Dietary Mitigation of Psychosocial Stress Effects on Health in Female Primates

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Psychosocial Stress and Disease

↑ Inflammation
↑ Depression
↑ Cardiovascular Disease
↑ Infectious Diseases - HIV/AIDS
↑ At least some Cancers

• Challenge: Develop effective population level intervention on stress effects on disease

Cohen et al., 2007; 2012
Life Stress is Increasing; Women - More Stress

72%: Stress Plateaued/Increased Over Last 5 Years

By Sex \((p<0.01)\)

Stress Over the Past 5 Years

Cohen and Janicki-Deverts 2012

Stress in America, APA 2012
Cynomolgus Monkeys: An Established Model of Diet-Induced Atherosclerosis

- Dietary fat/cholesterol → atherosclerotic plaques in coronary arteries like humans

- Atherosclerosis and its complications cause heart disease

- Sex differences like humans: females protected
- Menstrual cycles like women
- This model accurately predicted in women:
  - females with good menstrual cyclicity protected
  - loss of ovarian function → ↑ coronary atherosclerosis
## Western Diet Versus Regular Lab Chow

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\(^1\) *What We Eat*: Women 40-49, 2007-8

\(^3\) LabDiet Chemical Composition Diet 5037/8; significant source of soy isoflavones
Social Status Hierarchy

- In small social groups hierarchies are linear & stable over time
- In all studies monkeys consumed a Western-like diet

Shively and Kaplan, 1991
Subordinate Female Monkeys are Stressed

- Receive more aggression
- Groomed less
- More vigilant
- Spend more time alone
- Hypersecrete cortisol
- ↑Heart rate response to stress
- Poor ovarian function

Adams et al., 1985; Kaplan et al., 1986; Shively et al., 1997, 1998; Shively & Willard 2012
Social Subordination Stress Doubles Diet-Induced Coronary/Iliac Artery Atherosclerosis

Kaplan et al., 2002, 2012
In Women & Female Monkeys Stress Worsens CV & Other Health Outcomes

SOCIAL STRESS

↑ Depression
↑ Inflammation
↑ Ovarian dysfunction
↑ Visceral Fat Deposition

↑ Stroke & MI in Women
↑ Coronary & Carotid Artery Atherosclerosis in Female Monkeys

*Most of these data from subjects consuming Western diets*
Mediterranean Diet Associated With Improved CV Health In Observational Studies

Mediterranean Diet

↓ Depression  (Sanchez-Villegas et al., 2013)
↓ Inflammation  (Casas et al., 2014)
↓ Infertility  (Vujkovic et al., 2010)
↓ Abdominal fat deposition? & metabolic syndrome  
  (Funtikova et al, 2014; Daniele et al., 2013)
↓ Stroke & MI  (Estruch et al., 2013, Fung et al., 2009)
Mediterranean Diet

↑ Depression
↑ Inflammation
↑ Ovarian dysfunction
↑ Visceral Fat Deposition
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↑ Coronary & Carotid Artery Atherosclerosis in Female Monkeys

↓ Depression
↓ Inflammation
↓ Infertility
↓ Abdominal fat deposition?
↓ Metabolic syndrome
↓ Stroke & MI
Could a Western Diet Exaggerate Stress Responses Which in Turn Increase Disease?
Stress and Diet: What Do We Know?

- Rodent & Clinical Studies -
Cortisol Response to Stress Higher in Rats Consuming a High Fat Diet

- Short-term: 4 days high/low fat diet
- Diet: Unlike human (or rat); 40 vs 12% fat: corn + coconut oil
- The stressor mattered: no difference in response to extreme, only to mild stress

Stress: Extreme- 3 hrs tube; Mild – 2 hrs novel cage

Legendre and Harris, 2006
Stress May Exacerbate the Lipid Response to a High Fat Diet

• 8 weeks diet; stress last 21 days
• Variable extreme physical stressors
• Diet: Chow+ 10% lard, cholesterol, salt, sugar

Manting et al., 2011
Clinical Studies: Eating a High Fat Meal Exaggerates Cardiovascular Responses to Stress

- \( n=30 \)
- *crossover design*

Jakulj et al. 2007

<table>
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<tr>
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<th>Low-fat</th>
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<tbody>
<tr>
<td>MacDonalds</td>
<td>Cereal</td>
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<tr>
<td>Total/Sat fat, g</td>
<td>42/16</td>
<td>1.3/.8</td>
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<tr>
<td>Cholesterol, mg</td>
<td>270</td>
<td>15</td>
</tr>
<tr>
<td>Sodium, mg</td>
<td>2010</td>
<td>1904</td>
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<tr>
<td>Carbohydrate, g</td>
<td>73</td>
<td>172</td>
</tr>
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<td>Protein, g</td>
<td>31</td>
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Type of Fat May Buffer CV Responses to Stress

- n=20, randomized crossover feeding study. Each diet - 6 weeks
- Diets: **Typical American Diet; Linoleic Acid** enriched diet (walnuts, walnut oil); **Alpha Linoleic Acid** enriched diet (walnuts, walnut & flaxseed oil)
- **LA and ALA diets**: Walnuts replaced dairy/meat as protein sources; 1/2 total fat from plant sources
- Diets matched for total protein, fat, carbohydrate, cholesterol

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<tr>
<td>TAD</td>
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*West et al., 2010*

- Also stroke volume, cardiac output
- Flow Med Dilation ALA only
Stress and Diet: What We Know

• Rodent & Clinical Studies:
  • High saturated fat diet may exacerbate physiological stress responses
  • It might be type rather than quantity of fat
  • Weaknesses: small, short term feeding studies, not what people eat

• Observational Studies -
Population Studies

Western Diet Pattern
Greater Perceived Stress

↑ Cortisol Levels

Mediterranean Diet
Lower Perceived Stress

Boston Puerto Rican Health Study
n>1300; 70% women, Laugero et al., 2011

Melbourne Collaborative Cohort Study
n=8600; Hodge et al., 2012
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• Nonhuman Primates Studies-
Diet Effects on Physiological Stress Responses in NHPs: Western Diet Versus Regular Lab Chow

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Assessment of Autonomic Function Via Remote Telemetry

3-Lead Digital Transmitter

We get
- Interbeat Interval
- 24 hour digital ECG Tracing
- HR, HRV, Complexity
Diet Effects on Autonomic Function in Chronically Stressed Monkeys

- 42 female monkeys
- 6 mos monkey chow, followed by 34 mos Western Diet
- 24 hour Heart Rates Recorded by telemetry

Longitudinal Effects of Western Diet on 24 Hour Heart Rate in Female Monkeys
**Assessment of Hypothalamic-Pituitary-Adrenal Activity**

- **ACTH Challenge test**
  - Measures adrenal responsivity to ACTH
  - Suppress axis with large dose of dexamethasone
  - Give ACTH iv
  - Measure Cortisol response over 30 min
Diet Effects on Cortisol Response to ACTH in Female Macaques

**Prudent Diet**

- **Dom > Sub**
- **Dominant**
- **Subordinate**

Interpretation:
Blunted Stress R in chronically stressed subordinates

**Western Diet**

- **Sub > Dom**
- **Dominant**
- **Subordinate**

Interpretation:
Adrenal Hyperresponsiveness in Subs resulting in chronic hypercortisolemia

Emory-GA: Michopoulos et al., 2012
Rhesus M. mulatta
Interpretation:
Blunted Stress R in chronically stressed subordinates

Wake Forest – NC: Shively et al., 1998
Cynomolgus M. fascicularis
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• Nonhuman Primates Studies
  • Western diet appears to increase HR and cortisol secretion in chronically socially stressed subordinate monkeys
  • Weaknesses
    • Prudent diet comparison was with monkey chow – high in isoflavones which have tissue-selective estrogenic activity
    • No long term control diet group in HR study
    • Cortisol effects from post hoc comparison of 2 different studies
Stress and Diet: What We Don’t Have

• Randomized clinical trials of long-lasting effects of diet on stress physiology or stress-induced CVD

• Direct comparison of effects of Mediterranean versus Western diet pattern on stress physiology

• Mechanisms through which diet affects gene expression resulting in heightened stress responsivity
Central Hypothesis of our Current Preclinical NHP Trial

- Psychosocial stress-associated CV and other disease risk is due in part to Western diet exacerbation of stress reactivity
- Consumption of a Mediterranean diet will reduce physiological stress reactivity and mitigate the deleterious effects of stress on CV disease risk.

Overarching Hypothesis

![Graph showing endpoints worsened under stress and no stress conditions.](Image)
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1 *What We Eat*: Women 40-49, 2007-8  
2 Bedard et al., 2012  
3 LabDiet Chemical Composition Diet 5037/8  
4 About 256 mg/day
**Dietary Mitigation of Psychosocial Stress Effects on CV and CNS Health in Female Primates: Preclinical Trial Design**

**Western Diet**
- 12 dominant 12 subordinate

**Mediterranean Diet**
- 12 dominant 12 subordinate

- **Endpoints:**
  - Stress Responsivity
  - CV Risk Factors
  - Coronary/Carotid Atherosclerosis
  - Brain
  - Results: Spring 2017

- **Run-in diet:**
  - Monkey Chow

- **Preclinical Trial:**
  - 48 females
  - Social Groups Randomized

- **Duration:** 2 Years

**Grant:** RO1 HL087103-07
The Obesity Epidemic & Stress-Related Eating

36% Report Unhealthy Eating To Cope With Stress:
Women (43%) > Men (29%)

Barrier to Change?

Maybe Willpower is not the only Problem....

- Managing stress: 64% importance, 37% achievement
- Eating healthy: 60% importance, 35% achievement
- Being physically active or fit: 57% importance, 33% achievement

31% OF AMERICANS SAY THAT A LACK OF willpower STANDS IN THE WAY OF CHANGE*

*BASE: Change has been recommended or decided to make a change (n=1928)
Diet, Stress, and Reward: Impact on Eating

- **High-fat** diet decreases dopaminergic activity in striatum “reward center”
- **Chronic Stress** decreases dopaminergic activity in striatum “reward center”
- Result: Need more high fat food to get the same reward
- Leading to consumption of even more **high-fat** foods

Could Western Diet + Stress have synergistic effects on the mesolimbic dopamine system?

Tellez et al., 2013 Science - rats

Grant, Shively et al., 1998 - macaques
Diet Modification of Stress Responses: Public Health Significance

• Currently there is no effective population level intervention on psychosocial stress effects on disease

• Population level diet modification possible
  – The National Cholesterol Education Program (NCEP)
    • Reduced cholesterol consumption in US
  – Recent FDA product labeling mandates
    • Reduced trans fat intake in US

• If hypothesis supported we will have a cost-effective population level intervention on stress

• This diet modification also will have many other beneficial effects on health

RO1 HL087103-07
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- Tom Morton, PhD
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