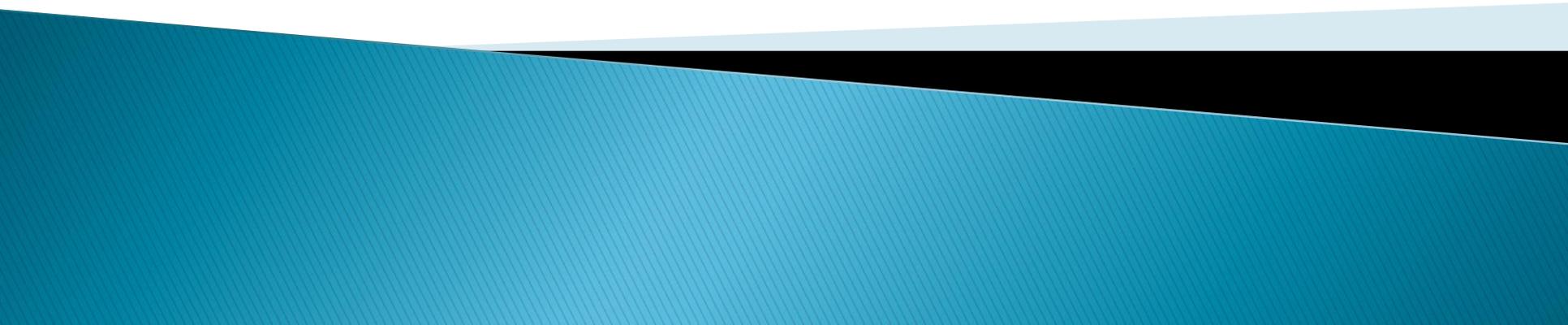


A Biological Mechanism for Adverse Maternal-child Outcomes in Disadvantaged Populations

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This work was supported by the National Institutes of Health, National Institute of Nursing Research (R01NR011278)



Chronic Stress

Increased chronic stress and lifetime stressful experiences increase the risk of poor birth and infant outcomes (Institute of Medicine, 2007)

Minority and low income women experience increased chronic stress and increased number of lifetime of stressful experiences (Geronimus, 2006; Duru et al, 2012)

Growing evidence supports that chronic stress - directly or in interaction with host genetic susceptibility and/or infection - is an important contributor to racial disparities in health outcomes for mothers and infants(Kramer et al, 2011)



The Stress Response in Pregnant and Postpartum Women

Mental and physical stress activate the neuroendocrine immune response – to neutralize the stressor

(1) Sympathetic nervous system (SNS)

Prepares body to respond – fight or flight

Increase WBC production of pro-inflammatory cytokines:

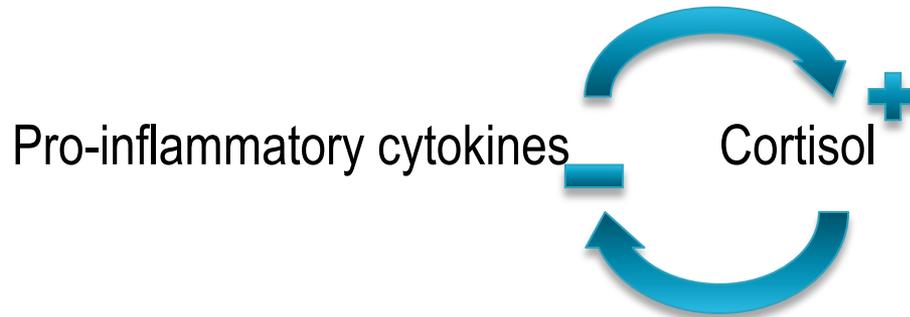
- Protect against infection & increases healing
- Increase risk of preterm delivery
- If chronic: gestational hypertension, pre-eclampsia, diabetes
- Acts as a strong stimulus of HPA axis to increase cortisol secretion

(2) Hypothalamic-pituitary-adrenal (HPA) axis

Stimulates cortisol secretion to mobilize resources and attention

- Increases risk of premature delivery
- If chronic: Increases risk gestational diabetes, anxiety, and fetal programming for hypertension, obesity, diabetes, anxiety

Cytokine-Glucocorticoid Feedback Circuit



This happens via cortisol binding to glucocorticoid receptors (GR) on WBCs

Derails cellular signaling pathways and transcription factors (NFκB) that control production of pro-inflammatory cytokines

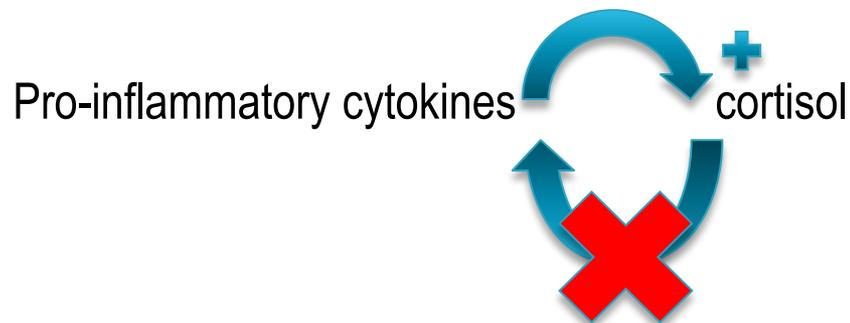
With Exposure to Chronic Stress

Cells may develop functional **glucocorticoid resistance (GR)**

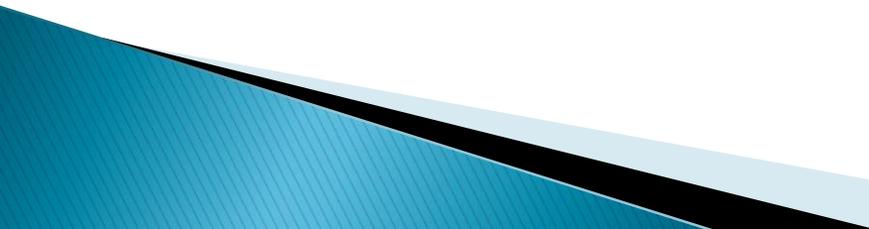
- Cortisol cannot limit WBC cytokine production
 - Cytokine production becomes dysregulated
- Cortisol partially escapes negative feedback

Cortisol levels increase

- Partially due to pro-inflammatory cytokine interference with GR signaling at multiple sites



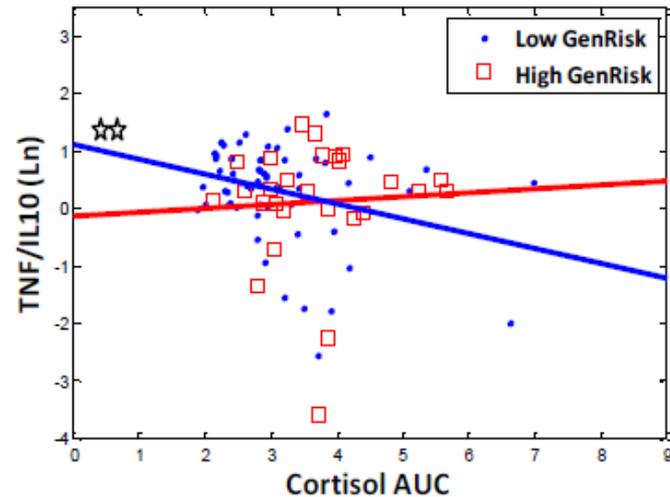
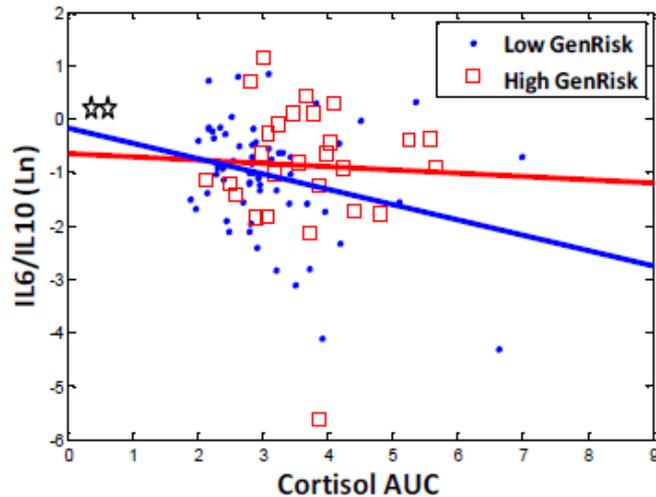
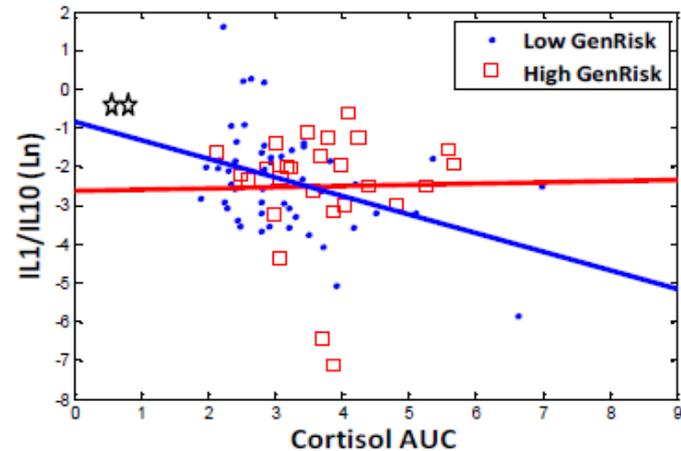
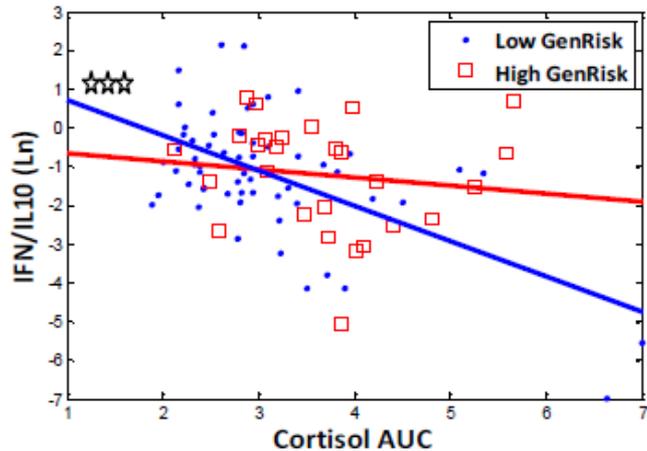
Glucocorticoid Resistance in Other Populations

- Parents of children with cancer (Miller, Cohen, Ritchey, 2002)
 - Spouses of adults with cancer (Miller et al., 2008)
 - Women with a history of PTSD (Pace et al., 2012)
 - Individuals with lifetime exposure to low SES (Cohen et al., 2012)
- 

Our previous research: Cytokine-Glucocorticoid Feedback Dysregulation during Pregnancy

- Pregnant women disadvantaged due to race/ethnicity or income show dysregulation in the cytokine-glucocorticoid feedback circuit when compared to Caucasian or higher income women.
 - (Corwin et al. (2013) Immune dysregulation and glucocorticoid resistance in minority and low income pregnant women. *Psychoneuroendocrinology, In Press*)

Cytokine–glucocorticoid feedback circuit:
All slopes significant (* $p < 0.05$, ** $p < .001$, *** $p < .0001$)
for low risk but not high risk women



Does the pattern of cytokine–glucocorticoid dysregulation continue after delivery?

- ▶ Hypothesis: Minority and low–income women will demonstrate dysregulation of the cytokine–glucocorticoid feedback response over the first 6–months following delivery
 - ▶ All women in our study were healthy
 - ▶ The inflammatory response and the HPA response differ during pregnancy compared to the postpartum period.
- 

Methods

- Nurse-conducted home visits prenatal weeks 32-36 and postpartum at:
 - 1-week
 - 2-weeks
 - 1-month
 - 2-months
 - 3-months
 - 6- months
- At each visit, subjects completed questionnaires:
 - Demographic
 - Perceived Stress Scale (PSS)
 - Edinburgh Prenatal Depression Scale (EPDS)
- And provided a blood sample for measurement of:
 - Pro-inflammatory cytokines:
Interleukin 1-beta (IL-1 β), IL-6, tumor-necrosis factor-a (TNF- α), and
interferon-gamma (IFN- γ)
 - Anti-inflammatory cytokine: IL-10

Methods

- During preceding day subjects collected saliva samples:
 - Upon awakening
 - 30-minutes post-awakening
 - 11:00 AM
 - 4:00 PM
 - 8:00 PM
- To improve validity /reliability of saliva collection
 - Subjects called preceding night
 - Subjects called 5-minutes before each collection
 - Utilize MEMS Caps
 - Extra compensation if answered phone & MEMS Caps accurate

Prenatal Inclusion/Exclusion Criteria

Prenatal:

- No chronic illness (including immune or endocrine disease)
- Not taking prescribed or OTC medications except prenatal vitamins
- Non-smokers

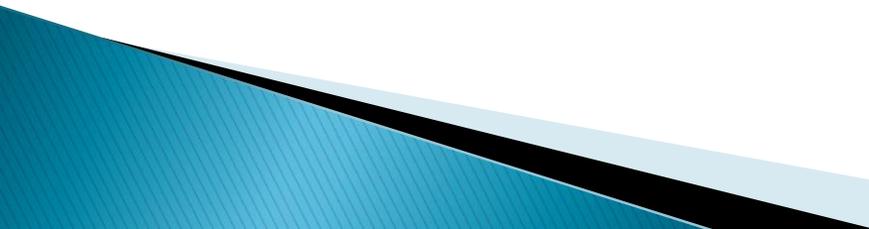
Postpartum:

- ▶ Vaginal birth
- ▶ No maternal hemorrhage or transfusion
- ▶ Mother and infant left hospital together within 72 hours

Statistical Analysis

- For statistical comparisons subjects grouped 3 ways:
 - Caucasian or racial minority (“Race”) – self report
 - High or low income – (“Income”)- self report of government assistance, i.e., WIC
 - Presence or absence of either of the 2 risk factors: being minority or low income vs. Caucasian and higher income (high or low “General Risk”)

Statistical Analysis

- Demographic variables compared:
 - Two sample t-test or Chi-square test/Fisher's Exact Test
 - Cytokine levels and pro- to anti-inflammatory ratios:
 - Multiple linear regression (controlling for other relevant factors)
 - Diurnal cortisol rhythm and cortisol area under the curve (AUC):
 - Hierarchical modeling (linear mixed model)
 - Association between cortisol AUC & cytokine ratios:
 - Pearson partial correlations
- 

Results



Table 1. Demographic and clinical characteristics of subjects (N=191)

	RACE			INCOME			GENERAL RISK		
	Minority (N=47)	Caucasian (N=144)	p- value	Low (N=48)	High (N=142)	p- value	High risk (N=68)	Low risk (N=122)	p- value
	Mean(SD)	Mean(SD)		Mean(SD)	Mean(SD)		Mean(SD)	Mean(SD)	
age	26.81(5.55)	29.77(4.70)	0.001	24.21(4.52)	30.67(4.15)	<0.001	26.10(5.21)	30.67(4.23)	<0.001
BMI	24.04(7.04)	24.17(4.60)	NS	26.20(5.47)	23.46(5.07)	0.002	24.69(6.61)	23.85(4.40)	NS
Marital Status	N(%)	N(%)	<.001	N(%)	N(%)	<.001	N(%)	N(%)	<0.001
Other	1(2.1%)	1(0.7%)		2(4.2%)	0(0%)		2(2.9%)	0(0%)	
Single	15(31.9%)	13(9.0%)		23(47.9%)	5(3.5%)		23(33.8%)	5(4.1%)	
Married	27(57.5%)	125(86.8%)		18(37.5%)	133(93.7%)		37(54.4%)	114(93.4%)	
Partnered	4(8.5%)	4(2.8%)		4(8.3%)	4(2.8%)		5(7.4%)	3(2.5%)	
Separated	0(0%)	1(0.01%)		1(2.1%)	0(0%)		1(1.5%)	0(0%)	

Notes: SD=standard deviation

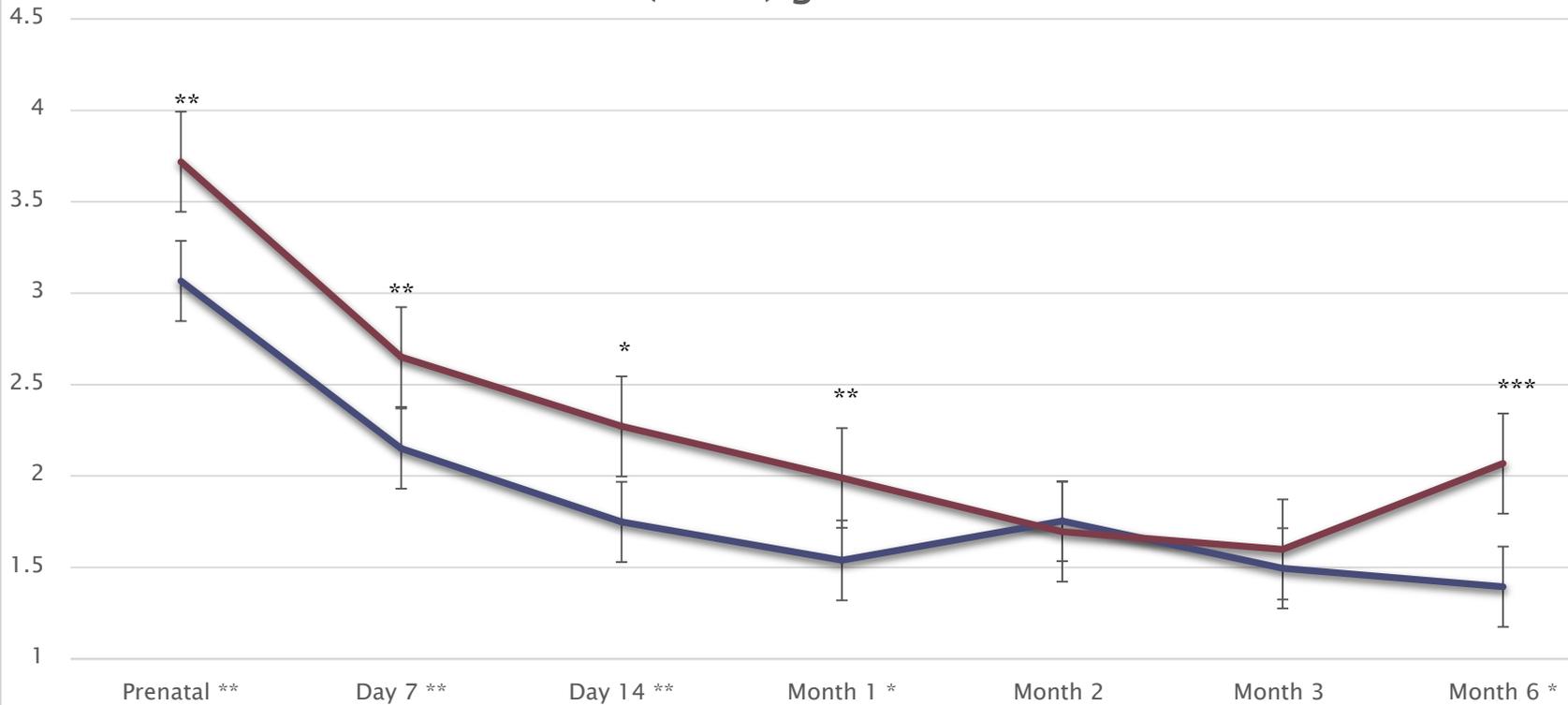
Self-report of perceived stress (PSS) and depressive symptoms (EPDS) in high (N=46) versus low (N=87) general risk pregnant and postpartum women (mean_±SD). (All data corrected for age & marital status)

	Prenatal	Day 7	Day 14	Month 1	Month 2	Month 3	Month 6
<u>PSS</u>							
Low stress	19.1 (5.7)	15.3(23.3)	17.0(5.9)	17.1(7.8)	18.2(6.4)	18.0(6.5)	18.5(7.2)
High Stress	22.5(6.8) (p=.004)	19.8(6.4) (NS)	17.8(10.0) (NS)	17.3(14) (NS)	19.4(8.5) (NS)	19.6(8.5) (NS)	19.6(8.5) (NS)
<u>EPDS</u>							
Low stress	4.1(3.3)	4.4(3.7)	3.3(3.1)	3.4(3.1)	3.1(2.7)	2.9(2.7)	3.1(3.1)
High Stress	5.6(4.2) (p=.047)	3.5(3.3) (NS)	3.4(3.1) (NS)	3.7(3.8) (NS)	3.1(3.1) (NS)	4.0(4.1) (NS)	3.4(3.6) (NS)

Average daily cortisol concentration (Area Under the Curve [AUC]) in high (N=36) versus low (N= 68) general risk pregnant and postpartum women (mean_±SE). (All data is corrected for appropriate variables)

	Prenatal	Day 7	Day 14	M 1	M 2	M 3	M6
AUC							
Low stress	3.02(0.1)	2.12(0.1)	1.75(0.1)	1.55(0.1)	1.74(0.1)	1.52(0.1)	1.41(0.1)
High Stress	3.77(0.2) (p=.003)	2.64(0.1) (p=.006)	2.25(0.2) (p=.001)	1.93(0.1) (p=.019)	1.62(0.1) (NS)	1.57(.1) (NS)	2.00(0.3) (p=.012)

Daily average salivary cortisol (area under the curve [AUC]) from the 3rd trimester through 6-months postpartum in high (n=36) versus low (n=68) general risk women.



*p<.05, **p<.01, ***p<.001

— Low Stressed Women — High Stressed Women

IL-6 (pg/ml) and IL-6/IL-10 ratio in high (N= 41) versus low (N=79) general risk pregnant and postpartum women. (mean_±SE). (All data corrected for appropriate variables)

	Prenatal	Day 7	Day 14	M 1	M 2	M 3	M6
IL-6 (ug/ml)							
Low stress	1.69(.12)	2.81(0.2)	1.64(.1)	1.95(0.2)	1.50(0.1)	1.25(0.1)	1.37(0.1)
High Stress	2.43(0.6) (NS)	3.47(0.8) (NS)	2.52(0.6) (p=.079)	2.26(0.6) (NS)	2.69(0.9) (p=.081)	3.99(1.6) (p=.004)	2.71(0.5) (p=.024)
IL-6/IL10							
Low stress	0.63(0.1)	0.88(0.1)	2.27(1.7)	1.38(0.7)	0.76(0.2)	0.6(0.1)	0.6(0.1)
High Stress	0.89(0.1) (NS)	1.07(0.2) (NS)	0.91(0.2) (NS)	0.79(0.1) (NS)	0.88(0.1) (p=.07)	1.0(0.2) (p=.056)	1.06(0.2) NS

Implications

- Postpartum minority or low income women experience signs of cytokine-glucocorticoid dysregulation
 - Limits a woman's ability to regulate inflammation
 - Limits a woman's ability to regulate cortisol secretion
 - Increases risk of poor outcomes for mothers and infants
- Postpartum minority or low income women have significantly elevated daily cortisol levels compared to Caucasian and upper income women
- **Implications:** more study is needed to determine if this profile is present before pregnancy or continues after delivery: **If it is then...**
 - Does GR explain the health disparities (hypertension, diabetes, cancer depression) we see related to social disadvantage in the general population?



Acknowledgements

Primary Study Team:

Emory

Ying Guo, PhD

The Ohio State University

Donna McCarthy, PhD

Runfeng Jing, MD

University of Colorado

Nancy Lowe, CNM, PhD

Brian Stafford, MD, MPH

Mary Weber, PhD

Laurel Ware, RN

Dalhousie University

Kathleen Pajer, MD, MPH

Thank you

Questions?

The end so far



Self-report of stress (PSS) and depressive symptoms (EPDS) in low (N=87) versus high (N=46) risk of stress and Caucasian (N=104) versus minority (N=30) pregnant and postpartum women (mean_±SD). (All data corrected for age & marital status)

	Prenatal	Day 7	Day 14	Month 1	Month 2	Month 3	Month 6
<u>PSS</u>							
Low stress	19.1 (5.7)	15.3(23.3)	17.0(5.9)	17.1(7.8)	18.2(6.4)	18.0(6.5)	18.5(7.2)
High Stress	22.5(6.8) (p=.004)	19.8(6.4) (NS)	17.8(10.0) (NS)	17.3(14) (NS)	19.4(8.5) (NS)	19.6(8.5) (NS)	19.6(8.5) (NS)
Caucasian	19.6(5.9)	16.2(21.1)	17.5(6.1)	17.6(7.9)	18.3(6.6)	18.4(7.0)	18.7(7.3)
Minority	22.4(7.1) (p=.041)	19.5(7.2) (NS)	16.6(11.4) (NS)	15.6(16) (NS)	19.7(9.2) (NS)	18.9(8.3) (NS)	19.4(8.9) (NS)
<u>EPDS</u>							
Low stress	4.1(3.3)	4.4(3.7)	3.3(3.1)	3.4(3.1)	3.1(2.7)	2.9(2.7)	3.1(3.1)
High Stress	5.6(4.2) (p=.047)	3.5(3.3) (NS)	3.4(3.1) (NS)	3.7(3.8) (NS)	3.1(3.1) (NS)	4.0(4.1) (NS)	3.4(3.6) (NS)
Caucasian	4.3(3.4)	4.1(3.5)	3.4(3.0)	3.5(3.1)	3.0(2.7)	3.1(3.2)	3.0(3.1)
Minority	5.5(4.4) (NS)	3.7(3.8) (NS)	3.8(3.4) (NS)	3.6(4.2) (NS)	3.3(3.4) (NS)	3.6(3.6) (NS)	3.7(3.8) (NS)

Figure 2. cytokine–glucocorticoid feedback circuit:
All slopes significant (* $p < 0.05$, ** $p < .001$, *** $p < .0001$)
for low risk but not high risk women

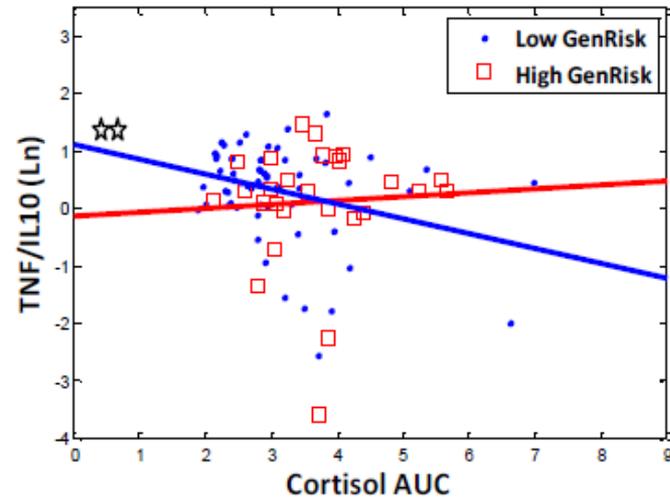
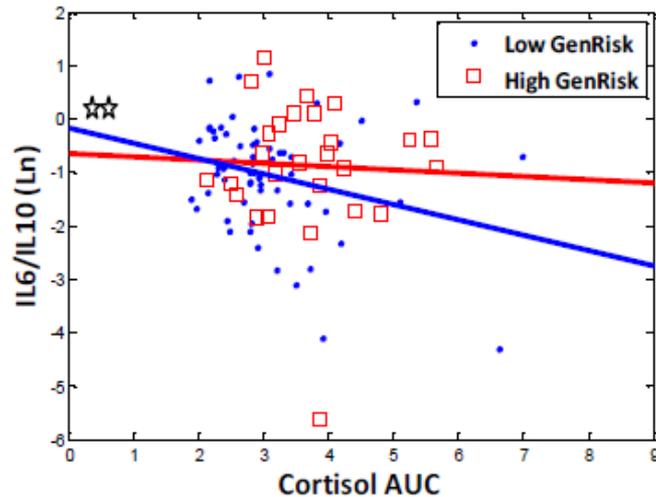
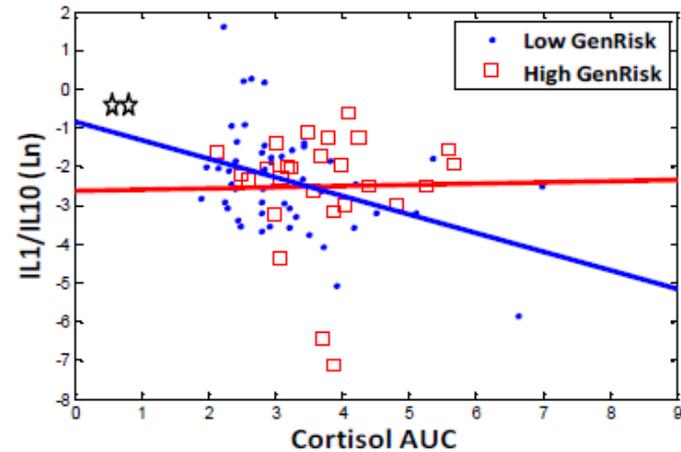
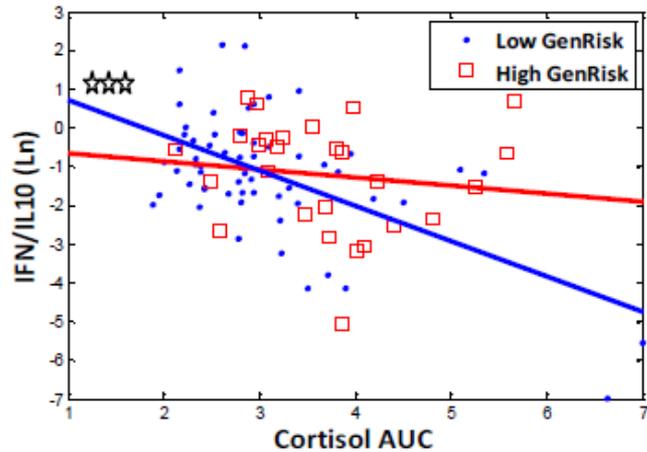
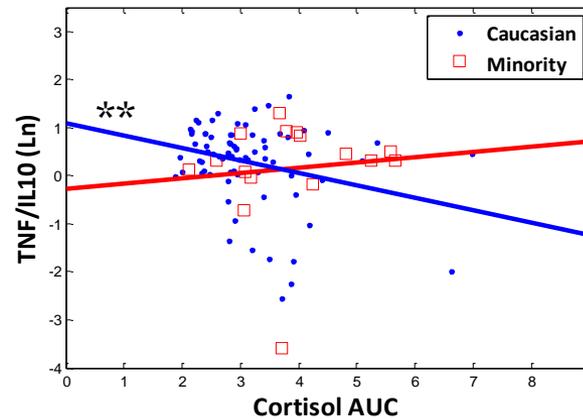
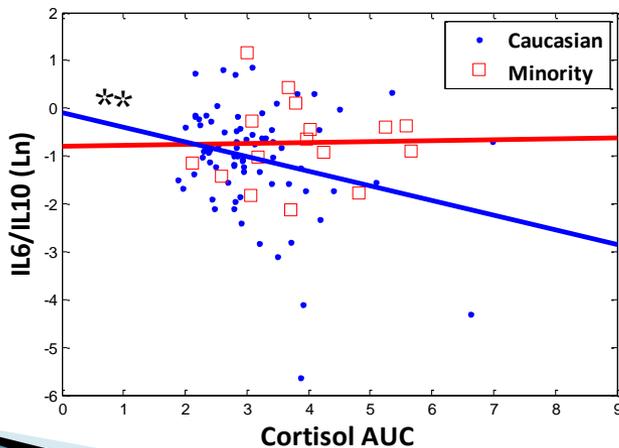
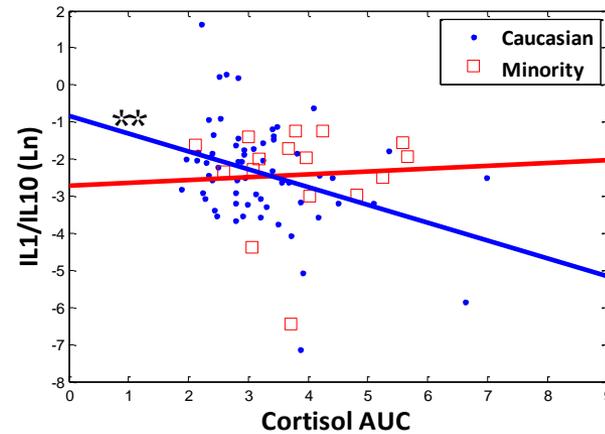
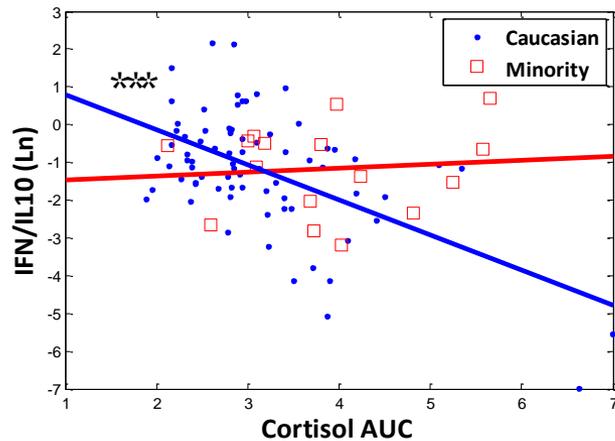
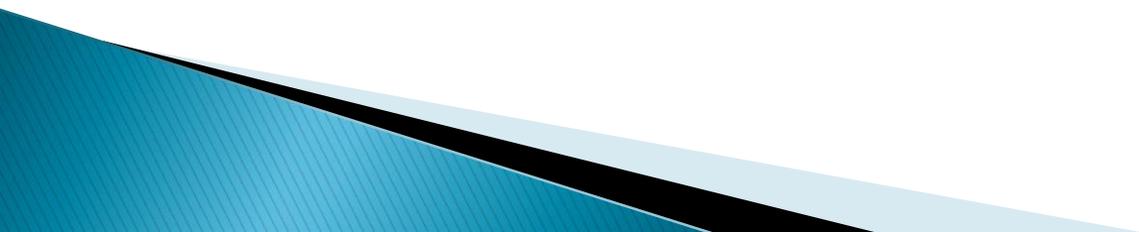


Figure 3. cytokine–glucocorticoid feedback circuit:
All slopes significant ($*p \leq 0.05$, $**p \leq .001$, $***p \leq .0001$)
for Caucasian but not minority women





Daily average salivary cortisol (area under the curve [AUC]) from the 3rd trimester through 6 months postpartum in minority (n=20) and Caucasian (n=77) women

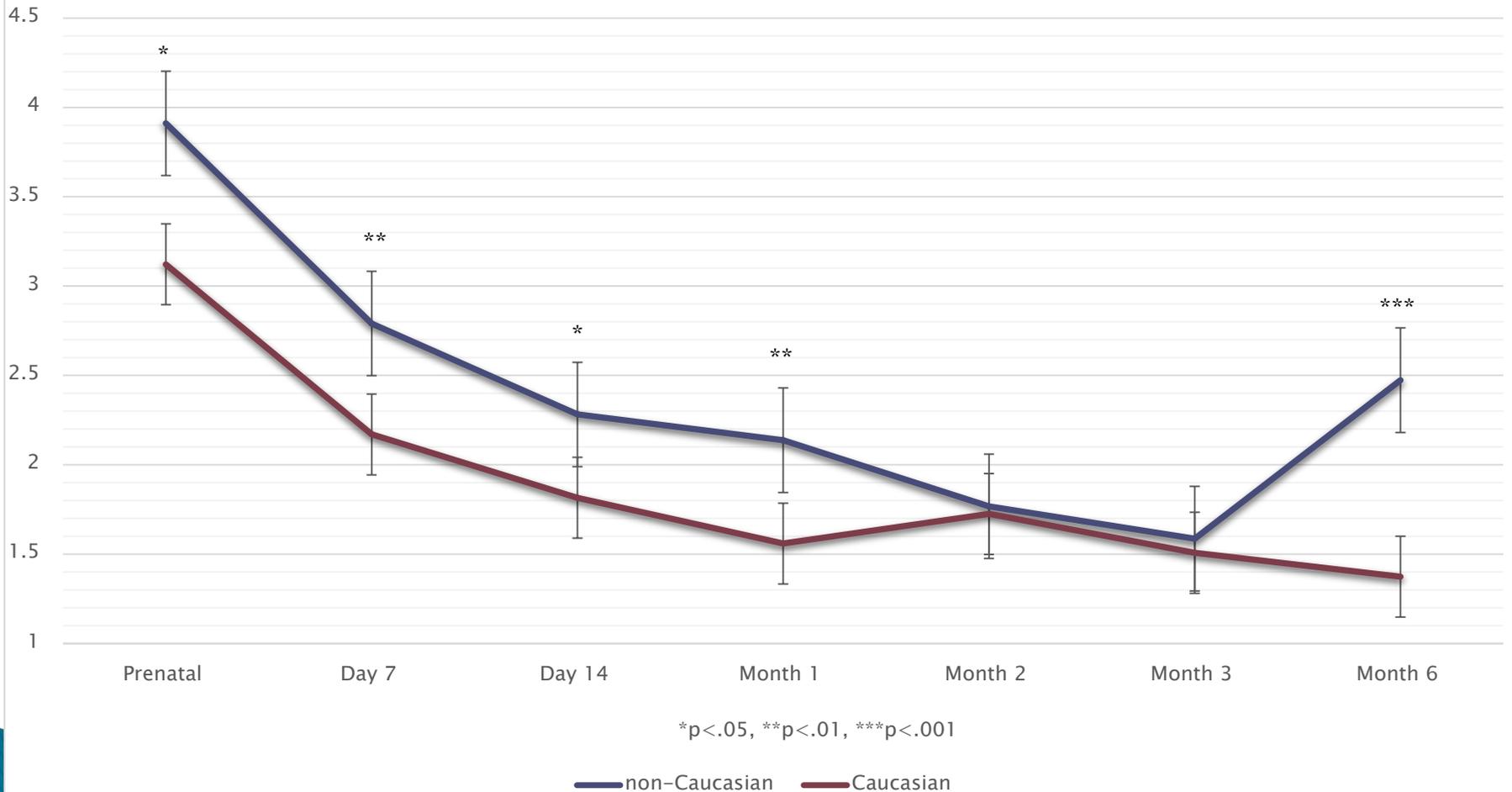
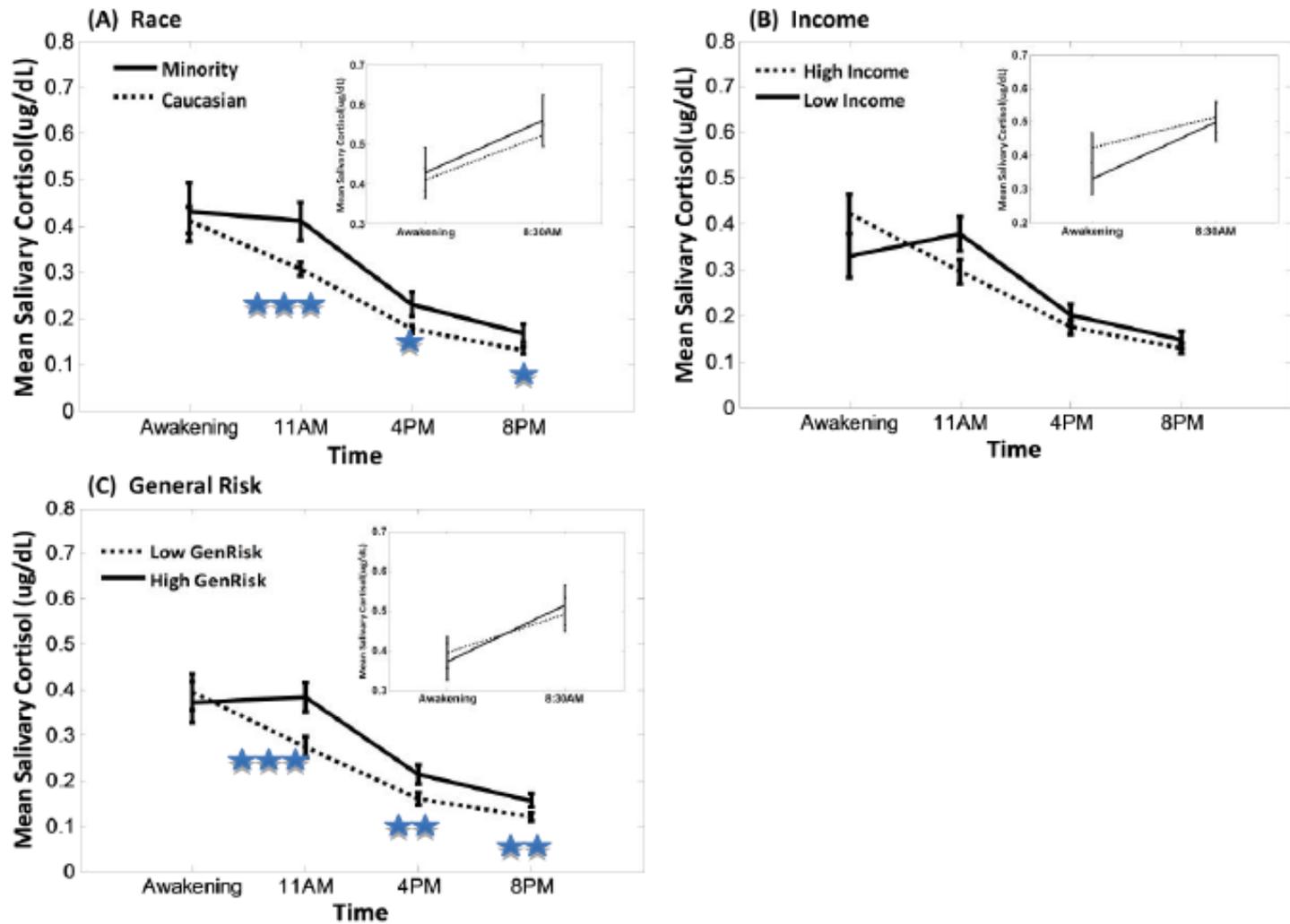


Figure 1. Model-based Mean salivary cortisol ($\mu\text{g}/\text{dL}$) at each time point for subject subgroups. Error bars represent standard error of the mean.



Proposed Study Design

- ▶ Recruit pregnant AA women beginning during the late 2nd trimester and follow longitudinally until offspring are 2-years of age.
 - Collect biological samples and data from women 5 times:
 - prenatal weeks 28-32,
 - within 48-hours after childbirth,
 - and 3-, 6-, 12-months after childbirth
 - Collect data from offspring 4 times:
 - at birth - cord blood
 - and 3-, 6-, 12-months of age