

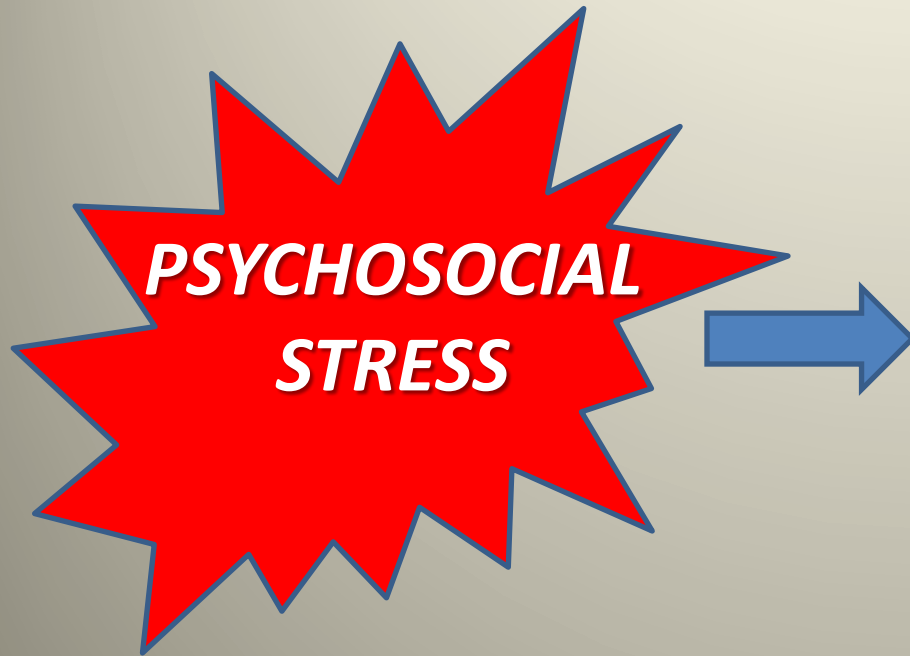
Dietary Mitigation of Psychosocial Stress Effects on Health in Female Primates

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Wake Forest School of Medicine**



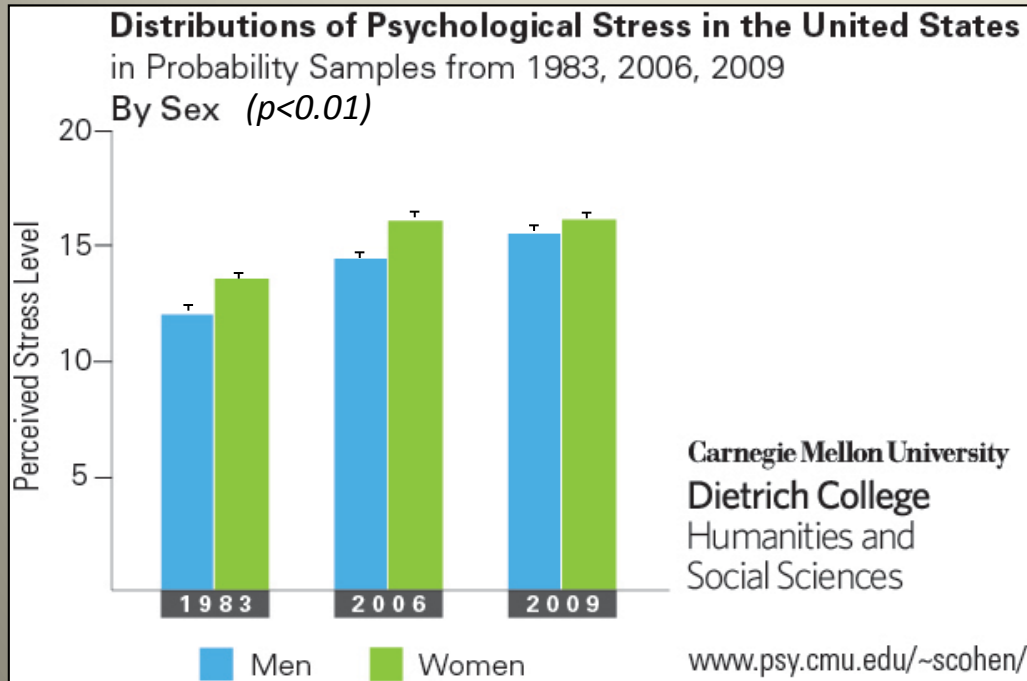
Psychosocial Stress and Disease



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

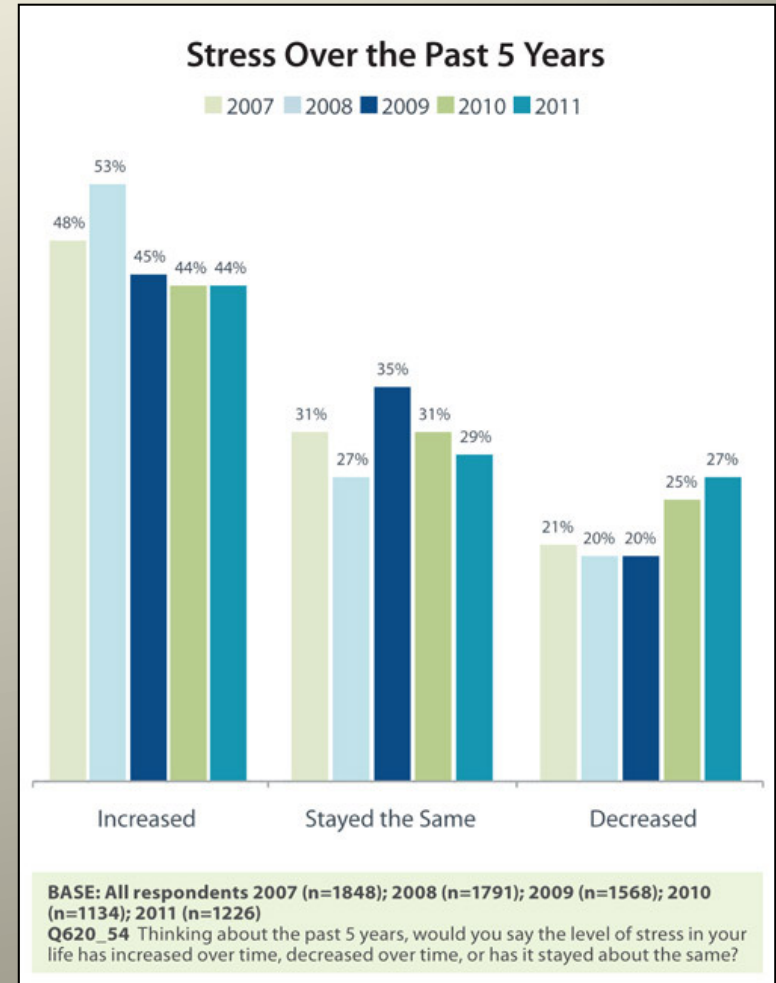
- Challenge: Develop effective population level intervention on stress effects on disease

Life Stress is Increasing; Women - More Stress



Cohen and Janicki-Deverts 2012

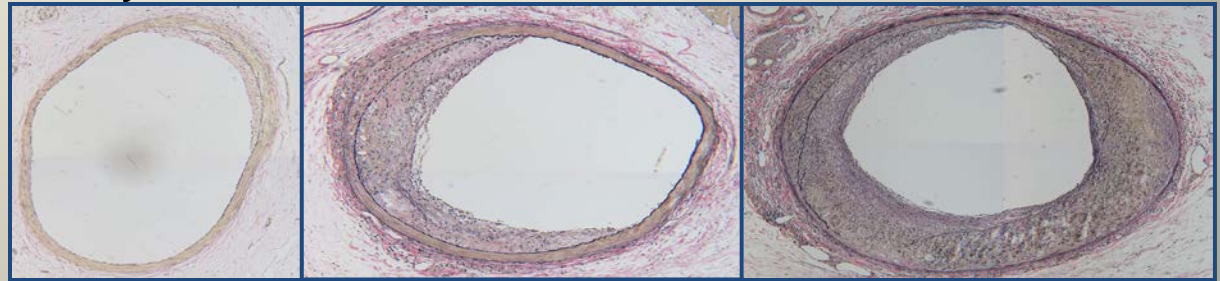
72%: Stress Plateaued/Increased Over Last 5 Years



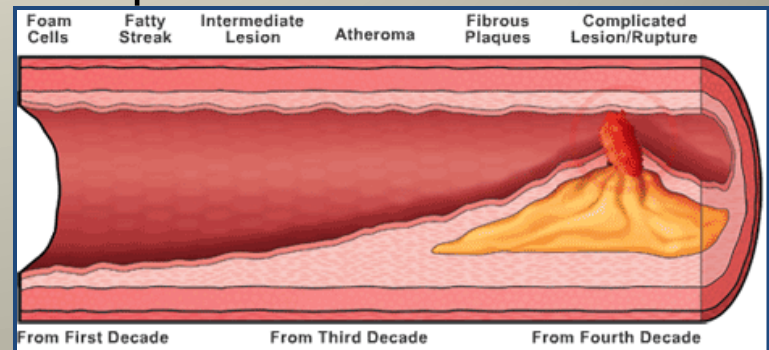
Stress in America, APA 2012

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



Macaca fascicularis

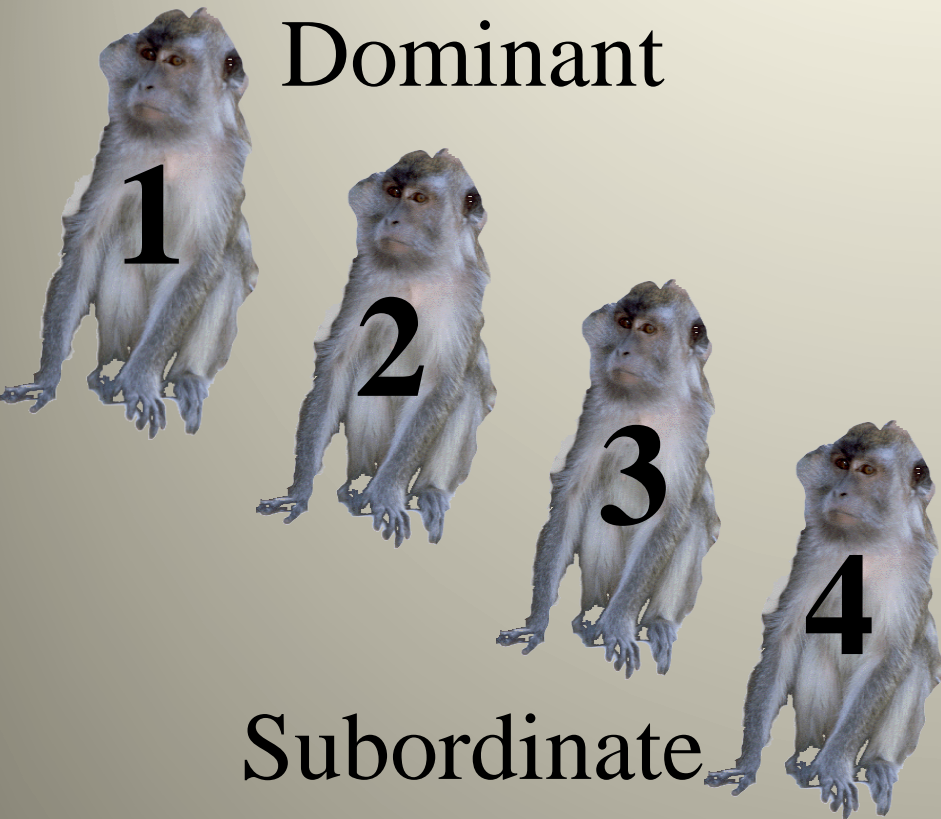
Western Diet Versus Regular Lab Chow

Diet Composition	Western ¹	Lab Chow ³
	% of Calories	% of Calories
Protein	15 (mostly animal sources)	18 (all plant sources)
Carbohydrate	50	69
Fat	34 (mostly animal sources)	13 (all plant sources)
	% of Total Fats	% of Total Fats
Saturated	32	26
Monounsaturated	35	28
Polyunsaturated	21	32
ω6:ω3 Fatty Acids	15:1	12:1
Cholesterol (mg/Cal)	0.14/ 256 mg/day	trace
Fiber (% of diet)	8	4.5
Salt (g/100g diet)	0.6	0.25

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

Subordinate Female Monkeys are Stressed

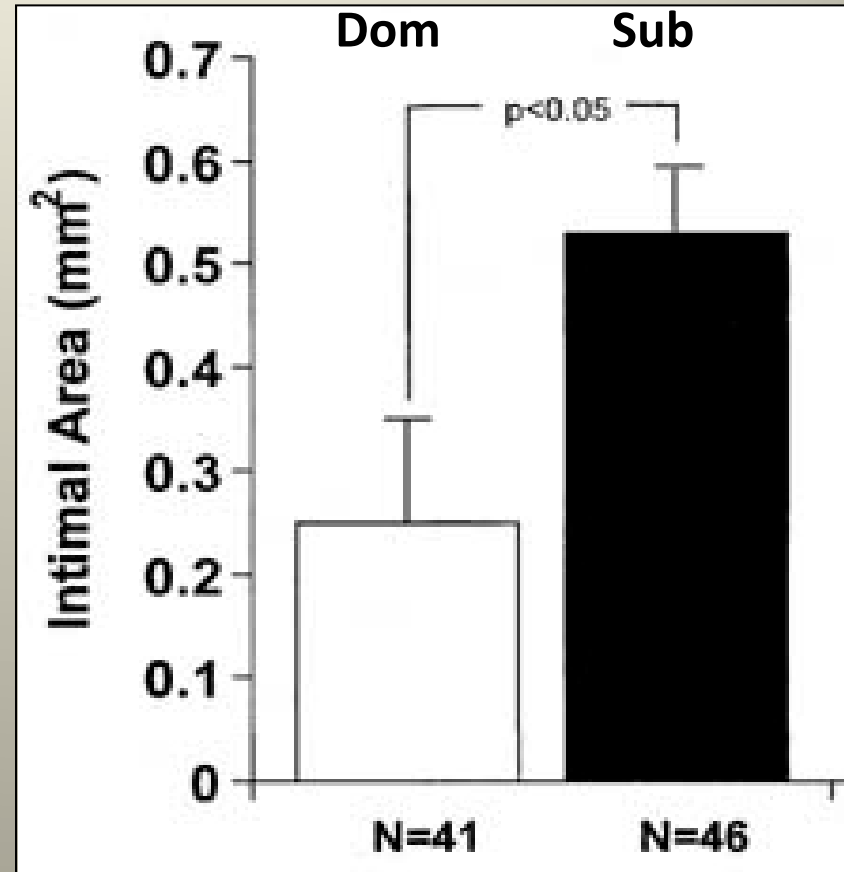
- Receive more aggression
- Groomed less
- More vigilant
- Spend more time alone
- Hypersecrete cortisol
- ↑Heart rate response to stress
- Poor ovarian function



Social Subordination Stress Doubles Diet-Induced Coronary/Iliac Artery Atherosclerosis

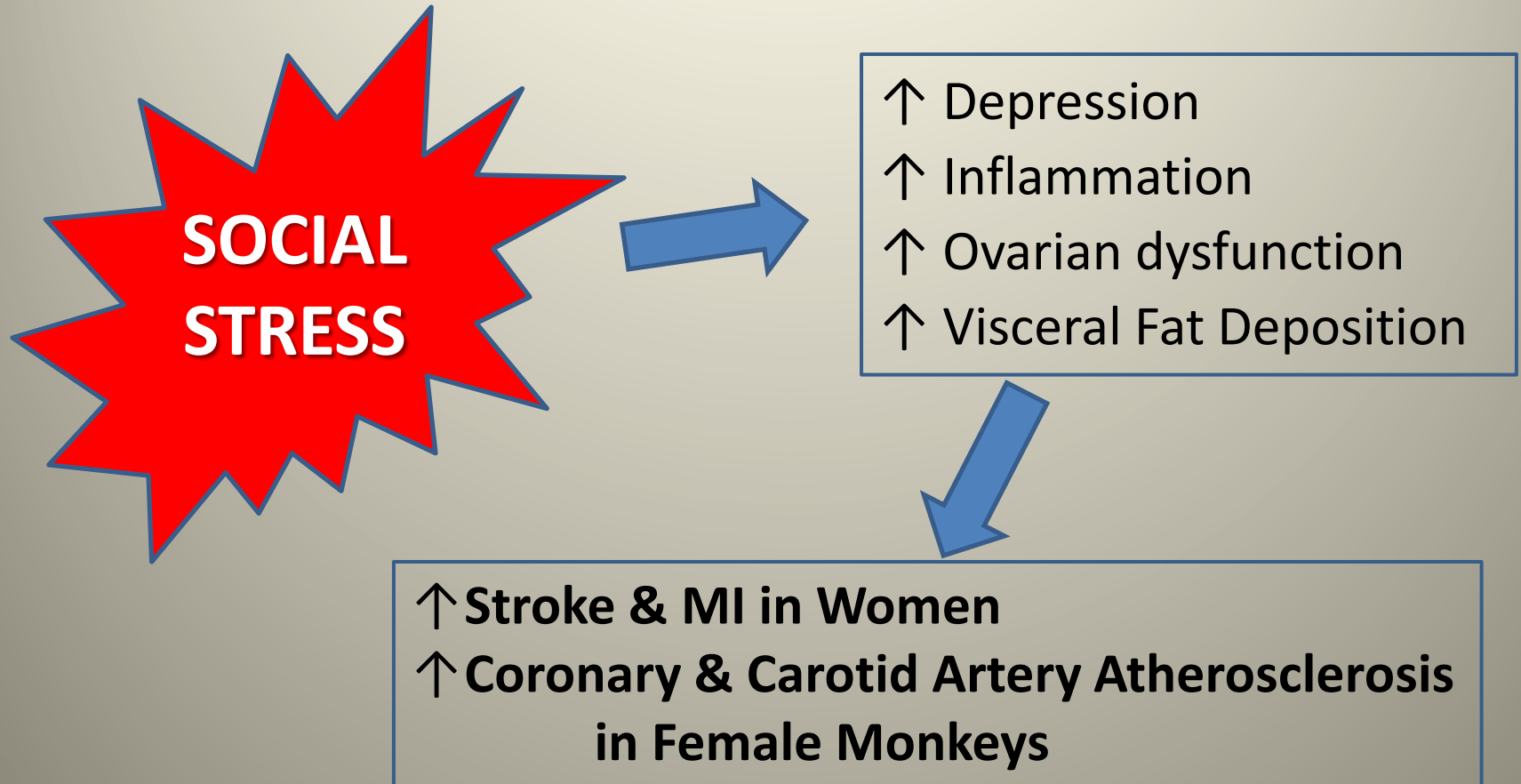
Dominant

Subordinate



Kaplan et al., 2002, 2012

In Women & Female Monkeys Stress Worsens CV & Other Health Outcomes



**** 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*)

**SOCIAL
STRESS**



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

Mediterranean Diet



↓ Depression
↓ Inflammation
↓ Infertility
↓ Abdominal fat deposition?
↓ Metabolic syndrome
↓ **Stroke & MI**

Could a Western Diet Exaggerate Stress Responses Which in Turn Increase Disease?

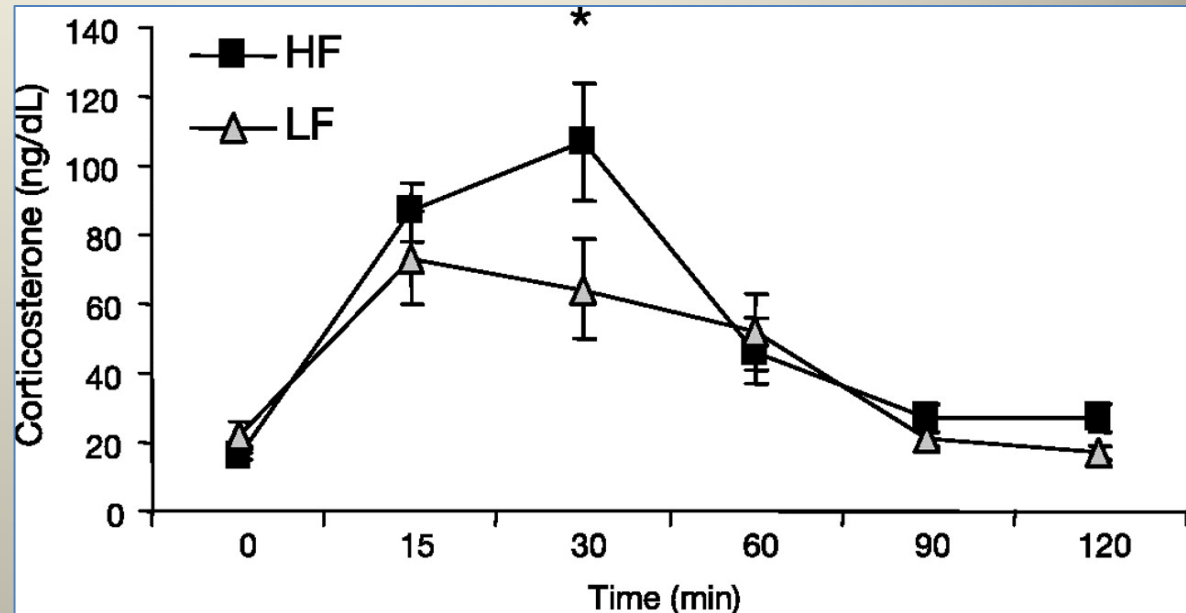


Stress and Diet: What Do We Know?

- **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;



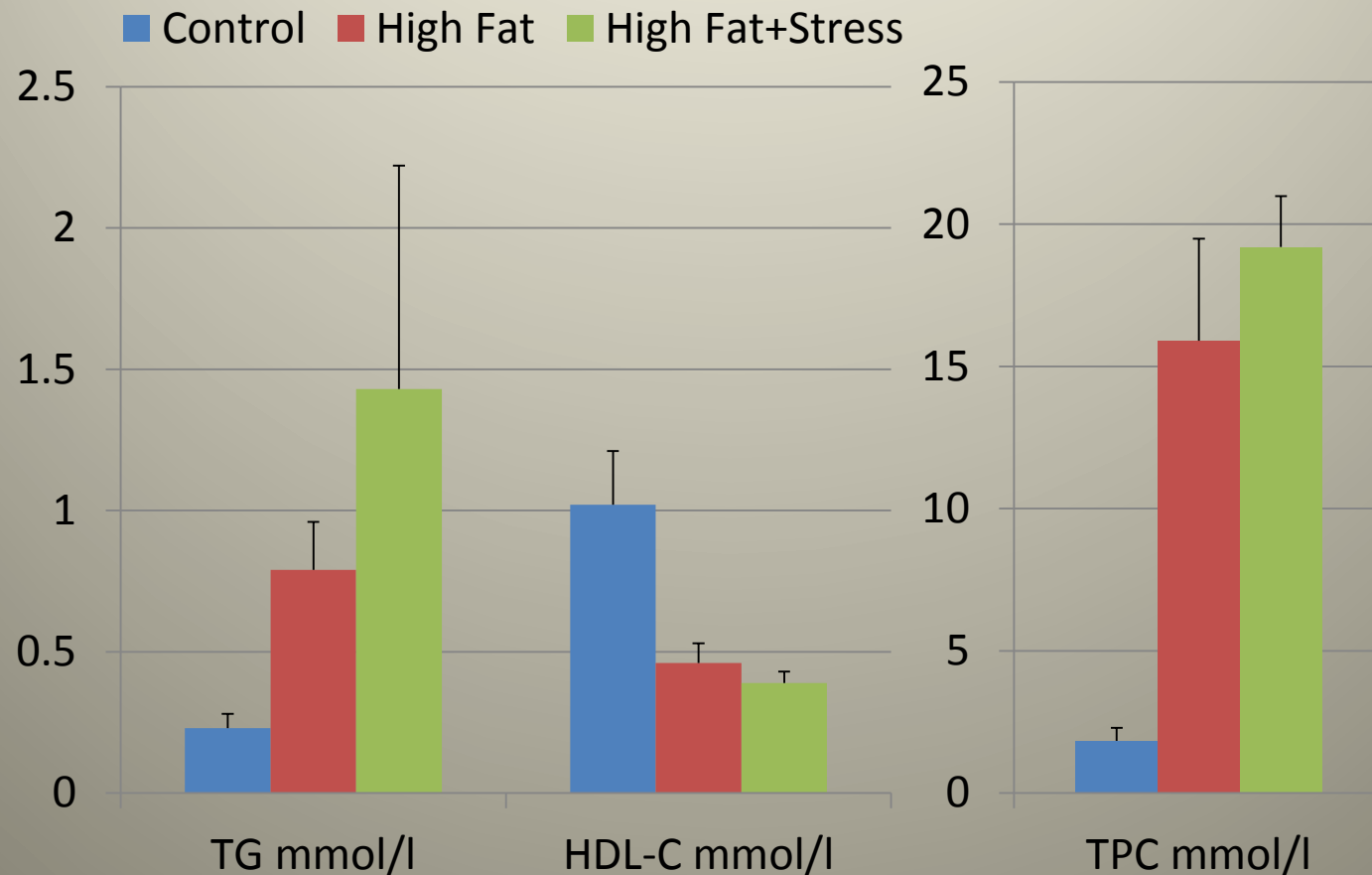
Mild – 2 hrs novel cage



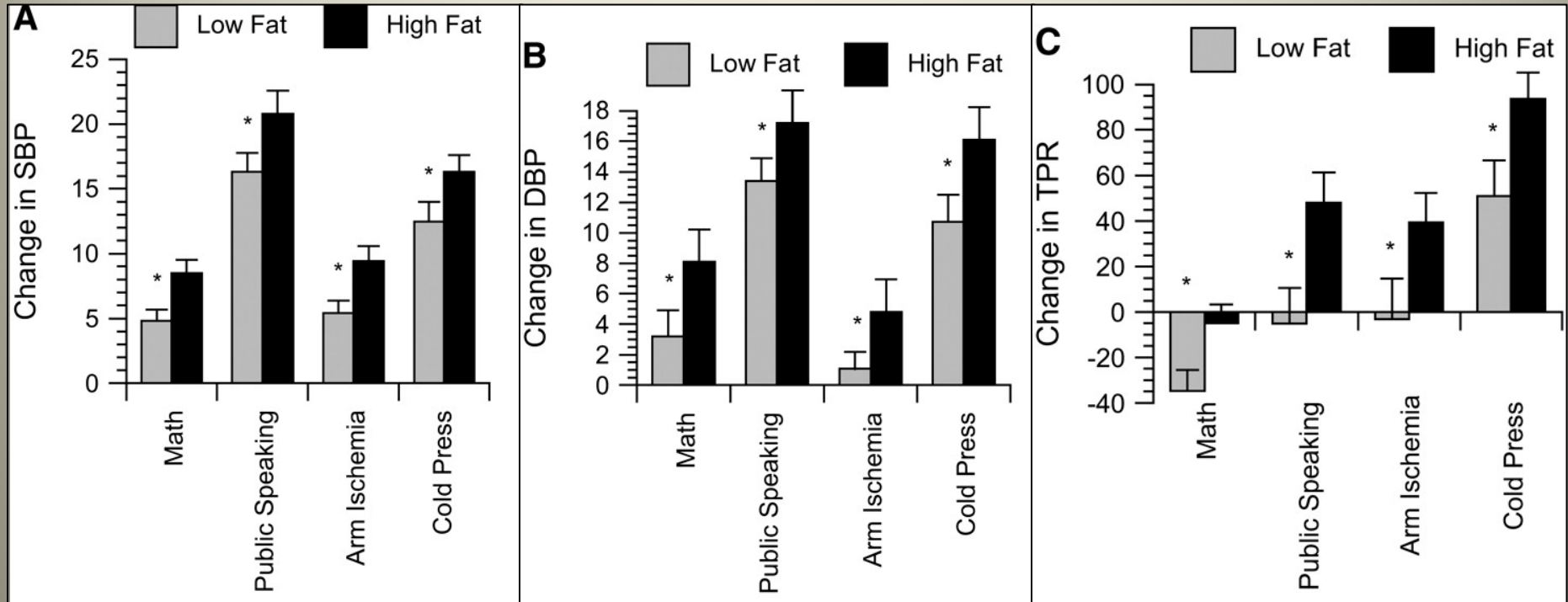
Stress May Exacerbate the Lipid Response to a High Fat Diet



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



Clinical Studies: Eating a High Fat Meal Exaggerates Cardiovascular Responses to Stress



- $n=30$
- *crossover design*
Jakulj et al. 2007

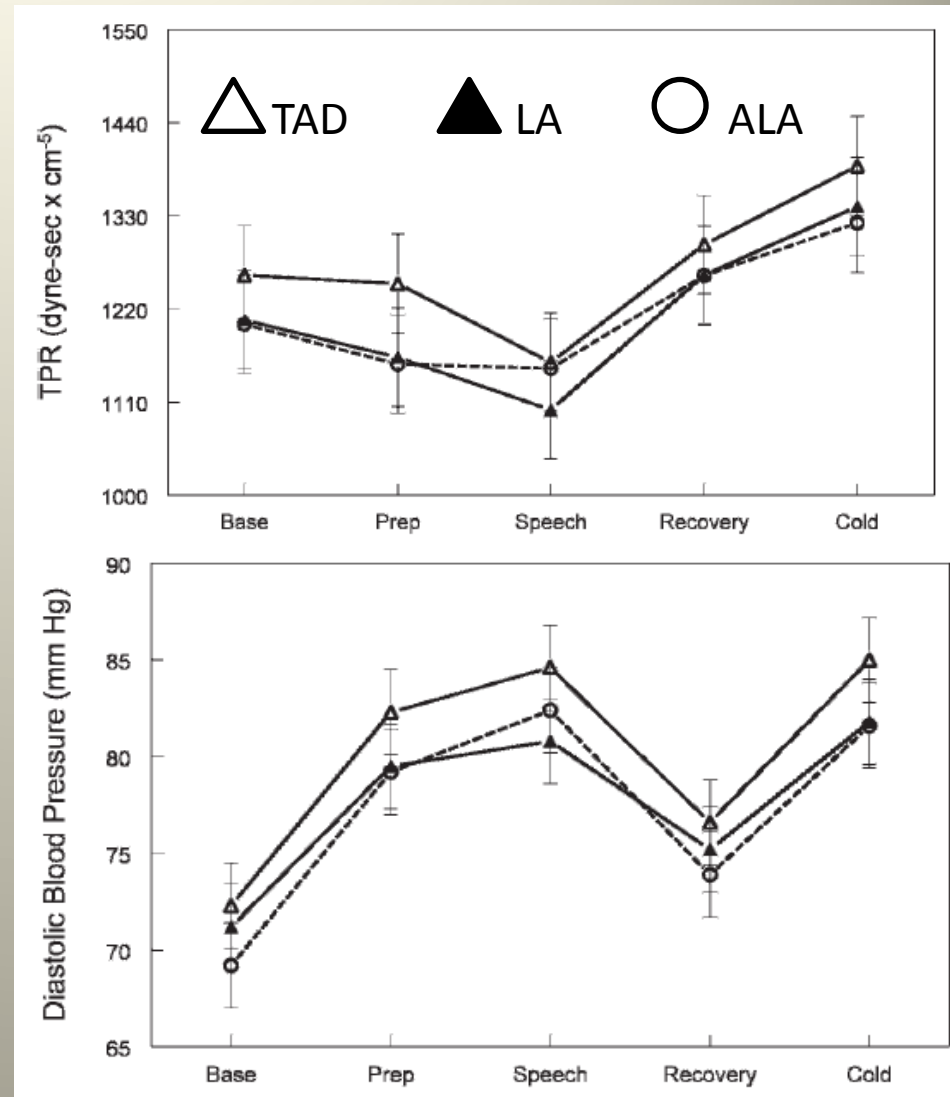
	High-fat	Low-fat
	MacDonalds	Cereal
Total/Sat fat, g	42/16	1.3/.8
Cholesterol, mg	270	15
Sodium, mg	2010	1904
Carbohydrate, g	73	172
Protein, g	31	15

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

	% SFA	% PUFA	% LA	% ALA	LA/ALA	
TAD	13	9	8	0.8	9.5	
LA	8	16	13	3.6	3.5	↑Ω-6
ALA	8	16	10	6.5	1.6	↑Ω-3

West et al., 2010



- Also stroke volume, cardiac output
- Flow Med Dilation ALA only

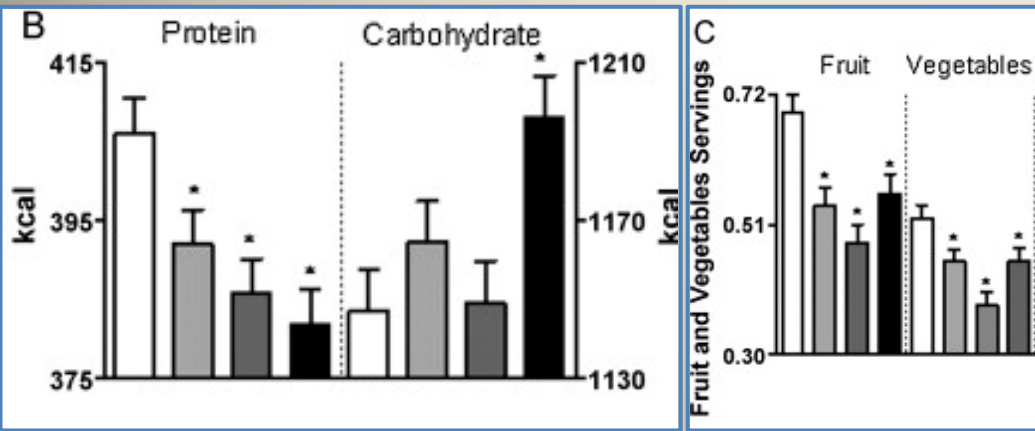
Stress and Diet: What We Know

- **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 -**

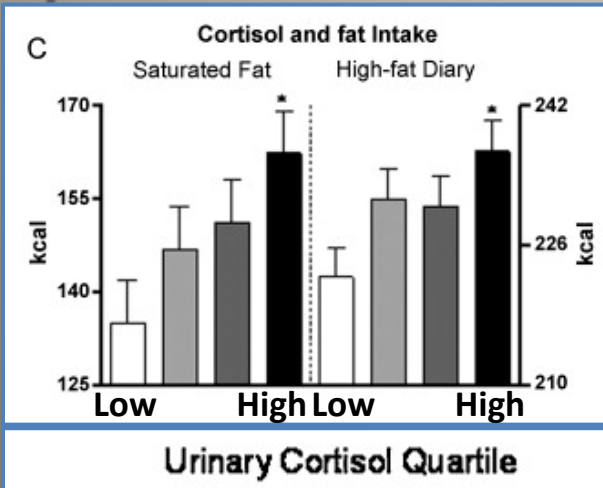
Population Studies

Western Diet Pattern

Greater Perceived Stress



↑ Cortisol Levels

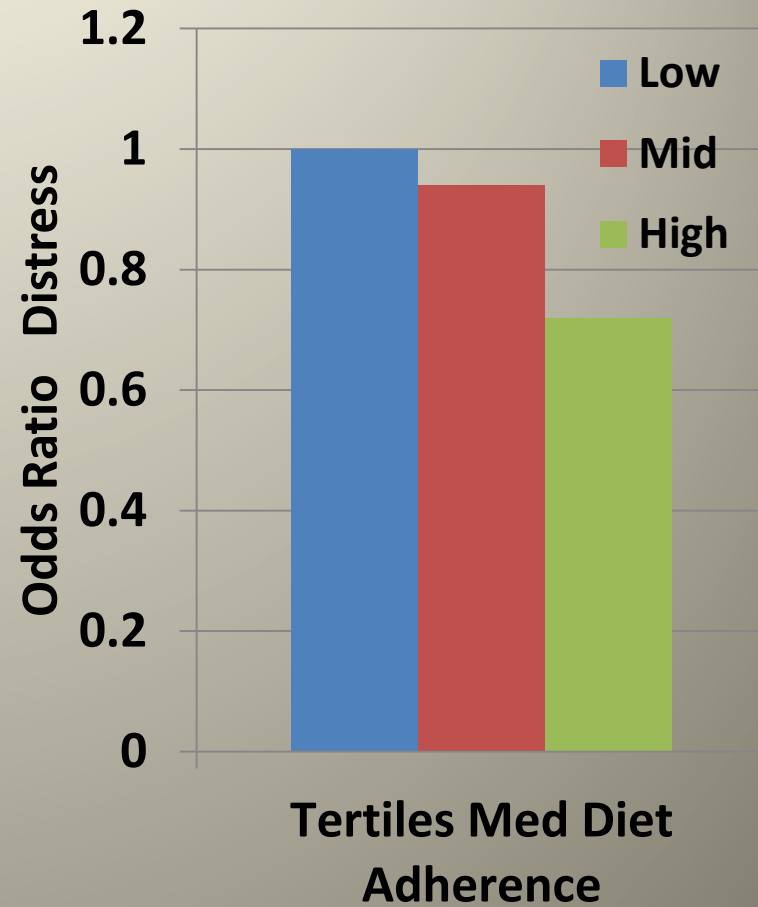


Perceived Stress Quartile

- Lowest
- Middle Lowest
- Middle Highest
- Highest

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*

Stress and Diet: What We Know

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- **Observational Studies**
 - Western diet pattern associated with greater perceived stress, cortisol; Mediterranean diet pattern associated with lower perceived stress
 - Strength: *These diets are actually what people eat*
 - Weaknesses: Self-reported diet & stress, retrospective, actual nutrient intake unknown
- **Nonhuman Primates Studies-**

Diet Effects on Physiological Stress Responses in NHPs: Western Diet Versus Regular Lab Chow

Diet Composition	Western ¹	Lab Chow ³
	% of Calories	% of Calories
Protein	15 (mostly animal sources)	18 (all plant sources)
Carbohydrate	50	69
Fat	34 (mostly animal sources)	13 (all plant sources)
	% of Total Fats	% of Total Fats
Saturated	32	26
Monounsaturated	35	28
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ω6:ω3 Fatty Acids	15:1	12:1
Cholesterol (mg/Cal)	0.14/ 256 mg/day	trace
Fiber (% of diet)	8	4.5
Salt (g/100g diet)	0.6	0.25

¹ *What We Eat: Women 40-49, 2007-8*

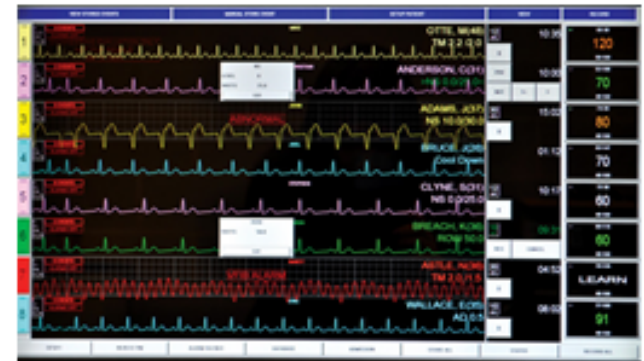
³ LabDiet Chemical Composition Diet 5037/8;
significant source of soy isoflavones

Assessment of Autonomic Function Via Remote Telemetry

3-Lead Digital Transmitter



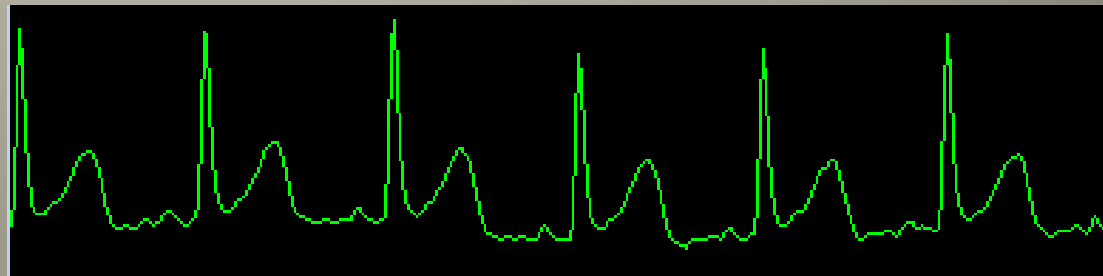
Life Sensing Instrument Telemetry System



10 Channel Receiver

We get

- Interbeat Interval
- 24 hour digital ECG Tracing
- HR, HRV, Complexity



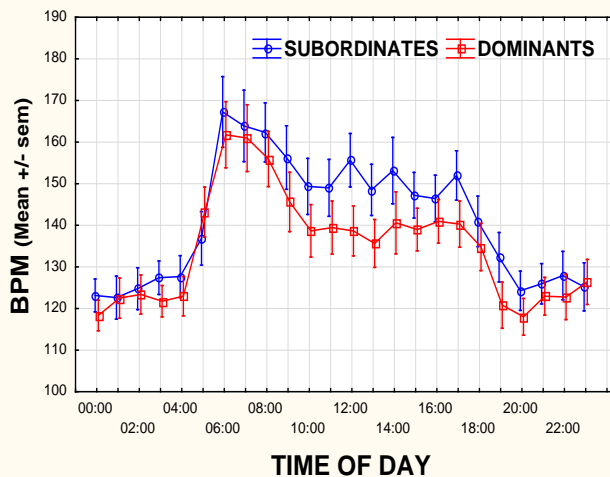
Diet Effects on Autonomic Function in Chronically Stressed Monkeys

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

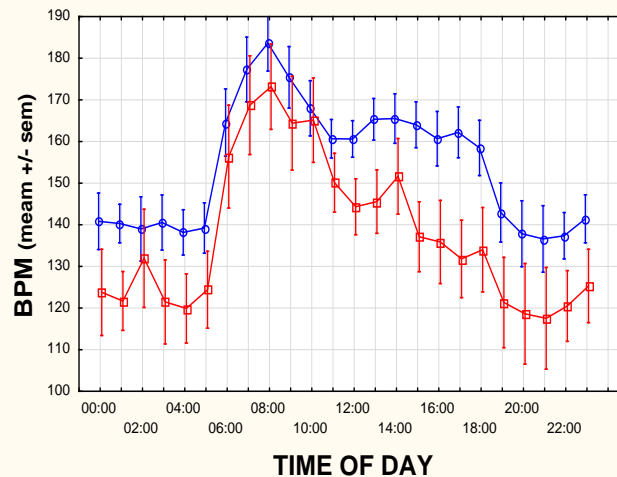
Longitudinal Effects of Western Diet on 24 Hour Heart Rate in Female Monkeys



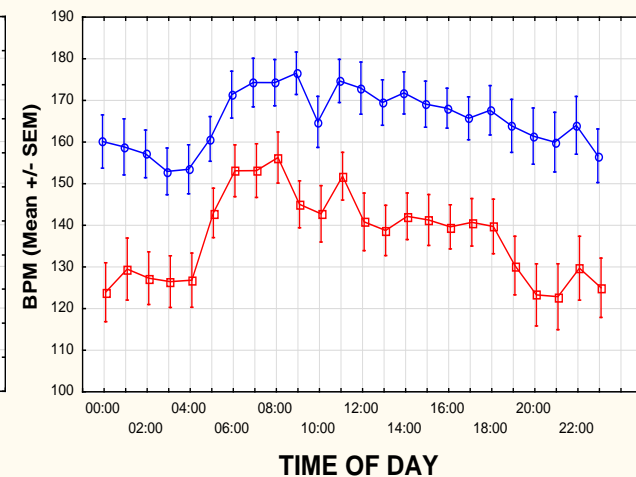
PRUDENT DIET 6 MONTHS



WESTERN DIET 18 MONTHS



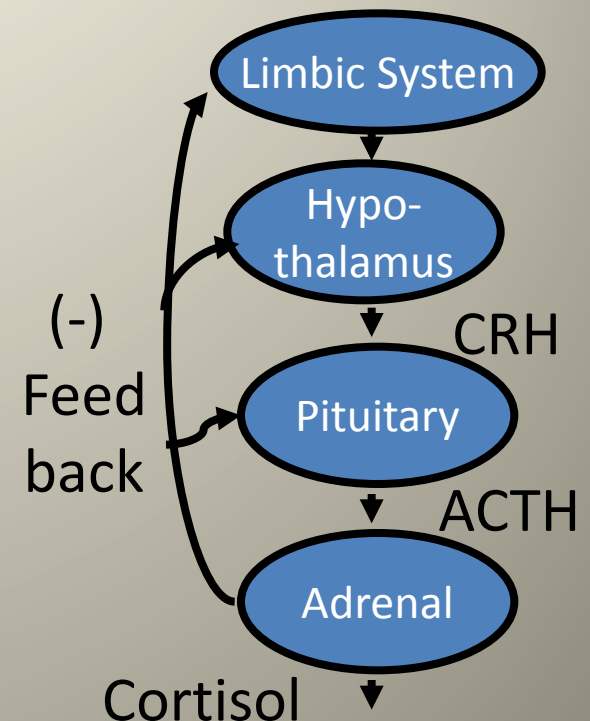
WESTERN DIET 34 MONTHS



Assessment of Hypothalamic-Pituitary-Adrenal Activity

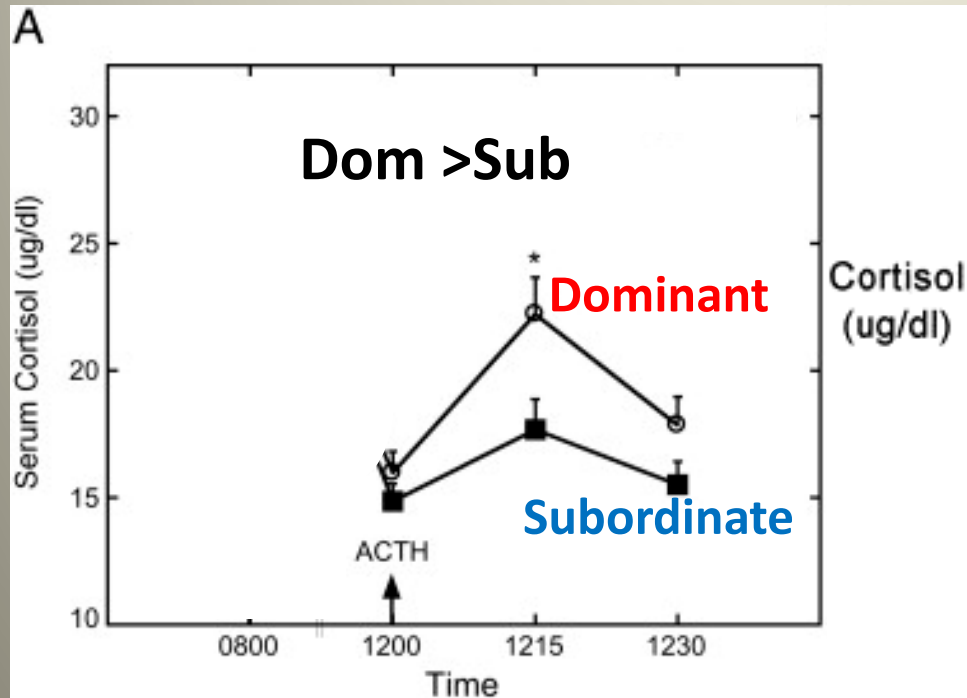
- **ACTH Challenge test**

- Measures adrenal responsiveness to ACTH
- Suppress axis with large dose of dexamethasone
- Give ACTH iv
- Measure Cortisol response over 30 min



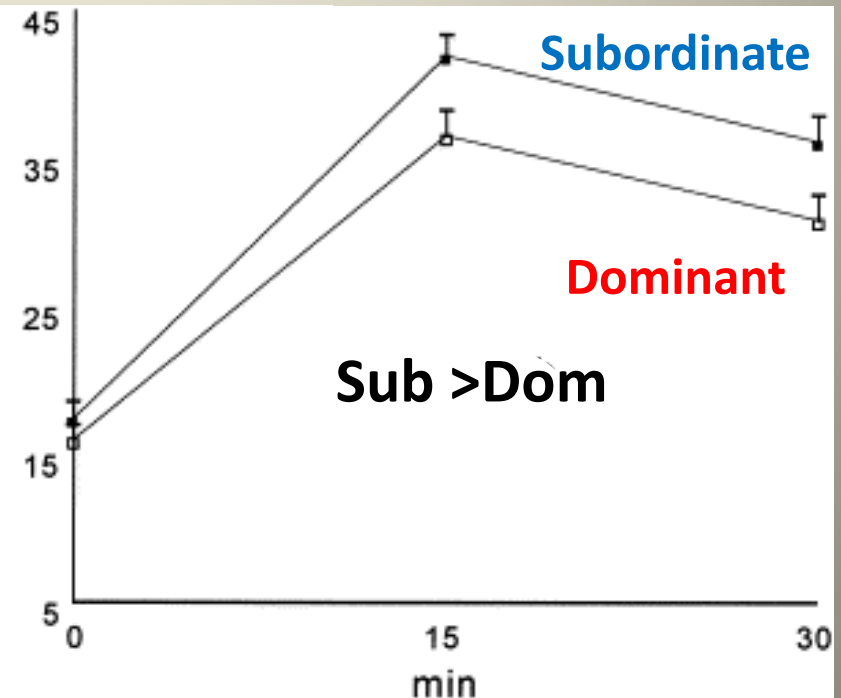
Diet Effects on Cortisol Response to ACTH in Female Macaques

Prudent Diet



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

Western Diet



Wake Forest – NC : Shively et al., 1998
Cynomolgus M. fascicularis
Interpretation:
Adrenal Hyperresponsiveness in Subs
resulting in chronic hypercortisolemia

Stress and Diet: What We Know

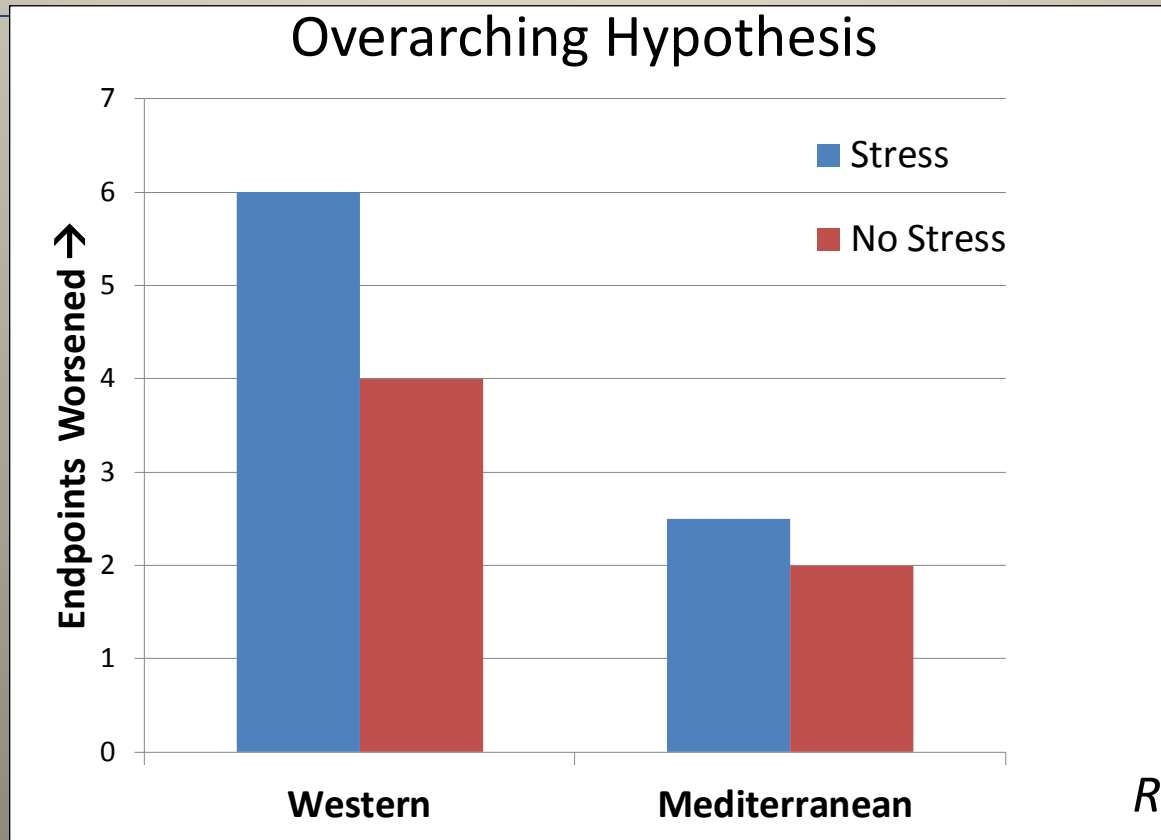
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 - Western diet pattern associated with greater perceived stress, cortisol; Mediterranean diet pattern associated with lower perceived stress
 - Strength: *These diets are actually what people eat*
 - Weaknesses: Self-reported diet & stress, retrospective, actual nutrient intake unknown
- **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.*



Diet Compositions

Diet Composition	Western ¹	Mediterranean ²	Lab Chow ³
	% of Calories	% of Calories	% of Calories
Protein	16	16	18
Carbohydrate	54	51	69
Fat	31	33	13
	% of Total Fats	% of Total Fats	% of Total Fats
Saturated	39	18	26
Monounsaturated	36	54	28
Polyunsaturated	24	15	32
ω6:ω3 Fatty Acids	15:1	3:1	12:1
Cholesterol (mg/Cal)	0.16 ⁴	0.15 ⁴	trace
Fiber (% of diet)	9	13	4.5
Salt (g/100g diet)	0.75	0.15	0.25

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



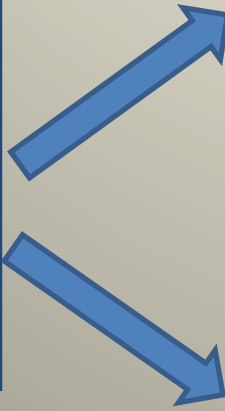
----- 2 Years ----->

Mediterranean Diet

12 dominant 12 subordinate



48 females
Social Groups
Randomized
Preclinical Trial
Run-in diet-
Monkey Chow



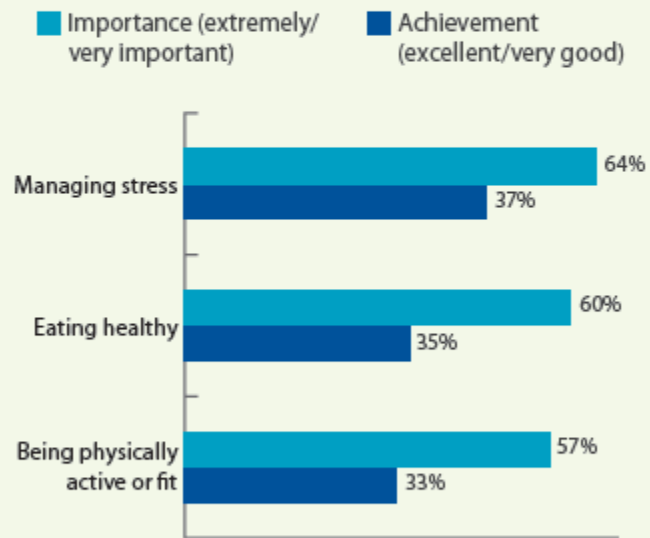
Endpoints:

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

The Obesity Epidemic & Stress-Related Eating

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

DESPITE BELIEVING THAT HEALTHY BEHAVIORS ARE IMPORTANT, AMERICANS STRUGGLE TO REACH HEALTHY LIVING GOALS.



BASE: All respondents 2012 (n=2020)

Q7005 How important are each of the following to you?

Q7010 How well are you doing at achieving each of these?

Barrier to Change?

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)

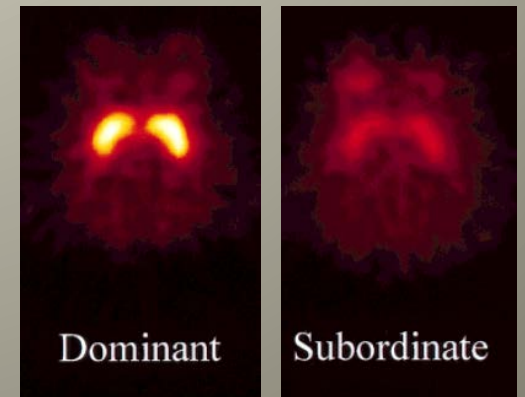
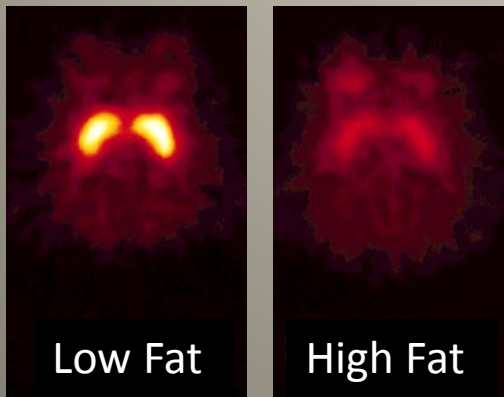
Maybe Willpower is not the only Problem....

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?



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

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- ◆ Tom Register, PhD
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- ◆ Tom Morton, PhD
- ◆ Bob Mach, PhD
- ◆ Jim Daunais, PhD
- ◆ Bob Kraft, PhD
- ◆ Don Gage, PhD



SURGEON GENERAL'S

WARNING:

The Standard American Diet causes approximately two-thirds of the deaths due to disease in America.



- ◆ Beth Uberseder
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