



# The Role of Estradiol in Modifying Circadian Rhythms, Sleep Regularity, and Risk for Depression During the Pubertal Transition

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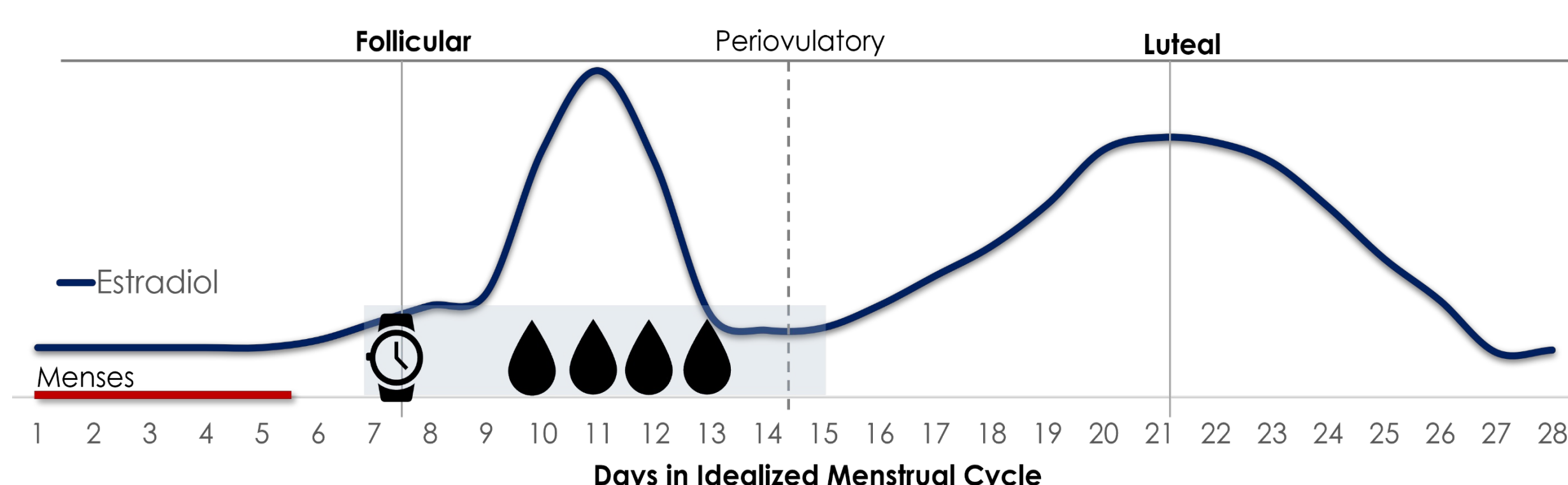
## Introduction

- During the pubertal transition (mid-puberty):
  - dramatic reproductive hormone fluctuations<sup>1</sup>
  - developmental circadian delay
  - significant changes in sleep/wake patterns<sup>2</sup>
- Starting at puberty, female adolescents are **3x more likely to develop depression<sup>3</sup>** and **2x more likely to experience sleep disorders<sup>4</sup>** compared with males = involvement of sex hormones
- Greater sleep irregularity is associated with affective impairment<sup>5</sup>

## Objective

Characterize the pathophysiological impact of estradiol on sleep disturbances, endocrine rhythm dysregulation, and depressive symptoms in peripubertal female adolescents

## Methods



### Enrollment

- Female adolescents 11-14 years old
- Within 1-year post-menarche
- Chronotype preference<sup>a</sup>

### Menstrual Cycle 1

- Daily E1G<sup>b</sup> via dried urine
- Weekly CES-DC<sup>c</sup> and PROMIS sleep measures<sup>d</sup>

### Menstrual Cycle 2

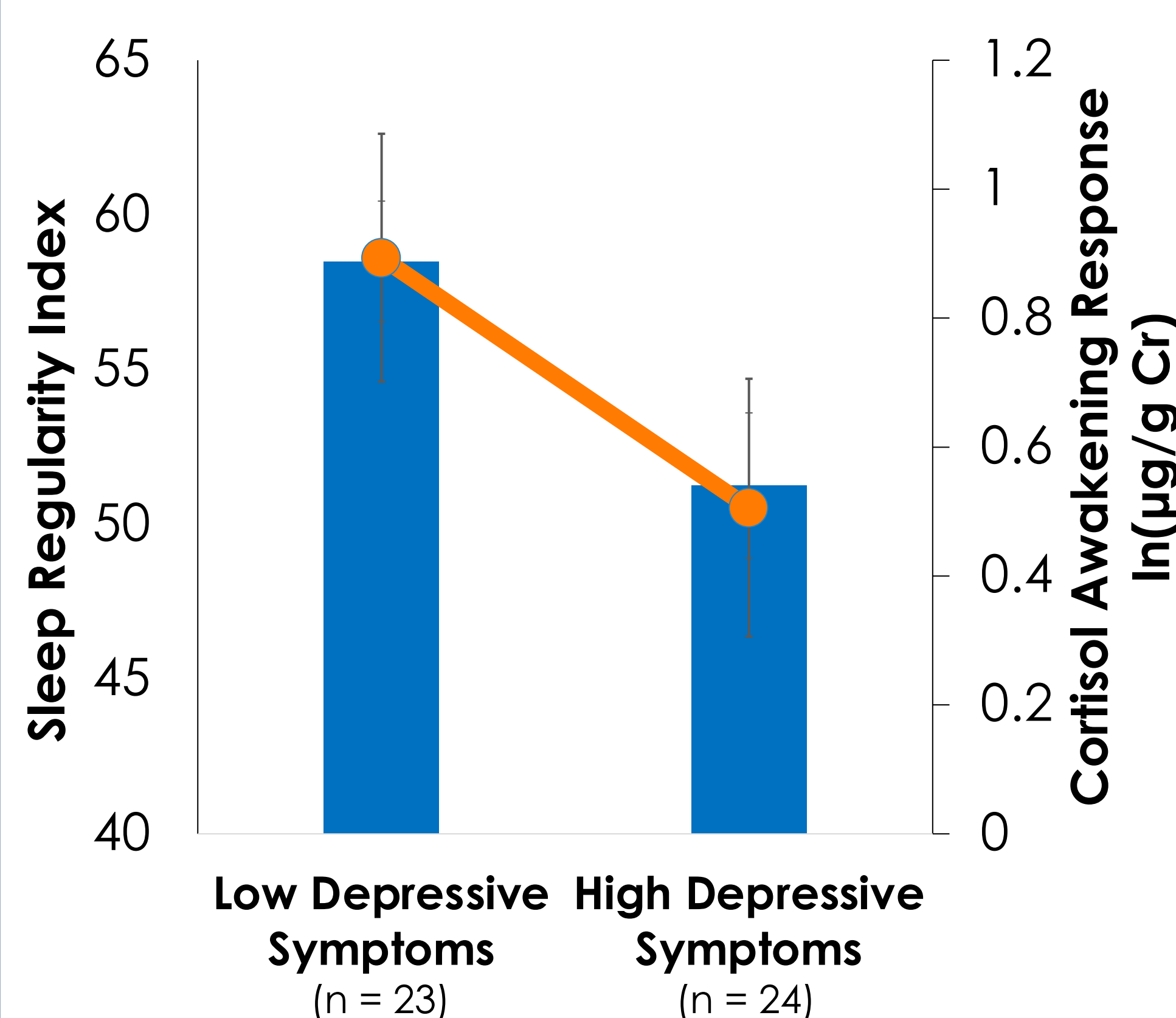
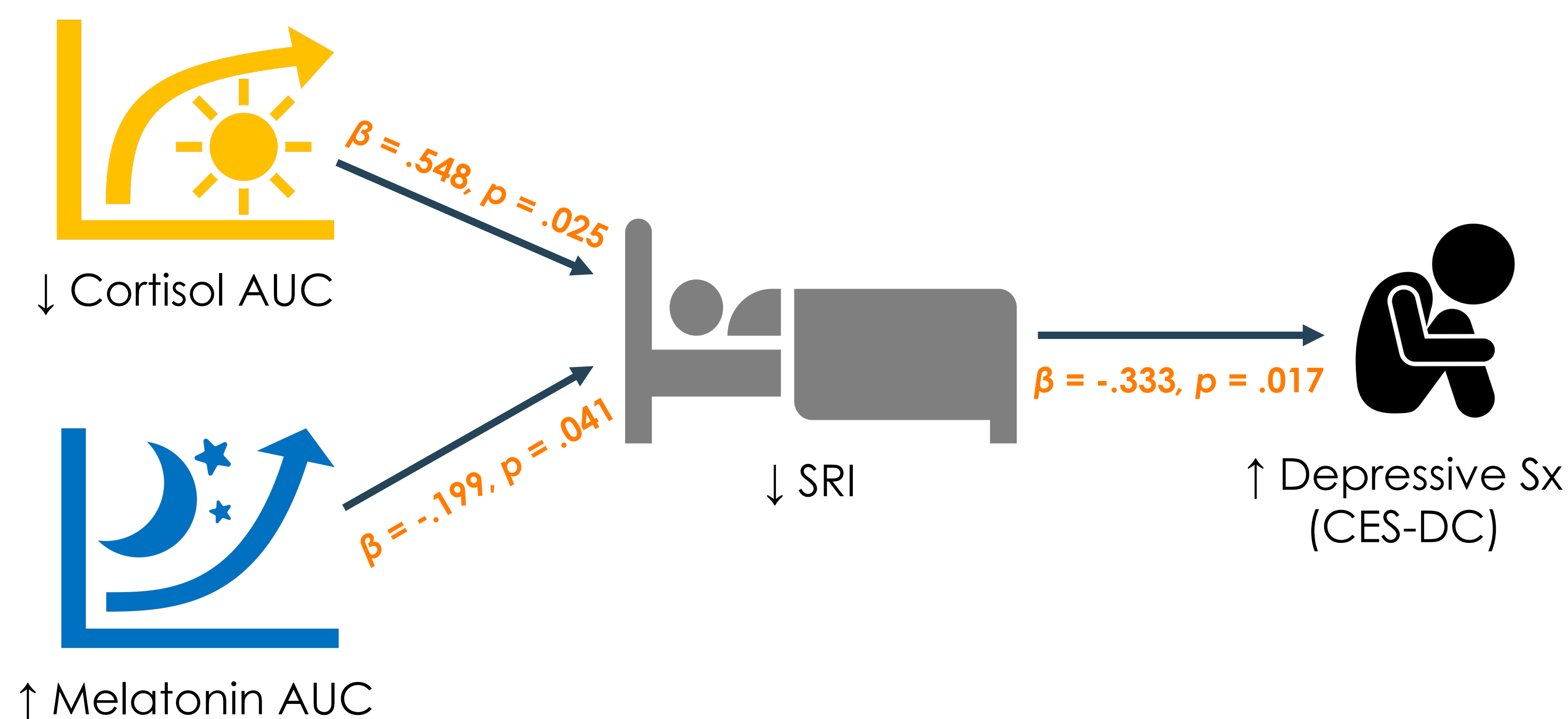
- Daily actigraphy<sup>e</sup> starting day 7
- Daily cortisol<sup>f,g</sup> and melatonin<sup>f</sup> via dried urine days 9-12

### Measures

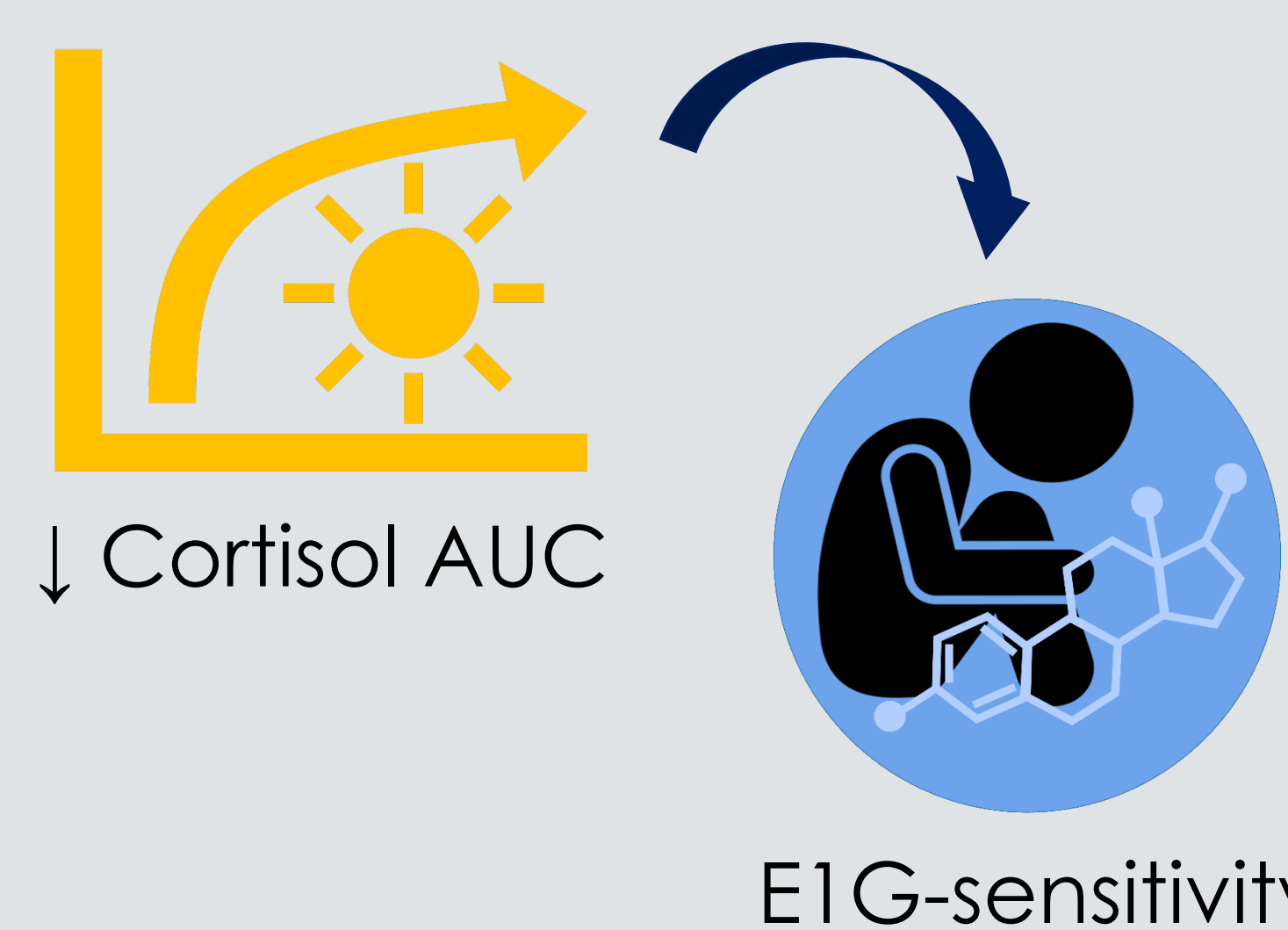
- Superscience Morningness/Eveningness Scale<sup>6</sup>**: scored 10–42, with higher scores indicating morningness preference and lower scores indicating eveningness preference; measure of chronotype
- E1G**: urinary metabolite of estradiol, collected once each morning; sensitivity analysis<sup>7</sup> determined mood sensitivity to E1G change
- Center for Epidemiological Studies Depression Scale for Children (CES-DC)<sup>8</sup>**: scored 0–60, with higher scores indicating greater depressive symptoms; used max score from weekly ratings
- PROMIS sleep measures<sup>9</sup>**: Sleep-Related Impairment and Sleep Disturbance surveys; higher scores indicate greater sleep impairment and disturbance, respectively; used max score from weekly ratings
- Sleep Regularity Index (SRI)<sup>10</sup>**: scored 0–100, with higher scores indicating more regular sleep; calculated from actigraphy scores
- Cortisol and melatonin AUC**: calculated from 4 samples collected just after waking, 30 min after waking, at dinnertime, and before bedtime
- Cortisol Awakening Response**: calculated from slope between first two time points of the day

## Results

Blunted cortisol and increased melatonin predict greater sleep irregularity, which further predicts depressive symptoms



Blunted cortisol predicts increased depression sensitivity to change in E1G ( $\beta = -.011, t = -3.432, p = .002$ )



Greater sleep irregularity, blunted cortisol, and increased melatonin may contribute to increased depressive symptoms in peripubertal female adolescents

## Participant Characteristics (n=47)

	Range	Mean (SD)
Age (years)	11–14	12.9 (1.0)
Chronotype Preference	14–39	27.3 (4.7)
Max Sleep-Related Impairment	37.9–73.2	56.8 (6.8)
Max Sleep Disturbance	45.9–72.6	58.4 (7.0)
SRI*	32.8–70.6	54.6 (11.0)
Max CES-DC**	4–41	19.5 (10.0)

\*In an adult study, SRI < 60.8 indicated irregular sleep<sup>10</sup>  
 \*\*CES-DC > 15 indicates clinically significant depressive symptoms<sup>8</sup>

**66% White, 13% Black or African-American, 9% Asian, 11% more than one race, 2% other; 11% Hispanic and/or Latina**

All participants were enrolled after onset of the COVID-19 pandemic.

## Discussion

- Results provide insight into the impact of COVID-19 on sleep and mood in female adolescents
- Approaches that aim to improve consistency of sleep schedules, such as light therapy, may be a promising treatment target for adolescent depression
- Disruptions in HPA diurnal rhythms may predict who is mood sensitive to changes in estradiol

## Acknowledgments

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**References:** 1. Walker et al., 2004; 2. Janfaza et al., 2006; 3. Angold, 1993; 4. de Zambotti et al., 2018; 5. Manglick et al., 2013; 6. Carskadon et al., 1993; 7. Andersen et al., 2022; 8. Faulstich et al., 1986; 9. NIH Toolbox; 10. Lunsford-Avery et al., 2018