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# CRITICAL ANALYSIS OF INFORMATION: AN EPIDEMIOLOGIC PERSPECTIVE

PERINATAL PROFESSIONAL CONFERENCE APRIL 21ST, 2017

PAST AND PRESENT PRACTICE: CARING FOR MODERN FAMILIES

KAREN SCHLIEP, PHD, MSPH, DIVISION OF PUBLIC HEALTH, DEPARTMENT OF FAMILY AND PREVENTIVE MEDICINE

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# OUTLINE

- Brief personal introduction
- Example: “Impact of stress on women and their offspring”
- How to critically evaluate the scientific literature
- Ways for you to get involved in research
  - PRAMs
  - Systematic Review
  - Secondary Data Analysis


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# Personal Introduction

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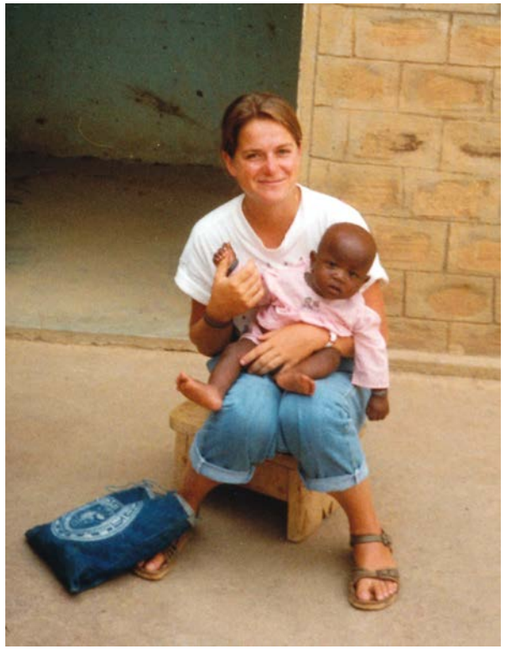
# A LITTLE ABOUT ME...

- BA, English, Carleton College (1984-1988)
- United States Peace Corps, Mali, West Africa (1990-1992)



# A LITTLE MORE ABOUT ME…

- BS, Biology (Minor, Chemistry), RA in Ecology Lab (1994-1997)
- Research Coordinator: University of Utah School of Medicine (2002-2012)
- MSPH/PhD, University of Utah School of Medicine (2005-2011)
- Postdoctoral Fellow, Epidemiology Branch, NICHD (2012-2015)

NATIONAL CANCER INSTITUTE
PLCO
Prostate, Lung, Colorectal, & Ovarian
CANCER SCREENING TRIAL

EAGeR
The Effects of Aspirin in Gestation & Reproduction

HOPE
HOME OBSERVATION OF PERICONCEPTIONAL EXPOSURES STUDY

FAZST
FOLIC ACID AND ZINC SUPPLEMENTATION TRIAL

BioCycle

ENDO

IMPACT OF DIET EXERCISE AND LIFESTYLE
IDEAL
FERTILITY STUDY

# AND HERE I AM NOW☺

- Assistant Professor, University of Utah; Asia Campus (2015-2016); SLC Campus, Fall 2016

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ASIA CAMPUS

# MY RESEARCH PASSION

Interplay between reproductive/pregnancy disorders, modifiable exogenous factors (exposome), non-modifiable endogenous factors (genome) and chronic disease pathogenesis.

# MOTIVATION FOR MY RESEARCH

# Impact of stress on women and their offspring

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# Introduction

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**Schliep KC**, et al. Perceived stress, reproductive hormones, and ovulatory function among premenopausal women: a prospective cohort study. *Epidemiology.* 2015;26:177-84.

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# PERCEIVED PSYCHOLOGICAL STRESS

- Psychological stress: individual **perceives** that external demands tax or exceed his or her ability to cope.

- 23% of US women reporting **high** levels of stress and 43% saying that their stress levels have **increased** over the last 5 years.
  - *Stress in America Survey* 2012

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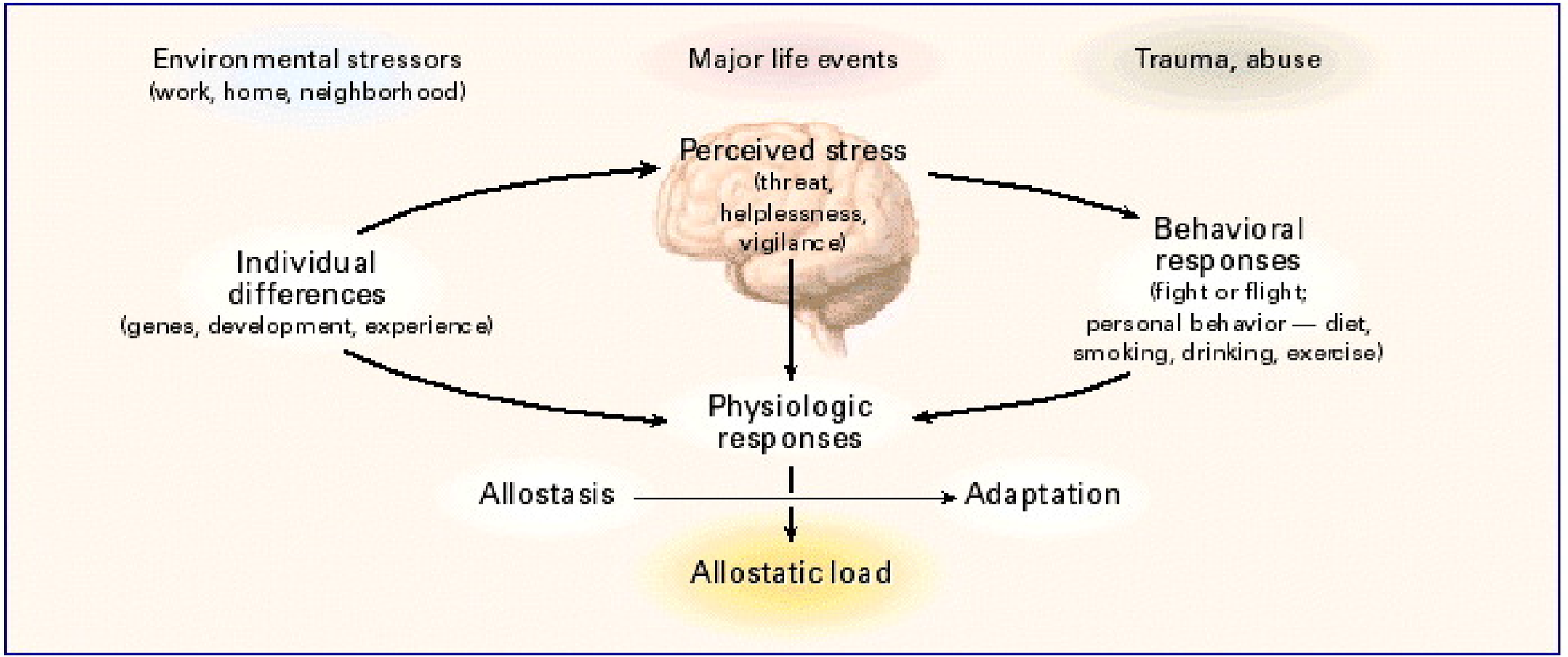
# ACUTE AND CHRONIC STRESS





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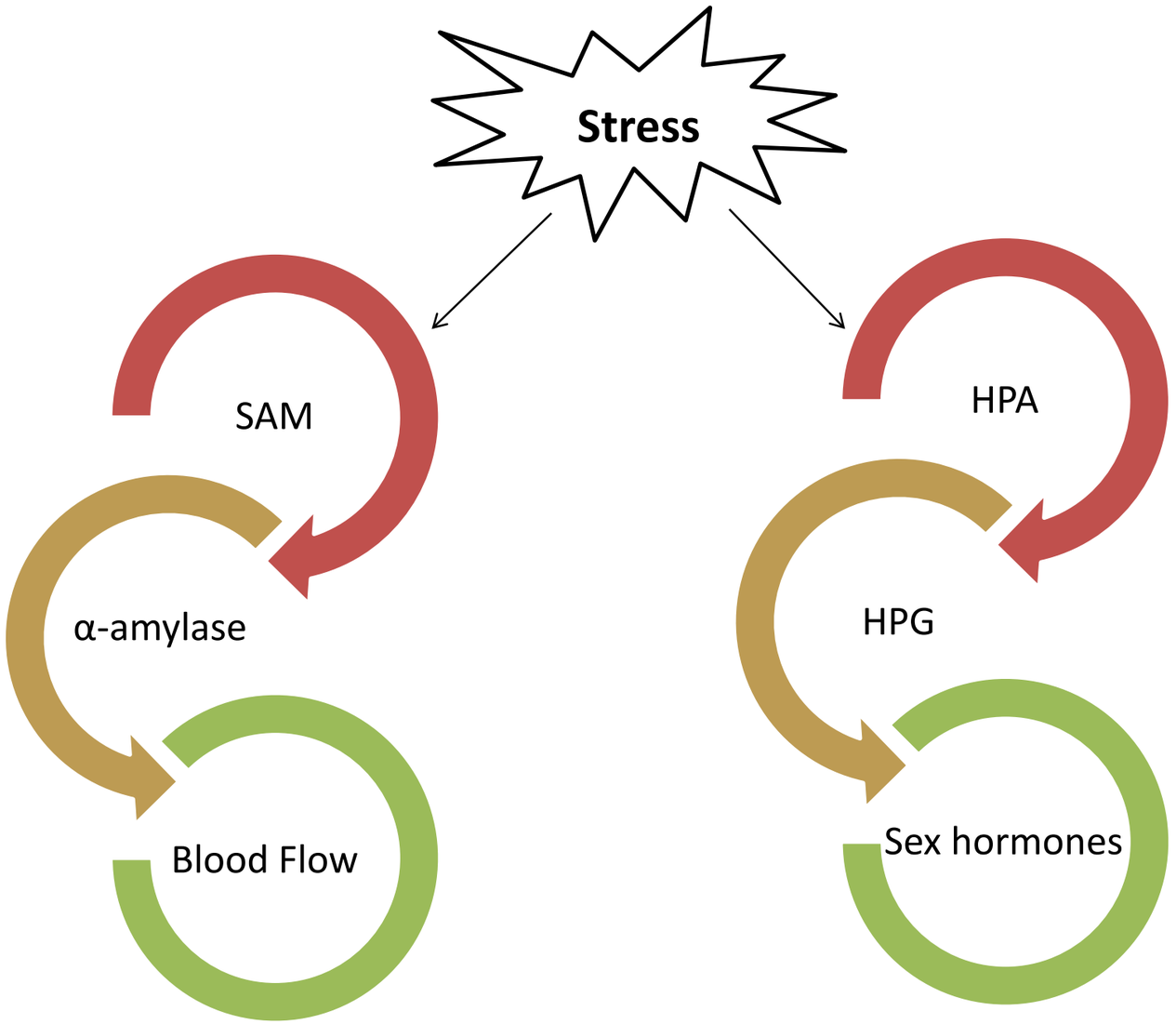
# STRESS AND REPRODUCTION





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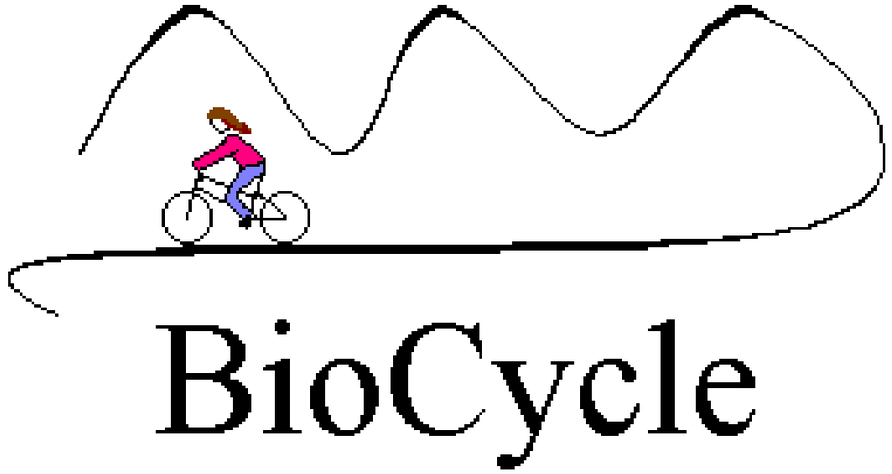
# OBJECTIVE

To examine the association between repeated measurements of perceived stress, reproductive hormone levels, and ovulatory function





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# Methods

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**Schliep KC**, et al. Perceived stress, reproductive hormones, and ovulatory function among premenopausal women: a prospective cohort study. *Epidemiology.* 2015;26:177-84.

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# STUDY POPULATION

- BioCycle Study (2005-2007): Followed 259 women from western NY region for up to 2 cycles
- Inclusion:
  - Ages 18-44
  - Regularly menstruating
- Exclusion:
  - Reproductive disorders
  - Self-reported obesity or underweight

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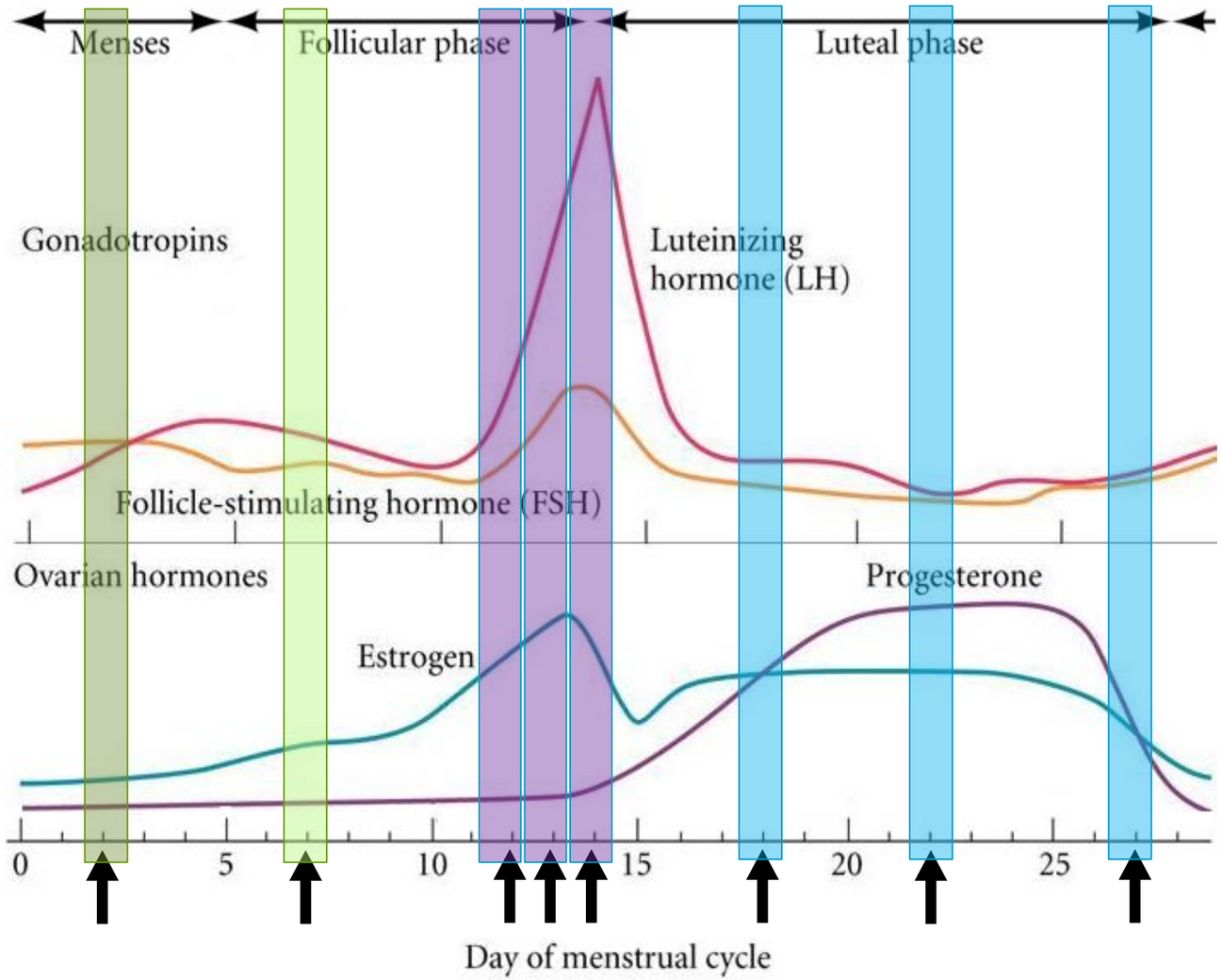
# HORMONE ASSESSMENT





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# HORMONE & ANOVULATION ASSESSMENT

- Total E2, Progesterone, LH, FSH and sex hormone binding globulin (SHBG) were assayed.
- Anovulation: ≤ 5ng/mL luteal progesterone and no LH peak at the mid- or late luteal visits.
- 94% of the 259 participants completed 7 or 8 clinic visits per cycle.


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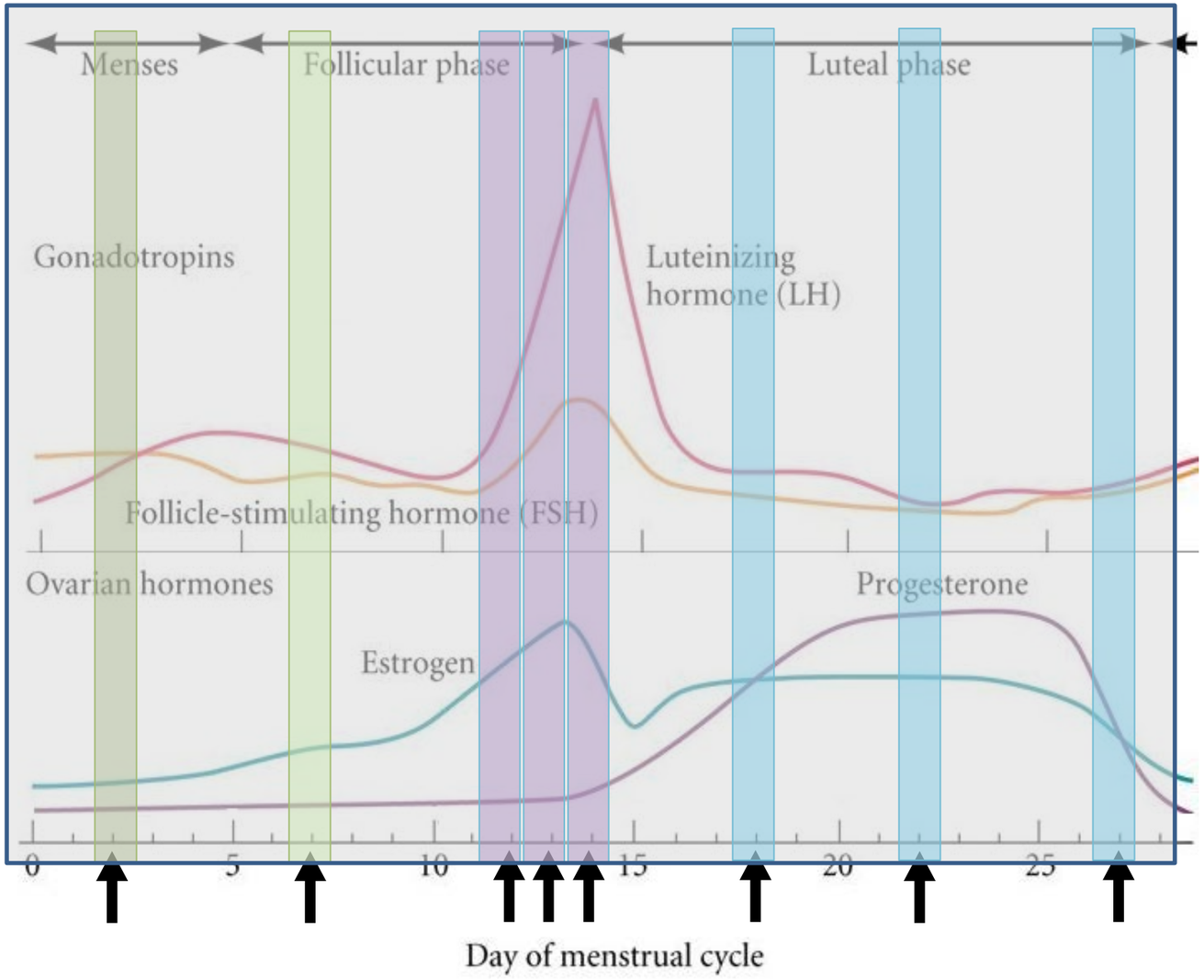
# STRESS ASSESSMENT




**Please rate your level of stress today:**

1 = not stressful
2 = a little stressful
3 = very stressful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# COVARIATE ASSESSMENT

- Age, race, income, education level, sexual and reproductive history, and depression (Center for Epidemiologic Studies Depression Scale) were obtained at baseline using standard questionnaires.
- At the end of the follow-up period, total percent body fat was measured using duel energy x-ray absorptiometry scans.


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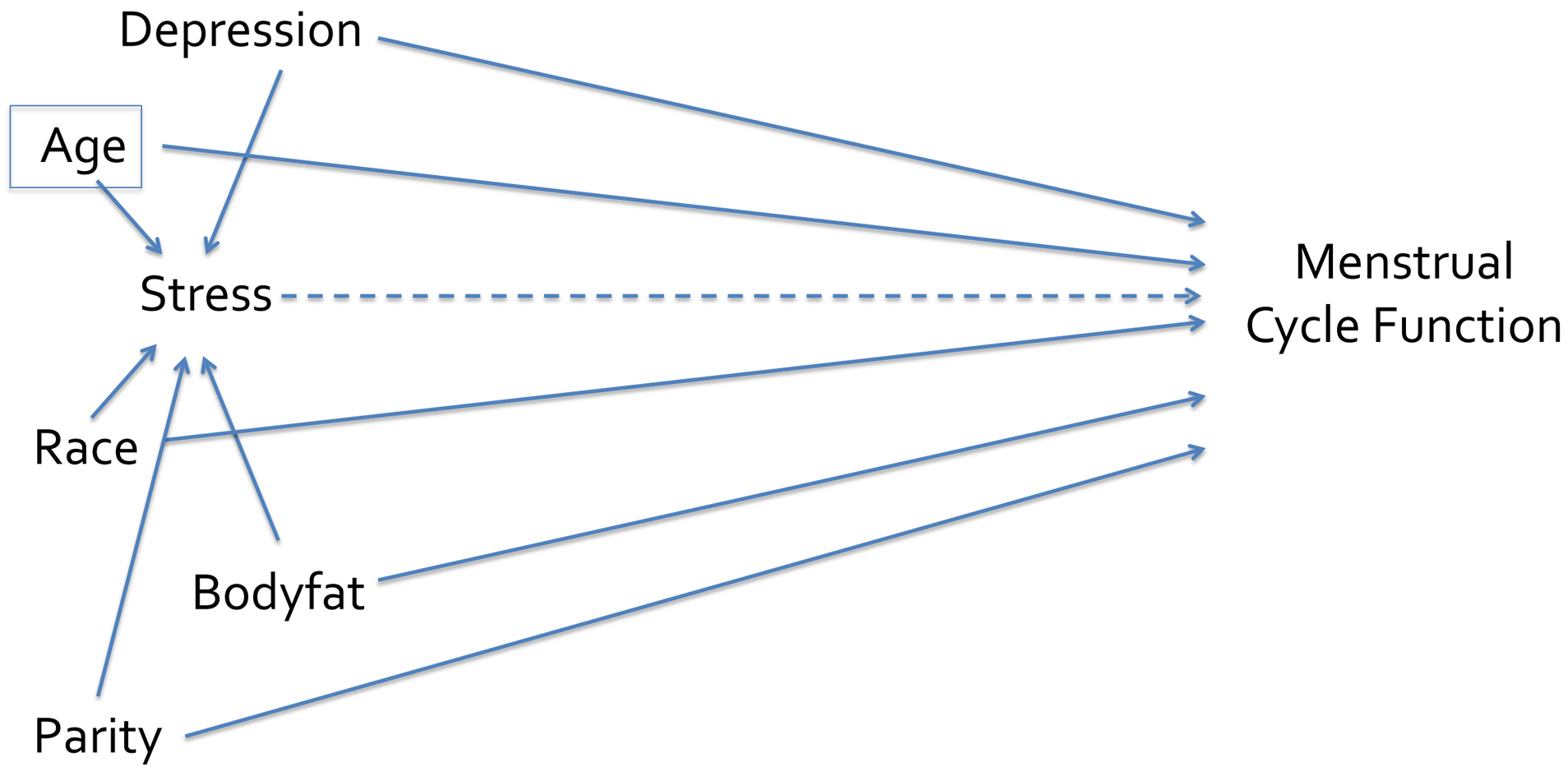
# POTENTIAL CONFOUNDERS: CHRONIC





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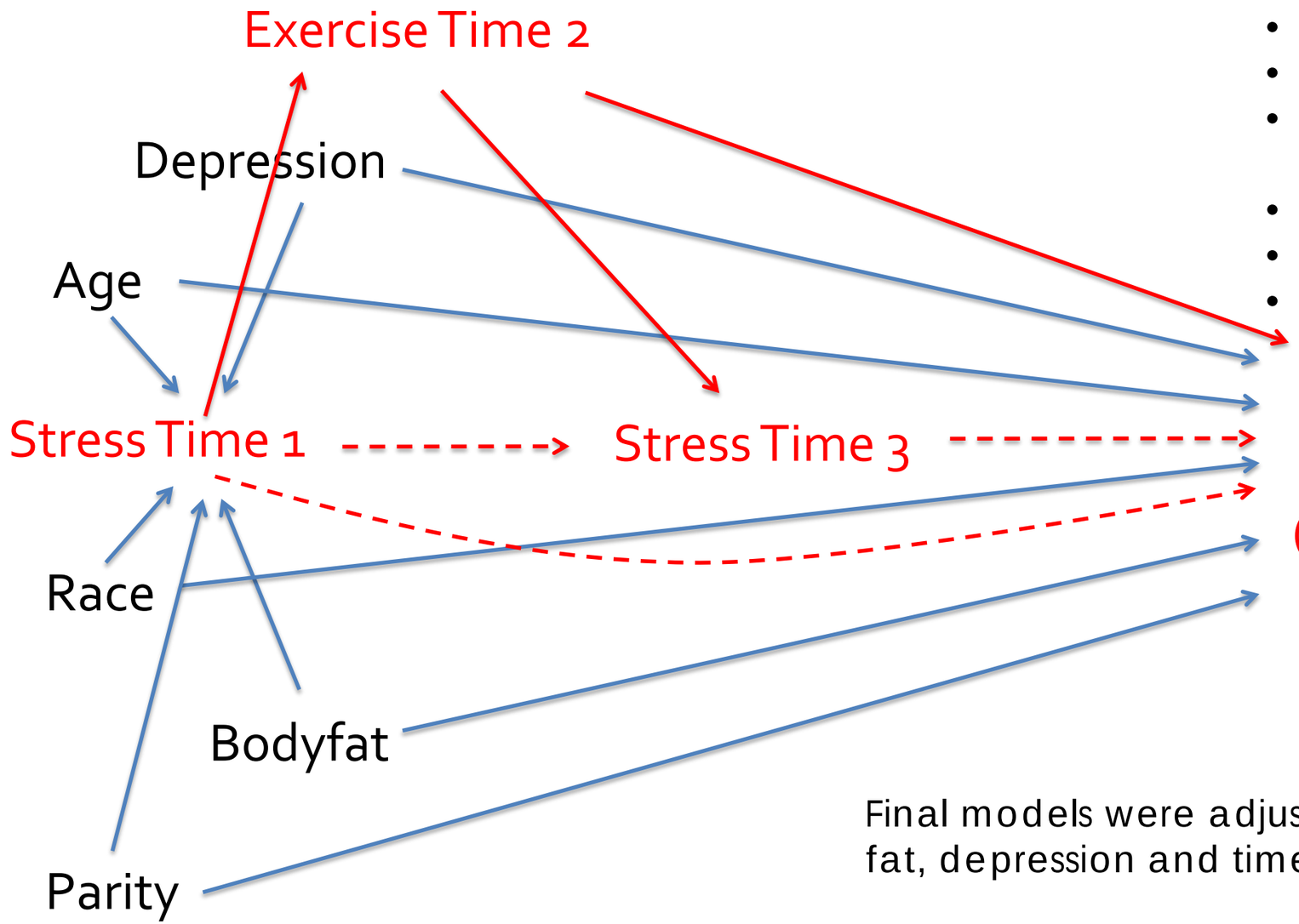
# POTENTIAL CONFOUNDERS: TIME VARYING




- sleep
- sexual activity
- pain or antibiotic medication use
- caffeine/alcohol/tobacco
- total energy and fiber intake
- diet score

Final models were adjusted for age, race, percent body fat, depression and time-varying vigorous exercise.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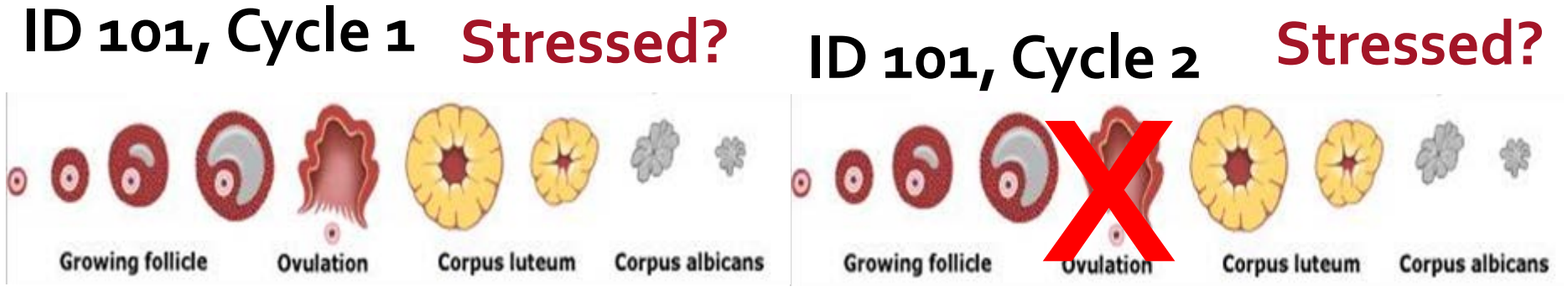
# STATISTICAL ANALYSIS

- Mixed models: to assess association between average daily stress, hormones and anovulation.
- Case crossover analysis on women who experienced both an ovulatory and anovulatory cycle (n=24).
  - *"The ultimate form of statistical adjustment for confounding by constant subject characteristics."*





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# Results

**Schliep KC**, et al. Perceived stress, reproductive hormones, and ovulatory function among premenopausal women: a prospective cohort study. *Epidemiology.* 2015;26:177-84.

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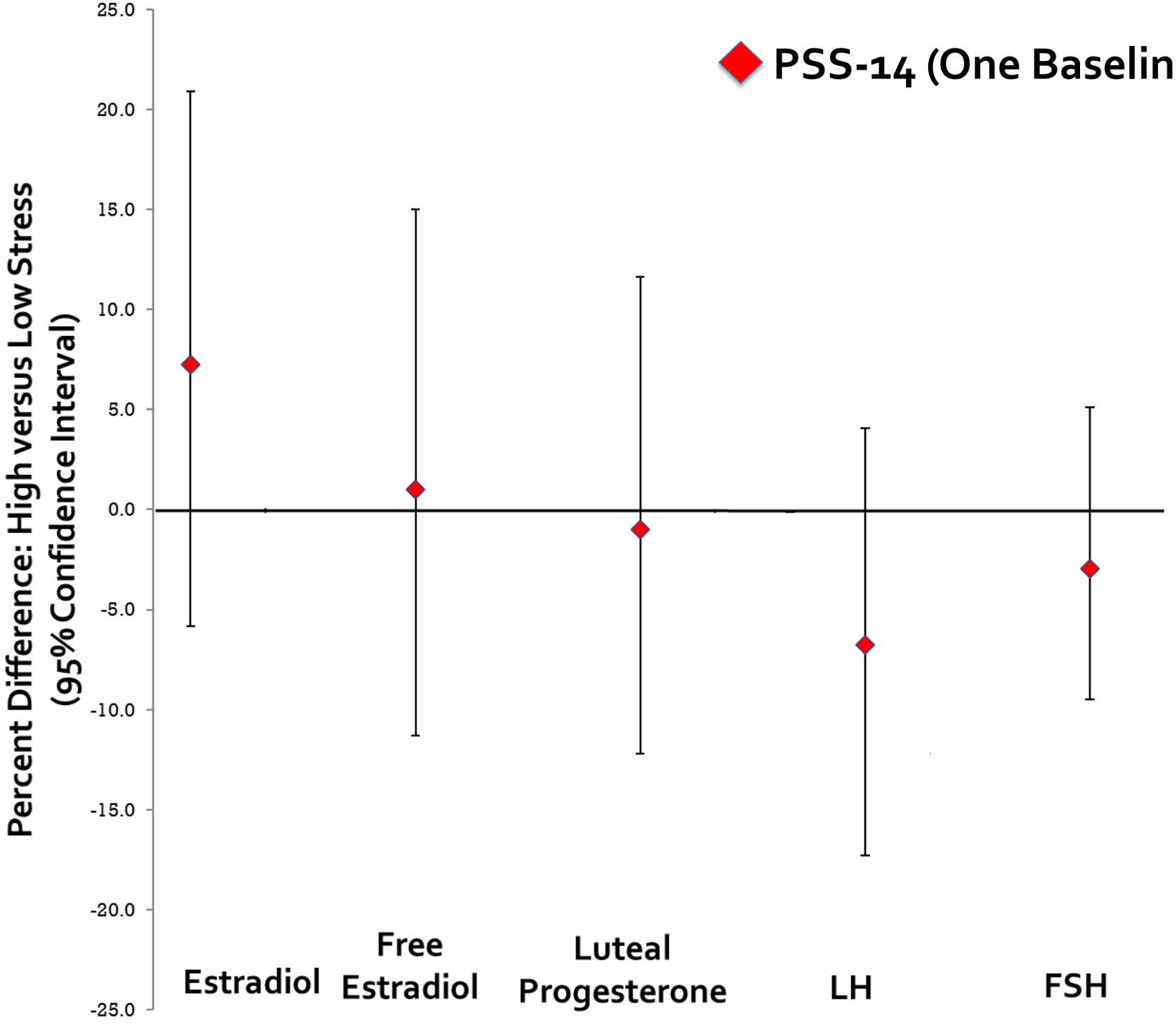
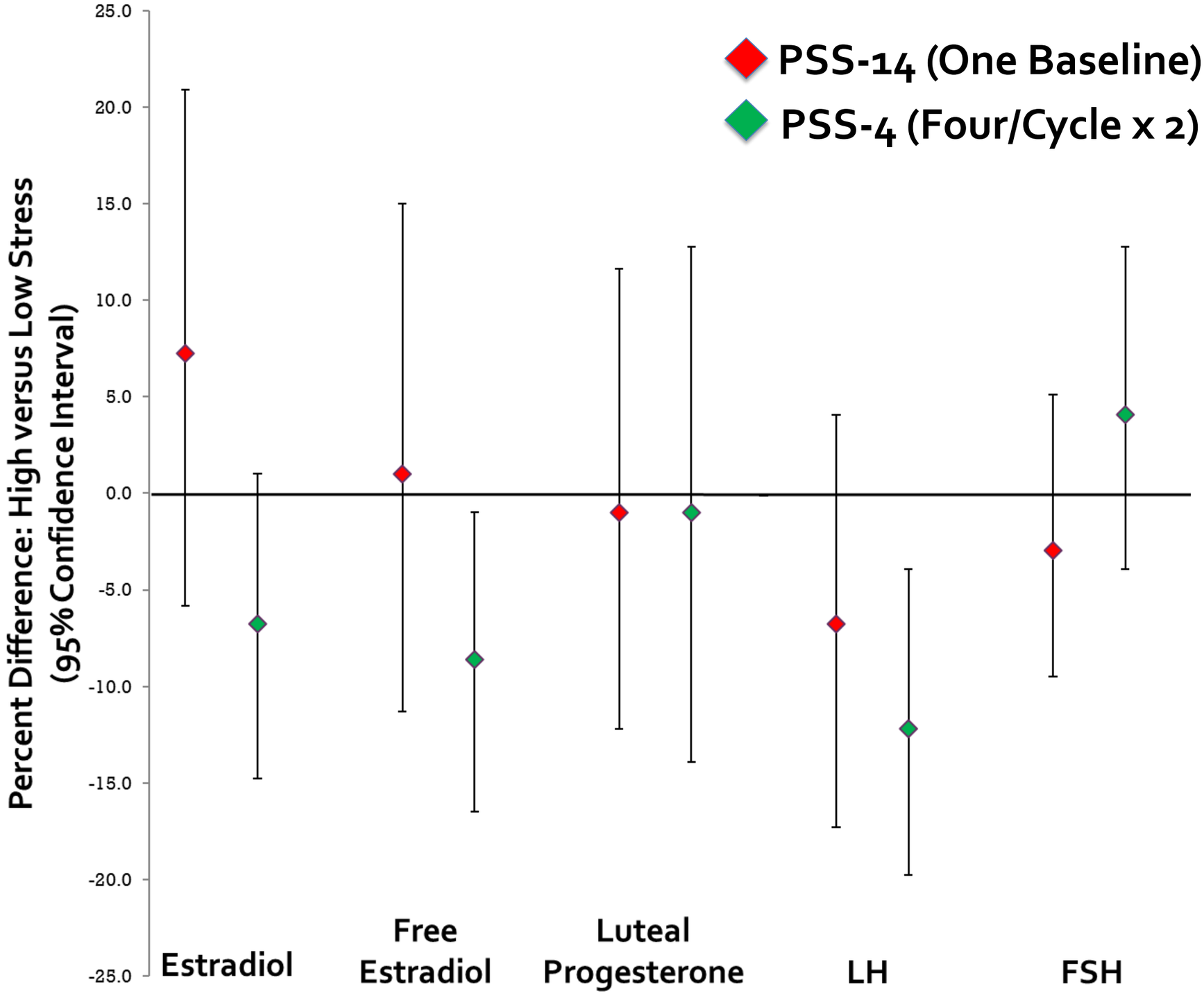
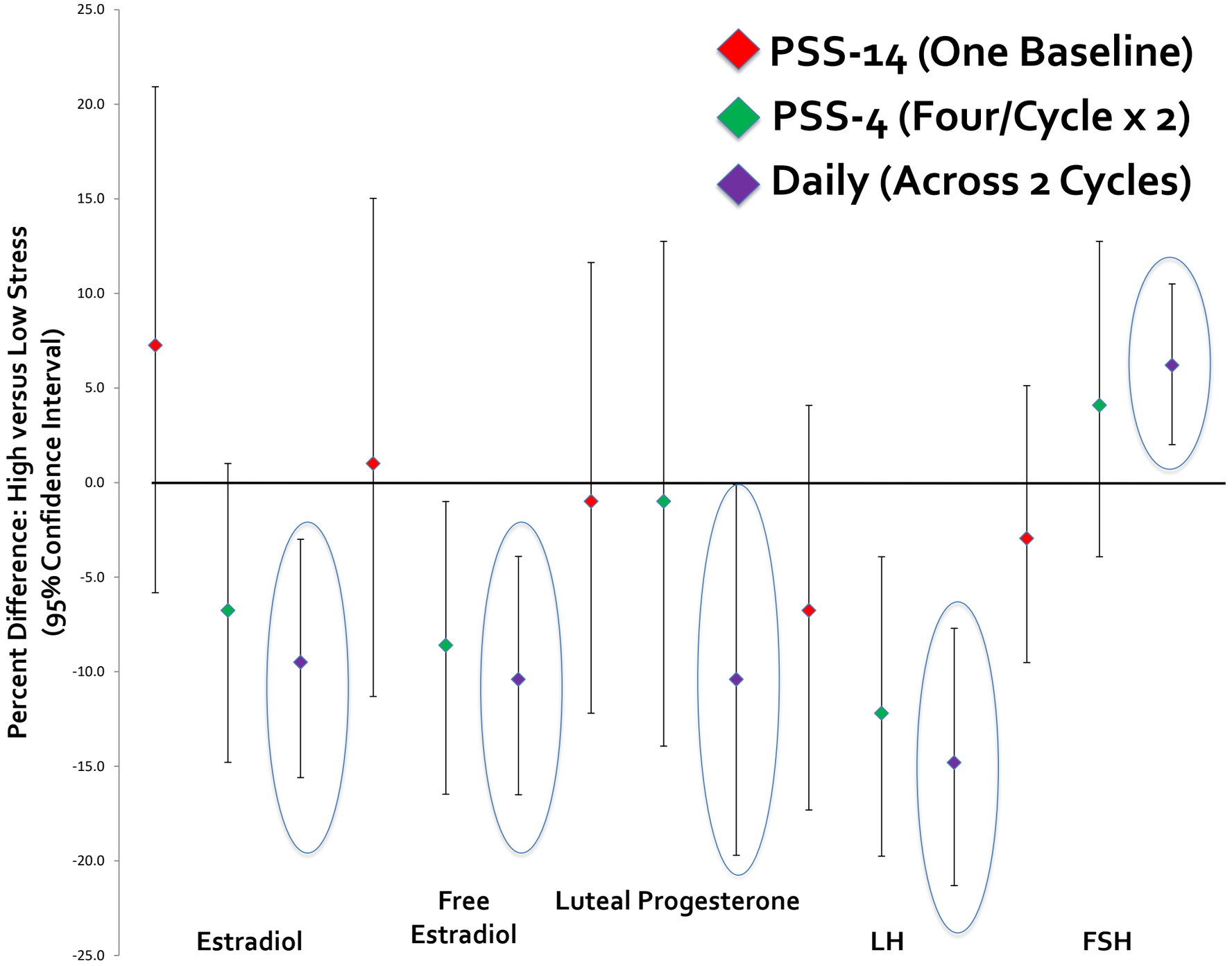
| | | Daily Stress Tertile | | | |
|---|---|---|---|---|---|
| | **Total Population** | **Low** | **Moderate** | **High** | ***P*-value** |
| Participants [*n* (%)] | 259 (100%) | 87 (33.6%) | 87 (33.6%) | 85 (32.8%) | |
| Age (years) | 27.3 ± 8.2 | 28.3 ± 8.4 | 27.0 ± 8.0 | 26.5 ± 8.2 | 0.34 |
| Race[*n* (%)] | | | | | |
| Caucasian | 154 (59) | 51 (33) | 47 (31) | 56 (36) | 0.27 |
| African American | 51 (20) | 20 (39) | 22 (43) | 9 (18) | |
| Asian | 37 (14) | 10 (27) | 12 (32) | 15 (41) | |
| Percent body fat | 29.5 ± 5.9 | 29.4 ± 5.9 | 29.1 ± 6.1 | 30.0 ± 5.8 | 0.95 |
| Depression score [median (IQR)] | 5 (1, 9) | 3 (0, 6) | 4 (1, 8) | 6 (3, 11) | <0.001 |
| Vigorous exercise (min/day) [median (IQR)] | 9.9 (2.3, 20.0) | 8.2 (0.7, 20.0) | 10.7 (3.2, 17.5) | 10.6 (2.8, 22.3) | 0.46 |
| Alcohol (g) [median (IQR)] | 0.08 (0.02, 3.5) | 0.08 (0.02, 3.9) | 0.07 (0.02, 2.3) | 0.14 (0.02, 4.2) | 0.49 |
| Caffeine (mg/day) [median (IQR)] | 53.6 (17.8, 147.7) | 51.7 (16.4, 147.7) | 71.1 (23.3, 156.2) | 49.7 (16.7, 134.1) | 0.69 |


PSS-14 (One Baseline)
Percent Difference: High versus Low Stress
(95% Confidence Interval)
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
Estradiol
Free Estradiol
Luteal Progesterone
LH
FSH


PSS-14 (One Baseline)
PSS-4 (Four/Cycle x 2)
Percent Difference: High versus Low Stress
(95% Confidence Interval)
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
Estradiol
Free Estradiol
Luteal Progesterone
LH
FSH

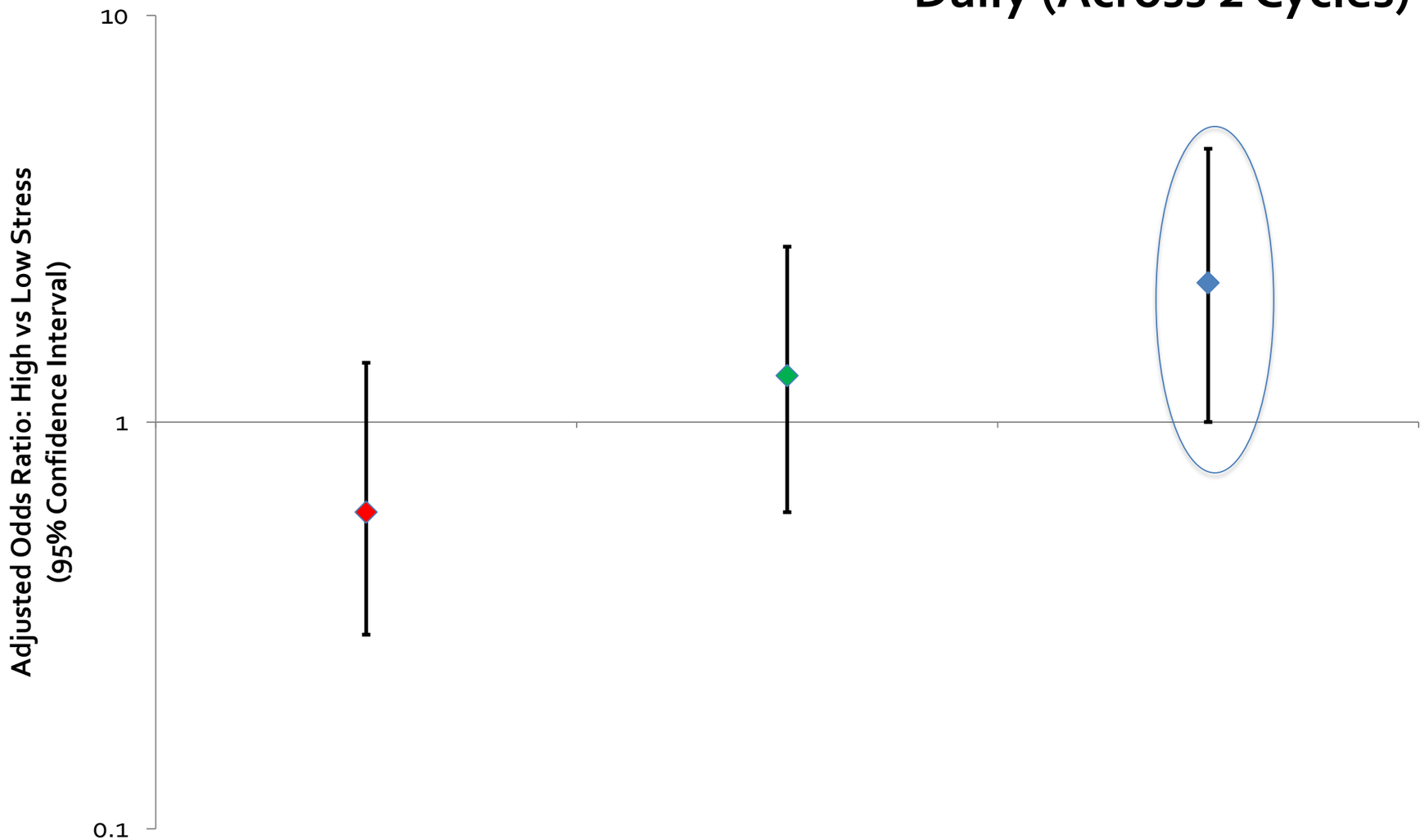

PSS-14 (One Baseline)
PSS-4 (Four/Cycle x 2)
Daily (Across 2 Cycles)
Percent Difference: High versus Low Stress
(95% Confidence Interval)
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
Estradiol
Free Estradiol
Luteal Progesterone
LH
FSH

# ANOVULATION

**PSS-14 (One Baseline)**

**PSS-4 (Four/Cycle x 2)**

**Daily (Across 2 Cycles)**



# STRESS AND SPORADIC ANOVULATION: CASE CROSSOVER ANALYSES

OR = 3.0; *P* = 0.24

| | |
|---|---|
| Stressed/Stressed **8** | Stressed/Anovulatory **6** |
| Stressed/Ovulatory **2** | Not Stressed/Not Stressed **6** |

22 women with one ovulatory and one anovulatory cycle with complete daily stress measures

# Discussion

**Schliep KC**, et al. Perceived stress, reproductive hormones, and ovulatory function among premenopausal women: a prospective cohort study. *Epidemiology.* 2015;26:177-84.

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# SUMMARY

- High daily perceived stress was significantly associated with **lower** total and free E2, LH, **higher** FSH, and an **increased** risk of sporadic anovulation

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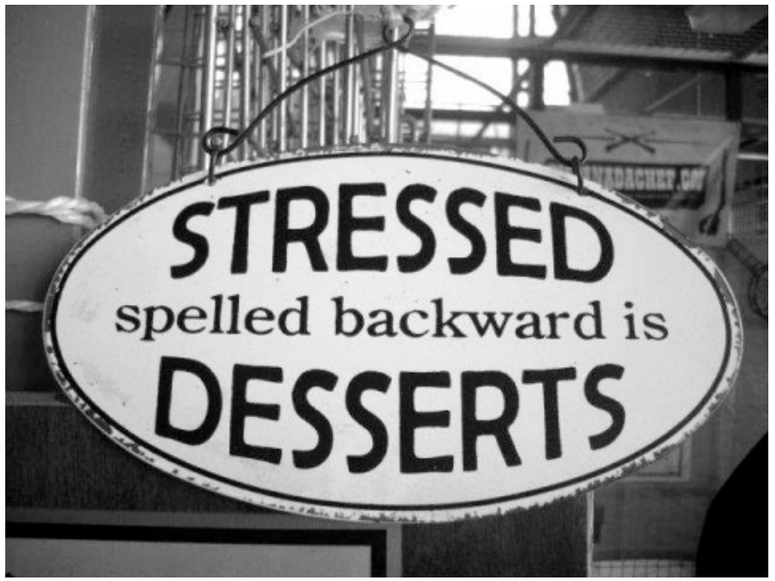
# CONCLUSION

- Recent, but not chronic, perceived stress is associated with alterations in reproductive hormone concentrations & sporadic anovulation
- Potential for healthy interventions.





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# LONG-TERM AFFECTS OF TRAUMA/STRESS

https://www.ted.com/talks/nadine_burke_harris_how_childhood_trauma_affects_health_across_a_lifetime


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# How to critically evaluate the scientific literature

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# the ebm project

tools for all of us to learn evidence-based medicine

HOME | FUNDAMENTALS OF EBM | THE 4A'S OF EBM | RMD 529B SMALL GROUPS | M3 | M4 | CLINICAL REASONING (BETA)

## the ebm project

Welcome to the ebm project. The goal of this site is to provide our students with the tools to critically evaluate medical literature. Starting with the basic concepts of physician numeracy (basic statistics and epidemiology) we move to asking clinical questions, searching for appropriate articles, critical appraisal of literature and finally applying the literature. Ultimately we hope to put examples of critically appraised topics online as well.

Follow

For Rush M2 students registered for RMD 529, please refer to our syllabus page. You can follow any updates or other communications on this updates page. If you click "Follow" in the bottom right of the screen, you will be emailed whenever we post any updates.

One more tip, some students prefer to watch the videos at 1.5x or 2.0x the normal speed. This is possible in YouTube if you use the HTML5 player. More information about this can be found here.

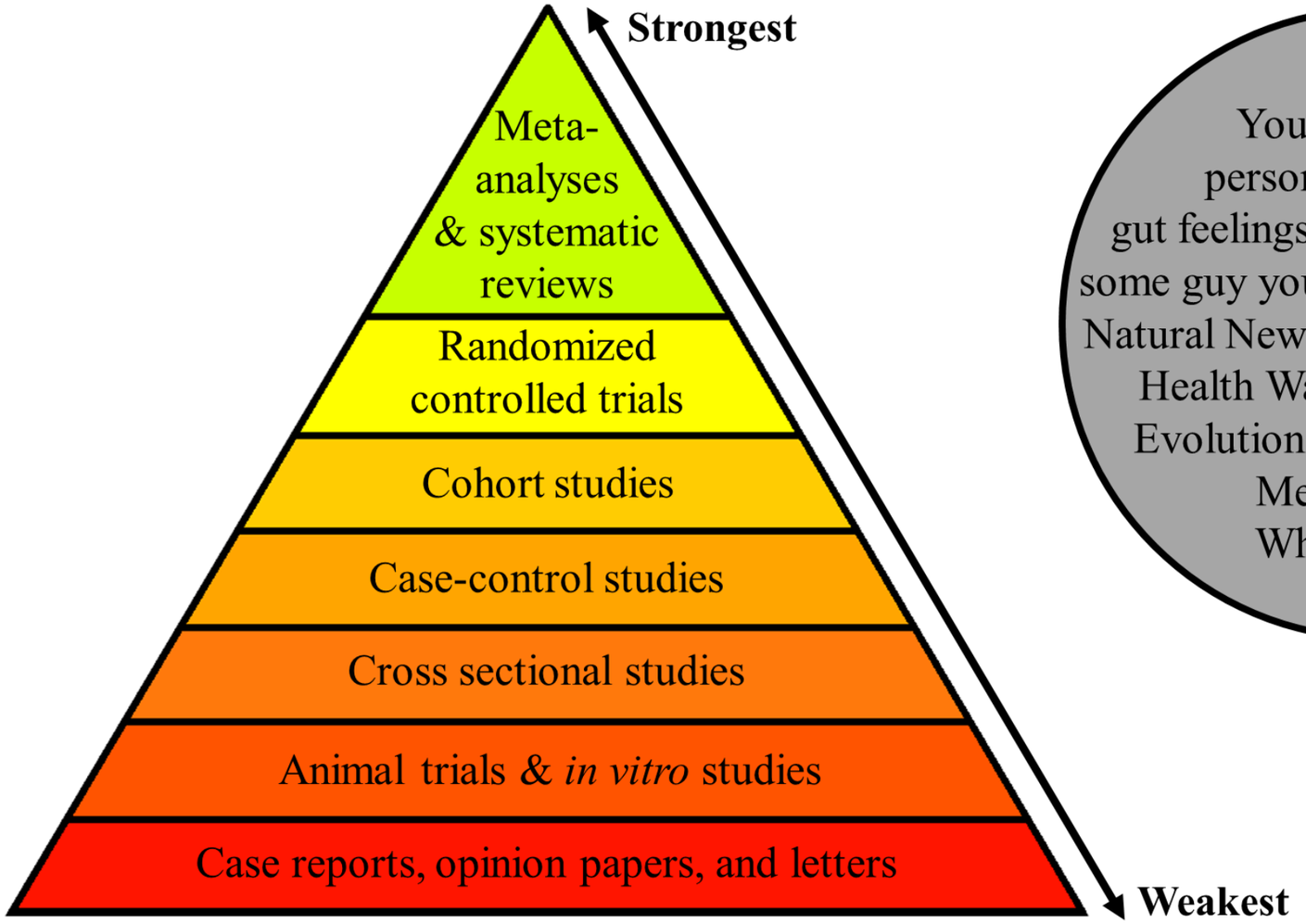
Our students include anyone who is interested, even ourselves. While we are developing this (and afterward as well), we invite your feedback on how we can make this better. Please put your insights, compliments and suggestions in the comments below (or on any other page).

Thanks,

Beth & Rahul

https://theebmproject.wordpress.com/

## Hierarchy of Scientific Evidence




## Not Scientific Evidence

Youtube videos, personal anecdotes, gut feelings, parental instincts, some guy you know, websites like Natural News, Info Wars, Natural Health Warriors, Collective Evolution, Green Med Info, Mercola.com, Whale.to, etc.

thelogicofscience.com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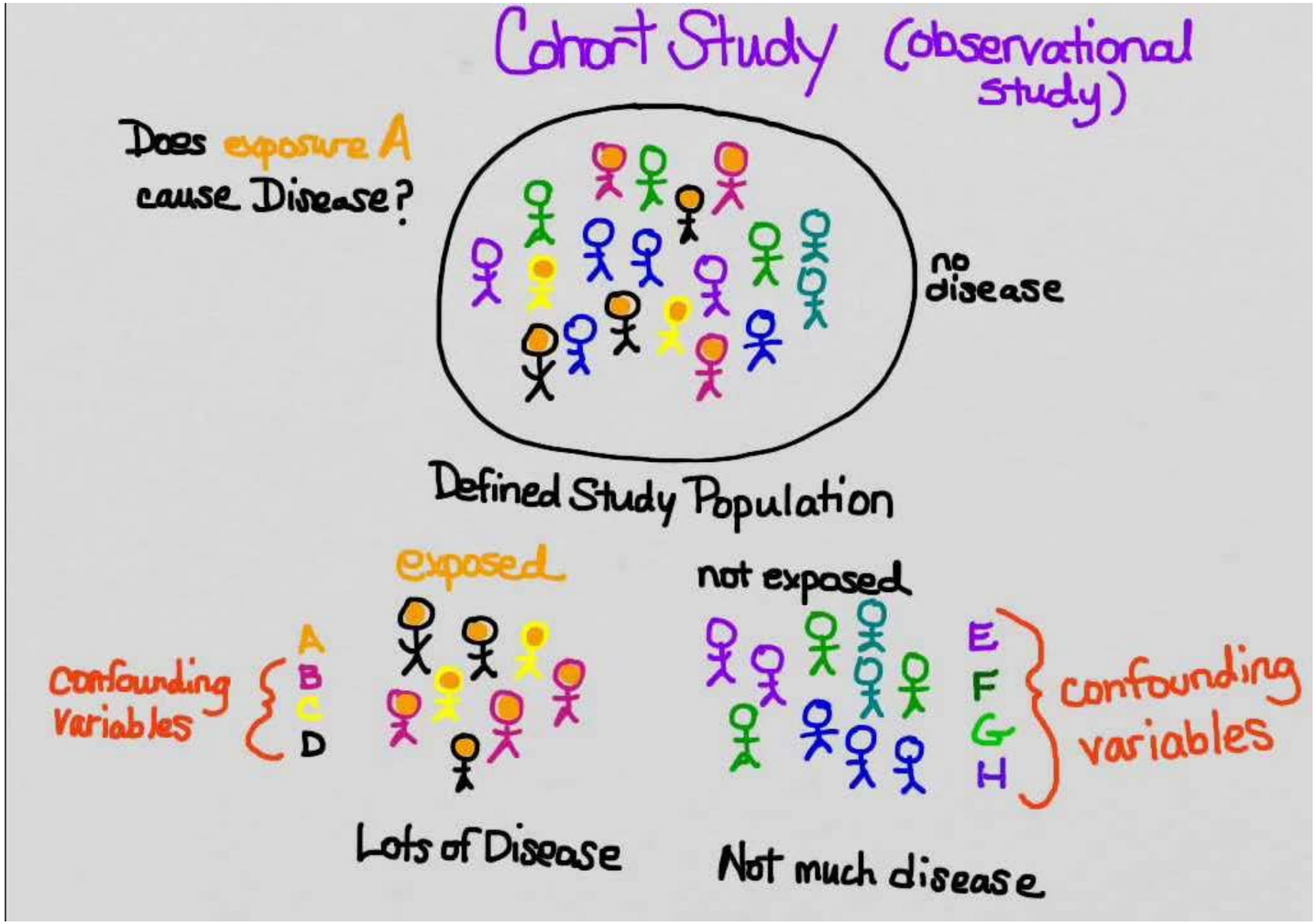
# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

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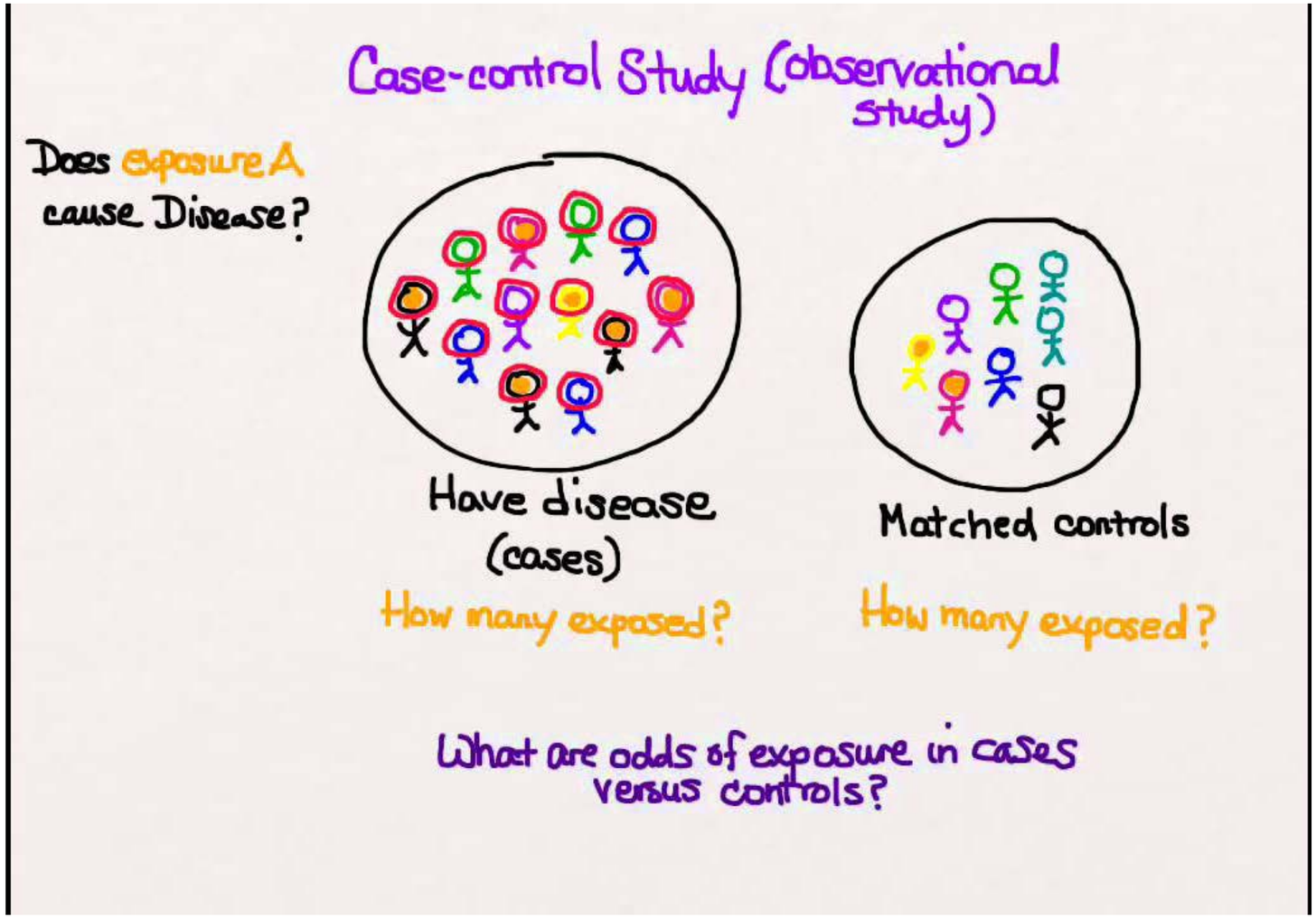


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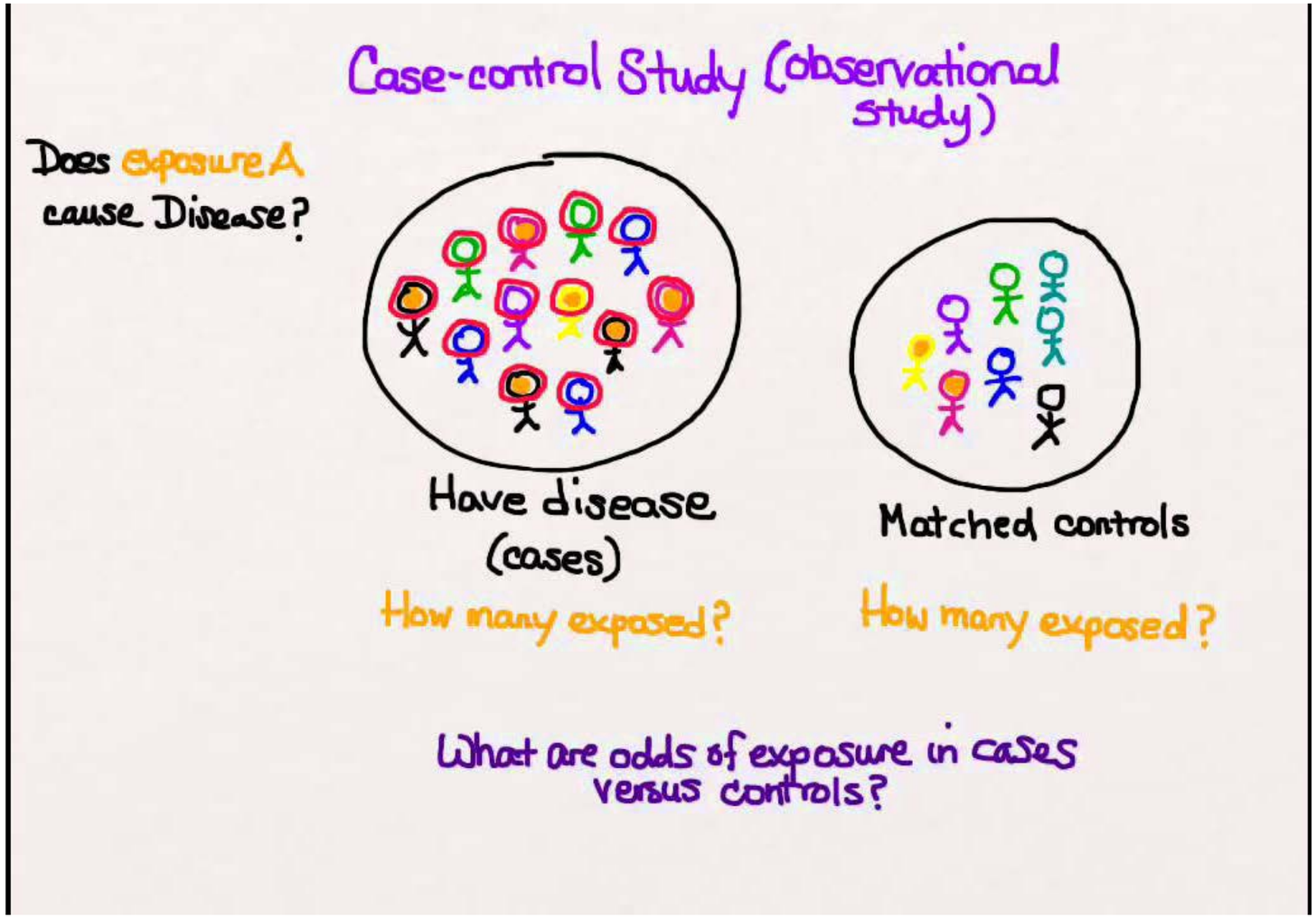


https://theebmproject.wordpress.com/


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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

Is selection bias present?

- In a cohort study, are participants in the exposed and unexposed groups similar in all important respects except for the exposure?
- In a case-control study, are cases and controls similar in all important respects except for the disease in question?

Grimes and Schulz, Bias and causal associations in observational research. *Lancet*. 2002, 359(9302):248-52.


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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

Is information bias present?

- In a cohort study, is information about outcome obtained in the same way for those exposed and unexposed?
- In a case-control study, is information about exposure gathered in the same way for cases and controls?

Grimes and Schulz, Bias and causal associations in observational research. *Lancet*. 2002, 359(9302):248-52.


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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

Is confounding present?

- Could the results be accounted for by the presence of a factor—eg, age, smoking, sexual behaviour, diet—associated with both the exposure and the outcome but not directly involved in the causal pathway?

Grimes and Schulz, Bias and causal associations in observational research. *Lancet*. 2002, 359(9302):248-52.


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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

If the results cannot be explained by these three biases, could they be the result of chance?

- What are the relative risk or odds ratio and 95% CI?
- Is the difference statistically significant, and, if not, did the study have adequate power to find a clinically important difference?

Grimes and Schulz, Bias and causal associations in observational research. *Lancet*. 2002, 359(9302):248-52.


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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

**If the results still cannot be explained away, then (and only then) might the findings be real and worthy of note.**

Grimes and Schulz, Bias and causal associations in observational research. *Lancet*. 2002, 359(9302):248-52.


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# Practice Time☺

**Abheiden** et al. Hypertensive disorders of pregnancy appear not to be associated with Alzheimer's Disease *Dementia and Cognitive Disorders.* 2015;5:375-385.

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# WHAT TO LOOK FOR IN OBSERVATIONAL STUDIES

- What type of study is this?
- Is selection bias present?
- Is information bias present?
- Is confounding present?
- If the results cannot be explained by these 3 biases, could they be the result of chance?
- What would you conclude re: evidence?


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# IS THERE ANY EPIDEMIOLOGIC EVIDENCE?

- **Only two** studies, both conducted in the **past year**:

**Case control study**

## Hypertensive Disorders of Pregnancy Appear Not to Be Associated with Alzheimer's Disease Later in Life

Abheiden, *Dement Geriatr Cogn Disord Extra* 2015;5:375–385

| | Women with AD (n = 104[a]) | Women without AD (n = 129[a]) | p |
|---|---|---|---|
| Hypertensive disorders of pregnancy | 15 (14.4) | 36 (27.9) | 0.11[a, b] |
| Pregnancy-induced hypertension | 11 (10.6) | 32 (24.8) | 0.03[a, b] |
| Preeclampsia | 4 (3.8) | 4 (3.1) | 1.00[a, b] |
| Eclampsia | 0 | 0 | – |

Data are presented as n (%). [a] After correction for age and BMI. [b] $\chi^2$.

# IS THERE ANY EPIDEMIOLOGIC EVIDENCE?

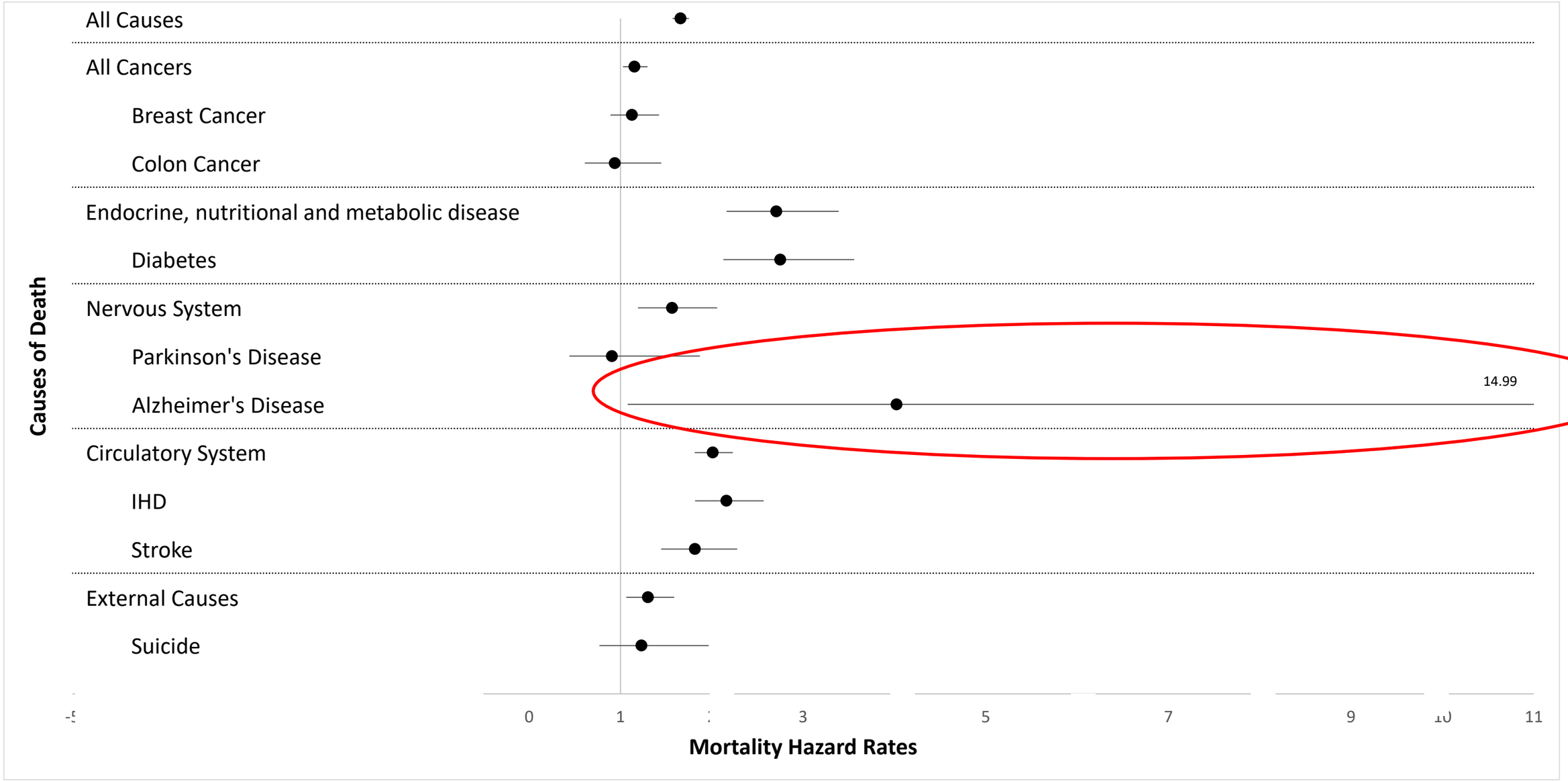
- **Only two** studies, both conducted in the **past year**:

All-Cause and Cause-Specific Mortality After Hypertensive Disease of Pregnancy

Theilen, Obstet Gynecol. 2016;128(2):238-244

**Retrospective cohort of UPDB death records. 60,850 exposed (PIH) women matched to 123,140 unexposed women (no PIH) by age, year of childbirth (cohort effect), and parity.**

# Risks of All-Cause and Cause-Specific Mortality Associated with Preeclampsia




• Hazard Ratios and 95% Confidence Intervals Estimated with Cox Regressions

| Risk of Mortality due to Alzheimer's Disease by Hypertensive Pregnancy Status | | |
|---|---|---|
| Exposure | n (%) | HR (95% CI) |
| **Unexposed** | 19 | |
| **Eclampsia** | 1 | 1.00 (0.03, 30.40) |
| **Preeclampsia** | 16 | 4.02 (1.08, 14.99) |

# Perfect Partnerships

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# PUBLICALLY AVAILABLE DATASETS

- Link between self-reported life stress(partner-related, traumatic, financial and emotiona development of preterm birth, small for gestational age, and preeclampsia.
- Maternal Oral Health Prior to Conception and Adverse Birth Outcomes
- How hospital interventions can impact breastfeeding initiation and success
- Predictors of post partum depression in representative sample of Utah mothers.


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# SYSTEMATIC REVIEWS: PRISMA AND PROSPERO

- PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.
- PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome.

http://www.prisma-statement.org/

https://www.crd.york.ac.uk/PROSPERO


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# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

# SECONDARY DATA ANALYSIS OF EXISTING STUDIES WITH UTAH MOTHERS AND CHILDREN

*Original Research*

**Trying to Conceive After an Early Pregnancy Loss**

*An Assessment on How Long Couples Should Wait*

*Karen C. Schliep, PhD, Emily M. Mitchell, PhD, Sunni L. Mumford, PhD, Rose G. Radin, PhD, Shvetha M. Zarek, MD, Lindsey Sjaarda, PhD, and Enrique F. Schisterman, PhD*

**Sexual and physical abuse and gynecologic disorders**

**K.C. Schliep[1,2,*], Sunni L. Mumford[2], Erica B. Johnstone[3], C. Matthew Peterson[3], Howard T. Sharp[3], Joseph B. Stanford[1], Zhen Chen[2], Uba Backonja[4], Maeve E. Wallace[5], and Germaine M. Buck Louis[2]**

EAGeR
The Effects of Aspirin in Gestation & Reproduction

>80% enrollees from UT in both the EAGeR and ENDO Studies☺

ENDO


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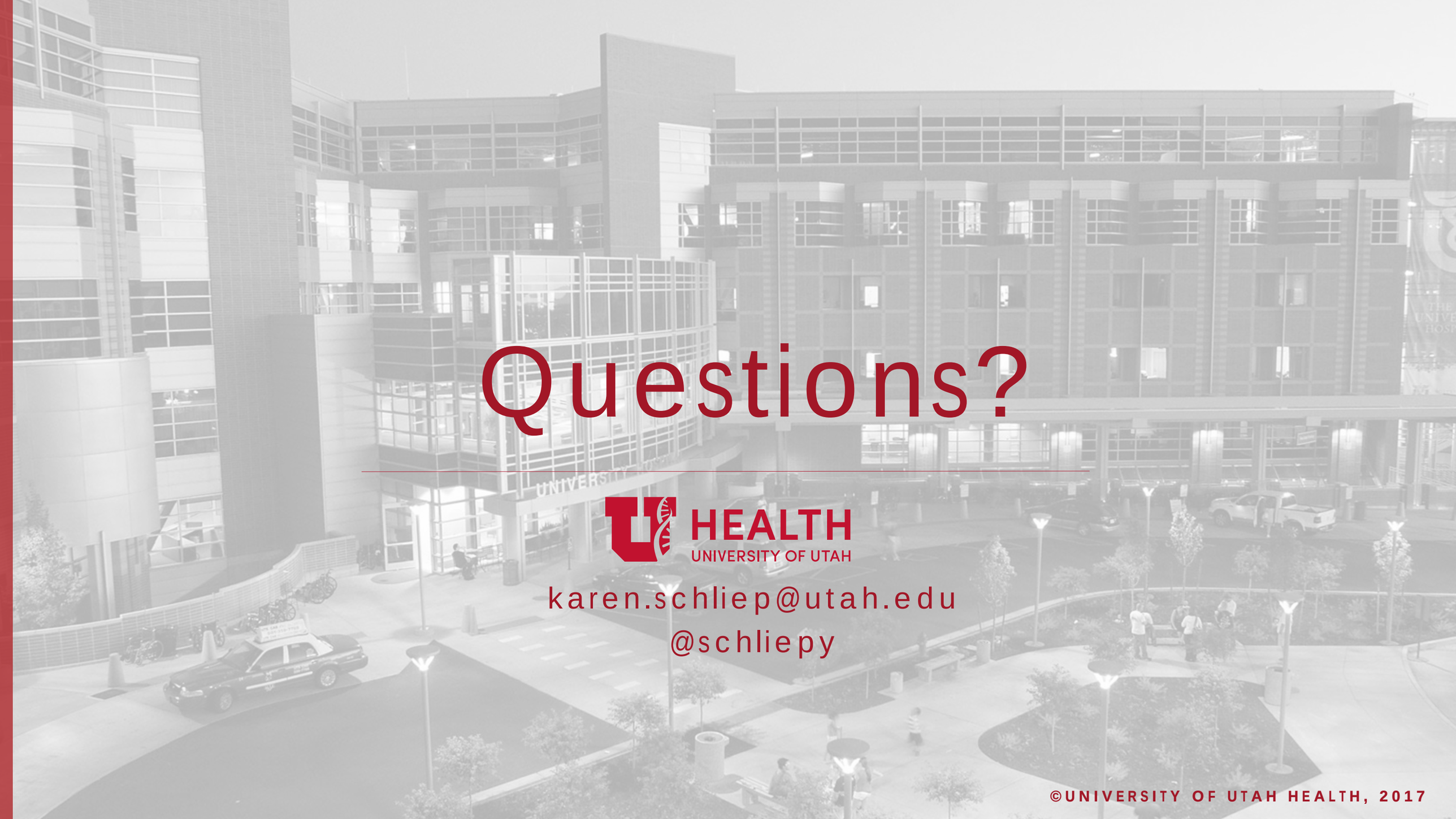

# Questions?

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