## COPE WEBINAR SERIES FOR HEALTH PROFESSIONALS

December 12, 2018

**The Evidence: Impact of Intermittent Fasting and Food Intake Timing on Cardiometabolic Disease and Cancer Risk**

**Moderator:** Lisa Diewald MS, RD, LDN
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Nursing Education Continuing Education Programming Research

VILLANOVA UNIVERSITY COLLEGE OF NURSING
MacDonald CENTER FOR OBESITY PREVENTION AND EDUCATION

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VILLANOVA UNIVERSITY M. LOUISE FITZPATRICK COLLEGE OF NURSING
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## OBJECTIVES

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1. Describe intermittent fasting, including the variety of intermittent fasting regimens and the challenges associated with implementation.
2. Identify the evidence-supported health effects of intermittent fasting, shorter fasting times, and food intake timing related to cancer, obesity, and type 2 diabetes
3. Discuss the use of fasting and food intake timing regimens that may be aligned with circadian rhythm.

## CE DETAILS

VILLANOVA UNIVERSITY COLLEGE OF NURSING
MacDonald CENTER FOR OBESITY PREVENTION AND EDUCATION

- Villanova University College of Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center Commission on Accreditation
- Villanova University College of Nursing Continuing Education/COPE is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration
- The American College of Sports Medicine's Professional Education Committee certifies that Villanova University College of Nursing Continuing Education, Center for Obesity Prevention and Education (COPE) meets the criteria for official ACSM Approved Provider status (10/2018-9/2021). Providership #698849

## CE CREDITS

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MacDonald CENTER FOR OBESITY PREVENTION AND EDUCATION

- This webinar awards 1 contact hour for nurses and 1 CPEU for dietitians
- Suggested CDR Learning Need Codes: 4040, 5000, 5160, 9020
- Level 2
- CDR Performance Indicators: 6.2.5, 8.3.6

THE EVIDENCE:
IMPACT OF INTERMITTENT FASTING AND FOOD INTAKE TIMING ON CARDIOMETABOLIC DISEASE AND CANCER RISK

Dorothy D. Sears , Ph.D.
Professor of Nutrition
College of Health Solutions
Arizona State University

## DISCLOSURE

Neither the planners or presenter have any conflicts of interest to disclose.

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## The Evidence: Impact of Intermittent Fasting and Food Intake Timing on Cardiometabolic Disease and Cancer Risk

Dorothy D. Sears, PhD
Professor of Nutrition
College of Health Solutions, Arizona State University

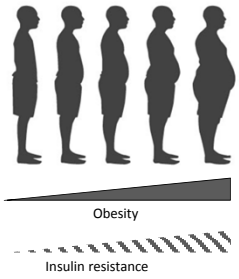
Adjunct Professor of Medicine and Family Medicine & Public Health
University of California, San Diego

ASU College of Health Solutions
Arizona State University

## Topics

- Obesity and insulin resistance
- Intermittent fasting & health
- Food intake timing & circadian rhythm
- Mechanisms and feasibility
- Conclusions & take-home messages

## Global Epidemic of Obesity

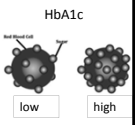



↑ Risk:
- Type 2 diabetes
- Fatty Liver (NAFLD)
- Cancer
- Cardiovascular disease

## Insulin Resistance

- Increasing prevalence world-wide
  - Affects ~1/3 of non-diabetic, U.S. population (80 million people)
  - "Pre-diabetes"
- Contributing risk factors
  - Genetics
  - Environment (obesity, diet, lifestyle behaviors)
- **A primary defect leading to type 2 diabetes**

## Insulin Resistance



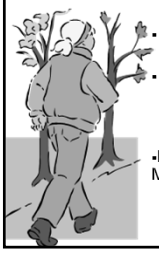

- Insulin action impaired
  - Liver, adipose tissue, muscle
    - Nutrient storage
  - Compensatory high insulin levels
  - Impaired blood glucose (glycemic) control
    - Elevated postprandial (i.e., after meal) glucose
    - Leads to "sugar-coating" of hemoglobin – hemoglobin A1c (HbA1c)
- Associated with elevated systemic inflammation
  - C-reactive protein
- Cancer risk factor - high glucose, insulin, & inflammation all promote tumor growth

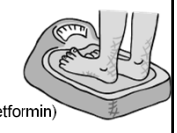
# Can't we just take a pill?

Yes, but there exist effective, non-drug alternatives!

## Lifestyle Intervention Can Prevent or Delay Type 2 Diabetes Onset

- Diabetes Prevention Program (DPP)
  - >3,000 pre-diabetic subjects
- Moderate diet modification & physical activity
  - 30 min walking almost every day
- Moderate weight loss (5-7%)
- 58% reduction in incidence
  - 71% reduction if >60yr
  - only 38% reduction with Rx (metformin)





- Now "NDPP" partially funded by the CDC and covered by Medicare. YMCA partnership

## Feeding Behaviors Can Modify Risk for Diseases Associated with Insulin Resistance & Inflammation

Type 2 diabetes

Cancer

Cardiovascular disease

Voluntary abstinence from food and drink (i.e., fasting) has been practiced from earliest antiquity by peoples scattered all over the world.


Renewed interest in fasting regimens has led to numerous popular press publications & diet promotions.




A December 10, 2018 internet search yielded more than 2.2 **BILLION** hits!

AHA SCIENTIFIC STATEMENT

## Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention

**A Scientific Statement From the American Heart Association**

St. Onge, M-P et al. Circulation 2017

*"Intentional eating with mindful attention to the timing and frequency of eating occasions could lead to healthier lifestyle and cardiometabolic risk factor management."*

American Heart Association. Learn and Live

## Intermittent Fasting & Chronic Disease

- Associated with improvements in weight and/or markers of chronic disease risk
- Strong evidence in mice, suggestive in humans
- Only 20, mostly under-powered, clinical trials
- Most human intermittent fasting regimens are not "real world" feasible
  - Not aligned with circadian rhythm light/dark cycle
  - Hunger, mood changes during daytime fasting
- **Our 2017 review**: Patterson RE & Sears DD, Metabolic Effects of Intermittent Fasting Annu Rev Nutr PMID: 28715993


## Intermittent Fasting Regimens Hypothesized to Benefit Health

| | |
|---|---|
| **Complete Alternate Day Fasting** | Alternating fasting days (no energy-containing foods or beverages consumed) with eating days (foods and beverages consumed ad-libitum). |

## Intermittent Fasting & Metabolic Risk: The Evidence in Humans

3 Trials Alternate Day Fasting (every other day)
- Samples: 8-30 non-obese adults
- Weight loss: reduction of 1-2.5% body weight
- Insulin: some studies, decreases of 52-81%

10 Trials Modified Alternate Day Fasting (e.g., 5:2 diet)
- 10-100 adults overweight/obese
- Weight loss: reduction of 3-10% body weight
- Insulin: some studies, decreases of 13-37%
- Triglycerides: some studies, decreases ~20%

Several studies of Religious Fasting (e.g., Ramadan)
- Temporarily improved lipid panel & glucose regulation

Patterson RE & Sears DD Annual Review of Nutrition (2017)
Metabolic Effects of Intermittent Fasting PMID: 28715993

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**Many hours of wake-time fasting – problematic for hunger, mood changes**

## Weight Loss Trial - 3-Arm RCT: Modified ADF vs. CR

- Trepanowski, et al., University of Illinois, Chicago
  - PMID 28459931, July 2017
  - N=100 (86 F/14 M); mean[SD] age, 44[11] years
  - Mean BMI 34 kg/m$^2$
  - 6-mo intervention, 6-mo maintenance
- ADF – 25% calorie needs on "fast", 125% calorie needs on "feast" days
- CR – 75% calorie needs on all days
- Control – no intervention
  - 1$^o$ outcome - weight change; 2$^o$ outcome - adherence, CVD risk biomarkers
- ADF not superior to CR for weight loss or maintenance, cardio-protection, or adherence
- ADF – poor compliance, highest drop-out rate (38%)
  - CR – good compliance, lower drop-out rate (29%)
  - Control drop-out rate (26%)

# Time-Restricted Feeding

## Human Trials of Time-Restricted Feeding

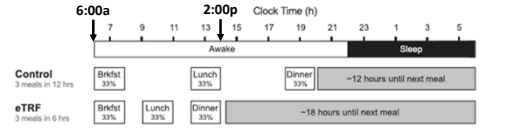
| First Author (Year) | Group Size (N) | Type of Participants | Intervention Duration & Type of Fasting | Comparison Group or Condition | Weight Change | Changes in Fasting Concentrations of Biomarkers | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Glucose Control Markers | Lipids | Inflammatory Markers |
| Carlson (2007)[15] Stote (2007)[86] | 10 F 5 M | Normal weight, middle-aged | 8 weeks: 1 meal per day | 8 weeks of 3 meals per day (cross over design) | ↓ | ↓ glucose NS insulin | ↓ LDL ↑ HDL ↑ TGs | NS leptin NS resistin NL BDNF |
| LeCheminant (2013)[83] | 29 M | Normal weight young men | 2 weeks: Nightly fasting period from 7 pm to 6 am (=11 hours) | 2 weeks of usual nightly fasting interval (cross over design) | ↓ | -- | -- | -- |
| Chowdhury (2016)[21] | 16 F 8 M | Obese adults | 1 day: Prolonged nighttime fasting until lunch meal (=13 hours) | 1 day of breakfast & lunch meals (cross over design) | -- | ↑ glucose ↑ insulin post-lunch | ↓ FFA post-lunch | ↓ leptin post-lunch |
| Chowdhury (2016)[22] | 15 F 8 M | Obese adults | 6 weeks: Prolonged nighttime fasting until lunch meal at noon | Control group: Inclusion of breakfast each morning | ↑in both groups; NS between groups | NS glucose NS insulin | ↑ Total cholesterol in both groups; NS between groups; NS LDL, HDL, TG, FFA | NS CRP NS IL-6 NS leptin NS adiponectin |

Abbreviations: ↓ denotes a statistically significant decrease ($p<0.05$); ↑ denotes a statistically significant increase ($p<0.05$); NS = not statistically significant ($p>0.05$); BDNF = brain-derived neurotrophic factor; CRP = C-reactive protein; F = female; FFA = free fatty acids; HbA1c = hemoglobin A1c; LDL = low-density lipoproteins; HDL = high-density lipoproteins; M = male; TG = triacylglycerides; TNF-α = tumor necrosis factor alpha.

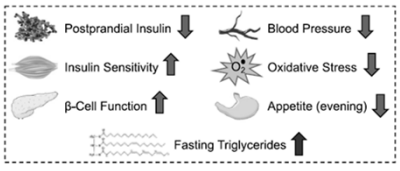
[a]No significant differences between fasting groups.

**Most aligned with circadian "wake" phase**
**Night fasting duration not controlled w/breakfast skipping**

## Early Time-Restricted Feeding: 2-Arm Crossover RCT (N=8 males w/pre-diabetes)

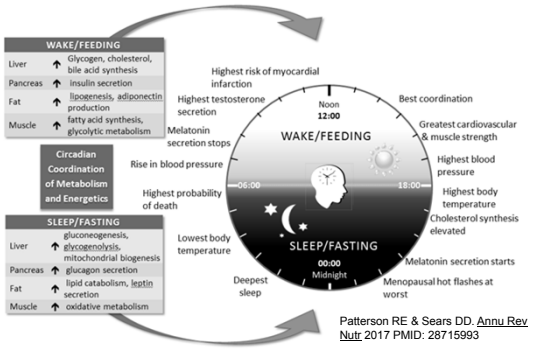



Isocaloric (no weight change), matched meals; 5 wk interventions w/1wk washout




Sutton, et al. Cell Metabolism May 2018

## Feeding & Fasting Alignment with the Circadian Clock

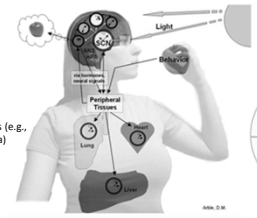



Patterson RE & Sears DD. Annu Rev Nutr 2017 PMID: 28715993

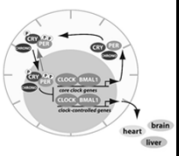
## Circadian Rhythms are Entrained by Light, Food, & Activity/Sleep

**Disrupted or misaligned circadian rhythms associated with**:

- Variety of cancers
- Obesity, type 2 diabetes
- Cardiovascular disease
- Inflammatory bowel disease
- Other immune-related disorders (e.g., rheumatoid arthritis and asthma)
- Neurodegenerative disorders
- Psychiatric illness
- Cognitive impairment
- Other disease states




**Clocks regulate biological processes in 24-hr cycles**




*Arble DM, Best Pract Res Clin Endocrinol Metab. 2010*

## Disruption of Circadian Clocks Increases Cancer Risk – Mouse Models

- Tumor suppression is controlled by the circadian clock
  - Gastric cancer cells (PMID: 30008892), prostate cancer cells (PMID: 19752089)
  - Regulates expression of oncogenes and tumor suppressors (e.g., p53)
- Disruption of the clock promotes tumor growth
  - ↑ oncogene potential - PMID: 20539819
  - ↑ cell growth and proliferation
  - ↓ apoptosis
  - ↑ lung tumorigenesis - PMID: 27476975
  - ↑ liver tumorigenesis - PMID: 28224616, 27432117
  - ↑ osteosarcoma and pancreatic adenocarcinoma - PMID: 16596304

| Clock genes expression | Breast cancer phenotype |
|---|---|
| CLOCK over expression | Increased breast cancer risk |
| Per1, per2 and per3 deficiency | Increased breast cancer risk |
| Cry deficiency | Disrupted cell cycle regulation |
| Bmal1 over-expression | Tumor suppression |

PMID: 24099911, 29946530,

## Eating Outside of Circadian Rhythm is Associated with Increased Risk of Chronic Disease

- Night shift workers, flight attendants
- Nighttime eating/snacking
  - Association with breast cancer incidence (2017; PMID 2832140)
- Mouse model studies of jet lag & daytime (sleep cycle) eating
- Weight loss is blunted if largest meal occurs in evening
  - Post-bariatric surgery (PMID: 26948400) and weight loss (PMID: 23357955) studies


↑ **Obesity, CVD, type 2 diabetes, cancer**

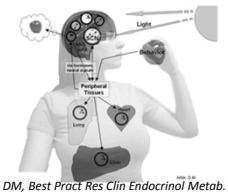
## Circadian Misalignment of Food Intake has Detrimental Metabolic Consequences

- Hormones that are active at night (e.g., melatonin and growth hormone interfere with insulin action to regulate nutrient storage.
- Efficacy of insulin decreases throughout the day and into the night.
- Thus, post-meal, blood glucose, lipid and insulin exposures are significantly greater after nighttime eating compared to daytime eating for calorie- and content-matched meals.
  - Higher blood lipids can promote atherosclerosis
  - Higher insulin and glucose can promote tumor growth
- Acutely and overtime, the presence of nutrient metabolites in the circulation out of "phase" with the circadian cycle will change or blunt metabolic pathways regulating fuel storage and cell growth.
  - Hemoglobin (& many other proteins) can become "sugar-coated" and damaged. HbA1c levels rise.
  - Cells producing insulin can become over-worked with decades of time.

## Eating in Alignment with Circadian Rhythm Associated with Reduced Risk of Chronic Disease

Patterson RE & Sears DD. Metabolic Effects of Intermittent Fasting Annu Rev Nutr 2017 PMID: 28715993

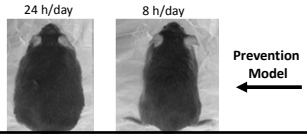
Manoogian EN & Panda S. Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res Rev 2016 PMID: 28017879



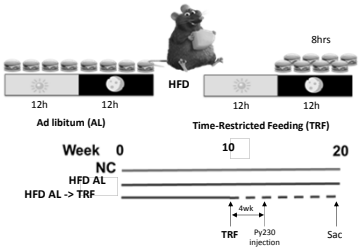

*Arble DM, Best Pract Res Clin Endocrinol Metab. 2010*

## Time-Restricted Feeding (TRF) Mouse Models

- Male mice (Panda; Salk), female mice (Webster, Sears & Ellies; UCSD MCC), others
- 24hr access to high fat diet (HFD AL) vs. TRF HFD (8hr access, nighttime)
- Prevention or intervention: TRF protects from obesity and associated metabolic disturbances associated with HFD <u>despite equivalent daily kcal intake!</u>
- Effective even when TRF mice have the weekend off!
- Hatori, et al., 2012 PMID: 22608008; Chaix, et al., 2014 PMID: 25470547; Zarrinpar, et al., 2014 PMID: 25470548; Chung, et al., 2016 PMID: 27832862




## Can TRF Inhibit Breast Cancer?




**R01 CA196853; PI – Nicholas Webster**

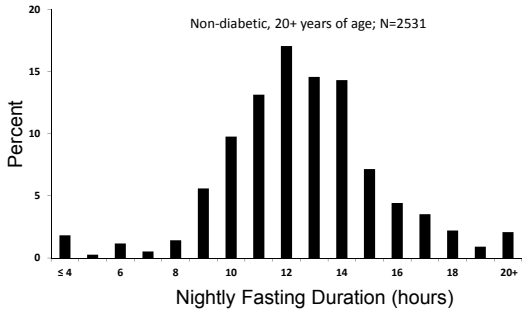
- "Time-Restricted Feeding and Breast Cancer"
  - Obese postmenopausal mouse models
- Co-Investigators – Lesley Ellies, Dorothy Sears
  - Lead Postdoctoral Fellow – Manasi Das

## What is the evidence in humans for benefit of prolonged nightly fasting (TRF)?

## Prolonged Nightly Fasting

- Nightly fasting - the time between dinner and breakfast, without interim caloric intake.
- Equivalent to TRF mouse model where food intake is in circadian alignment with active phase of the 24-hr day.
- Has the appeal of being easy to adopt and is minimally disruptive, since most of fasting hours are during sleep.
- Synchronous with circadian rhythms
  - Nutrients are powerful circadian clock stimuli (i.e., zeitgebers)
    - Signal the brain that sleep is not appropriate or needed.
    - Entrain peripheral clocks in metabolic tissues.
    - Asynchronous food intake (or fasting?) signals counteract circadian systems and leads to suboptimal metabolism
      - E.g., Melatonin impairs insulin ability to manage blood sugar

## Distribution of Nightly Fasting in NHANES Women 2009-2010




## Prolonged Nightly Fasting Associated with Improved Glycemic Control & Decreased Inflammation

- 2531 women from NHANES database with 24-hr food recall data (our focus for this work was breast cancer risk)
  - Regression models adjusting for age, education, race/ethnicity, eating episodes, evening calories, total Kcal/day, & BMI
- Glycemic Control – HbA1c
  - Each 3-hour increase in nighttime fasting duration was associated with a significant 20% reduced odds of elevated HbA1c (OR, 0.81; 95% CI, 0.68-0.97)
  - Marinac CR et al. (2015) CEBP; PMID: 25896523
- Inflammation – C-reactive protein (CRP)
  - Nighttime eating (5pm-midnight) was associated with 3% increase in CRP ($p<0.05$)
  - Longer nighttime fasting duration was associated with significantly lower CRP concentrations in women who eat <30% calories after 5pm ($p<0.05$)
  - Marinac, CR et al. (2015) PLoS ONE; PMID: 26305095.

## Fasting ≥13 Hours Per Night & Risk of Breast Cancer Recurrence

- 2337 breast cancer survivors in the Women's Healthy Eating and Living (WHEL) Study (7-yr prospective)
- Fasting <13 hr/night associated with 36% increased risk of cancer recurrence (HR, 1.36; 95% CI 1.05-1.76) compared to fasting ≥13 hr/night.
- Each 2-hr increase in the nightly fasting was associated with significantly lower HbA1c (β = –0.37; 95%CI, –0.72 to –0.01) and a longer duration of nighttime sleep (β = 0.20; 95%CI, 0.14-0.26).
- **First human study to demonstrate an association of prolonged nightly fasting with a clinical outcome.**

Marinac CR et al. (2016) JAMA Oncology; PMID: 27032109.

Article featured in the 2016 Research Highlights of the Epidemiology and Genomics Research Program (NCI, NIH) as it was deemed to have the greatest potential for scientific and/or public health impact.

## Prolonged Nightly Fasting and Metabolic Risk: Potential Mechanisms

Impacts on the Gut Microbiota:

- Has its own circadian rhythm and influences that of the host through metabolite production (e.g., bile acids, SCFAs) PMID: 26706567
- Fasting may induce changes in the microbiota that reduce risk factors such as excess adiposity, insulin resistance, and inflammation.

## Prolonged Nightly Fasting and Metabolic Risk: Potential Mechanisms

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- Fasting may induce changes in the microbiota that reduce risk factors such as excess adiposity, insulin resistance, and inflammation.

Behavioral Effects:

- Reduction in hours available for eating.
- Reduced nighttime food consumption.
- Changes in appetite, physical activity, and sleep.
  - Change in BMI, food intake quantity or quality may not be needed (mice!).

## Prolonged Nightly Fasting and Metabolic Risk: Potential Mechanisms

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Behavioral Effects:

- Reduction in hours available for eating.
- Reduced nighttime food consumption.
- Changes in appetite, physical activity, and sleep.
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Circadian Rhythm Alignment:

- Food signals entrain peripheral clocks in metabolic tissues
- Synchronize with microbiota and SCN rhythms
- Align food intake with metabolic and other hormone rhythms (insulin secretion & action, melatonin, growth hormone)

## Could Prolonged Nightly Fasting Practiced in a Real-World, Community-Based Setting Confer Benefits Similar to Time-Restricted Feeding in Mice?

## Is Prolonged Nightly Fasting Feasible in a Real-world, Community Setting?

## Prolonged Nightly Fasting: A Feasibility Pilot Study

**Objective**: Investigate feasibility of intervention

**Sample**: 20 Obese postmenopausal women (BMI ≥30kg/m$^2$)
50% Latinas
Eligibility: <12 hr fasting usual period

**Run-In:** 4-day Food Record, meal times recorded
On-line Questionnaire

**Where:** UCSD Moores Cancer Center
San Diego State University

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## Prolonged Nightly Fasting: A Feasibility Pilot Study

Educational Powerpoint on Nightly Fasting & Health

One-Month Intervention Period
- 2 weeks Telephone Counseling & Bedside Journal
- Goal to fast 12+ hours each night
- 2 weeks SMS system:
  - Participants texted "Start Fast" and "Stop Fast"
  - Reminders about when to eat first meal
  - Encouraging texts
  - Monitoring

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## Prolonged Nightly Fasting: A Feasibility Pilot Study

- **Results**: Mean baseline nightly fast: 10.6 hours
  Mean post-intervention fast: 13.2 hours
  Mean weight change: -1.1 pound/1 month
  Successful nights fasting 12+ hours: **95%**
- **Attitudes and Opinions**:
  - 90% said fast was easy
  - 90% said that they could fast more than 12 hours
  - 70% preferred SMS texting APP to telephone counseling
  - 100% would recommend study to friend
  - 90% found fasting very/somewhat pleasant

**Seems feasible – let's do it!**

## Conclusions & Take-Home Messages

- Accumulating evidence shows that short nightly fasting duration and nighttime eating are associated with cardiometabolic disease and cancer risk.
- Daily practice of fasting during inactive, “sleep” phases of the circadian clock is associated with improved metabolic and breast cancer outcomes.
- Suggestive evidence supports metabolic benefits and safety of intermittent fasting, however, compliance challenges exist for fasting during “active” phase of day.
- Evidence-based messaging about health-promoting, food intake timing could have a significant public health benefit

## Collaborators & Funding

- Ruth Patterson
- Satchin Panda
- Emily Manoogian
- Rob Knight
- Embriette Hyde
- Nick Webster
- Lesley Ellies
- Manasi Das
- Heekyung Chung
- Loki Natarajan
- Linda Gallo
- Sandahl Nelson
- Emilie Gross
- Catherine Marinac
- Sonia Ancoli-Israel
- Jacqueline Kerr
- Elena Martinez
- Sheri Hartman
- Elva Arredondo
- John Pierce
- Shirley Flatt
- Caitlin Breen
- Suneeta Godbole
- Consuelo Sauceda
- Deepak Kumar

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Questions?

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**Upcoming FREE Continuing Education Webinar**

**Stephanie P. Goldstein, Ph.D.**
Clinical Psychology Postdoctoral Fellow
Miriam Hospital Weight Control and Diabetes Center

**Are there different types of lapses from dietary prescriptions?**
**Implications for outcomes in behavioral obesity treatments**
Wednesday, January 23, 2019
12:00PM - 1:00PM EST

:

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## QUESTIONS & ANSWERS

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MacDonald CENTER FOR OBESITY PREVENTION AND EDUCATION

Moderator: Lisa K. Diewald MS, RD, LDN
Email: cope@villanova.edu
Website: www.willanova.edu/COPE