CYP gene variants show preliminary evidence of association with patient-reported outcomes in active-duty service members with chronic pain

Nick Ieronimakis, PhD

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Disclosures

- I have no financial disclosures or conflicts of interests with presented material in this presentation.

- The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.

- The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.

Joint Base Lewis-McChord – Tacoma, WA

- Home to Armies I Corp and Air Force 62nd Airlift Wing
- 4th largest military population (2nd largest by area)
  - 290,251 personnel, 30,364 active-duty military (OnceSource.mil)

>120lb / 54kg

~100lb / 45kg

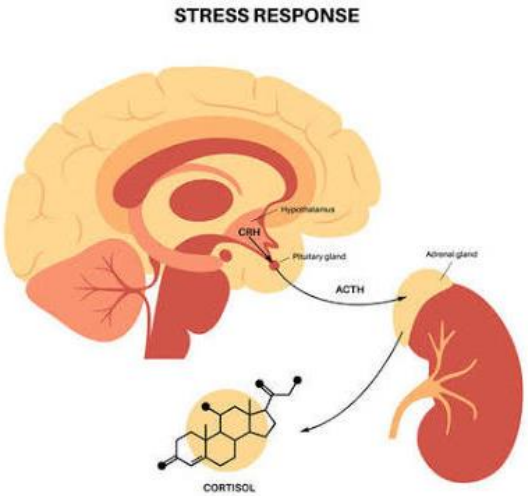
INTRODUCTION

- 1/3 of servicemembers experience chronic pain.
  - Impacts readiness, retention and quality of life
- Diagnosis of chronic pain is challenging
- Management relies primarily on self-reported measures
- Underlying mechanisms and individual factors unknown

BACKGROUND

- Chronic pain and stress intertwined
  - Lead to exaggerated psychological responses (catastrophizing)

- Heightened HPA activity or burnout
  - Primarily mediated by cortisol
  - Suppress anti-inflammatory responses
  - Linked to long term health effects
    - ✓ (diabetes, cardiovascular disease, hypertension)



BACKGROUND

Journal of Pain 33 (2025) 105458

Contents lists available at ScienceDirect

The Journal of Pain

journal homepage: www.jpain.org

Original Reports

Association of diurnal cortisol rhythm with chronic pain: Evidence from a prospective cohort study in community-dwelling adults

Yunlong Liang[a,*], Rui Li[b,c], Laura Fumagalli[a], Cara Booker[a]

[a] Institute for Social and Economic Research, University of Essex, Wivenhoe Park, Colchester, Essex, UK
[b] Center for Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, WA, United States
[c] Department of Anesthesiology & Pain Medicine, University of Washington School of Medicine, Seattle, WA, United States

Biological Research For Nursing
Volume 28, Issue 3, July 2026, Pages 384-394

https://doi.org/10.1177/10998004261423210

Mary Ann Liebert
A Part of Sage

Article

Evaluating Sex Differences in Biomarkers of Chronic Pain Among Active-Duty Personnel: An Exploratory Analysis of a Pragmatic Clinical Trial With a SMART Design

Sotaro Shimada, MHS, RN, PHN [1], Shannon Ledesma, PhD[2], Diane M. Flynn, MD, MPH[2], Nathan Tintle, PhD[1], Jeffrey C. Ransom, PhD, DNP[2], Honor M. McQuinn, DNP[2], Tyler DPT[2], Nicholas Ieronimakis, PhD[3], Dahee Wi, PhD, RN [1], Larisa A. Burke, MPH[1], A Steffen, PhD[1], and Ardith Z. Doorenbos, PhD, RN, FAAN[1,4]

STRESS
2024, VOL. 27, NO. 1, 2402954
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Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS

Diurnal cortisol patterns in chronic pain: Associations with work-family spillover, work, and home stress

Shin Ye Kim[a], Micah Iserman[b], Nguyen Nguyen[c] and Hannah Yoo[d]

[a]Department of Counseling Psychology, University of Wisconsin-Madison, Madison, WI, USA; [b]Data-Intensive Social Science Center, Yale University, New Haven, CT, USA; [c]Department of Educational Psychology, Texas A&M University, College Station, TX, USA; [d]Department of Psychological Sciences, Texas Tech University, Lubbock, TX, USA

BACKGROUND

Cortisol variability?

- Co-morbidities (PTSD, trauma, disease)
- Clinical characteristics (age, sex)
- Genetics
  - SNPs described in regulatory genes
    - ✓ CBG coding and release [1,2]
  - Synthesis enzymes cause disease
    - ✓ Congenital adrenal hyperplasia[3]
  - Unclear if variants always alter cortisol levels
  - Relation to chronic pain?

1. Neumann A. et al. Psychoneuroendocrilology. 2017. PMID 28843169.
2. Bolton JL. Et al. PLoS Genet. 2014. PMID
3. Menabo S. et al. Eur J Hum Genet. 2013. PMID 24022297.

Hypothesis

Variants underly cortisol levels and chronic pain in genes that code for synthesis enzymes

Objective

1. Evaluate SNPs relative to cortisol levels in servicemembers with chronic pain
2. Compare association with treatment and outcomes

METHODS – Participants

637 = IPMC Referrals

340 = Eligible

182 = Consented

118 = Samples

Inclusion Checklist:

1. ADSM with chronic pain ≥ 3-months duration
2. Dysfunction in daily social, vocational, and/or interpersonal activities
3. Able to commit the time required for interdisciplinary care

Exclusion Checklist

1. Major surgeries within past 6 months
2. Unstable psychological disorders
3. Active substance use disorder

METHODS – Participant Characteristics

Characteristic	N=118	%
Sex		
Male	93	79%
Female	25	21%
Age		
18-24	7	6%
25-34	57	46%
35-44	43	36%
>44	11	9%
Race		
White	78	66%
Black	24	20%
Asian	13	11%
Other	3	3%

Characteristic	N=118	%
Education		
High school/GED	30	25%
Some college	54	47%
College degree	29	24%
Married - Yes	74	63%
Tobacco use - Yes	20	17%

METHODS – Chronic Pain Measurements

PASTOR
PAIN ASSESSMENT SCREENING TOOL AND OUTCOMES REGISTRY

dvcipm.org

	WNL	Mild	Moderate	Severe
Pain Impact Score		8-27	28-34	35+
Pain interference	≤54.9	55-59.9	60-69.9	≥70
Depression	≤54.9	55-59.9	60-69.9	≥70
Anxiety	≤54.9	55-59.9	60-69.9	≥70
Fatigue	≤54.9	55-59.9	60-69.9	≥70
Anger	≤54.9	55-59.9	60-69.9	≥70
Sleep-related impairment	≤54.9	55-59.9	60-69.9	≥70

	Very high	High	Average	Low	Very Low
Satis w Partic in Social Roles & Activities	>70	60-69.9	40-59.9	30-39.9	<30
Physical functioning	>70	60-69.9	40-59.9	30-39.9	<30

nihpromis.org

- Fatigue
- Physical Functioning
- Pain Impact Score

METHODS – Saliva for Cortisol

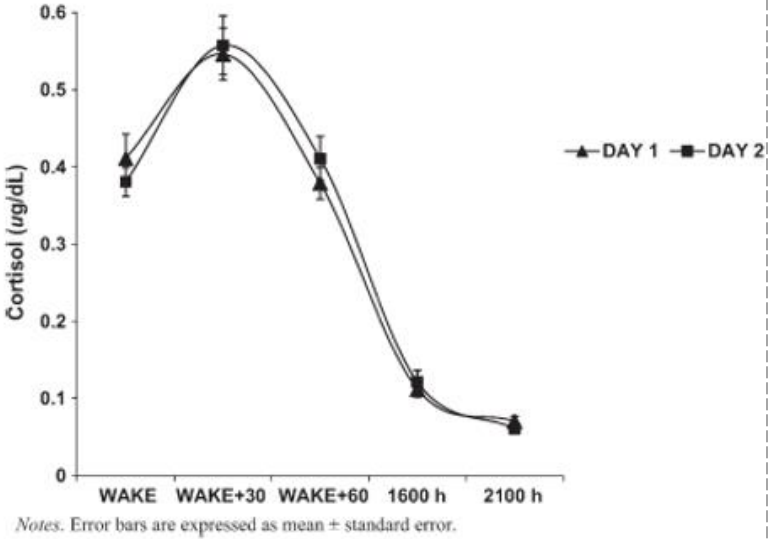
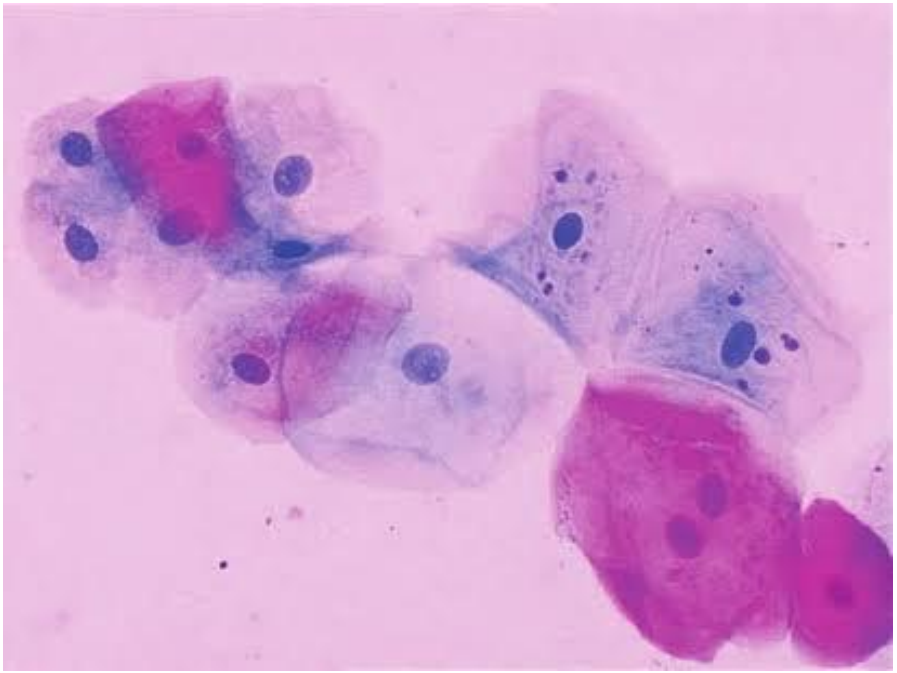


FIGURE 1. Daily cortisol profile of total sample: day 1 versus day 2.

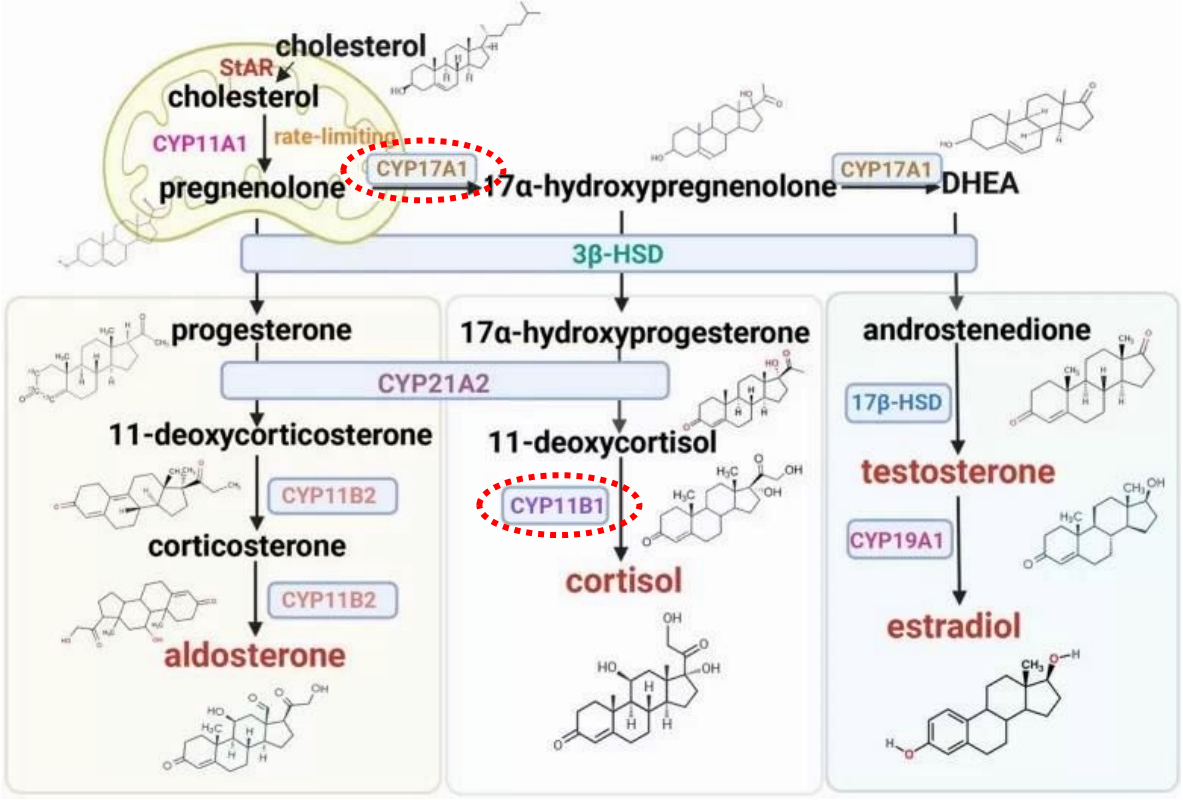
Taylor MK et al. 2016. PMID: 27849495

Wake up → **30 min post** → **afternoon**

METHODS – Collection DNA

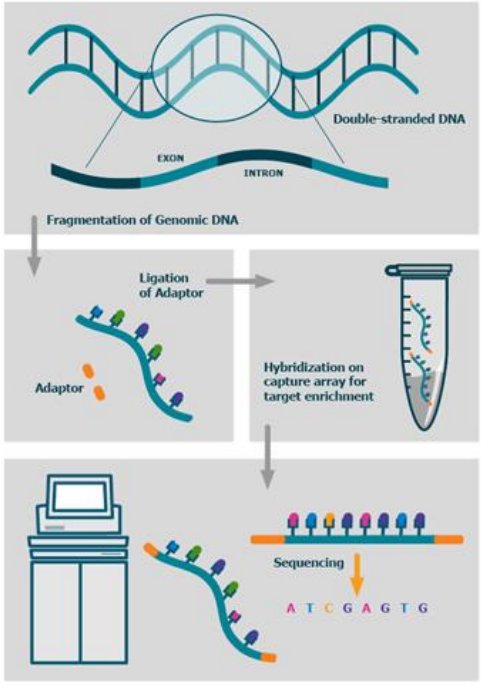


METHODS – Sequencing



Taylor MK et al. 2016. PMID: 27849495

Genome Sciences
UNIVERSITY OF WASHINGTON



Method – Analysis

Gene (chr numb.)	Genome location	SNP ID	MAF	Type of exonic variant
CYP11B1 (8)	142879181	rs5283	35%	Synonymous
	142879589	rs6410	46%	Synonymous
	22 variants		**<10%**	Synonymous
	21 variants		**<5%**	Synonymous (1 missense)
CYP17A1 (10)	102837167	rs6163	41%	Synonymous
	102837224	rs6162	44%	Synonymous
	11 variants		**<5%**	Synonymous

- Linear regression analysis models estimated individual variant associations
- Gene-wide rare variant burden scores for each outcome model adjusted to age, sex, race/ethnicity

RESULTS

		Pain Intensity	Pain Impact	Fatigue
Gene	**SNP/collapsing test**	**Adjusted beta (90% CI)**	**Adjusted beta (90% CI)**	**Adjusted beta (90% CI)**
CYP11B1	rs5283	**−0.43 (−0.83 to −0.04)***	−0.14 (−2.16 to 1.87)	0.28 (−2.16 to 2.71)
	rs6410	−0.20 (−0.59 to 0.20)	−0.11 (−2.10 to 1.89)	−1.42 (−3.79 to 0.94)
	MAF <5%	**−0.45 (−0.76 to −0.14)****	**−2.03 (−3.41 to −0.65)****	−1.49 (−3.19 to 0.21)
	MAF <10%	**−0.23 (−0.44 to −0.02)***	**−1.07 (−2.01 to −0.13)***	**−1.24 (−2.38 to −0.11)***
	All SNPs	**−0.18 (−0.34 to −0.01)***	−0.48 (−1.23 to 0.27)	−0.73 (−1.63 to 0.16)
CYP17A1	rs6163	−0.23 (−0.59 to 0.13)	**−1.83 (−3.58 to −0.08)***	**−2.69 (−4.77 to −0.61)****
	rs6162	−0.17 (−0.54 to 0.20)	−1.11 (−2.99 to 0.77)	**−2.30 (−4.5 to −0.11)***
	MAF <5%	−0.13 (−0.55 to 0.30)	−0.76 (−2.66 to 1.13)	−1.20 (−3.48 to 1.09)
	All SNPs	−0.01 (−0.19 to 0.17)	−0.51 (−1.32 to 0.30)	−0.95 (−1.92 to 0.02)

RESULTS

		Depression	Sleep	Cortisol
Gene	**SNP/collapsing test**	**Adjusted beta (90% CI)**	**Adjusted beta (90% CI)**	**Adjusted beta (90% CI)**
CYP11B1	rs5283	−1.75 (−4.85 to 1.35)	−0.28 (−2.76 to 2.19)	0.18 (−0.05 to 0.41)
	rs6410	−3.00 (−6.02 to 0.02)	**−3.76 (−6.08 to −1.43)*** **	0.18 (−0.04 to 0.41)
	MAF <5%	**−2.64 (−4.81 to −0.48)** **	**−2.07 (−3.84 to −0.30)***	**0.19 (0.04–0.35)** **
	MAF <10%	−1.07 (−2.54 to 0.41)	**−1.92 (−3.09 to −0.75)*** **	0.06 (−0.05 to 0.17)
	All SNPs	−1.09 (−2.24 to 0.06)	**−1.47 (−2.39 to −0.55)*** **	0.06 (−0.02 to 0.15)
CYP17A1	rs6163	**−3.60 (−6.24 to −0.96)** **	**−3.02 (−5.12 to −0.92)** **	0.17 (−0.04 to 0.37)
	rs6162	**−3.22 (−5.98 to −0.45)***	**−2.85 (−5.04 to −0.65)** **	0.12 (−0.09 to 0.33)
	MAF <5%	−1.23 (−4.18 to 1.72)	−1.29 (−3.69 to 1.11)	0.13 (−0.08 to 0.35)
	All SNPs	**−1.26 (−2.51 to −0.01)***	−0.87 (−1.89 to 0.16)	0.07 (−0.02 to 0.16)

CONCLUSION

- Mild association with salivary cortisol
  - May be attributed to synonymous variants
- Significant association with SNP and pain intensity, impact, depression and sleep
  - CYP11B2 with pain
  - CYP17A1 fatigue and depression
- Provide insight regarding biological processes in affected individuals
- Further research needed to understand genetic variants
  - Mechanisms and predictive value

Strengths

- Comprehensive longitudinal design
  - Integration of biomarkers with Pastor
- Active-duty population relatively free co-morbidities
- Focused analysis known genetic targets

Limitations

- Small numbers
- Limited genetic and biomarker analysis
  - Variants related to other hormones
- Associative not causal

IPMC Research Team

Dr. Ardith Doorenbos

Dr. Diane Flynn

Dr. Honor McQuinn

Ms. Kira Heartwick

Dr. Nathan Tintle

Dr. Jeffrey Ransom

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Thank You Soldiers!