Diurnal Cortisol Profile as a Predictor of Weight Change over 6 years: The Multiethnic Study of Atherosclerosis (MESA) Stress Study

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Hypothalamic-pituitary-adrenal (HPA) axis
- controls the response to stress
- participates in the regulation of many processes that affect energy storage and expenditure
The effector molecule of the HPA axis is cortisol production from the adrenal gland.
Subclinical Hypercortisolism and Obesity

Sleep Apnea
Sleep Deprivation

STRESS
Work Stress, Low SES, Anxiety, Depression, PTSD

Physical Abuse
Sexual Abuse
History of Trauma

50-70 Million Americans

↑ Cortisol
↓ Diurnal Cortisol Variability

OBESITY

57 Million Americans
STRESS
- Early adversity
- Interpersonal conflict
- Social isolation

HYPOTHALAMUS
- CRH

PITUITARY
- ACTH

ADRENAL GLAND
- Cortisol

OBESITY

Adapted from Miller et al, Biological Psychiatry, 2006.
Challenges to neuroendocrine assessment in population studies

- Epidemiological studies limited by imprecise measures of glucocorticoid exposure

- Gold standard: 24-hour urine free cortisol - cumbersome

- Hypothalamic and pituitary hormones
  - Pulsatile, labile
  - Limited utility in measurement directly or from stored samples

- Circadian variation in cortisol secretion
Challenges to neuroendocrine assessment in population studies

- Salivary cortisol
  - Non-invasive
  - Timed collection
  - Free-living state
  - Free cortisol measured
  - Stable for several days prior to processing (frozen, mailed)
Diurnal Cortisol Profile

A=Waking cortisol
B=Cortisol awakening response
C=Early decline
D=Late decline

Champaneri et al, Obesity, 2012
BMI is inversely associated with:

- Awakening cortisol area
- Early decline area (under curve)
- Late decline area under curve (among normal fasting glucose only)
Champaneri et al, *Obesity*, 2013

![Graph showing cortisol levels over hours since wake-up across different weight categories.](image)
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Hypothesis

Baseline diurnal cortisol pattern will be associated with change in BMI over 6 years.

A. Cortisol awakening response, early decline cortisol and late decline cortisol will be inversely associated with change in BMI

B. Nighttime salivary cortisol will be positively associated with change in BMI.
Description of the Multi-Ethnic Study of Atherosclerosis (MESA)

• Multi-center, longitudinal population based cohort study of occurrence and correlates of subclinical CVD and factors influencing its progression

• Six centers: Northwestern University, Wake Forest University, University of Minnesota, Columbia University, Johns Hopkins University, University of California-Los

• 6,000 men and women aged 45-85 years
  – 40% non-Hispanic White
  – 10% Chinese American
  – 30% African American
  – 20% Hispanic American
  – No history of clinical CVD
Study I

- 1000 MESA participants from UCLA and Columbia Field Centers
  - MESA Exams 3-4 (July 2004-Nov 2006)
  - White (25%), Black (33%), and Hispanic (40%), 52% women
- Sub-study of biological stress markers
- 6 samples/day collected over 3 consecutive weekdays (18 total)
  - Awakening, 30 minutes after awakening, 10 am, 12 pm or before lunch, 6 pm or before dinner, bedtime

Study II

- 2010-2012 (MESA Exam 5)
- Participants: Columbia (n=500), UCLA (n=500), JHU (n=500)
Methods II: Study Population for Longitudinal Analysis

- 580 multiethnic men and women
- Participated in MESA Stress I and II with repeated cortisol and BMI measurements
Methods III: Exposure

Components of Diurnal Cortisol Profile (log-transformed)

A=Waking cortisol
B=Cortisol awakening response
C=Early decline
D=Late decline

Champaneri et al, *Obesity*, 2012
Methods IV: Outcome

- Change in Body Mass Index (BMI) from MESA Stress I to MESA Stress II

BMI calculated as weight (kg) divided by height squared (m²)
Methods V: Statistical Analysis

• Linear mixed effects regression model to estimate adjusted associations of baseline cortisol diurnal parameters with percent change in BMI over 6 years. Modeling approach:
  – Accounts for within subject correlation between repeated measures
  – Allows for variable number of repeated measures within subject and variation in sample collection time

• Regression coefficients derived from our linear regression models represent the change in BMI over 6 years for each 1-unit increase in log of the cortisol variable
Methods VI: Potential Confounders

- Adjustments for Covariates:
  - Base model: age, race, sex, diabetes status, wake up time
  - Full model: base + socioeconomic status (income and education), smoking and medications that could potentially affect cortisol measures: beta blockers, steroids, HRT
Significance

STRESS
low ses, work stress, anxiety, depression

↑ cortisol
↓ diurnal cortisol variability

Lipolysis
FFA release

INSULIN RESISTANCE

CENTRAL OBESITY

Accumulation of visceral fat

TYPE 2 DIABETES & HYPERTENSION

CARDIOVASCULAR DISEASE
Limitations:

MESA excluded individuals with known clinical cardiovascular disease, so the results will be generalizable to patients without clinical cardiovascular disease.
Remember:

“STRESSED” is “DESSERTS” spelled backwards
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- My Family
Methods: Statistical Analysis

- We will first calculate the change in BMI over 6 year for each participant and the model whether baseline cortisol predicts the BMI change (in other words, if you have higher baseline cortisol AUC, do you have a greater BMI change over 6 years?)

- Cortisol daily samples will be modeled as a function of time (years) since baseline, time (hour) of sample collection in a day, percent change in BMI and the interaction of percent change in BMI with time since baseline.