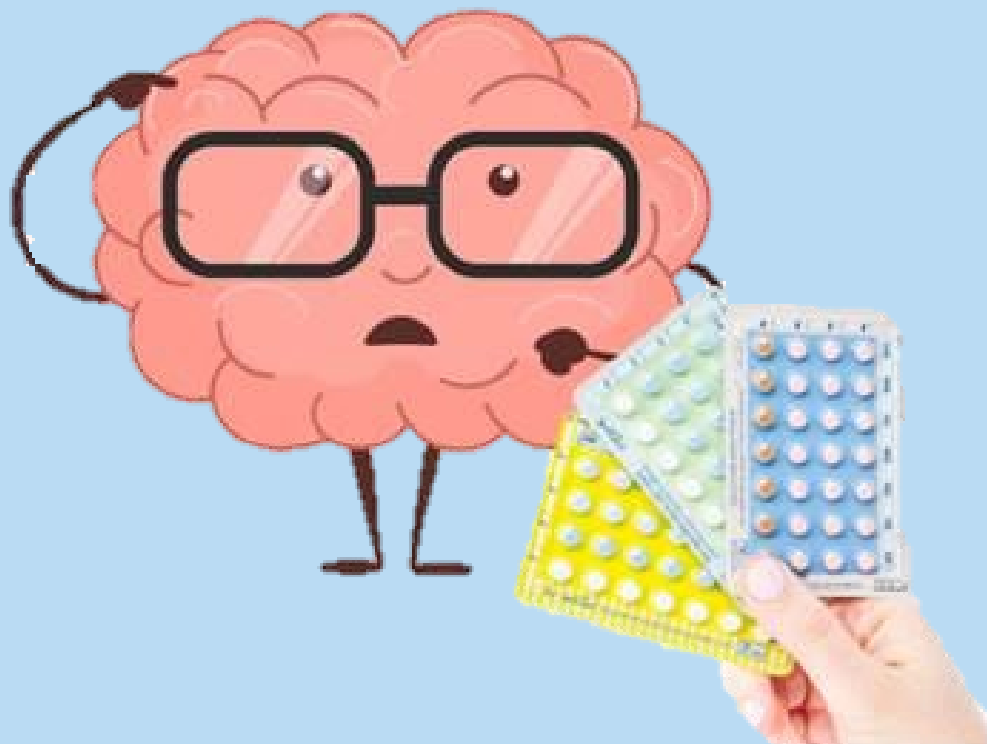


Hormonal Contraceptive Use & Depression

Unintended consequences, biological mechanisms, and precision medicine approaches to women's health

Summer Mengelkoch, PhD



What are Hormonal Contraceptives (HCs)?



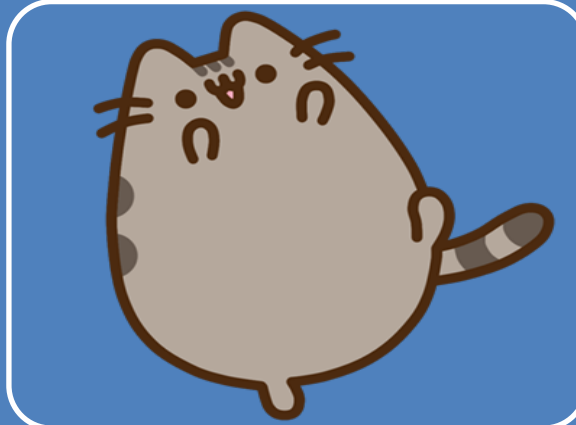
- HCs prevent pregnancy through hormonal administration of estradiol and/or progestins
- 200+ products on the market today
 - Pills, patches, shots, implants, intrauterine devices (IUDs)
- HCs are widely used:
 - >300 million HC users worldwide
 - Used by >80% of reproductive-aged women in the US at some point in their lives
- HCs are safe and effective
 - HCs have many positive effects on women's health, mental health, and well-being

Unintended Consequences of HC Use



- Common hormonal contraceptive (HC) related side effects include:
 - Weight gain, mood changes, decreased sexual desire, & acne
- HC use impacts women's psychologies & behaviors:
 - Memory, emotional processing, libido, neural reward reactivity, stress reactivity, & mood

Do HCs Increase Depression Risk?



HC use is associated with reduced depression risk

- Population study: Toffol et al., 2012
- For some women: e.g., Cheslack-Postava et al., 2015; Rasgon et al., 2003
- For some periods of HC treatment: e.g., Lundin et al., 2017



No meaningful effects of HCs on depression (with caveats for adolescents and high -risk groups)

- Review & meta-analysis: de Wit et al., 2021
- Population study: Lundin et al., 2022
- Progestin only review: Worley et al., 2018



HC use associated with increased depression risk

- Population studies:
 - Particularly for adolescents: Skovlund et al., 2016
 - Causal evidence, new HC users: Johansson et al., 2023
- American college students: Gregory et al., 2018

Why is HC Research Inconsistent?

Person-Specific Factors

- Age
- Age of onset & duration of use
- Mental health history
 - Genetic predispositions
- Current and early life stress
- Physical health history
- Nutrition

HC-Specific Factors

- Progestin type
- Mode of administration
- Dosages



Methodological Issues

- Causality
 - Self-selection
 - Survivorship biases
- Mean differences obscure heterogeneity in responses
- Silo effects
- Theoretical gaps: understanding depression



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne



Moving beyond the mean: Promising research pathways to support a precision medicine approach to hormonal contraception

Sarah E. Hill^{1,*}, Summer Mengelkoch

¹Texas Christian University, United States



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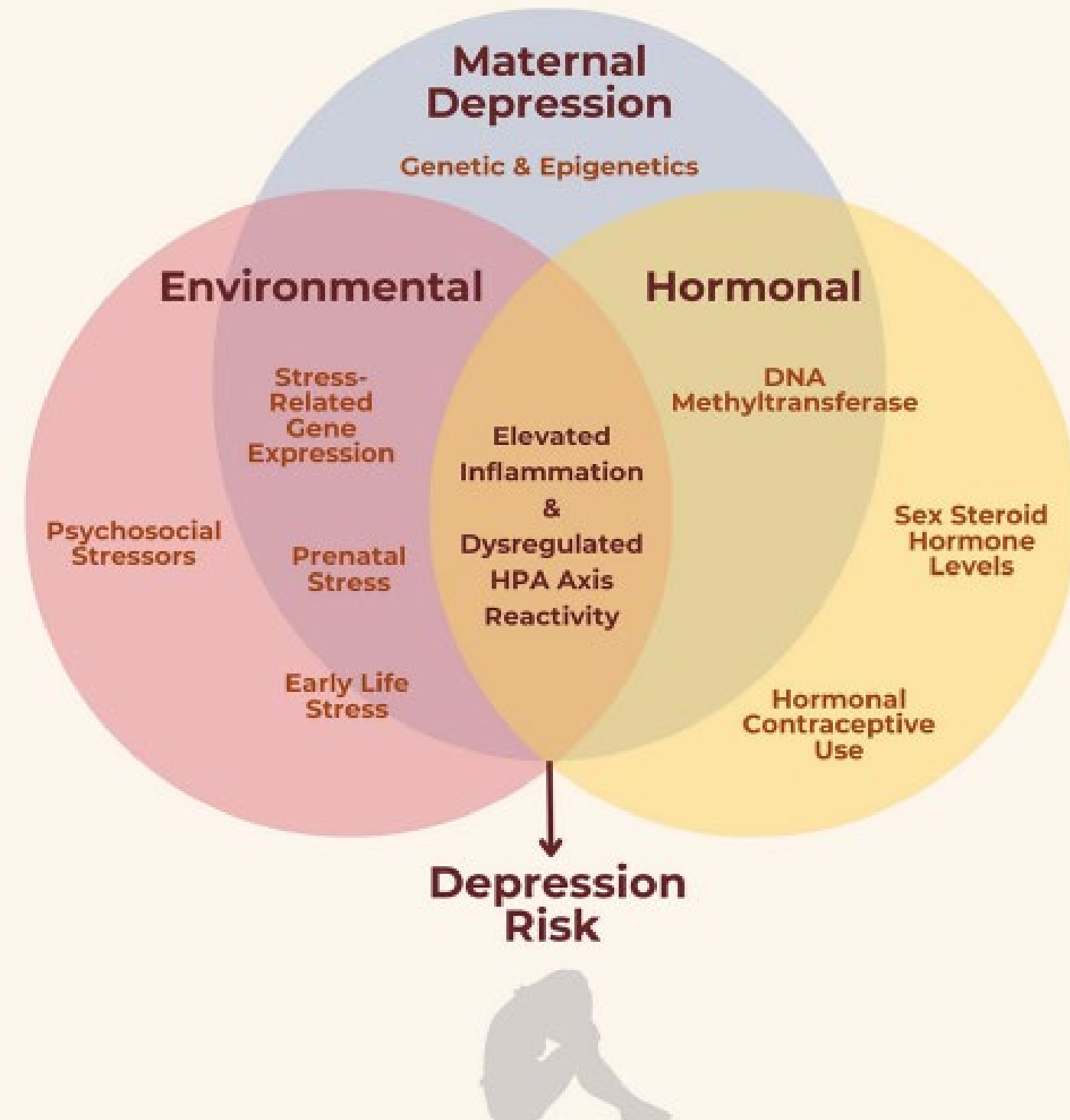
Sarah E. Hill^{1,*}, Summer Mengelkoch

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Sex Differences in Depression Risk

- Women twice as likely to experience depression (vs. men) from puberty until post-menopause
 - Risk is greater during hormonal transitions
- Stress predicts depression



Overlapping mechanisms contributing to high rates of female depression

Current Psychiatry Reports (2024) 26:157–165
<https://doi.org/10.1007/s11920-024-01490-8>

REVIEW

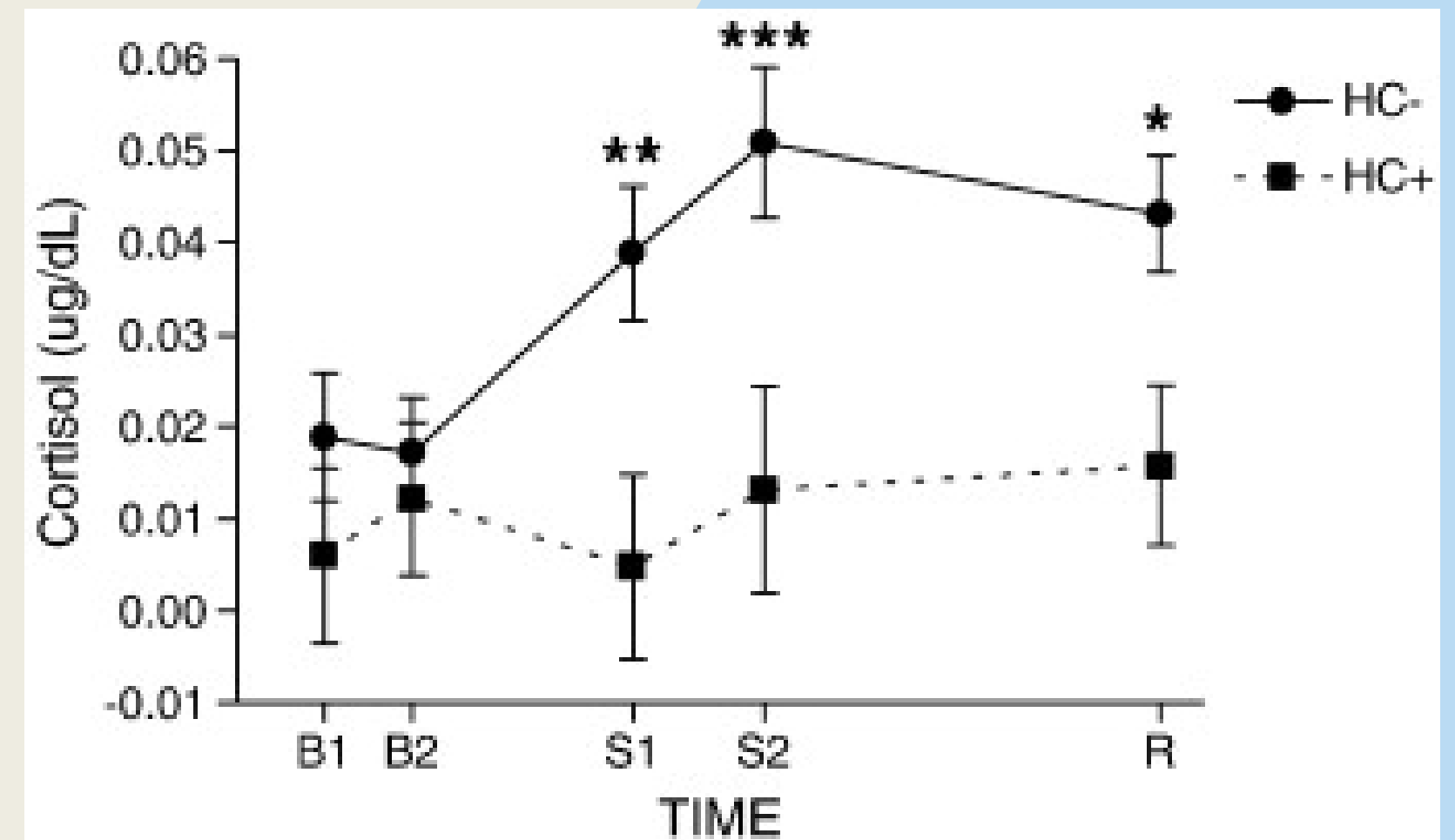


Sex Differences in Stress Susceptibility as a Key Mechanism Underlying Depression Risk

Summer Mengelkoch¹ · George M. Slavich¹

HC Users Have a Blunted Cortisol Response to Acute Stress

- Women taking HCs exhibit a blunted cortisol response to:
 - Social stress tasks, the cold-pressor & socially evaluated cold-pressor tests, & Naltrexone (a drug that increases cortisol levels when administered)



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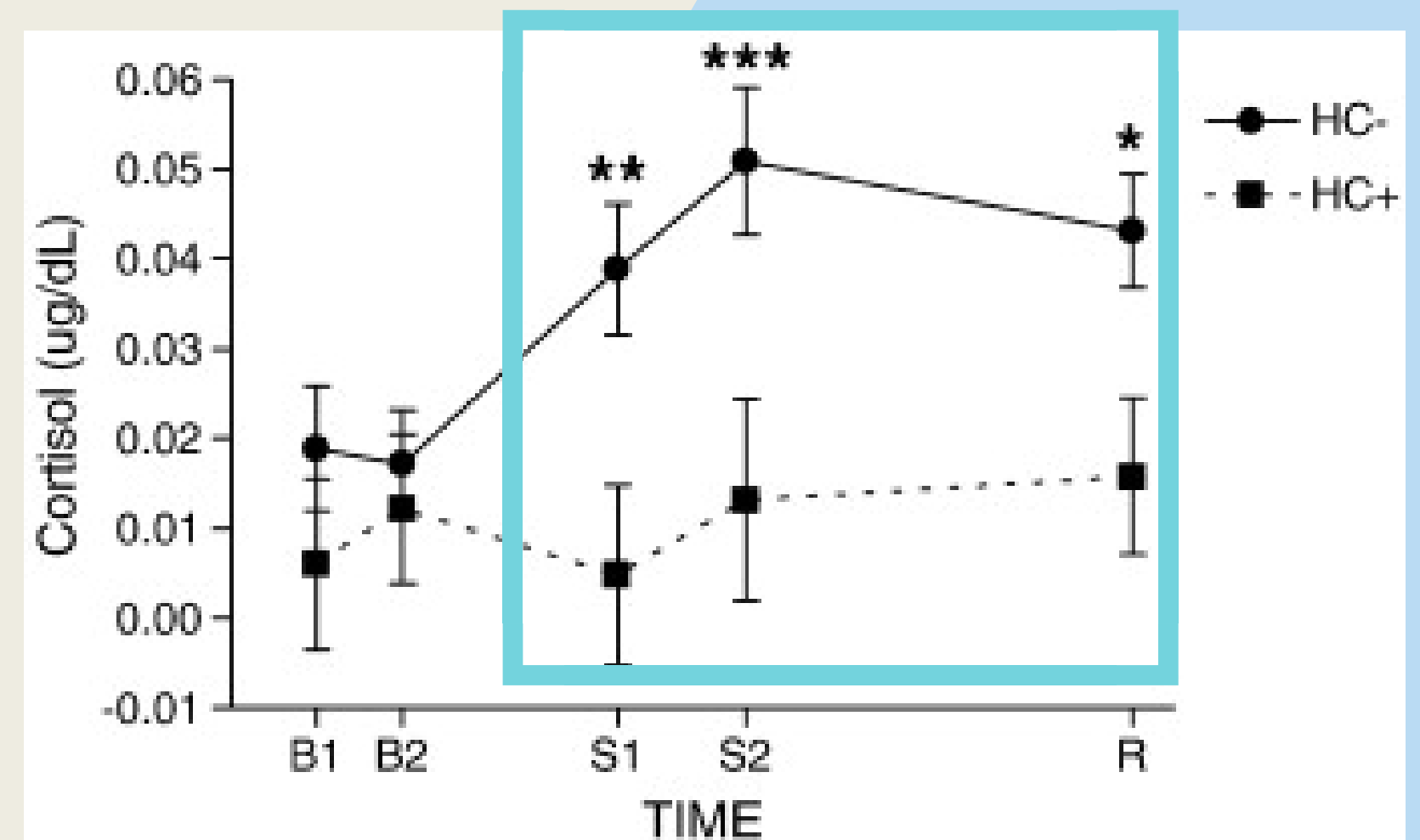
Hormonal contraceptive use diminishes salivary cortisol response to psychosocial stress and naltrexone in healthy women

Daniel J.O. Roche^{a,b}, Andrea C. King^{a,b}, Andrew J. Cohoon^{c,d}, William R. Lovallo^{c,d,*}

^a Department of Psychiatry and Behavioral Sciences, University of Chicago, Chicago, IL 60637, USA
^b Committee on Neurobiology, University of Chicago, Chicago, IL 60637, USA
^c Behavioral Sciences Laboratories, VA Medical Center, Oklahoma City, OK 73104, USA
^d Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, USA

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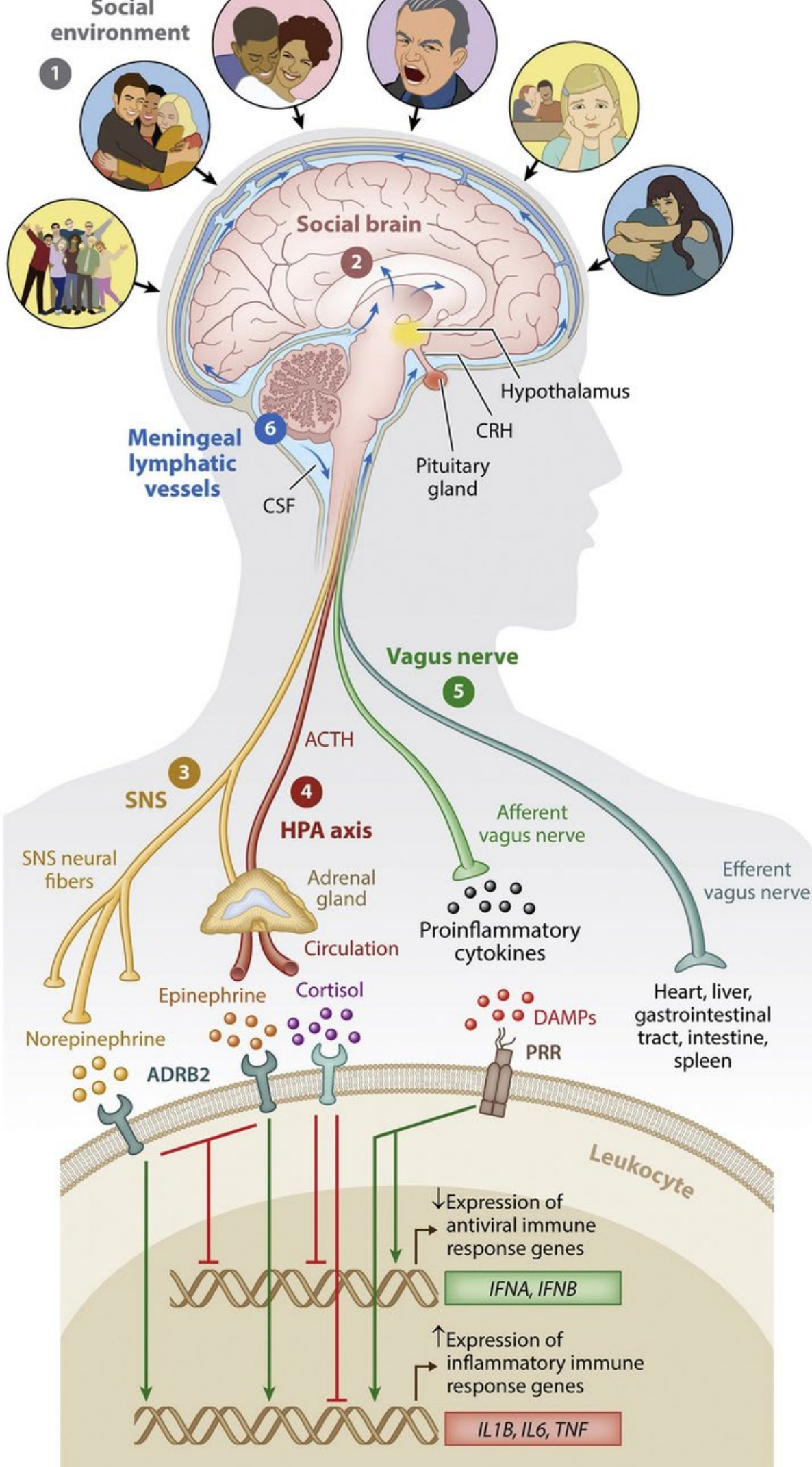
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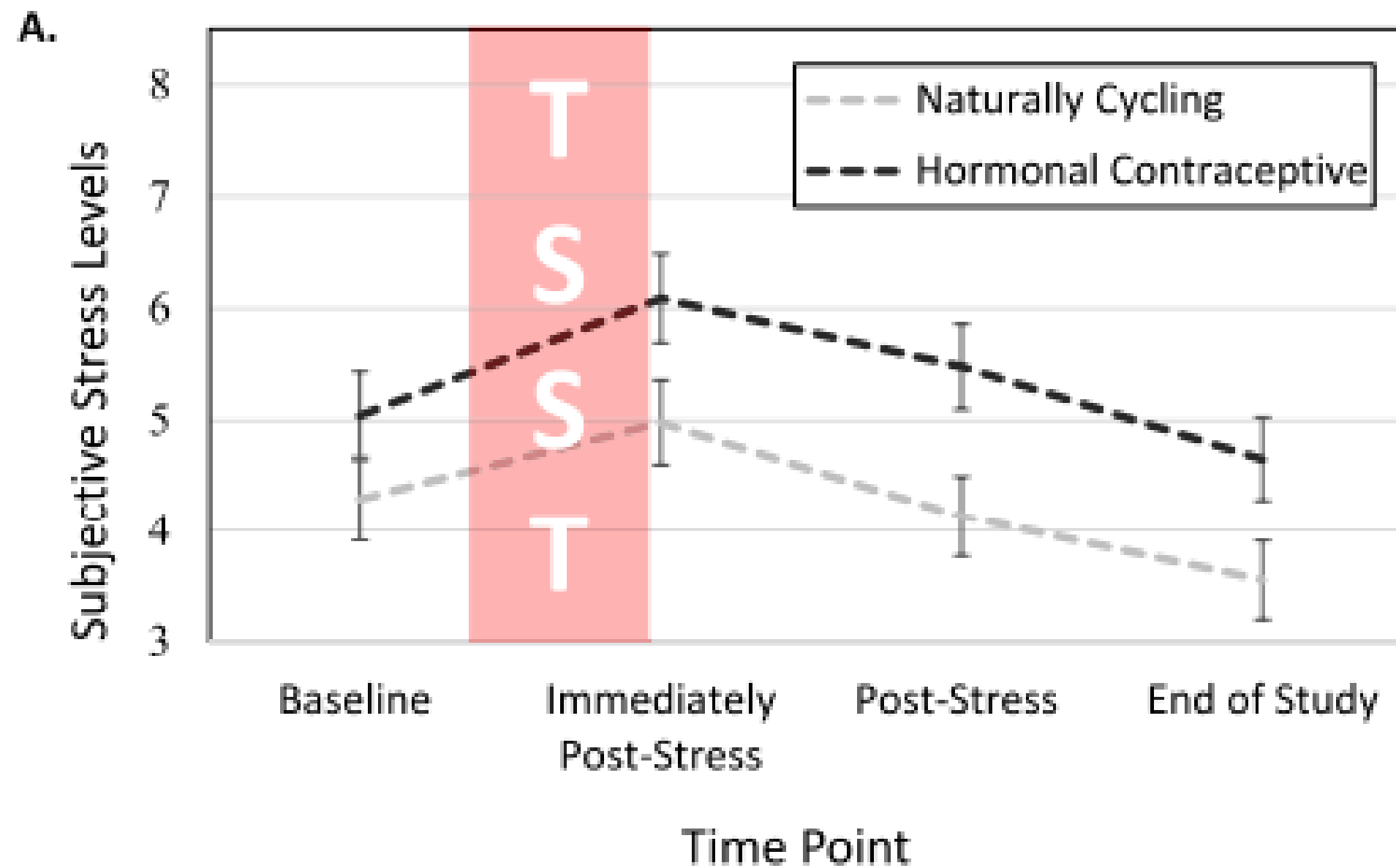
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HC Use & Inflammation

- HC users have elevated C -reactive protein (CRP), a marker of systemic inflammation, compared to naturally cycling women
 - Elevated CRP increases risks for cardiovascular disease, depression, & many diseases of aging
- HC users do not exhibit elevated basal levels of proinflammatory cytokines
- HC users have an altered cortisol response to stress
 - Do HC users have an altered inflammatory response to stress?

HC Users Report More Stress



Descriptive Statistics for Participant Demographics of Data Analytic Sample (N = 127)

Variable	M (SD)
Age (18-37)	19.31 (1.95)
BMI (16.78-38.98)	21.94 (3.55)
Hormonal Contraceptive Use	
Naturally Cycling: 52.8% (n = 67)	
First Generation: 17.3% (n = 22)	
Second Generation: 8.7% (n = 11)	
Third Generation: 21.3% (n = 27)	
Race/Ethnicity	
White: 63.8% (n = 81)	
Black/African American: 3.1% (n = 4)	
Hispanic: 17.3% (n = 22)	
Asian/Pacific Islander: 6.3% (n = 8)	
Multiracial/Other: 9.5% (n = 12)	

Note. BMI = body-mass index.

HC Users have Different Inflammatory Stress Responses

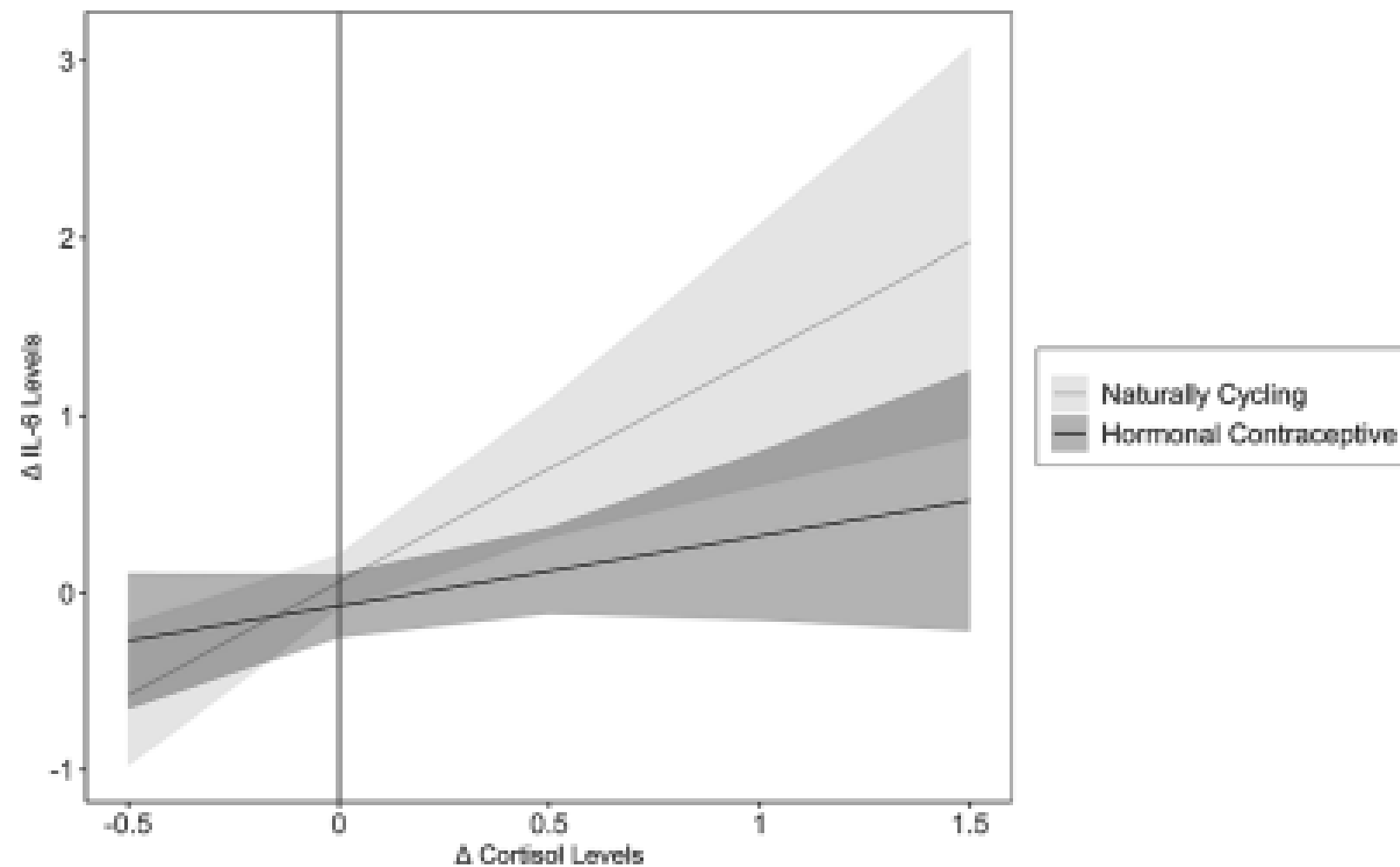


Fig. 3. Association between Changes in Cortisol and changes in IL-6, moderated by Hormonal Contraceptive Use. In naturally cycling women, cortisol changes and changes in IL-6 were positively associated with each other, whereas this was not the case for hormonal contraceptives users. IL-6 = interleukin-6. Shadows indicate 95% confidence intervals.

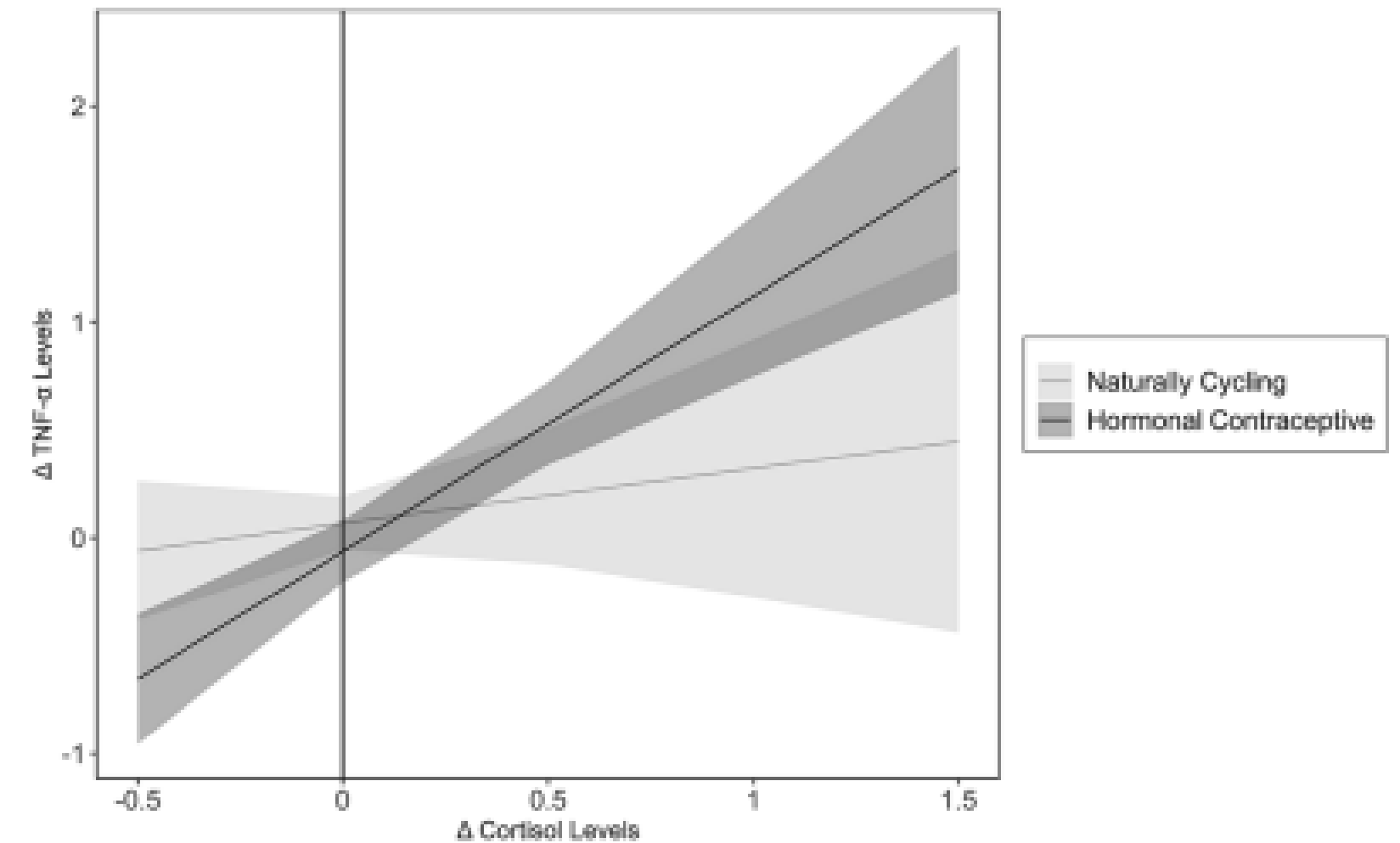


Fig. 4. Association between Changes in Cortisol and changes in TNF- α , moderated by Hormonal Contraceptive Use. In women using hormonal contraceptives, cortisol changes and changes in TNF- α levels were positively associated with each other, whereas this was not the case for naturally cycling women. TNF- α = tumor necrosis factor- α . Shadows indicate 95% confidence intervals.

HC Users Report Negative Mood with Cortisol Increase

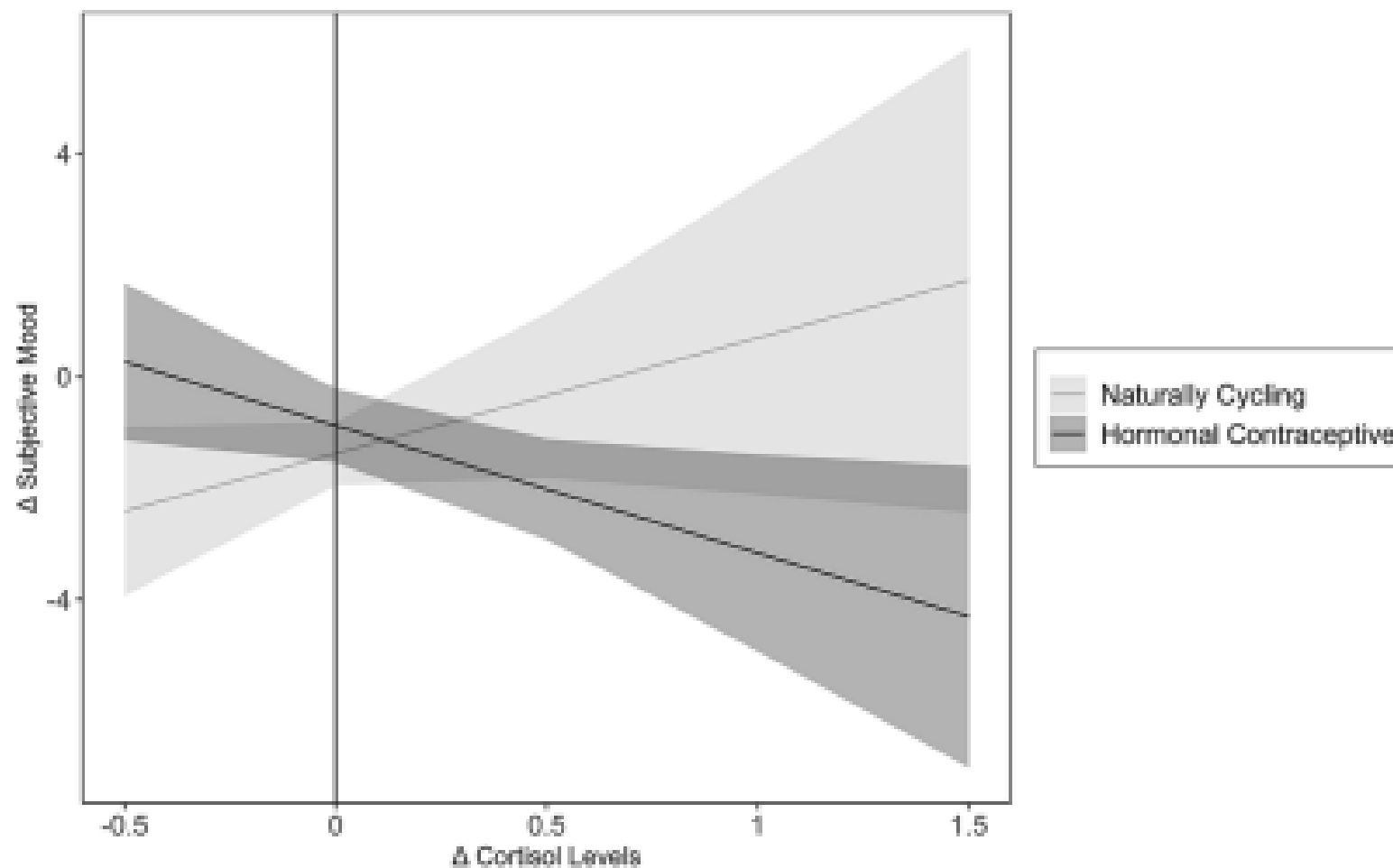
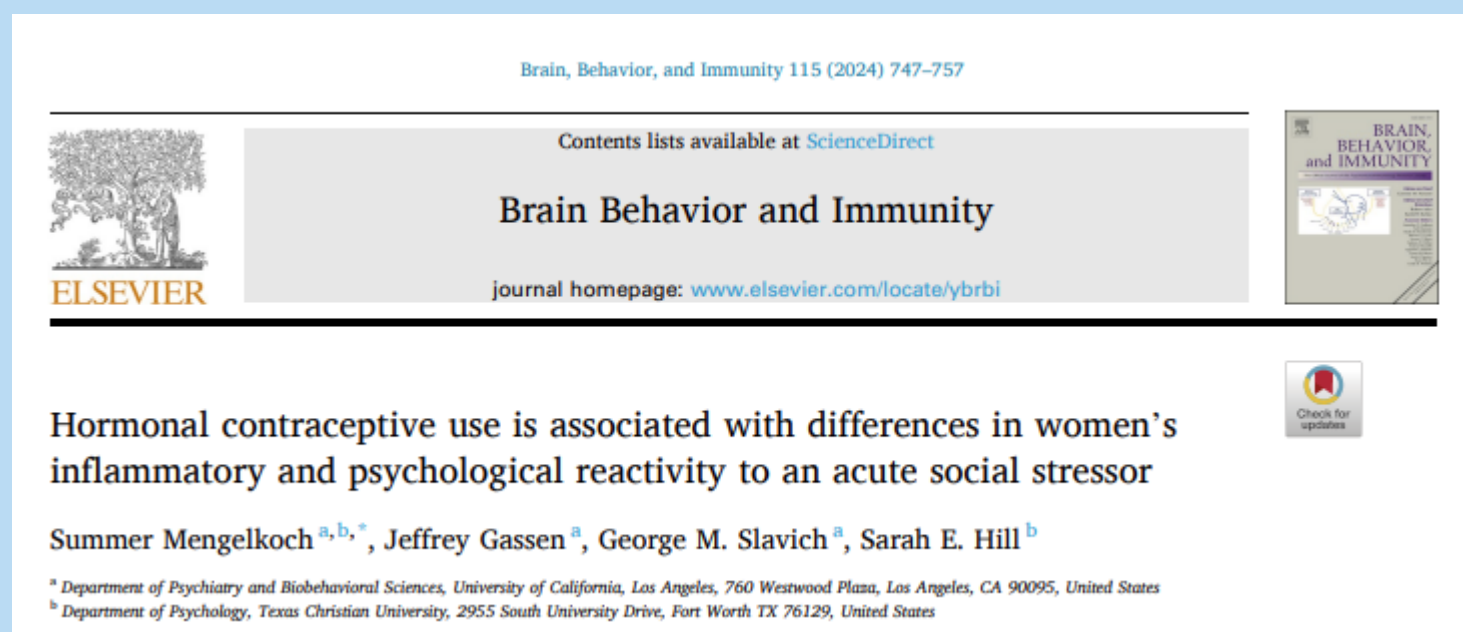


Fig. 5. Association between Changes in Cortisol and changes in subjective positivity of mood, moderated by Hormonal Contraceptive Use. In women using hormonal contraceptives, changes in cortisol and changes in subjective positivity of mood were negatively associated with each other, whereas the opposite pattern emerged for naturally cycling women. Shadows indicate 95% confidence intervals.

Take aways:

- Oral HC use impacts stress reactivity
- Altered stress reactivity may increase depression risk in HC users



Practical Implications

Mindful prescribing of HCs is necessary (weigh costs & benefits)

- Risk assessment at onset
- Monitor side effects for 3 -24 months
 - If side effects emerge, consider different contraceptive options
- Listen to and trust women




Box 2. Different types of HCs.

Type of Progestin	HC Type and Progestin Generation	Androgenic and Progestational effects	Metabolic Half-Life
Norethindrone/ Norethisterone acetate	1st gen oral HC; hormone therapy	Moderately androgenic, moderately progestational	34.8h
Ethinodiol acetate	1st gen oral HC; hormone therapy	Low androgenicity, highly progestational	N / A
Medroxy-progesterone acetate	Depo-Provera (injectable); 1st gen HC; hormone therapy	Moderate- to highly androgenic, highly progestational	40 – 60h
Levonorgestrel	2nd gen oral HC; Hormonal IUD; emergency contraception	Highly androgenic, highly progestational	26h
Norgestrel	2nd gen oral HC; hormone therapy	Highly androgenic, highly progestational	21h
Desogestrel / Etonogestrel	3rd gen oral HC; Nexplanon (implant); Nuva Ring (insertable); hormone therapy	Low androgenicity, highly progestational	23 – 25h
Gestodene	3rd gen oral HC; hormone therapy	Low androgenicity, highly progestational	12 – 15h
Norgestimate	3rd gen oral HC; hormone therapy	Low androgenicity, highly progestational	12 – 30h
Drospirenone	4th gen oral HC; hormone therapy	Anti-androgenic and little progestational activity	30h
Dienogest	4th gen oral HC; hormone therapy	Anti-androgenic and little progestational activity	10h

Note: gen=generation; HC=hormonal contraceptive.

A Precision Medicine Approach to Contraceptive Use

 TUUNE™

Your Focus

Birth Control

Pregnancy

Your Cycle

Medical History

What's your main goal?

If you're looking for emergency birth control, unfortunately we will not be able to help you. Please visit your local pharmacy or speak to your doctor as soon as possible.






















I'd like to start a new birth control

I have a hormone-related issue I'd like to improve

I'm just exploring my options and I'd love to understand my hormones better

BACK



Recommended	Alternative 1	Alternative 2
<div> Kariva Combined pill • 9 generic versions Ethinyl estradiol (0.02mg / 0mg / 0.01mg) Desogestrel (0.15mg / 0mg / 0mg)</div>	<div> Mirena Hormonal IUD • 2 generic versions Levonorgestrel (52mg)</div>	<div> Nuvaring Vaginal ring • 1 generic version Ethinyl estradiol (0.015mg) Etonogestrel (0.12mg)</div>
<div>✓ Could improve period pain</div>	<div>? May improve / worsen period pain</div>	<div>? May improve / worsen period pain</div>
<div>✓ May improve heavy / long periods</div>	<div>✓ May improve heavy / long periods</div>	<div>✓ May improve heavy / long periods</div>
<div>✓ May improve acne / spots</div>	<div>X May worsen acne / spots</div>	<div>X May worsen acne / spots</div>
<div>✓ May improve fatigue</div>	<div>✓ May improve fatigue</div>	<div>? Unknown for fatigue</div>
<div>✓ May improve anxiety</div>	<div>X May worsen anxiety</div>	<div>? Unknown for anxiety</div>
<div>X May worsen sleep quality</div>	<div>X May worsen sleep quality</div>	<div>X May worsen sleep quality</div>
<div>X May worsen breast tenderness</div>	<div>X May worsen breast tenderness</div>	<div>X May worsen breast tenderness</div>
<div>✓ May improve depression</div>	<div>X May worsen depression</div>	<div>? May improve / worsen depression</div>
<div>✓ May improve bloating</div>	<div>X May worsen bloating</div>	<div>? Unknown for bloating</div>
<div>✓ May improve mood changes</div>	<div>X May worsen mood changes</div>	<div>? May improve / worsen mood changes</div>
<div>✓ May improve PMS symptoms</div>	<div>X May worsen PMS symptoms</div>	<div>✓ May improve PMS symptoms</div>
<div> Take daily</div>	<div> Can last up to 7 years for pregnancy prevention</div>	<div> Lasts 3 weeks</div>
<div> You can have regular periods</div>	<div> You might have regular periods</div>	<div> You can keep your period but we recommend you skip them</div>
<div> 91% pregnancy prevention with typical use</div>	<div> 99.8% pregnancy prevention with typical use</div>	<div> 91% pregnancy prevention with typical use</div>
<div> No medical procedure needed</div>	<div> Medical procedure needed</div>	<div> No medical procedure needed</div>
<div> Blood clot risk of 9-12/10,000 women per year</div>	<div> Blood clot risk of 2/10,000 women per year</div>	<div> Blood clot risk of 9-12/10,000 women per year</div>
<div> Return to baseline fertility ~0 to 3 months after stopping</div>	<div> Return to baseline fertility ~0 to 2 months after stopping</div>	<div> Return to baseline fertility ~0 to 3 months after stopping</div>
<div>✓ Good option</div>	<div>✓ Good option</div>	<div>✓ Good option</div>
<div>More information about this option</div>	<div>More information about this option</div>	<div>More information about this option</div>

Comprehensive screening of goals, health history, reproductive health, informs personalized, physician reviewed recommendations



Mengelkoch et al. *BMC Digital Health* (2023) 1:36
<https://doi.org/10.1186/s44247-023-00034-z>

BMC Digital Health

RESEARCH

Open Access

Tuuned in: use of an online contraceptive decision aid for women increases reproductive self-efficacy and knowledge; results of an experimental clinical trial

Summer Mengelkoch¹, Matthew Espinosa¹, Stephen A. Butler², Laura Joigneau Prieto², Emma Russell², Chris Ramshaw², Shardi Nahavandi² and Sarah E. Hill^{1*}




Key Points

- Millions of women use HCs
 - We need to understand the unintended consequences of HC use
- Some HC use, in some women, is associated with increased depression risk
 - Altered stress reactivity in HC users is a potential mechanism through which HC use increases depression risk
- Practice mindful prescribing of HCs
 - Screen women for risk factors
- A precision medicine approach to HC treatment could:
 - Reduce healthcare burden on providers
 - Improve outcomes for HC users
 - Reduce the rates of depression in reproductive -aged women

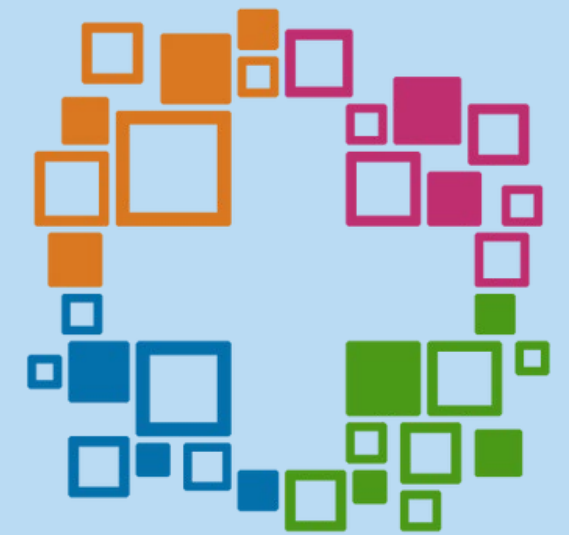




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California Initiative to Advance
Precision Medicine



Thank you!

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