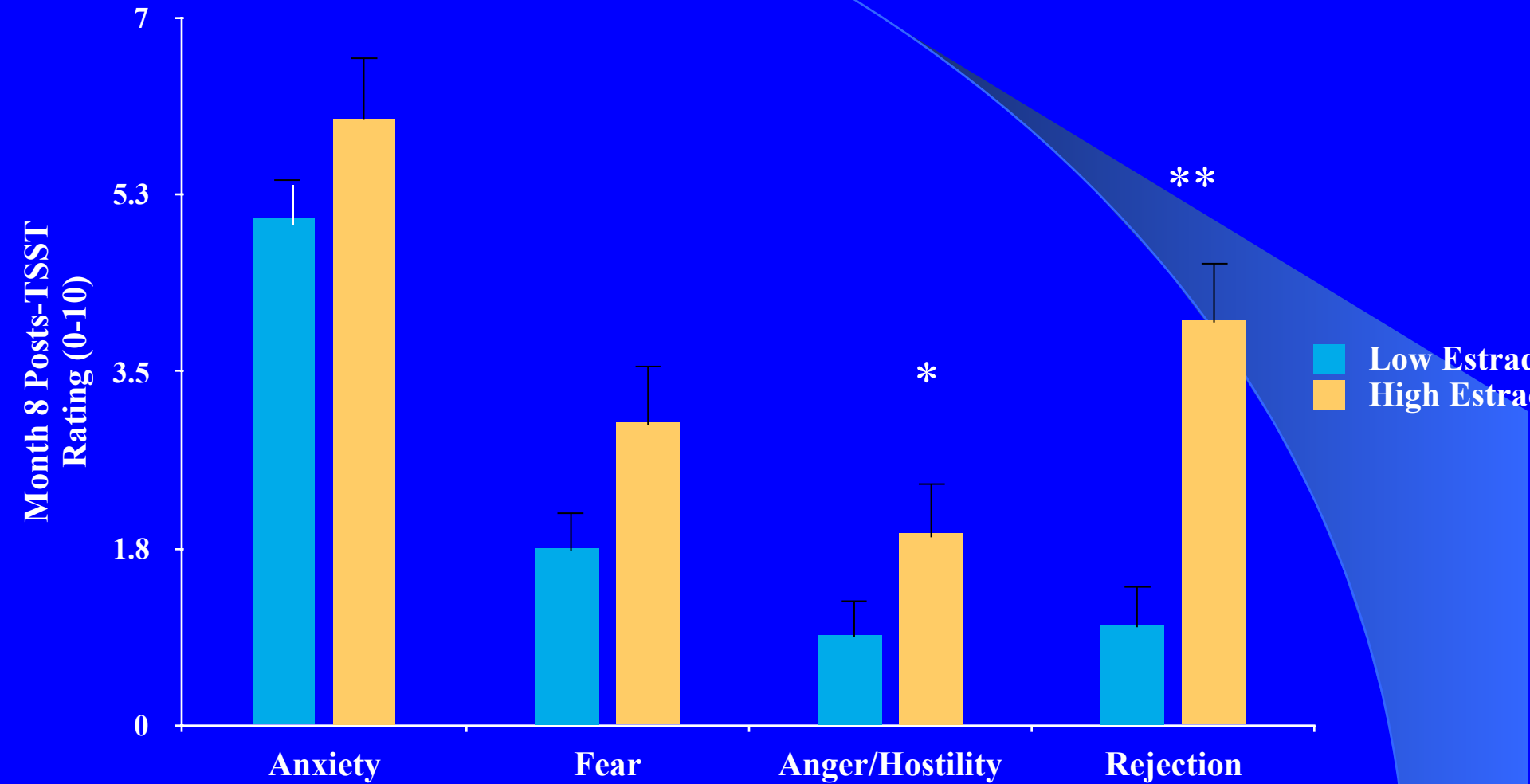
The Trier Social Stress Test



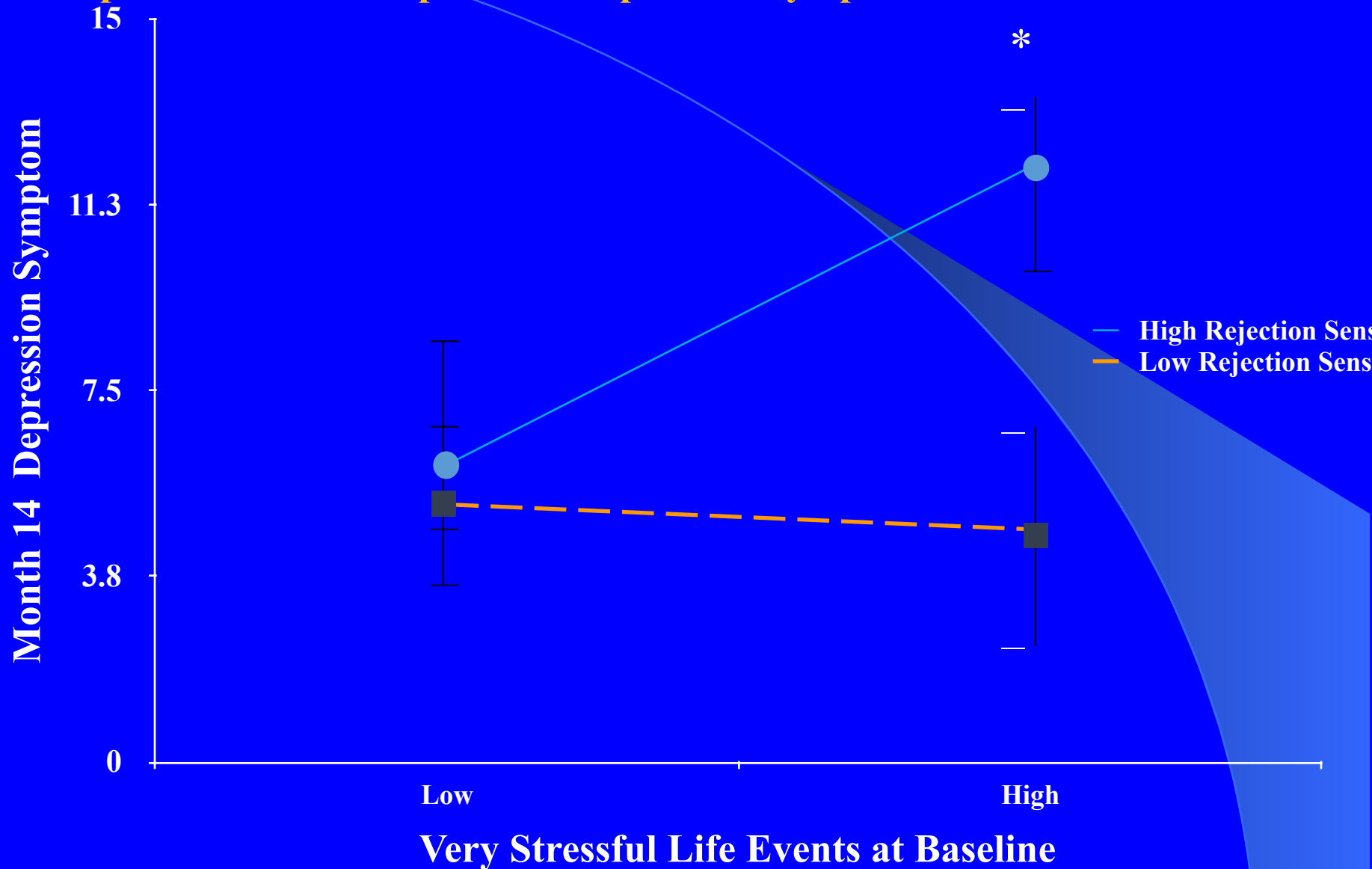
Women in the Late Menopause Transition (more erratic hormones) Show Greater Cortisol Reactivity to Stress



Greater estradiol variability over 8 months predicts more negative emotional responses to psychosocial stress

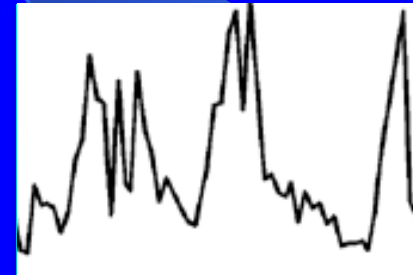
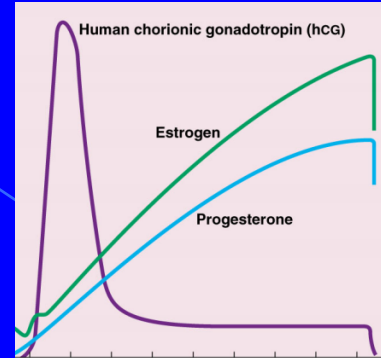


High rejection sensitivity in combination with stressful life events predicts the development of depression symptoms over 14 months



Biobehavioral Model of Reproductive Mood Disorders

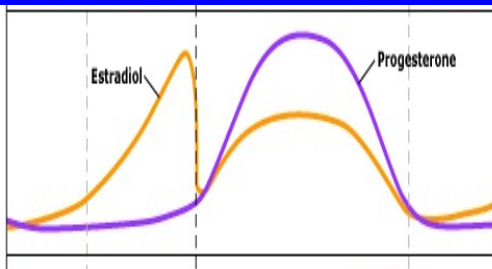
Early Life
Adversity



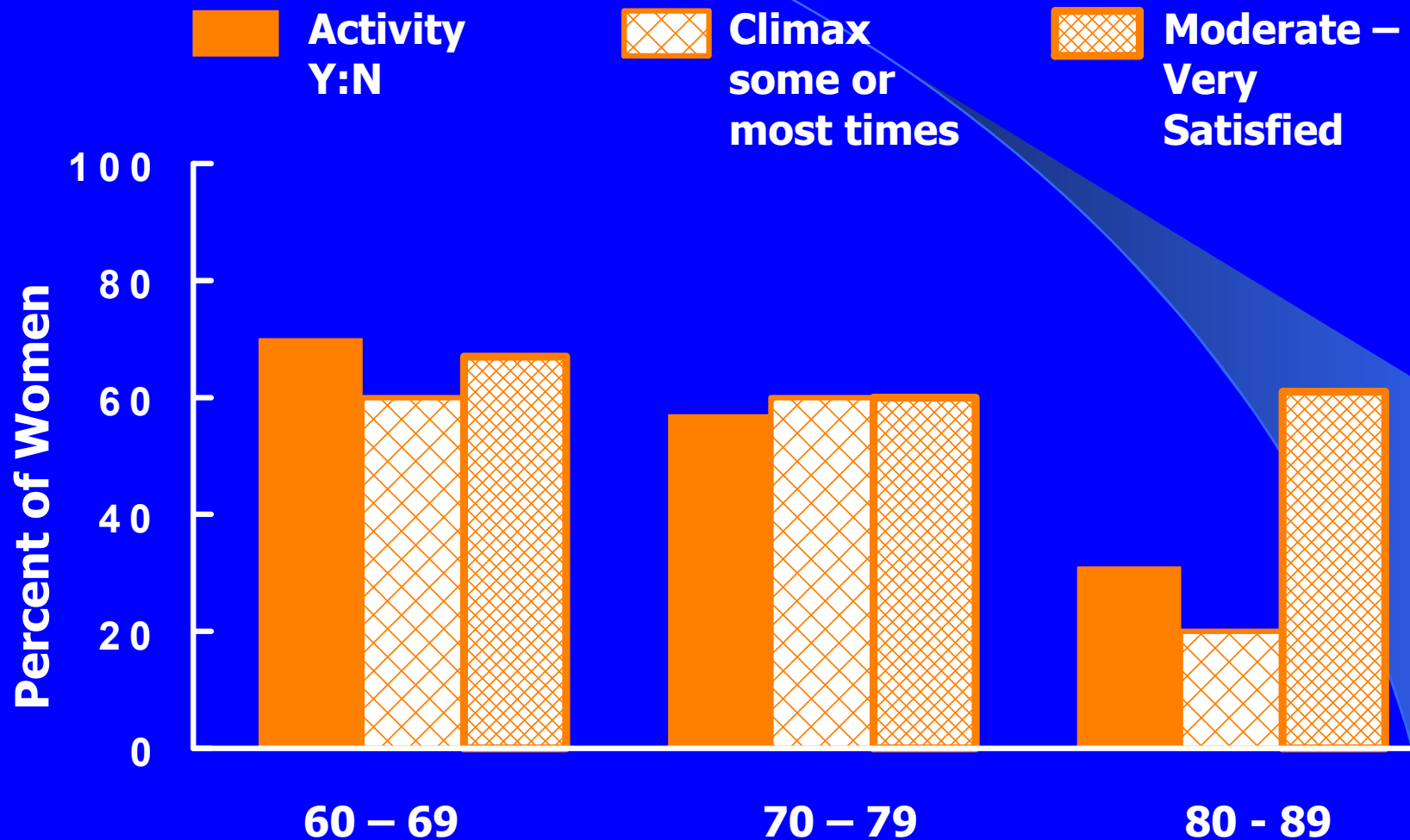
HPA & SNS
Stress Response
Dysregulation

Stressful Life
Events

Reproductive
Mood
Disorders



Sexual Function and Satisfaction in Women 60 – 89 years of age



Collaborators

- **David Rubinow, M.D., Director, UNC Center for Women's Mood Disorders**
- **Samantha Meltzer-Brody, M.D.**
- **Jane Leserman-Madison, Ph.D.**
- **Alan Hinderliter, M.D.**

Former and Current Postdoctoral Fellows

- **Tory Eisenlohr-Moul, Ph.D.**
- **Jennifer Gordon, Ph.D.**
- **Adomas Bunevicius, M.D., Ph.D.**
- **Shannon Crowley, Ph.D.**