Are You Tired of Being Tired?

Filomena Trindade, MD, MPH, ABFM, ABOIM

April 25, 2018

Lahnor Powell, ND, MPH

Medical Education Specialist - Atlanta

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Filomena Trindade, MD, MPH

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Technical Issues & Clinical Questions

- Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

- We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.

DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

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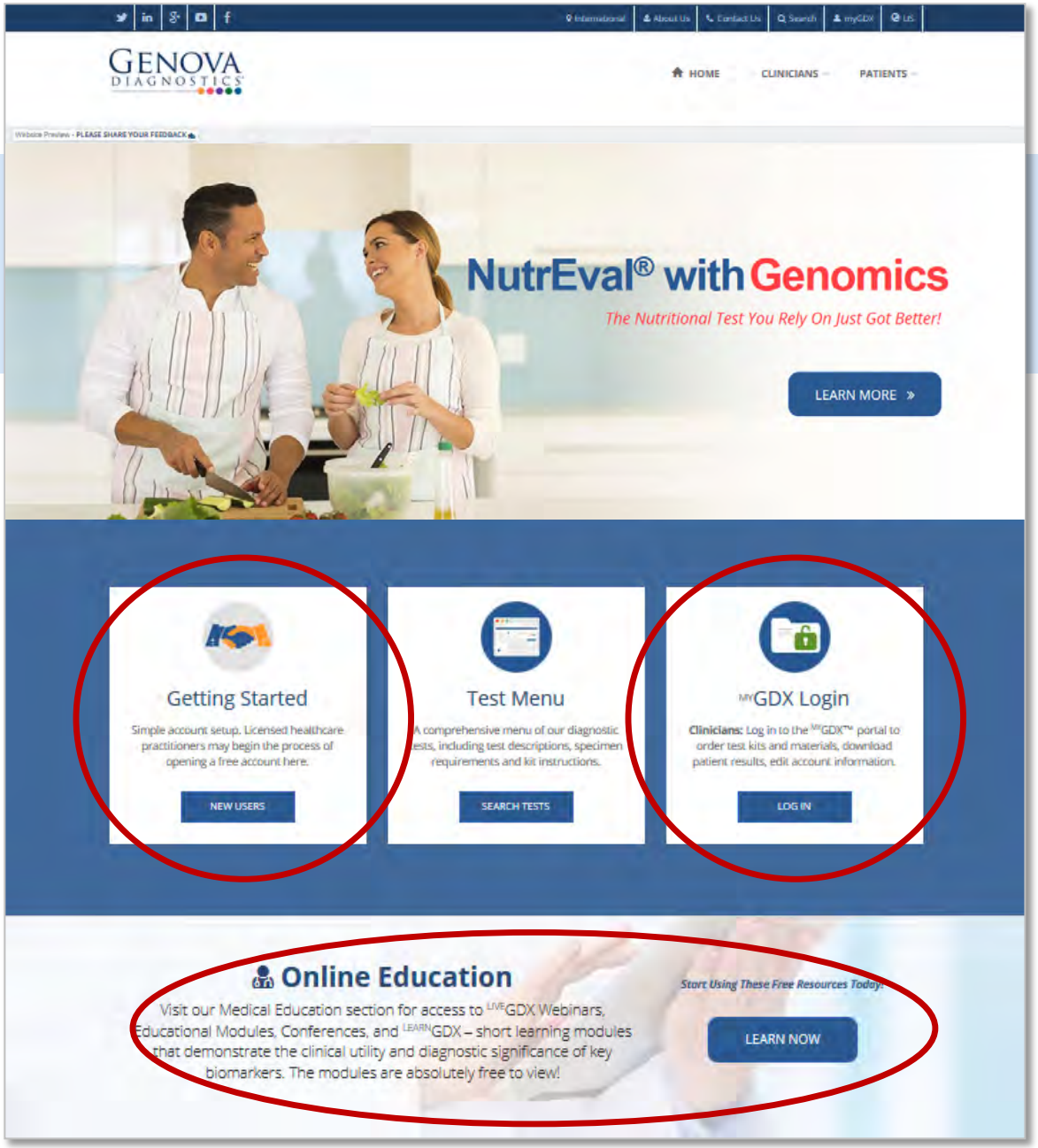
Need More Resources?

Ensure you have an account!



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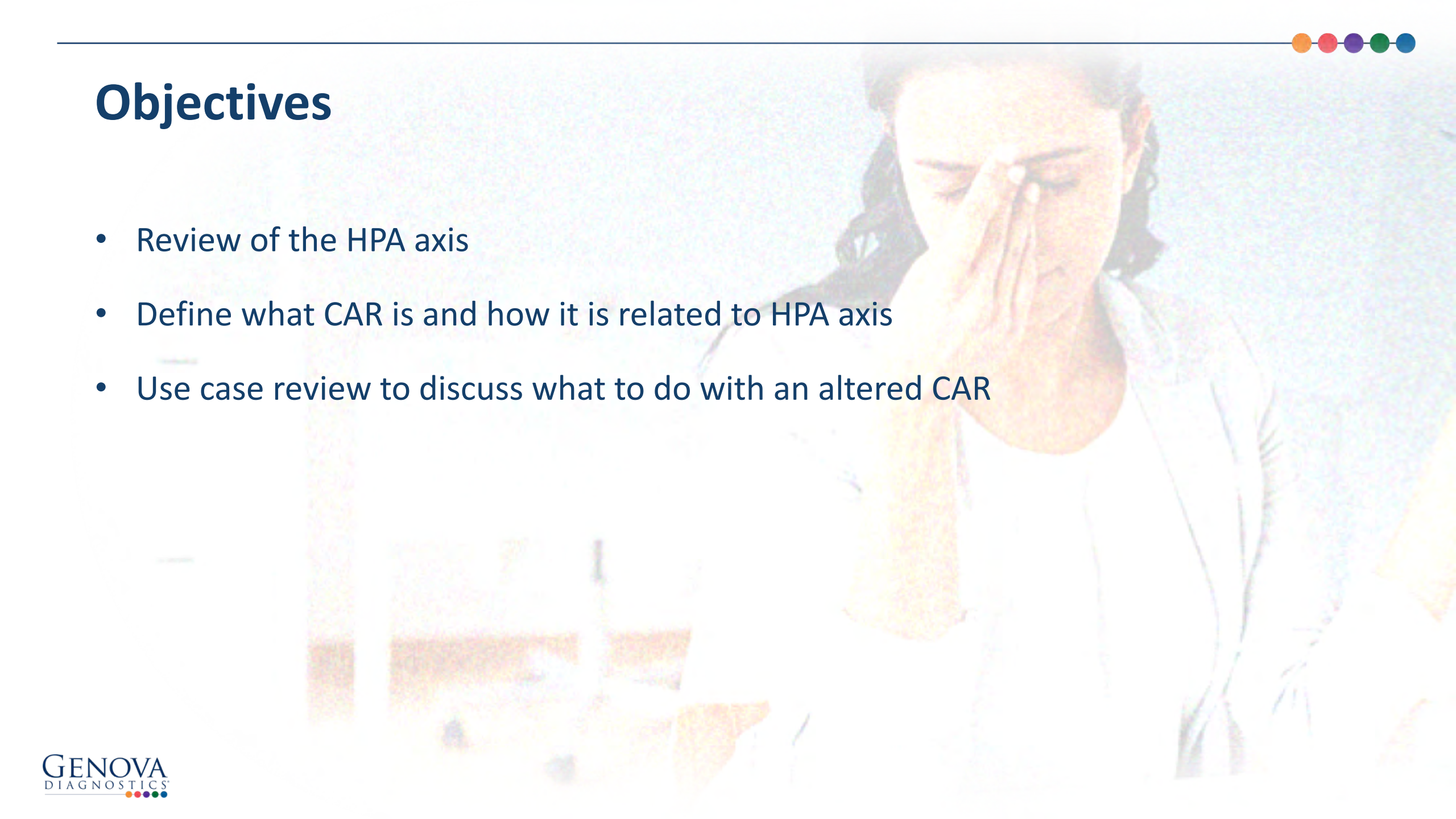
Are You Tired of Being Tired?

Filomena Trindade, MD, MPH, ABFM, ABOIM

April 25, 2018

Objectives

- Review of the HPA axis
- Define what CAR is and how it is related to HPA axis
- Use case review to discuss what to do with an altered CAR



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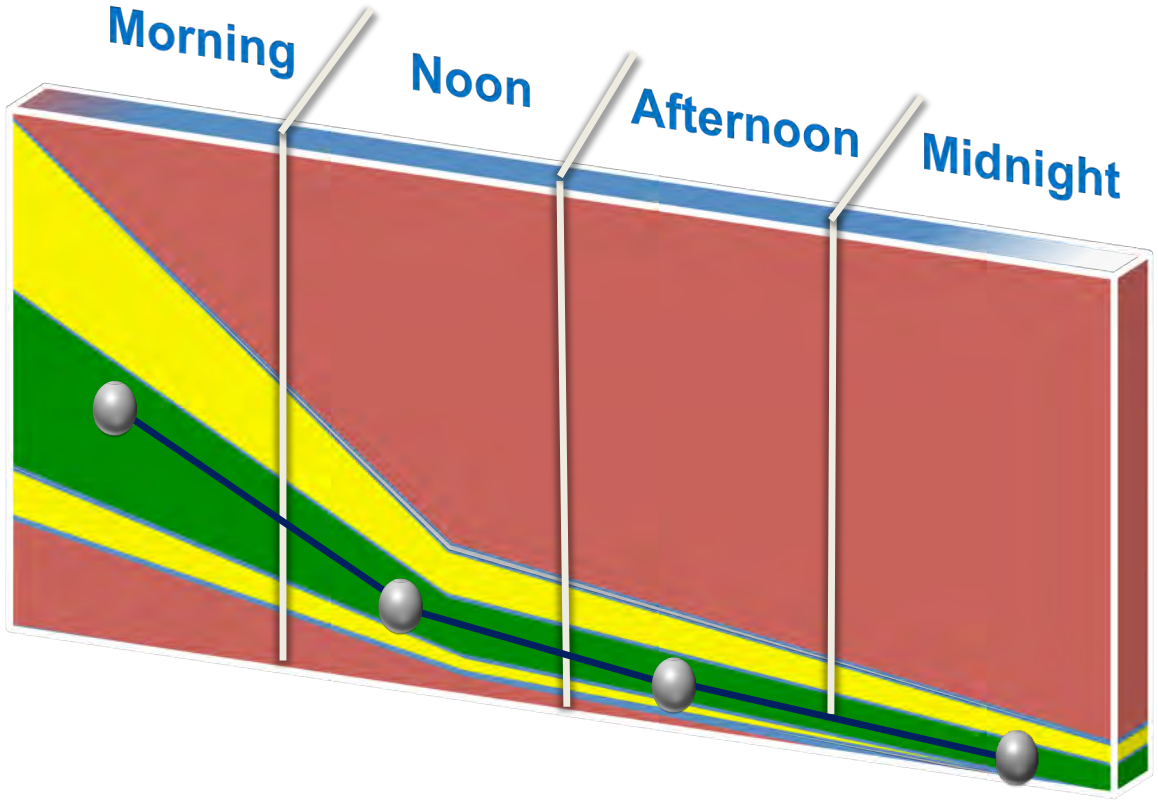
Diurnal Cortisol Testing: Normal

Cortisol



Salivary testing – most common method

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Selye's General Adaptation Syndrome: The Three Stages of Stress

- Arousal (STAGE 1)
  - Rapid increases in catecholamines (alarm molecules)
  - Slower increases of corticosteroids (stress steroids)
- Adaptation (STAGE 2)
  - Sustained increased levels of corticosteroids and alarm molecules
  - Altered glucose tolerance, blood pressure, thyroid and sex hormone metabolism
- Exhaustion (STAGE 3)
  - Degenerative diseases characterized by the adverse influence of corticosteroids and alarm molecules

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Selye H. 1956. The stress of life. New York: McGraw-Hill Book Co.

Correlation with Laboratory Values

- Stage 1 - Alarm phase / normal adaptation
  - Both cortisol and DHEA increase with stress
  - Cortisol can elevate at any or multiple points
  - DHEA may be normal or elevated
- Stage 2 - Resistance phase / early decompensation
  - Cortisol increases; more persistent patterning
  - DHEA can be normal, elevated, or may start to gradually decline
- Stage 3 - Exhaustion phase / late decompensation
  - Adrenal insufficiency - low cortisol and DHEA
  - Depression and exhaustion

What is the Cortisol Awakening Response (CAR)?

- The **Cortisol Awakening Response** (CAR) is an increase of about 50% in **cortisol** levels occurring around 30 (30-45 per some studies) minutes after **awakening** in the morning
- Gradual decline of cortisol throughout the day, reaching a nadir in late evening
- Inter-individual variability in both the **cortisol** profile and CAR in response to physical **stress**
- **CAR** response within a given individual seems to be consistent, as long as confounding variables are properly controlled, such as time of waking, sex, and age

CAR-continued

- First established by Pruessner, et al, in 1997
- Previous studies have suggested that the daily CAR provides energy in anticipation of upcoming demands

Adam EK, et al. Psychoneuroendocrinology. 2009;34:1423—36.
Fries E, et al. Int J Psychophysiol. 2009;72(1):67-73.
Hellhammer DH, et al. Psychoneuroendocrinology. 2007; 32(1):80-6.
Kudielka BM, et al. Psychoneuroendocrinology. 2003;28:35–47.
Pruessner JC, et al. Life Sci. 1997;61:2539–49.

Cortisol Sampling Time Point

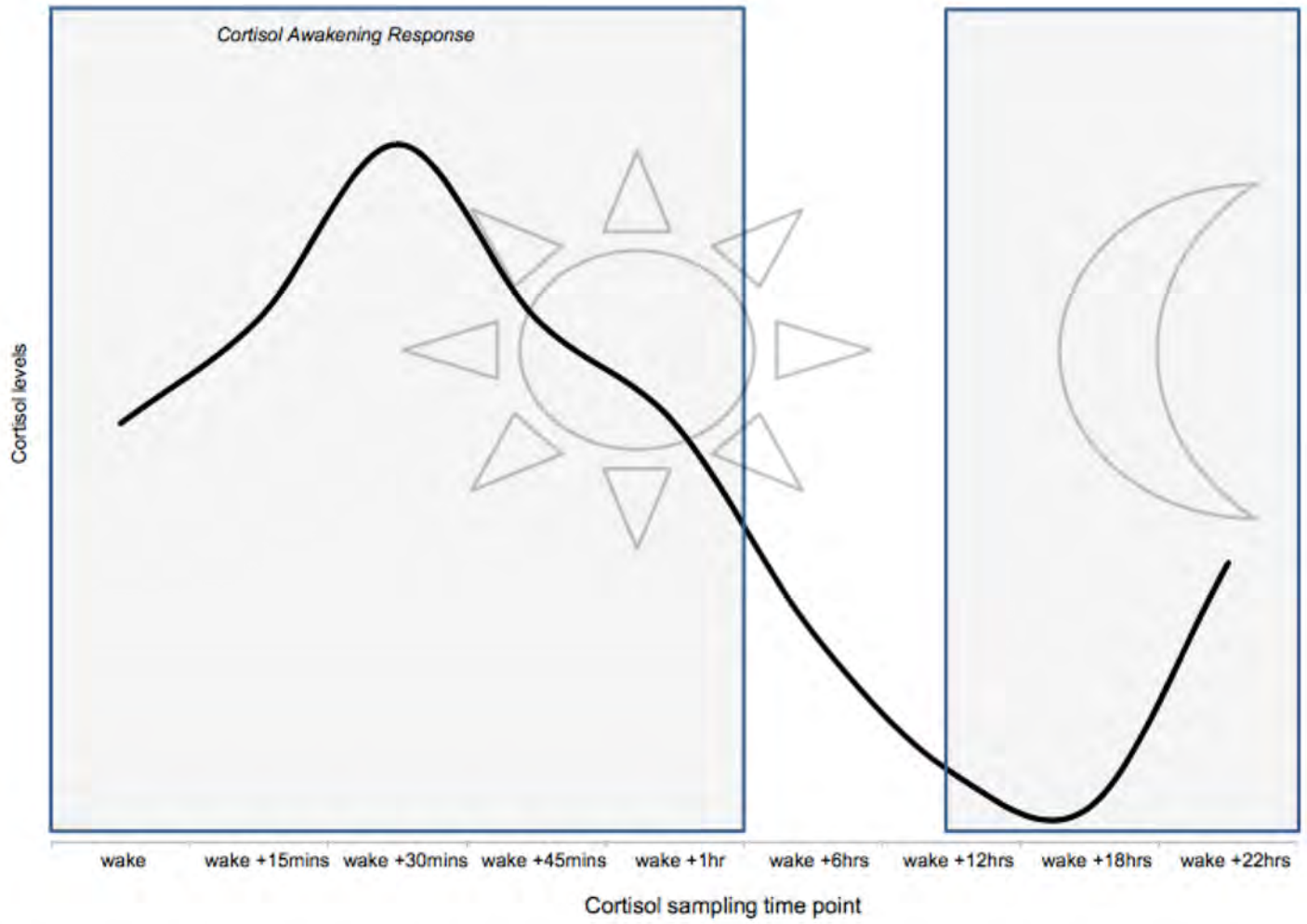

Fig. 1. A typical cortisol awakening response (CAR) and diurnal cortisol profile over a twenty-four hour period in healthy individuals. The first shaded area represents the cortisol awakening response and the second shaded area represents cortisol levels during sleep.

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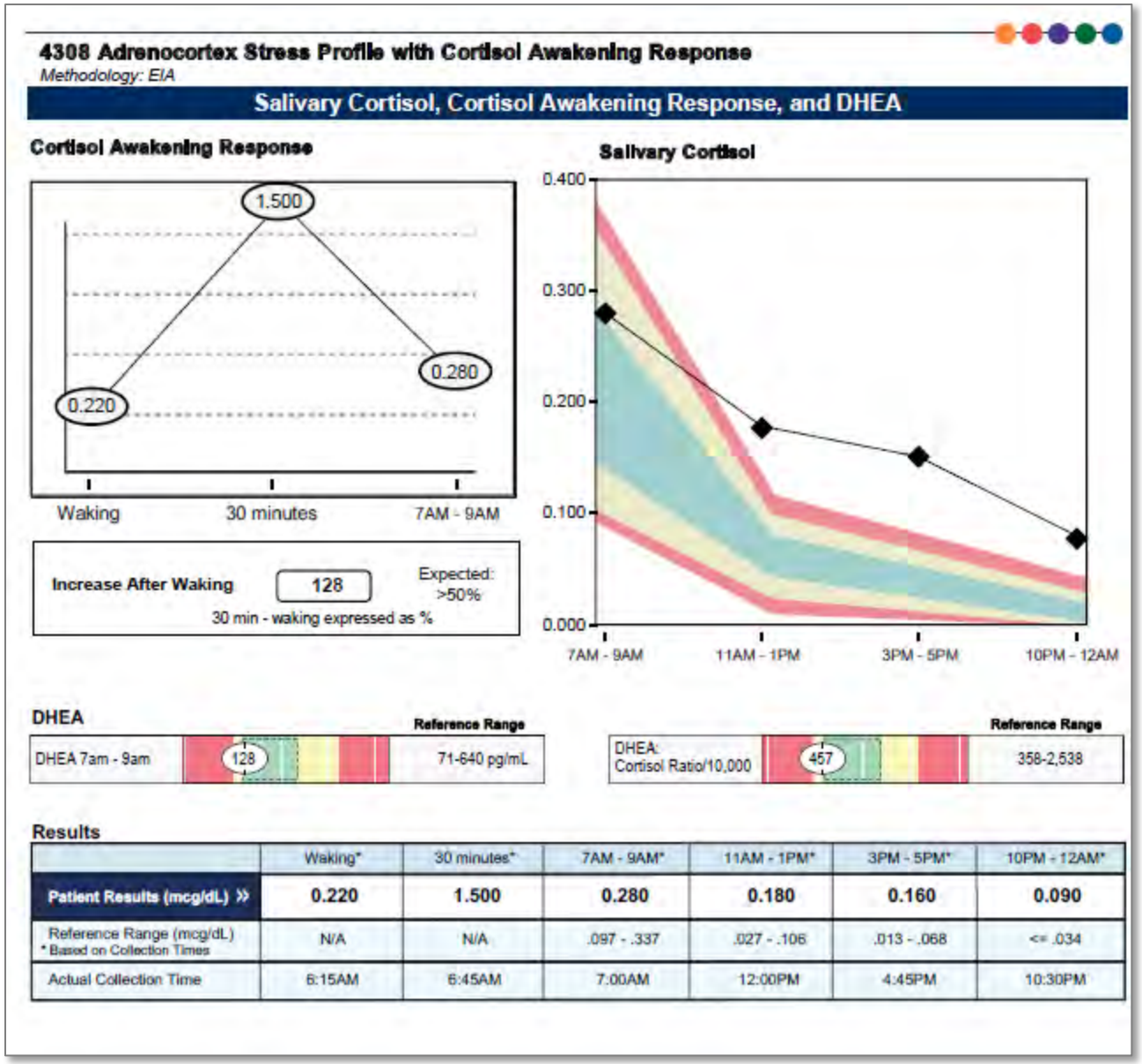
Sleep Medicine Reviews 18 (2014) 215e224.

Scenario #1



4308 Adrenocortex Stress Profile with Cortisol Awakening Response

Methodology: EIA

Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response

Increase After Waking 128 Expected: >50%

30 min - waking expressed as %

Salivary Cortisol

DHEA

		Reference Range
DHEA 7am - 9am	128	71-640 pg/mL

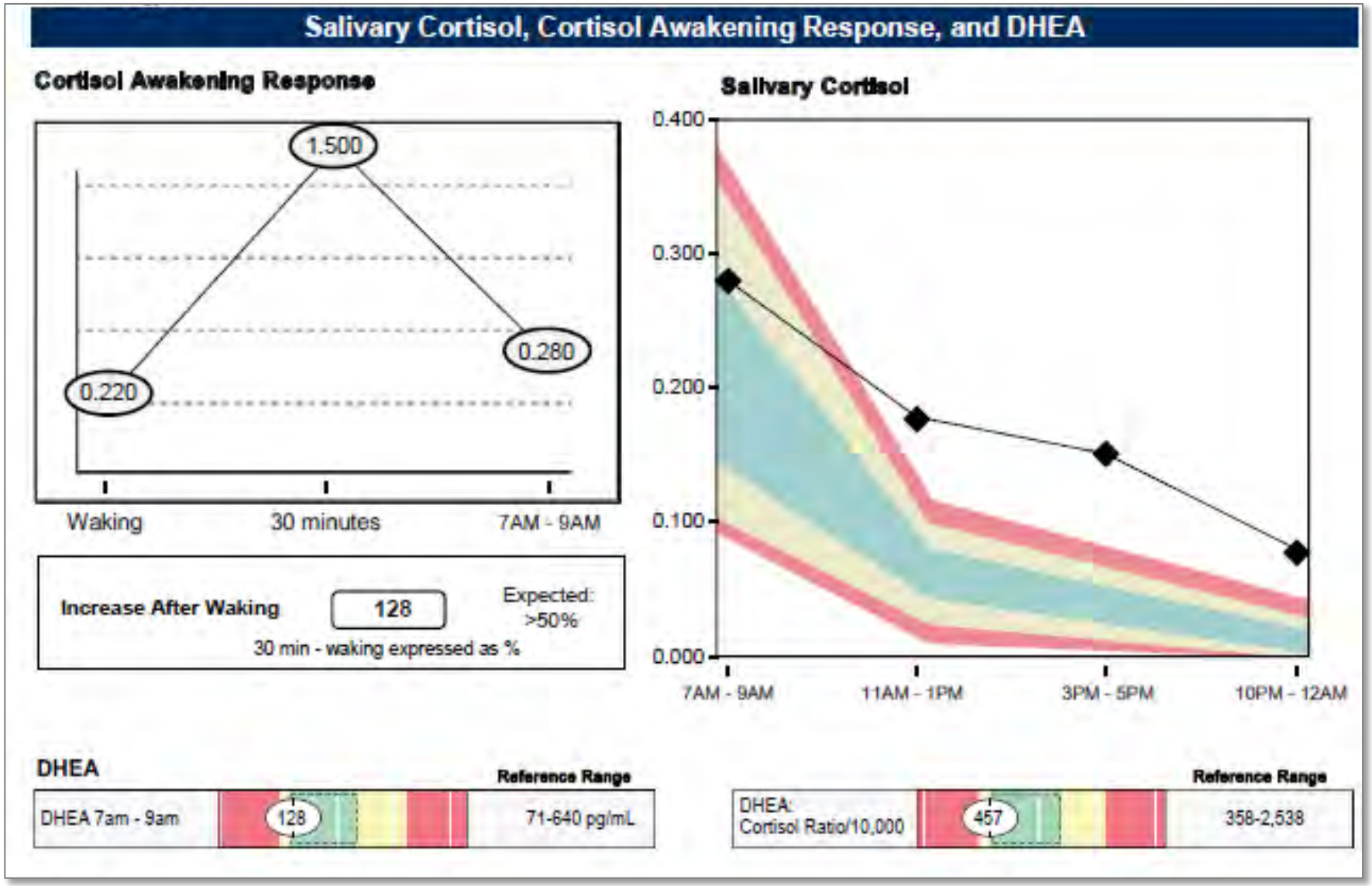
		Reference Range
DHEA: Cortisol Ratio/10,000	457	358-2,538

Results

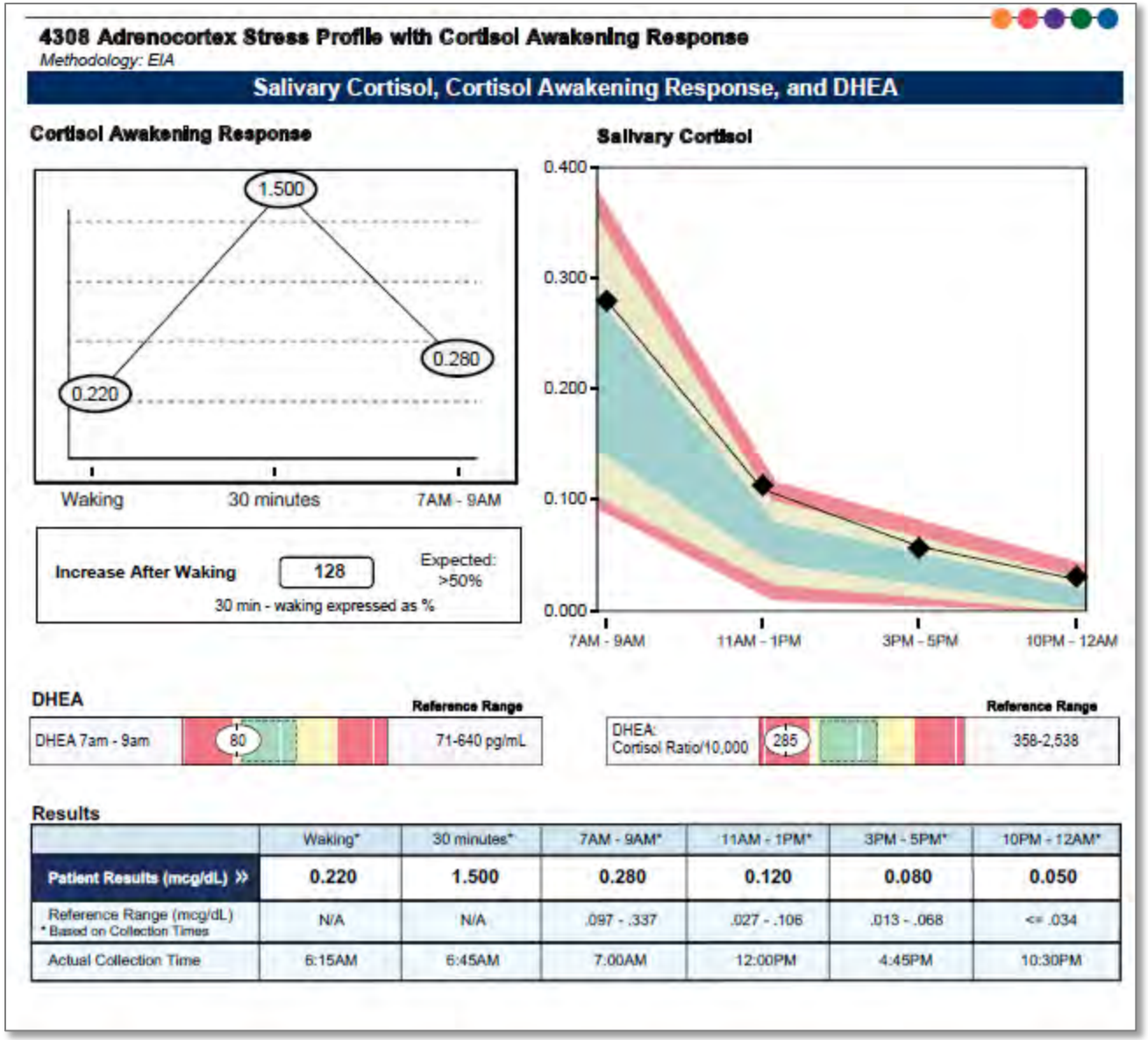
	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) »	**0.220**	**1.500**	**0.280**	**0.180**	**0.160**	**0.090**
Reference Range (mcg/dL) * Based on Collection Times	N/A	N/A	.097 - .337	.027 - .106	.013 - .068	<= .034
Actual Collection Time	6:15AM	6:45AM	7:00AM	12:00PM	4:45PM	10:30PM

GENOVA DIAGNOSTICS

Scenario #1


Salivary Cortisol, Cortisol Awakening Response, and DHEA
Cortisol Awakening Response
1.500
0.280
0.220
Waking
30 minutes
7AM - 9AM
Increase After Waking
128
Expected:
>50%
30 min - waking expressed as %
Salivary Cortisol
0.400
0.300
0.200
0.100
0.000
7AM - 9AM
11AM - 1PM
3PM - 5PM
10PM - 12AM
DHEA
Reference Range
DHEA 7am - 9am
128
71-640 pg/mL
Reference Range
DHEA:
Cortisol Ratio/10,000
457
358-2,538

Scenario #2



4308 Adrenocortex Stress Profile with Cortisol Awakening Response

Methodology: EIA

Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response

Increase After Waking 128 Expected: >50%

30 min - waking expressed as %

Salivary Cortisol

DHEA

		Reference Range
DHEA 7am - 9am	80	71-640 pg/mL

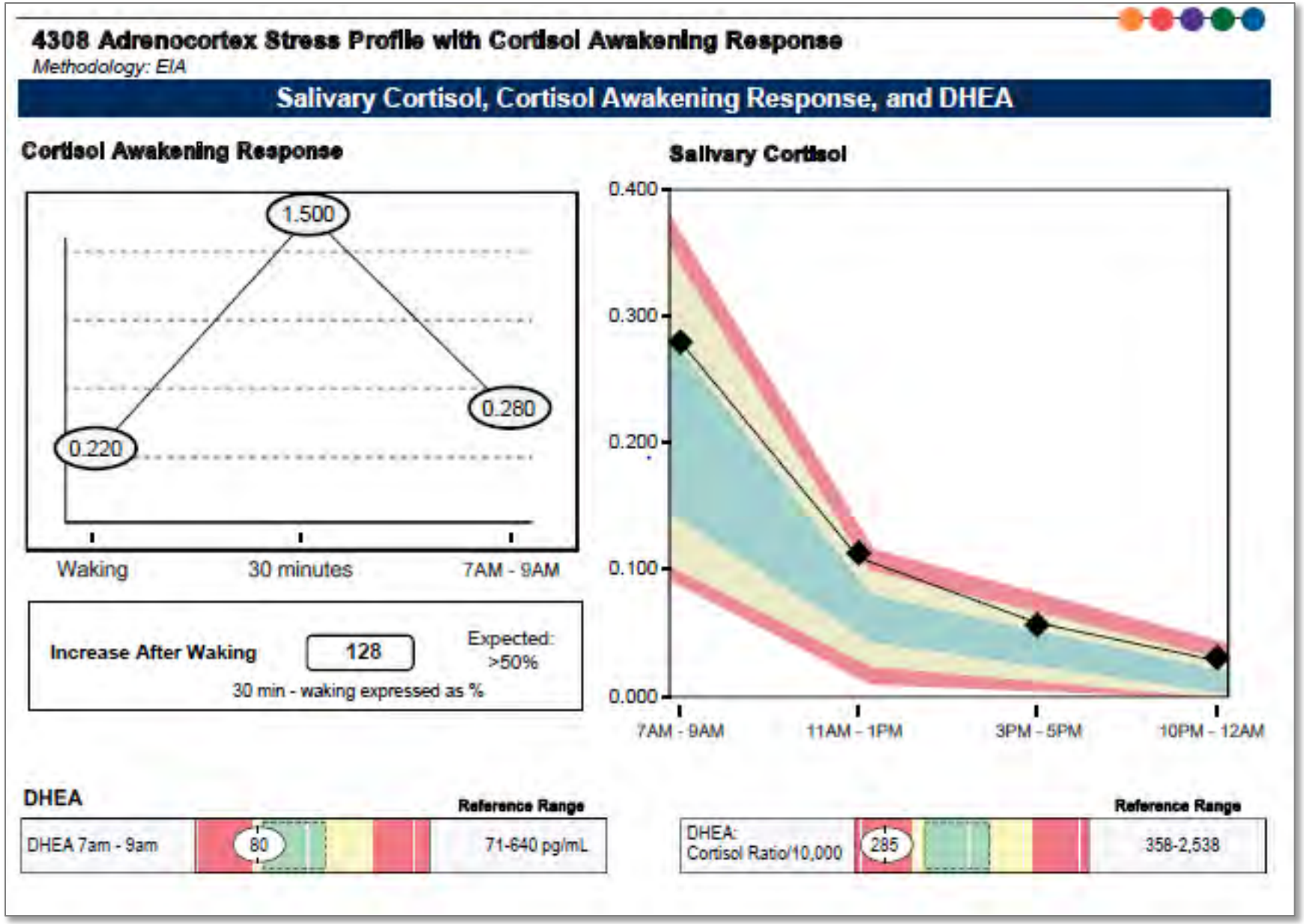
		Reference Range
DHEA: Cortisol Ratio/10,000	285	358-2,538

Results

	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) »	**0.220**	**1.500**	**0.280**	**0.120**	**0.080**	**0.050**
Reference Range (mcg/dL) * Based on Collection Times	N/A	N/A	.097 - .337	.027 - .106	.013 - .068	<= .034
Actual Collection Time	6:15AM	6:45AM	7:00AM	12:00PM	4:45PM	10:30PM

GENOVA DIAGNOSTICS

Scenario #2



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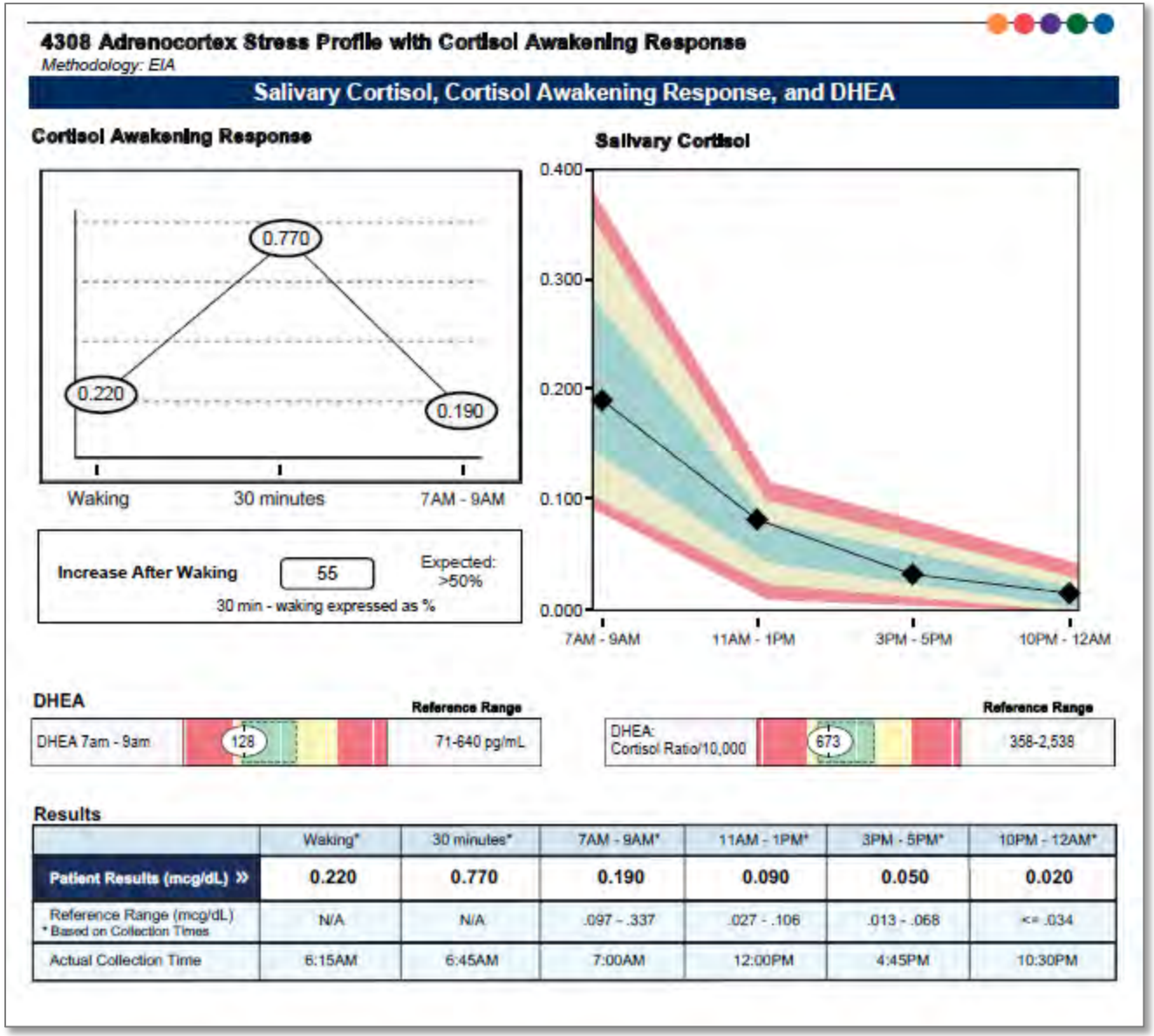
Scenario #3



4308 Adrenocortex Stress Profile with Cortisol Awakening Response

Methodology: EIA

Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response

Increase After Waking 55 Expected: >50%

30 min - waking expressed as %

Salivary Cortisol

DHEA

		Reference Range
DHEA 7am - 9am	128	71-640 pg/mL

		Reference Range
DHEA: Cortisol Ratio/10,000	673	358-2,538

Results

	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) »	**0.220**	**0.770**	**0.190**	**0.090**	**0.050**	**0.020**
Reference Range (mcg/dL) * Based on Collection Times	N/A	N/A	.097 - .337	.027 - .106	.013 - .068	<= .034
Actual Collection Time	6:15AM	6:45AM	7:00AM	12:00PM	4:45PM	10:30PM

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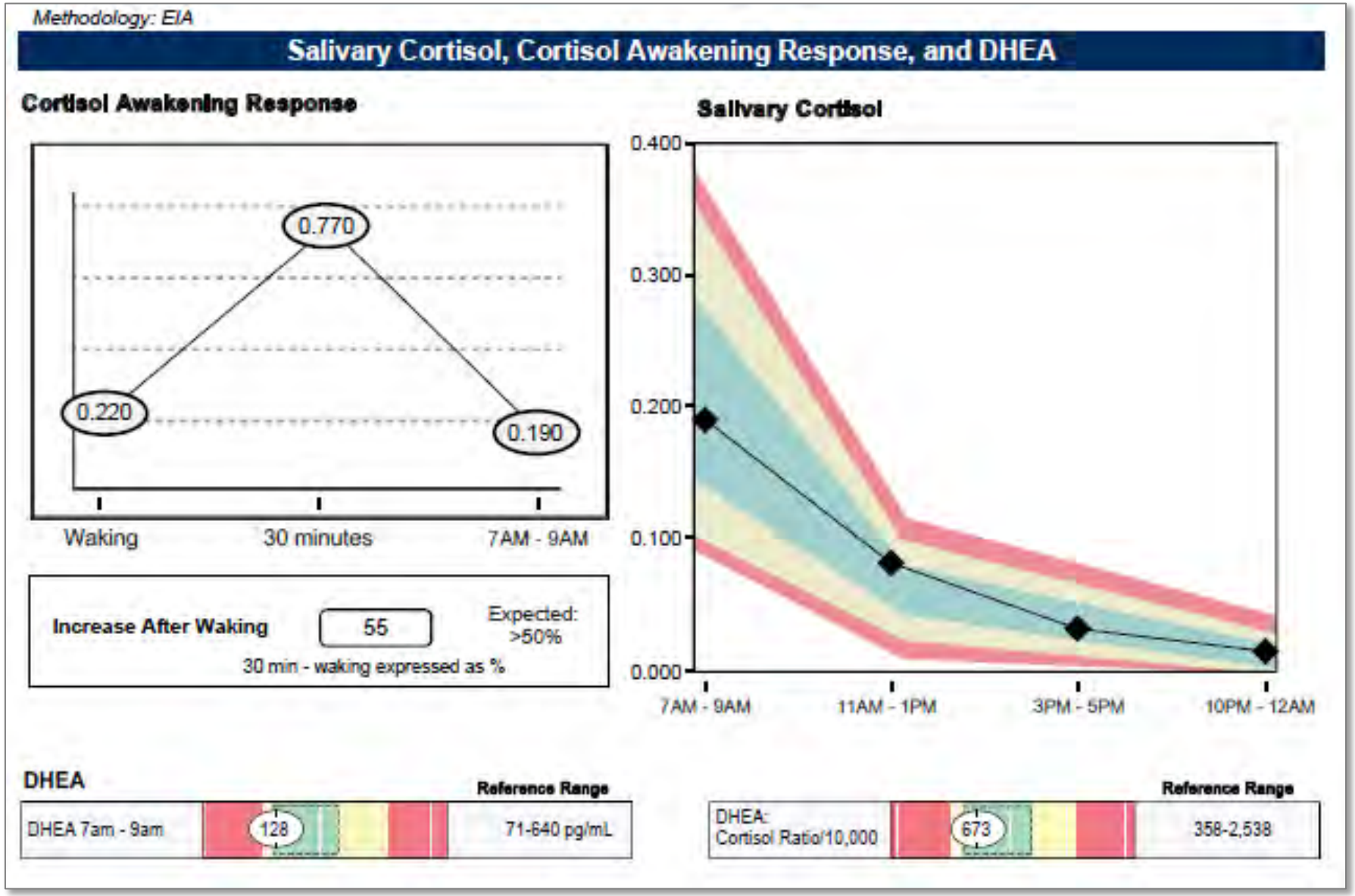
Scenario #3


Methodology: EIA
Salivary Cortisol, Cortisol Awakening Response, and DHEA
Cortisol Awakening Response
0.770
0.220
0.190
Waking
30 minutes
7AM - 9AM
Increase After Waking
55
Expected: >50%
30 min - waking expressed as %
Salivary Cortisol
0.400
0.300
0.200
0.100
0.000
7AM - 9AM
11AM - 1PM
3PM - 5PM
10PM - 12AM
DHEA
Reference Range
DHEA 7am - 9am
128
71-640 pg/mL
Reference Range
DHEA: Cortisol Ratio/10,000
673
358-2,538

Scenario #3

DHEA

		Reference Range
DHEA 7am - 9am	128	71-640 pg/mL

		Reference Range
DHEA: Cortisol Ratio/10,000	673	358-2,538

Results

	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) >>	**0.220**	**0.770**	**0.190**	**0.090**	**0.050**	**0.020**
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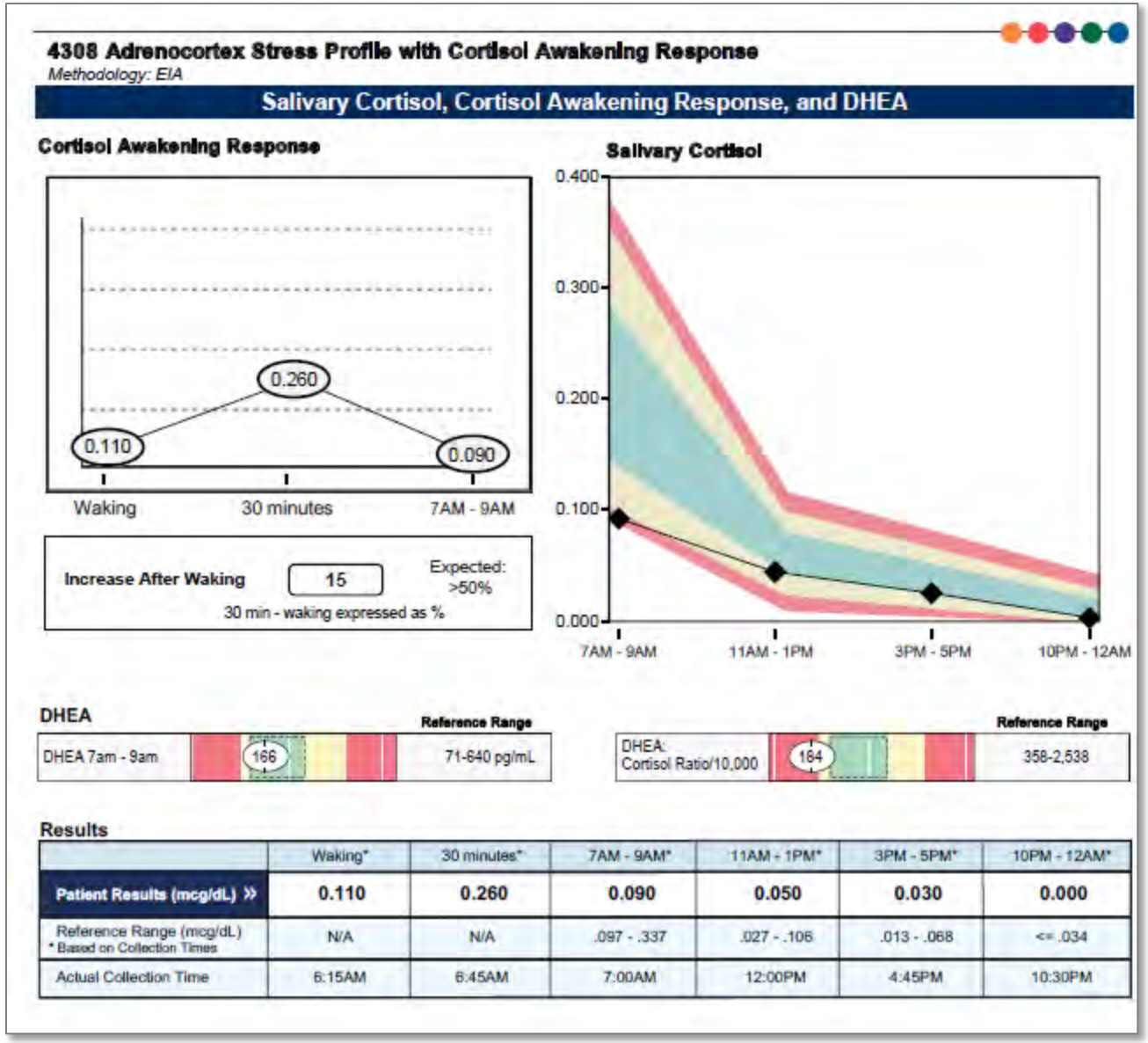
Scenario #4



4308 Adrenocortex Stress Profile with Cortisol Awakening Response

Methodology: EIA

Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response

Increase After Waking 15 Expected: >50%

30 min - waking expressed as %

Salivary Cortisol

DHEA

		Reference Range
DHEA 7am - 9am	166	71-640 pg/mL

		Reference Range
DHEA: Cortisol Ratio/10,000	184	358-2,538

Results

	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) »	**0.110**	**0.260**	**0.090**	**0.050**	**0.030**	**0.000**
Reference Range (mcg/dL) * Based on Collection Times	N/A	N/A	.097 - .337	.027 - .106	.013 - .068	<= .034
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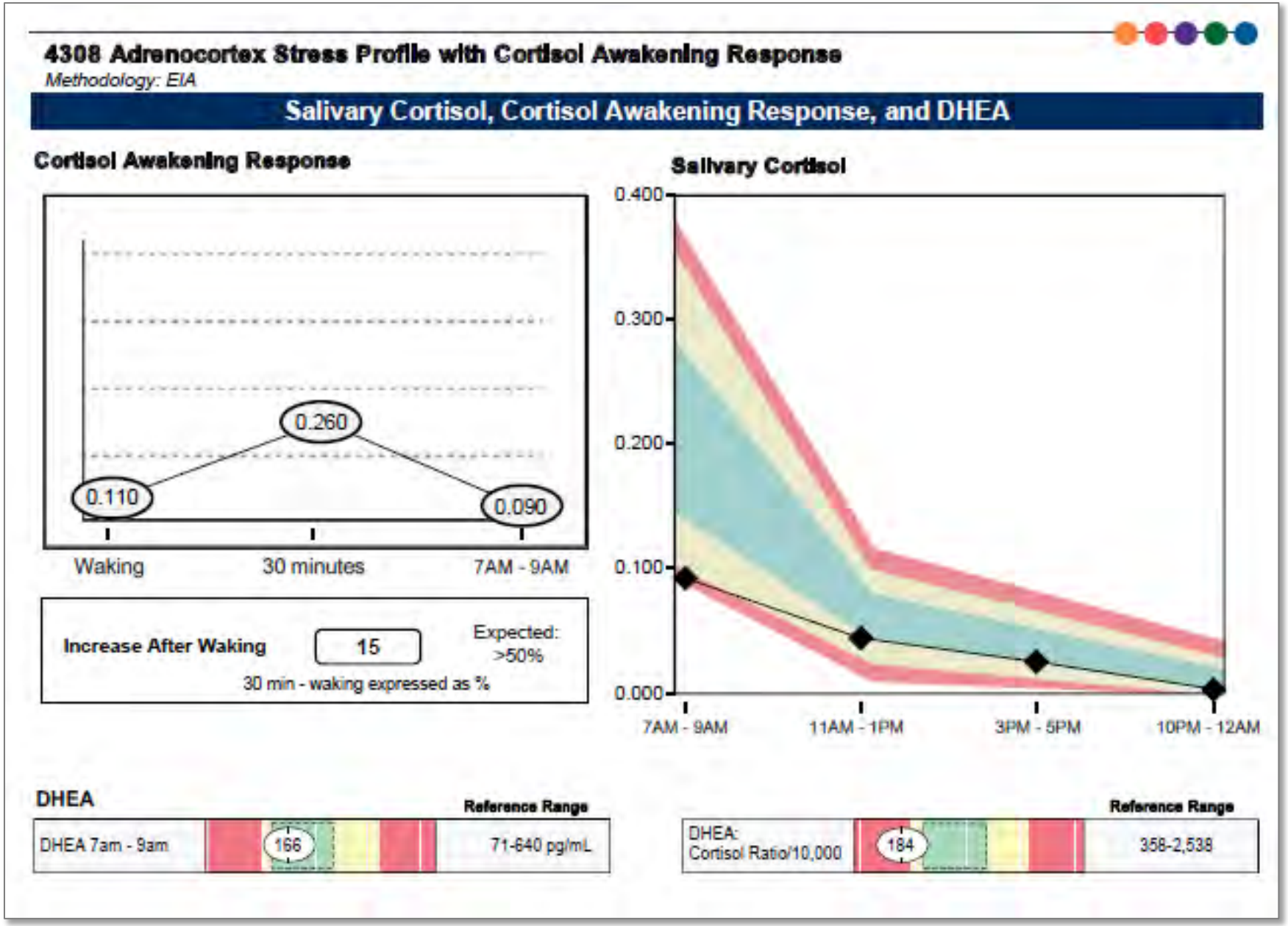
4308 Adrenocortex Stress Profile with Cortisol Awakening Response
Methodology: EIA
Salivary Cortisol, Cortisol Awakening Response, and DHEA
Cortisol Awakening Response
0.260
0.110
0.090
Waking
30 minutes
7AM - 9AM
Increase After Waking
15
Expected: >50%
30 min - waking expressed as %
Salivary Cortisol
0.400
0.300
0.200
0.100
0.000
7AM - 9AM
11AM - 1PM
3PM - 5PM
10PM - 12AM
DHEA
Reference Range
DHEA 7am - 9am
166
71-640 pg/mL
DHEA: Cortisol Ratio/10,000
184
358-2,538

Scenario #4

DHEA

		Reference Range
DHEA 7am - 9am	166	71-640 pg/mL

		Reference Range
DHEA: Cortisol Ratio/10,000	184	358-2,538

Results

	Waking*	30 minutes*	7AM - 9AM*	11AM - 1PM*	3PM - 5PM*	10PM - 12AM*
Patient Results (mcg/dL) »	**0.110**	**0.260**	**0.090**	**0.050**	**0.030**	**0.000**
Reference Range (mcg/dL) * Based on Collection Times	N/A	N/A	.097 - .337	.027 - .106	.013 - .068	<= .034
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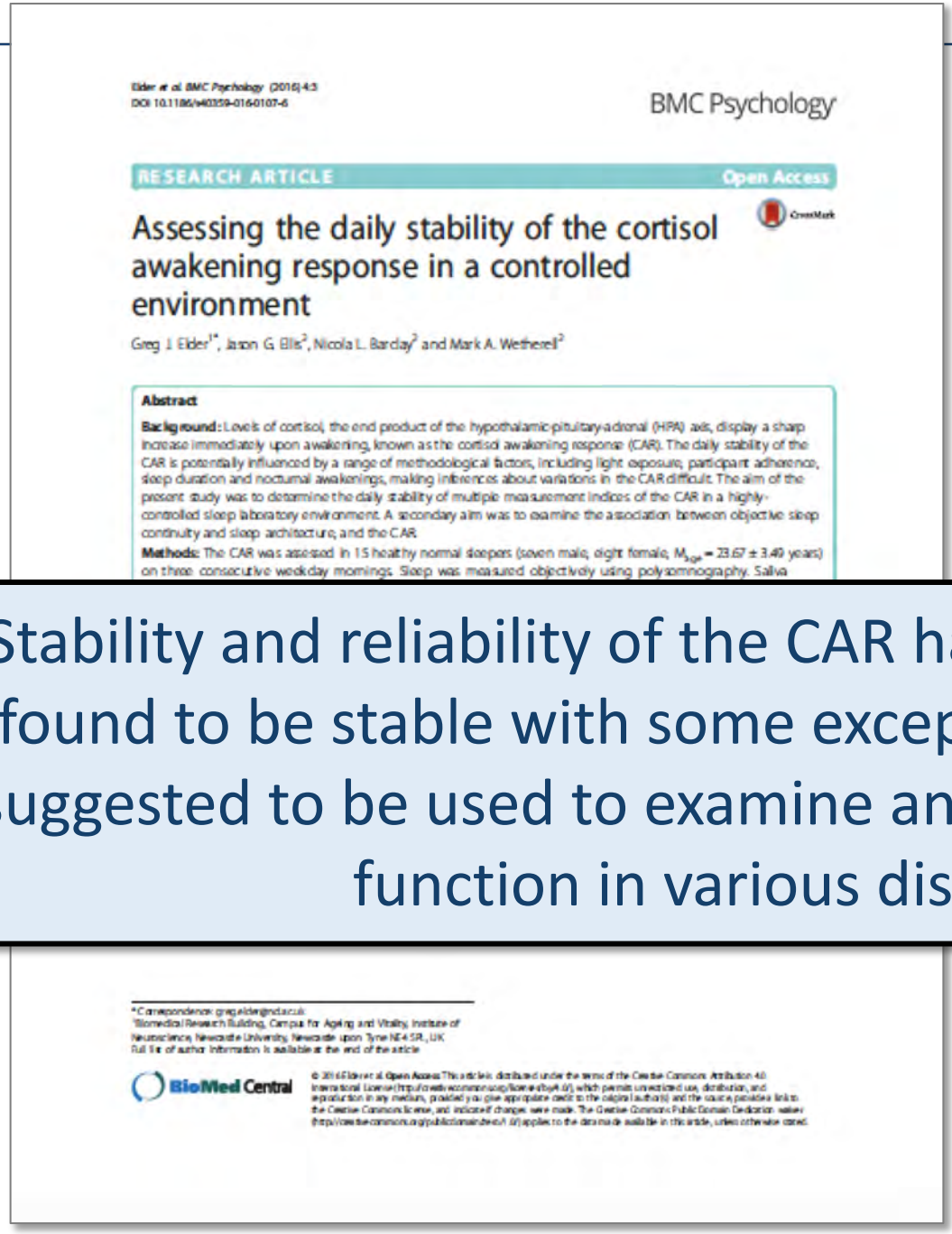

Elder et al. BMC Psychology (2016) 4:3
DOI 10.1186/s40359-016-0107-6

BMC Psychology

RESEARCH ARTICLE Open Access

Assessing the daily stability of the cortisol awakening response in a controlled environment

Greg J. Elder[1*], Jason G. Ellis[2], Nicola L. Barclay[2] and Mark A. Wetherell[2]

Abstract

Background: Levels of cortisol, the end product of the hypothalamic-pituitary-adrenal (HPA) axis, display a sharp increase immediately upon awakening, known as the cortisol awakening response (CAR). The daily stability of the CAR is potentially influenced by a range of methodological factors, including light exposure, participant adherence, sleep duration and nocturnal awakenings, making inferences about variations in the CAR difficult. The aim of the present study was to determine the daily stability of multiple measurement indices of the CAR in a highly-controlled sleep laboratory environment. A secondary aim was to examine the association between objective sleep continuity and sleep architecture, and the CAR.

Methods: The CAR was assessed in 15 healthy normal sleepers (seven male, eight female, M_{age} = 23.67 ± 3.49 years) on three consecutive weekday mornings. Sleep was measured objectively using polysomnography. Saliva

Stability and reliability of the CAR has been studied and found to be stable with some exceptions and has been suggested to be used to examine and asses the HPA axis function in various disorders

*Correspondence: greg.elder@ncl.ac.uk
Biomedical Research Building, Campus for Ageing and Vitality, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne NE4 5PL, UK
Full list of author information is available at the end of the article

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Neurosci Biobehav Rev. 2010 Sep;35(1):97-103. doi: 10.1016/j.neubiorev.2009.12.011. Epub 2009 Dec 22.

The cortisol awakening response: more than a measure of HPA axis function.

Clow A[1], Hucklebridge F, Stalder T, Evans P, Thorn L.

⊕ Author information

Abstract

In most healthy people morning awakening is associated with a burst of cortisol secretion: the cortisol awakening response (CAR). It is argued that the CAR is subject to a range physiological regulatory influences that facilitate this rapid increase in cortisol secretion. Evidence is presented for reduced adrenal sensitivity to rising levels of ACTH in the pre-awakening period, mediated by an extra-pituitary pathway to the adrena… …on is considered… …es a combinatio… …nal sensitivity t… …y pathway. A…

PMID: 20026…

[Indexed for M…

"In most healthy people morning awakening is associated with a burst of cortisol secretion: the cortisol awakening response (CAR). It is argued that the CAR is subject to a range of physiological regulatory influences that facilitate this rapid increase in cortisol secretion."

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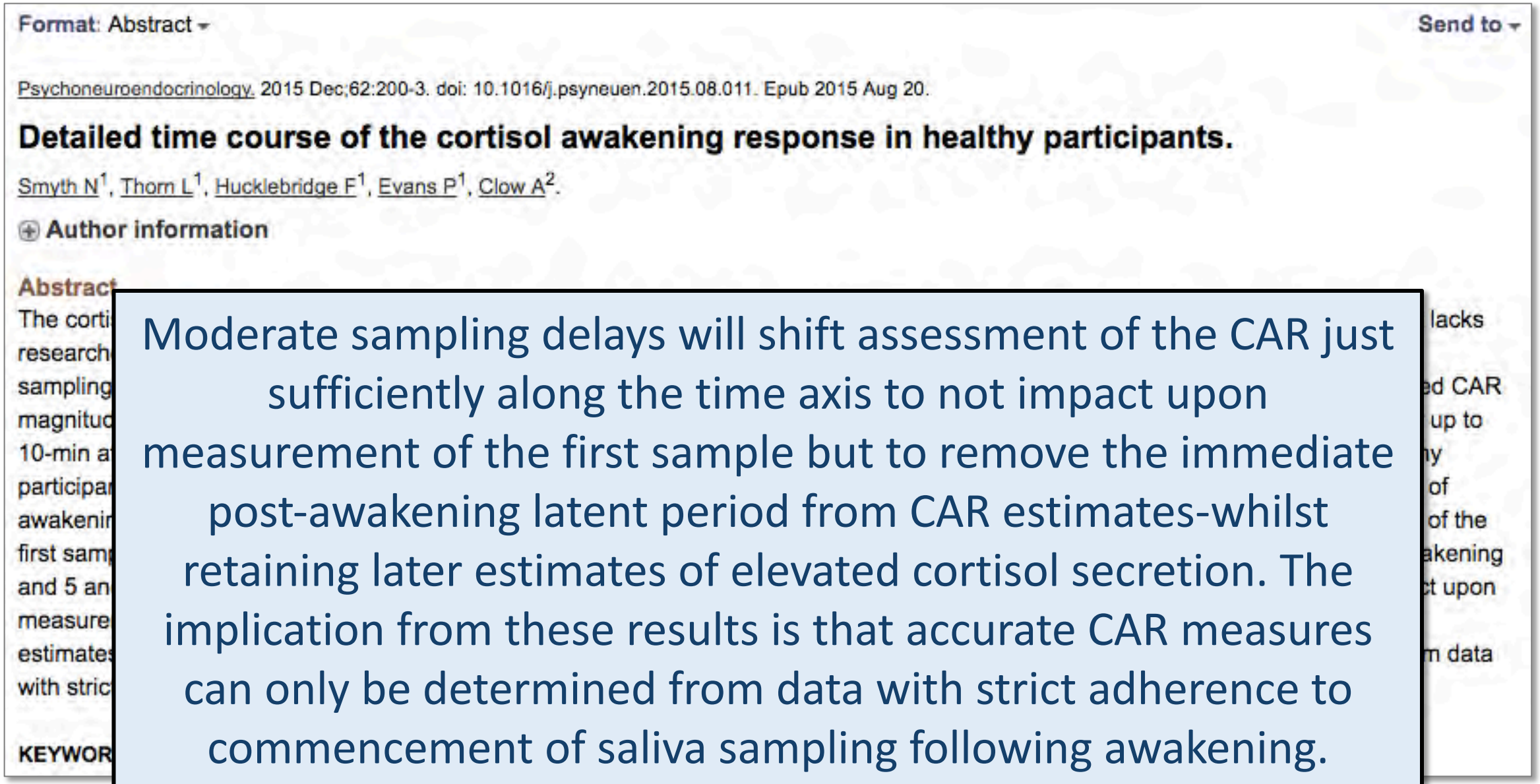

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Psychoneuroendocrinology. 2015 Dec;62:200-3. doi: 10.1016/j.psyneuen.2015.08.011. Epub 2015 Aug 20.

Detailed time course of the cortisol awakening response in healthy participants.

Smyth N[1], Thorn L[1], Hucklebridge F[1], Evans P[1], Clow A[2].

⊕ Author information

Abstract

The corti… lacks
research…
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magnitud… up to
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particip… of
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and 5 an… t upon
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estimates… m data
with stric…

KEYWOR…

Moderate sampling delays will shift assessment of the CAR just sufficiently along the time axis to not impact upon measurement of the first sample but to remove the immediate post-awakening latent period from CAR estimates-whilst retaining later estimates of elevated cortisol secretion. The implication from these results is that accurate CAR measures can only be determined from data with strict adherence to commencement of saliva sampling following awakening.

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What are the Causes of Adrenal Dysfunction and Alteration of the CAR?

- Traumatic emotional events
  - Stress at work
  - Early Life Emotional/Physical/Sexual abuse
- Physical trauma
- Chronic sleep deprivation
- Infections
- Dysbiosis/Microbiota changes
- Aging
- Inflammatory diseases
- Toxins
- Acute physical illness
- EMF/Dirty Electricity
- Nutritional insufficiencies
- Food intolerance or sensitivity
- Altered biotransformation
- Hormone Imbalance
- Genetics/SNPs

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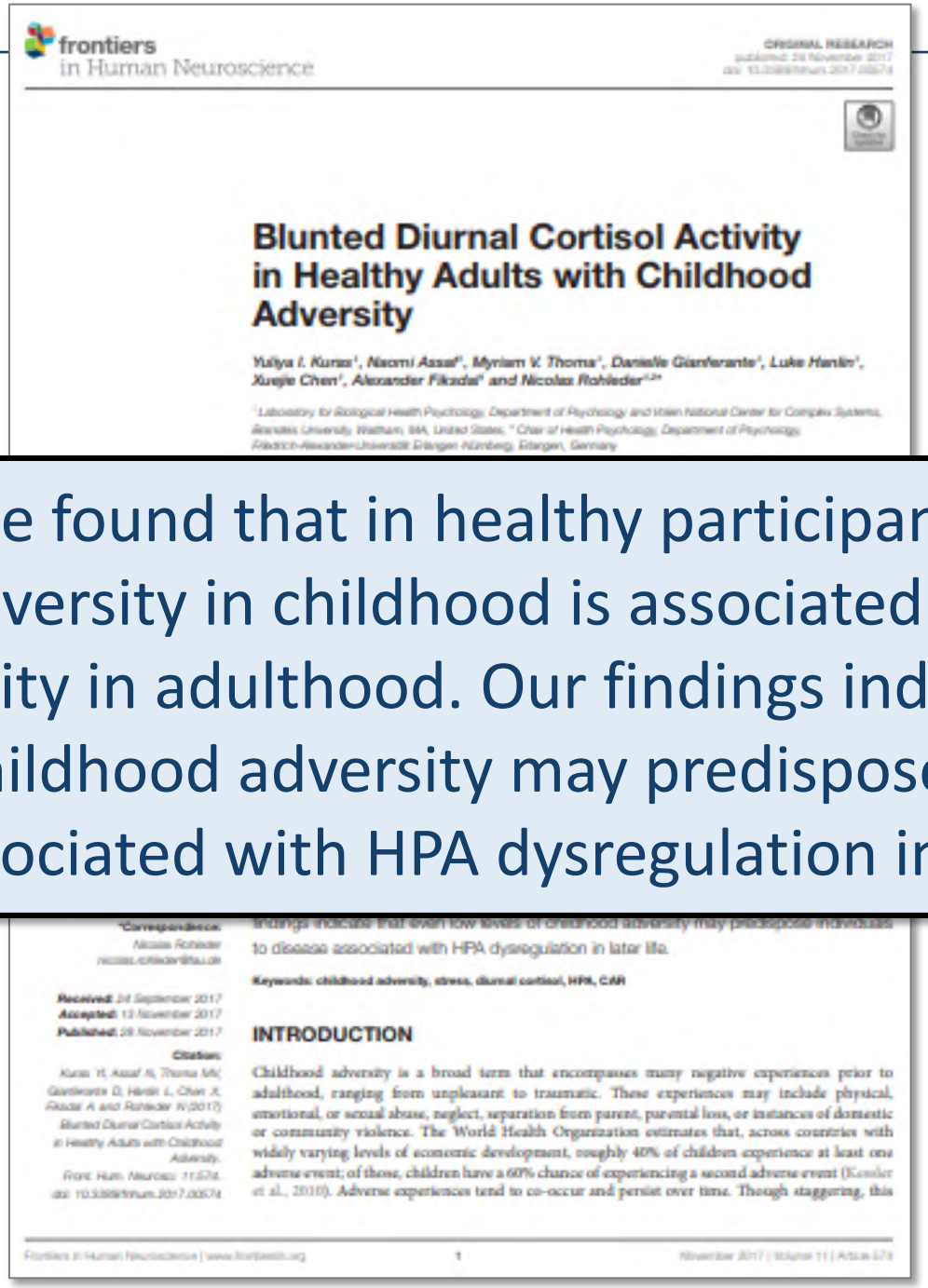

frontiers in Human Neuroscience

ORIGINAL RESEARCH

Blunted Diurnal Cortisol Activity in Healthy Adults with Childhood Adversity

Yuliya I. Kuras[1], Naomi Assaf[1], Myriam V. Thoma[1], Danielle Gianferante[1], Luke Hanlin[1], Xuejia Chen[1], Alexander Fikadu[1] and Nicolas Rohleder[1,2]*

[1] Laboratory for Biological Health Psychology, Department of Psychology and Klein National Center for Complex Systems, Brandeis University, Waltham, MA, United States, [2] Chair of Health Psychology, Department of Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

"Overall, we found that in healthy participants, low-to-moderate adversity in childhood is associated with altered basal HPA activity in adulthood. Our findings indicate that even low levels of childhood adversity may predispose individuals to disease associated with HPA dysregulation in later life."

*Correspondence:
Nicolas Rohleder
nicolas.rohleder@fau.de

Received: 24 September 2017
Accepted: 13 November 2017
Published: 28 November 2017

Citation:
Kuras YI, Assaf N, Thoma MV, Gianferante D, Hanlin L, Chen X, Fikadu A and Rohleder N (2017) Blunted Diurnal Cortisol Activity in Healthy Adults with Childhood Adversity. Front. Hum. Neurosci. 11:574. doi: 10.3389/fnhum.2017.00574

findings indicate that even low levels of childhood adversity may predispose individuals to disease associated with HPA dysregulation in later life.

Keywords: childhood adversity, stress, diurnal cortisol, HPA, CAR

INTRODUCTION

Childhood adversity is a broad term that encompasses many negative experiences prior to adulthood, ranging from unpleasant to traumatic. These experiences may include physical, emotional, or sexual abuse, neglect, separation from parent, parental loss, or instances of domestic or community violence. The World Health Organization estimates that, across countries with widely varying levels of economic development, roughly 40% of children experience at least one adverse event; of those, children have a 60% chance of experiencing a second adverse event (Kessler et al., 2010). Adverse experiences tend to co-occur and persist over time. Though staggering, this

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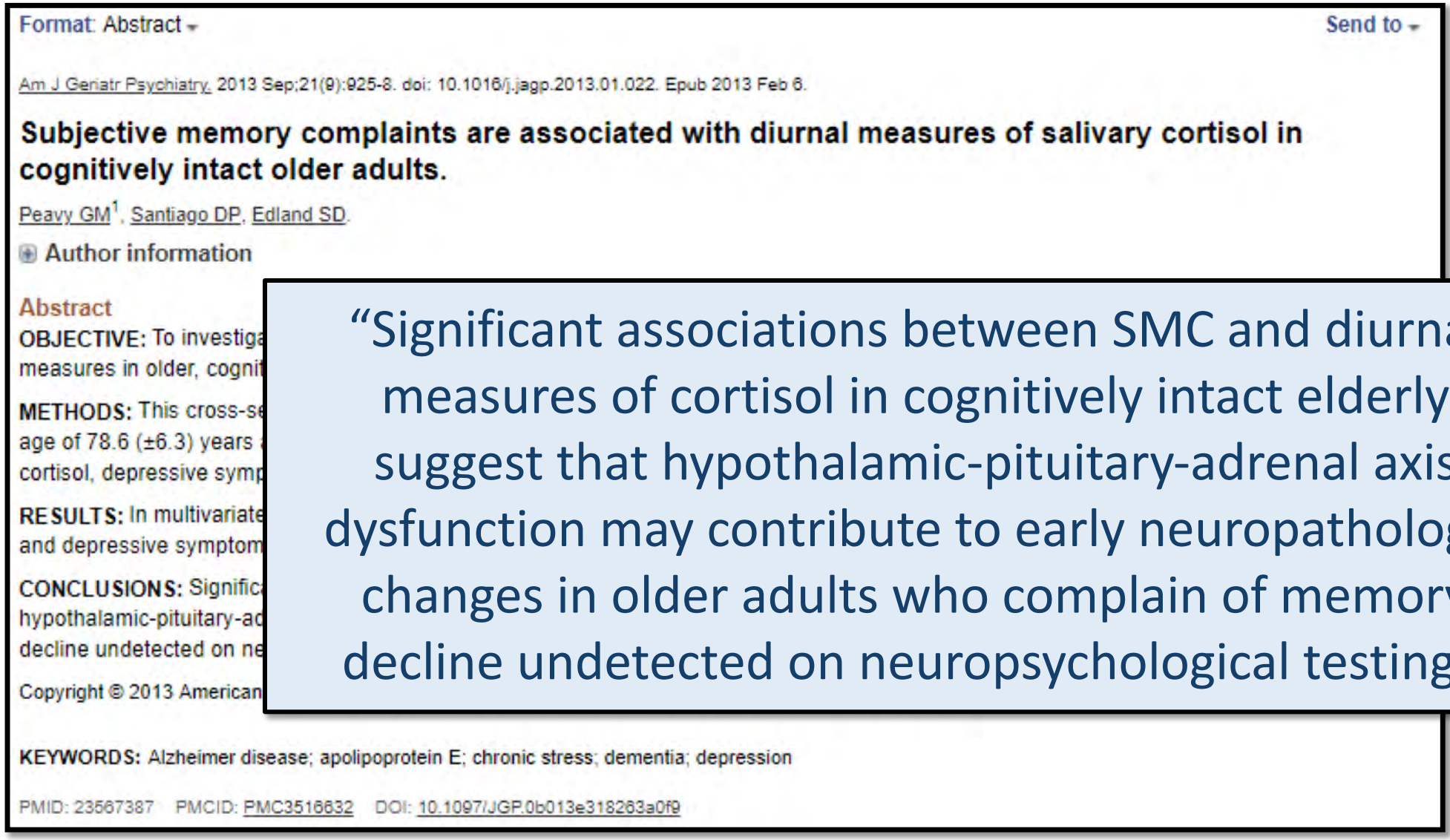

Format: Abstract ▾ Send to ▾

Am J Geriatr Psychiatry. 2013 Sep;21(9):925-8. doi: 10.1016/j.jagp.2013.01.022. Epub 2013 Feb 6.

Subjective memory complaints are associated with diurnal measures of salivary cortisol in cognitively intact older adults.

Peavy GM[1], Santiago DP, Edland SD.

Author information

Abstract

OBJECTIVE: To investiga
measures in older, cogni

METHODS: This cross-se
age of 78.6 (±6.3) years
cortisol, depressive symp

RESULTS: In multivariate
and depressive symptom

CONCLUSIONS: Signific
hypothalamic-pituitary-ad
decline undetected on ne

"Significant associations between SMC and diurnal measures of cortisol in cognitively intact elderly suggest that hypothalamic-pituitary-adrenal axis dysfunction may contribute to early neuropathologic changes in older adults who complain of memory decline undetected on neuropsychological testing."

KEYWORDS: Alzheimer disease; apolipoprotein E; chronic stress; dementia; depression

PMID: 23567387 PMCID: PMC3516632 DOI: 10.1097/JGP.0b013e318283a0f9

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Am J Geriatr Psychiatry. 2013 Sep;21(9):925-8. doi: 10.1016/j.jagp.2013.01.022. Epub 2013 Feb 6.

Subjective memory complaints are associated with diurnal measures of salivary cortisol in cognitively intact older adults.

Peavy GM[1], Santiago DP, Edland SD.

Author information

Abstract

OBJECTIVE: To investigate the relationship between subjective memory complaints (SMC) and the stress hormone cortisol using diurnal measures in older, cognitively intact subjects.

METHODS: This cross-sectional study co
age of 78.6 (±6.3) years and diagnosis o
cortisol, depressive symptoms, episodic

RESULTS: In multivariate logistic regress
and depressive symptoms were significa

CONCLUSIONS: Significant associations
hypothalamic-pituitary-adrenal axis dysfu
decline undetected on neuropsychologic

KEYWORDS: Alzheimer disease; apolipoprotein E; chronic stress; dementia; depression

PMID: 23567387 PMCID: PMC3516632 DOI: 10.1097/JGP.0b013e318283a0f9

"Therefore, targeting HPA axis dysfunction in the earliest stages of neurodegeneration could lead to disease modification prior to clinical manifestations and loss of independence."

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Format: Abstract Send to

Alzheimer Dis Assoc Disord. 2012 Jul-Sep;26(3):260-6. doi: 10.1097/WAD.0b013e3182389a9c.

The influence of chronic stress on dementia-related diagnostic change in older adults.

Peavy GM[1], Jacobson MW, Salmon DP, Gamst AC, Patterson TL, Goldman S, Mills PJ, Khandrika S, Galasko D.

Author information

Abstract

Increased susceptibility of the aging brain to both chronic stress and incipient dementia-related neuropathology may accelerate cognitive decline. We investigated associations between chronic stress and diagnostic change in 62 individuals (mean age, 78.7 y) participating in an Alzheimer disease research center longitudinal study. The subjects, diagnosed at baseline as cognitively normal (CN) or with mild cognitive impairment (MCI), were followed for an average of 2.5 years. Senior neurologists, blind to detailed measures of stress and cognition, assigned diagnoses annually. Logistic regressi
cortisol levels) predicted the conversion to MC
follow-up. Sixteen converted from cognitively n
MCI to dementia. The cortisol awakening resp
measures were not associated with the progre
the change to MCI. Mechanisms associated w
diagnostic change to dementia. These findings
different stages of susceptibility.

PMID: 22037597 PMCID: PMC3290680 DOI: 10.1097/WAD.0b013e3182389a9c

"The cortisol awakening response, with age and education, was associated with a diagnostic change to MCI."

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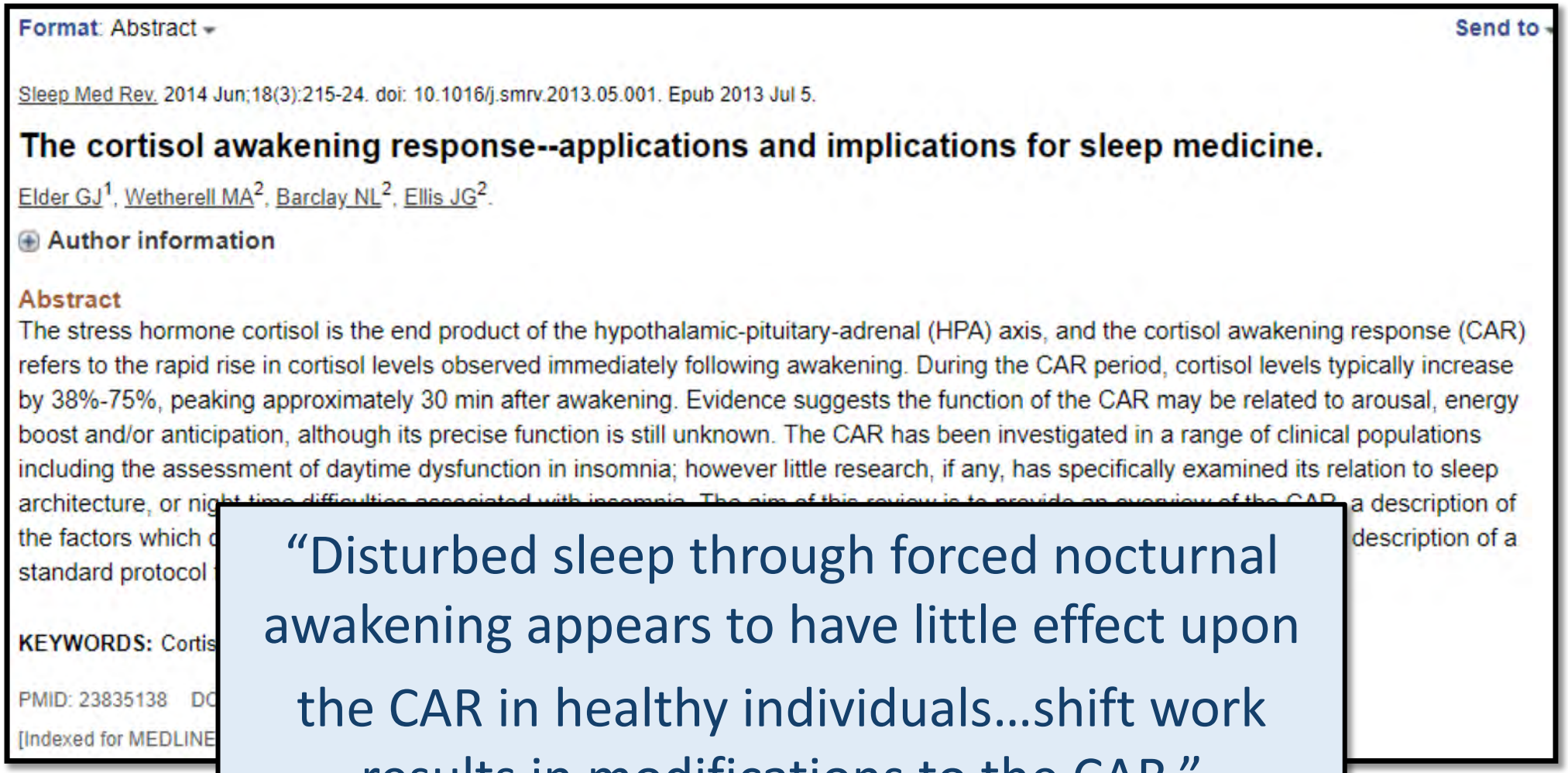

Format: Abstract

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Sleep Med Rev. 2014 Jun;18(3):215-24. doi: 10.1016/j.smrv.2013.05.001. Epub 2013 Jul 5.

The cortisol awakening response--applications and implications for sleep medicine.

Elder GJ[1], Wetherell MA[2], Barclay NL[2], Ellis JG[2].

Author information

Abstract

The stress hormone cortisol is the end product of the hypothalamic-pituitary-adrenal (HPA) axis, and the cortisol awakening response (CAR) refers to the rapid rise in cortisol levels observed immediately following awakening. During the CAR period, cortisol levels typically increase by 38%-75%, peaking approximately 30 min after awakening. Evidence suggests the function of the CAR may be related to arousal, energy boost and/or anticipation, although its precise function is still unknown. The CAR has been investigated in a range of clinical populations including the assessment of daytime dysfunction in insomnia; however little research, if any, has specifically examined its relation to sleep architecture, or night-time difficulties associated with insomnia. The aim of this review is to provide an overview of the CAR, a description of the factors which d description of a standard protocol

KEYWORDS: Cortis

PMID: 23835138 DO

[Indexed for MEDLINE

"Disturbed sleep through forced nocturnal awakening appears to have little effect upon the CAR in healthy individuals…shift work results in modifications to the CAR."

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Psychoneuroendocrinology. 2015 Dec;62:327-35. doi: 10.1016/j.psyneuen.2015.08.021. Epub 2015 Aug 28.

Diurnal salivary cortisol, glycemia and insulin resistance: The multi-ethnic study of atherosclerosis.

Joseph JJ[1], Wang X[2], Spanakis E[3], Seeman T[4], Wand G[1], Needham B[5], Golden SH[6].

Author information

Abstract

Hypercortisolism is associated with insulin resistance (IR) and diabetes mellitus (DM); however, to our knowledge prior studies have not examined the association of diurnal cortisol curve features with measures of glycemia or IR in a population-based setting. Using log-transformed salivary cortisol data on 850 ethnically diverse men and women from the Multi-Ethnic Study of Atherosclerosis, we investigated the cross-sectional association of cortisol curve features with (1) glycemia in those with and without DM and (2) IR, in non-diabetic subjects.

"Among participants with DM, cortisol curve parameters suggestive of higher hypothalamic-pituitary-adrenal (HPA) axis activity and dysfunction were associated with higher HbA1c. In non-diabetic participants, greater HPA activity was paradoxically associated with lower insulin resistance."

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Ann N Y Acad Sci. 2017 Mar;1391(1):20-34. doi: 10.1111/nyas.13217. Epub 2016 Oct 17.

Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus.

Joseph JJ[1], Golden SH[1].

Author information

Abstract

Controversy e… shown to increase the r… on of stress with diabetes … involved in adaptation tha… and the autonomic ne… ns for responding to… rtisol curve, including a bl… is also associated wi… HPA axis dysregulation…

"Depression is associated with cross-sectional and longitudinal alterations in the diurnal cortisol curve, including a blunted cortisol awakening response and flattening of the diurnal cortisol curve. Flattening of the diurnal cortisol curve is also associated with insulin resistance and type 2 diabetes mellitus."

KEYWORDS: …

PMID: 27750377 PMCID: PMC5334212 DOI: 10.1111/nyas.13217

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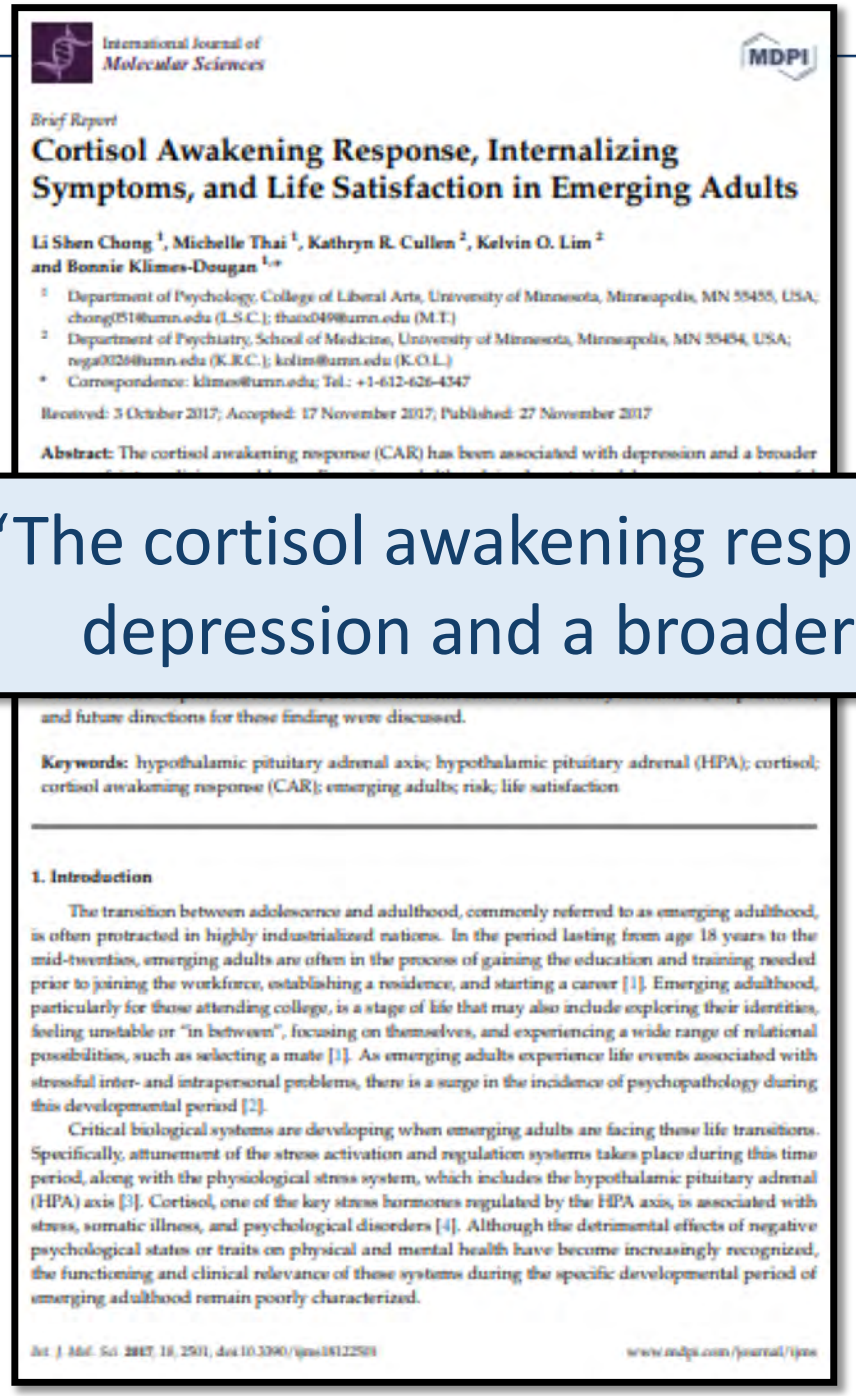

International Journal of Molecular Sciences

MDPI

Brief Report

Cortisol Awakening Response, Internalizing Symptoms, and Life Satisfaction in Emerging Adults

Li Shen Chong [1], Michelle Thai [1], Kathryn R. Cullen [2], Kelvin O. Lim [2] and Bonnie Klimes-Dougan [1,*]

[1] Department of Psychology, College of Liberal Arts, University of Minnesota, Minneapolis, MN 55455, USA; chong0518@umn.edu (L.S.C.); thaix049@umn.edu (M.T.)

[2] Department of Psychiatry, School of Medicine, University of Minnesota, Minneapolis, MN 55454, USA; rega0026@umn.edu (K.R.C.); kolim@umn.edu (K.O.L.)

* Correspondence: klimes@umn.edu; Tel.: +1-612-626-4347

Received: 3 October 2017; Accepted: 17 November 2017; Published: 27 November 2017

Abstract: The cortisol awakening response (CAR) has been associated with depression and a broader

and future directions for these finding were discussed.

Keywords: hypothalamic pituitary adrenal axis; hypothalamic pituitary adrenal (HPA); cortisol; cortisol awakening response (CAR); emerging adults; risk; life satisfaction

1. Introduction

The transition between adolescence and adulthood, commonly referred to as emerging adulthood, is often protracted in highly industrialized nations. In the period lasting from age 18 years to the mid-twenties, emerging adults are often in the process of gaining the education and training needed prior to joining the workforce, establishing a residence, and starting a career [1]. Emerging adulthood, particularly for those attending college, is a stage of life that may also include exploring their identities, feeling unstable or "in between", focusing on themselves, and experiencing a wide range of relational possibilities, such as selecting a mate [1]. As emerging adults experience life events associated with stressful inter- and intrapersonal problems, there is a surge in the incidence of psychopathology during this developmental period [2].

Critical biological systems are developing when emerging adults are facing these life transitions. Specifically, attunement of the stress activation and regulation systems takes place during this time period, along with the physiological stress system, which includes the hypothalamic pituitary adrenal (HPA) axis [3]. Cortisol, one of the key stress hormones regulated by the HPA axis, is associated with stress, somatic illness, and psychological disorders [4]. Although the detrimental effects of negative psychological states or traits on physical and mental health have become increasingly recognized, the functioning and clinical relevance of these systems during the specific developmental period of emerging adulthood remain poorly characterized.

"The cortisol awakening response (CAR) has been associated with depression and a broader range of internalizing problems."

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Int J Mol Sci. 2017 Oct 24;18(10). pii: E2226. doi: 10.3390/ijms18102226.

Diurnal Hypothalamic-Pituitary-Adrenal Axis Measures and Inflammatory Marker Correlates in Major Depressive Disorder.

Doolin K[1], Farrell C[2], Tozzi L[3,4], Harkin A[5], Frodl T[6], O'Keane V[7,8].

⊕ Author information

Abstract

Dysregulation of the hypothalamic-pituitar
Depressive Disorder (MDD). Cortisol is of
levels. Some methods of cortisol measure
relatively inert cortisone, therefore this stu
catalyzing enzyme 11β-hydroxysteroiddeh
known to regulate the body's immune syst
were collected from 57 MDD patients and 40 healthy controls at five post-wakening time points (0, +30, +60, +720 and +750 min).
Glucocorticoid concentrations were measured by liquid chromatography mass spectrometry. Whole blood mRNA expression of several inflammatory markers was measured by quantitative polymerase chain reaction. This study replicated the common finding of elevated morning cortisol and reduced CAR reactivity in MDD and found no differences in cortisone or 11β-HSD1 mRNA measures. There was a negative association between interleukin 1-β (IL-1β) mRNA and morning cortisol reactivity within the depressed group, indicating that dysregulation of the HPA axis and immune system may be interconnected.

KEYWORDS: cortisol awakening response; hypothalamic-pituitary-adrenal axis; immune system; inflammation; major depressive disorder

PMID: 29064428 PMCID: PMC5666905 DOI: 10.3390/ijms18102226

"This study replicated the common finding of elevated morning cortisol and reduced CAR reactivity in MDD"

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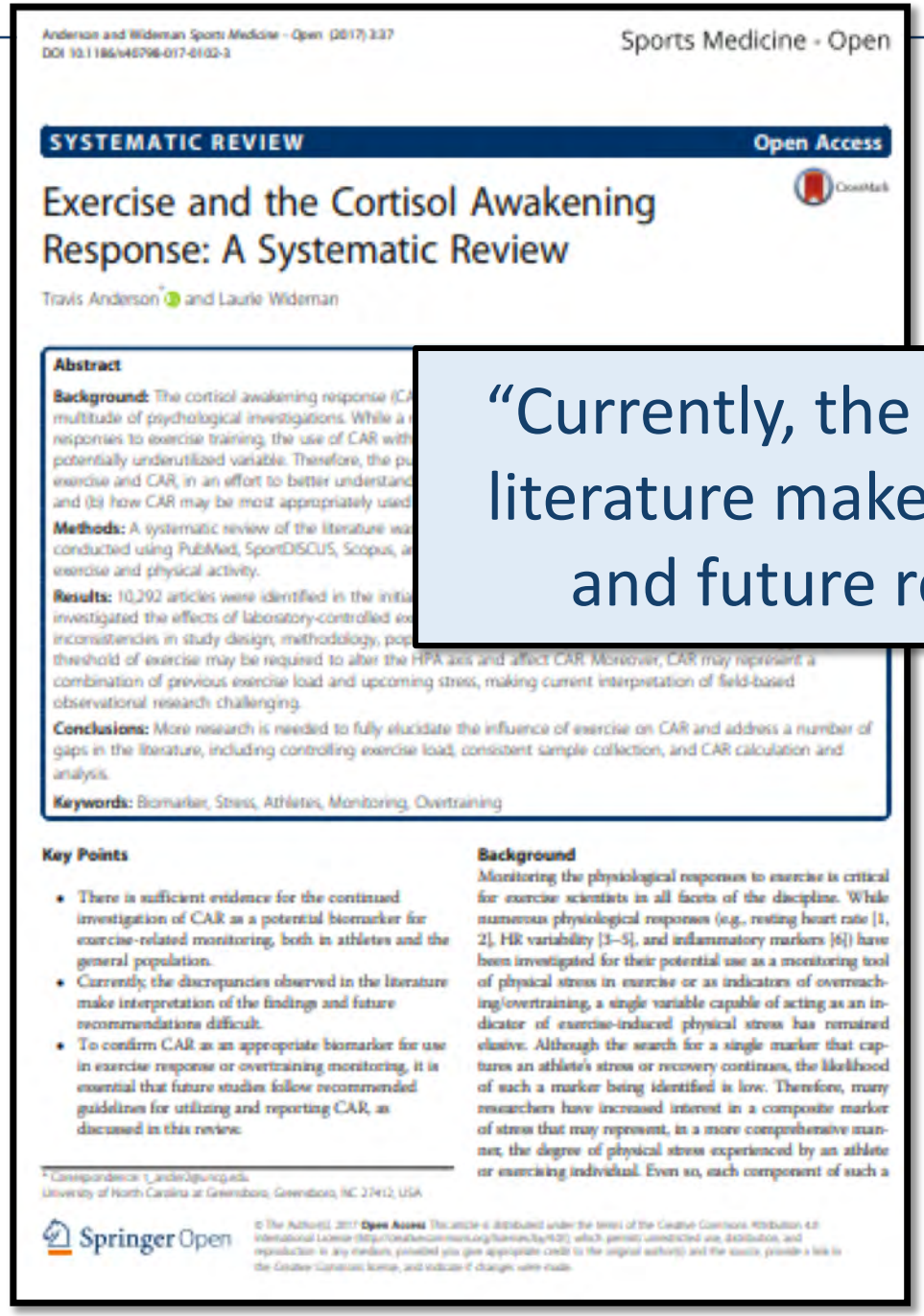

Anderson and Wideman Sports Medicine - Open (2017) 3:37
DOI 10.1186/s40798-017-0102-3

Sports Medicine - Open

SYSTEMATIC REVIEW Open Access

Exercise and the Cortisol Awakening Response: A Systematic Review

Travis Anderson* and Laurie Wideman

Abstract

Background: The cortisol awakening response (CA
multitude of psychological investigations. While a
responses to exercise training, the use of CAR with
potentially underutilized variable. Therefore, the pu
exercise and CAR, in an effort to better understand
and (b) how CAR may be most appropriately used

Methods: A systematic review of the literature wa
conducted using PubMed, SportDISCUS, Scopus, a
exercise and physical activity.

Results: 10,292 articles were identified in the initia
investigated the effects of laboratory-controlled ex
inconsistencies in study design, methodology, pop
threshold of exercise may be required to alter the HPA axis and affect CAR. Moreover, CAR may represent a combination of previous exercise load and upcoming stress, making current interpretation of field-based observational research challenging.

Conclusions: More research is needed to fully elucidate the influence of exercise on CAR and address a number of gaps in the literature, including controlling exercise load, consistent sample collection, and CAR calculation and analysis.

Keywords: Biomarker, Stress, Athletes, Monitoring, Overtraining

Key Points

- There is sufficient evidence for the continued investigation of CAR as a potential biomarker for exercise-related monitoring, both in athletes and the general population.
- Currently, the discrepancies observed in the literature make interpretation of the findings and future recommendations difficult.
- To confirm CAR as an appropriate biomarker for use in exercise response or overtraining monitoring, it is essential that future studies follow recommended guidelines for utilizing and reporting CAR, as discussed in this review.

Background

Monitoring the physiological responses to exercise is critical for exercise scientists in all facets of the discipline. While numerous physiological responses (e.g., resting heart rate [1, 2], HR variability [3–5], and inflammatory markers [6]) have been investigated for their potential use as a monitoring tool of physical stress in exercise or as indicators of overreaching/overtraining, a single variable capable of acting as an indicator of exercise-induced physical stress has remained elusive. Although the search for a single marker that captures an athlete's stress or recovery continues, the likelihood of such a marker being identified is low. Therefore, many researchers have increased interest in a composite marker of stress that may represent, in a more comprehensive manner, the degree of physical stress experienced by an athlete or exercising individual. Even so, each component of such a

* Correspondence: t_ander2@uncg.edu
University of North Carolina at Greensboro, Greensboro, NC 27412, USA

"Currently, the discrepancies observed in the literature make interpretation of the findings and future recommendations difficult."

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Front Hum Neurosci. 2017 Jun 26;11:315. doi: 10.3389/fnhum.2017.00315. eCollection 2017.

Yoga, Meditation and Mind-Body Health: Increased BDNF, Cortisol Awakening Response, and Altered Inflammatory Marker Expression after a 3-Month Yoga and Meditation Retreat.

Cahn BR[1,2], Goodman MS[3], Peterson CT[4,5], Maturi R[6,7], Mills PJ[4].

⊕ Author information

Abstract

Thirty-eight individuals (mean age: 34.8 years old
intervention for psychometric measures, brain de
inflammatory cytokines. Participation in the retrea
as increases in mindfulness. As hypothesized, in
awakening response (CAR) were also observed.
at both the pre-retreat ($r = 0.40$, $p < 0.05$) and po
smaller pre- to post-retreat increases in plasma B
the yoga and meditation practices, we found that
inflammatory cytokine Interleukin-12 was reduce
cytokines, including Interferon Gamma (IFN-γ), Tumor Necrosis Factor (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Interleukin-8 (IL-8) were increased after the retreat. Given evidence from previous studies of the positive effects of meditative practices on mental fitness, autonomic homeostasis and inflammatory status, we hypothesize that these findings are related to the meditative practices throughout the retreat; however, some of the observed changes may also be related to other aspects of the retreat such as physical exercise-related components of the yoga practice and diet. We hypothesize that the patterns of change observed here reflect mind-body integration and well-being. The increased BDNF levels observed is a potential mediator between meditative practices and brain health, the increased CAR is likely a reflection of increased dynamic physiological arousal, and the relationship of the dual enhancement of pro- and anti-inflammatory cytokine changes to healthy immunologic functioning is discussed.

KEYWORDS: BDNF; cortisol; inflammation; inflammatory markers; meditation; stress; yoga

PMID: 28694775 PMCID: PMC5483482 DOI: 10.3389/fnhum.2017.00315

"Participation in the retreat was found to be associated with decreases in self-reported anxiety and depression as well as increases in mindfulness."

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What are the Causes of Adrenal Dysfunction and Alteration of the CAR?

- Traumatic emotional events
  - Stress at work
  - Early life emotional/physical/sexual abuse
- Physical trauma
- Chronic sleep deprivation
- Infections
- Dysbiosis/microbiota changes
- Aging
- Inflammatory diseases
- Toxins
- Acute physical illness
- EMF/dirty electricity
- Nutritional insufficiencies
- Food intolerance or sensitivity
- Altered biotransformation
- Hormone imbalance
- Genetics/SNPs

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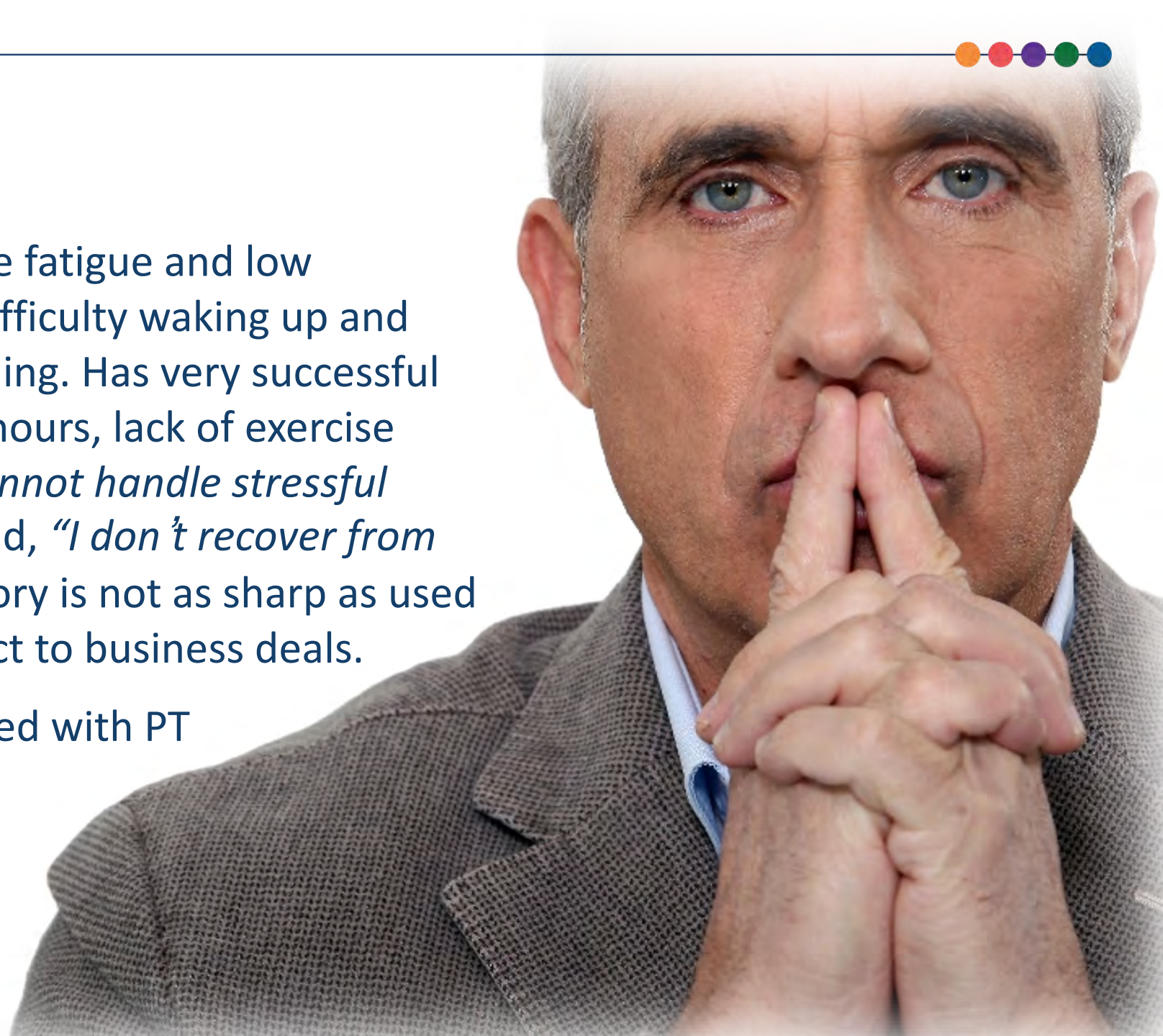
My Clinical Approach to Treatment of Adrenal Dysfunction

The 3 or 4 Tiered Approach:

- **Tier #1: The Foundation**
  - Lifestyle modification-KEY
  - Nutritional support with wholesome food (fresh, whole, unprocessed, organic, colorful - phytonutrient spectrum (servings, fermented, high fiber, nuts and seeds)
  - Targeted dietary interventions – personalize your elimination diet and plan
  - Mind / body / spirit equilibrium
  - Exercise: adjust for stage
- **Tier #2: Supplements/nutraceuticals**
- **Tier #3: Botanicals/adaptogens**
  - Adjust for stage or hypo vs hyper cortisol
- **Tier #4: Hormonal replacement**

Case Study

- 54 yo male with progressive fatigue and low motivation. Having more difficulty waking up and "getting going" in the morning. Has very successful own business. Works long hours, lack of exercise except walking. Finding *"cannot handle stressful situations like I used to"* and, *"I don't recover from stress like I used to."* Memory is not as sharp as used to be especially with respect to business deals.
- PMH: Low back pain resolved with PT
- Meds: none



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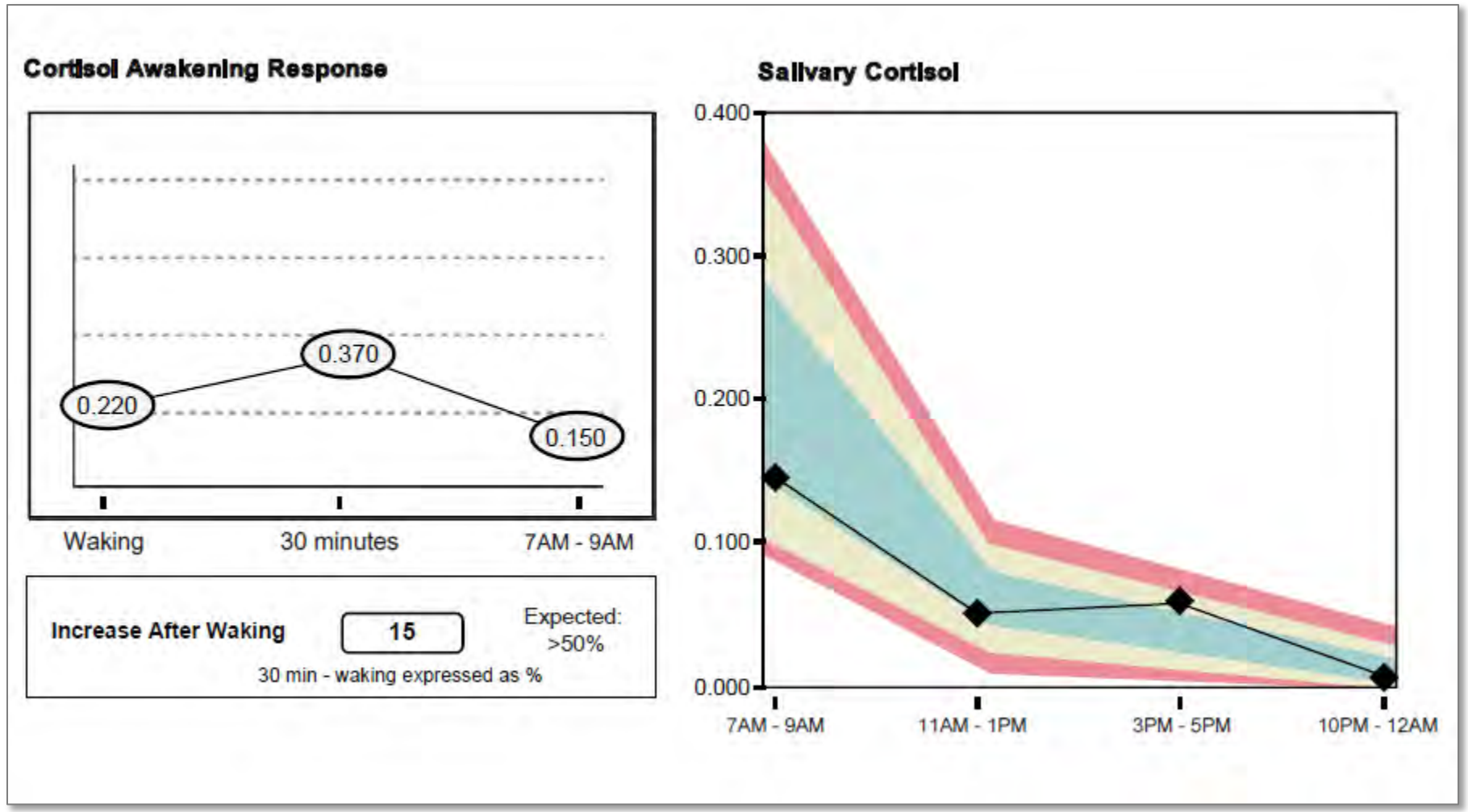
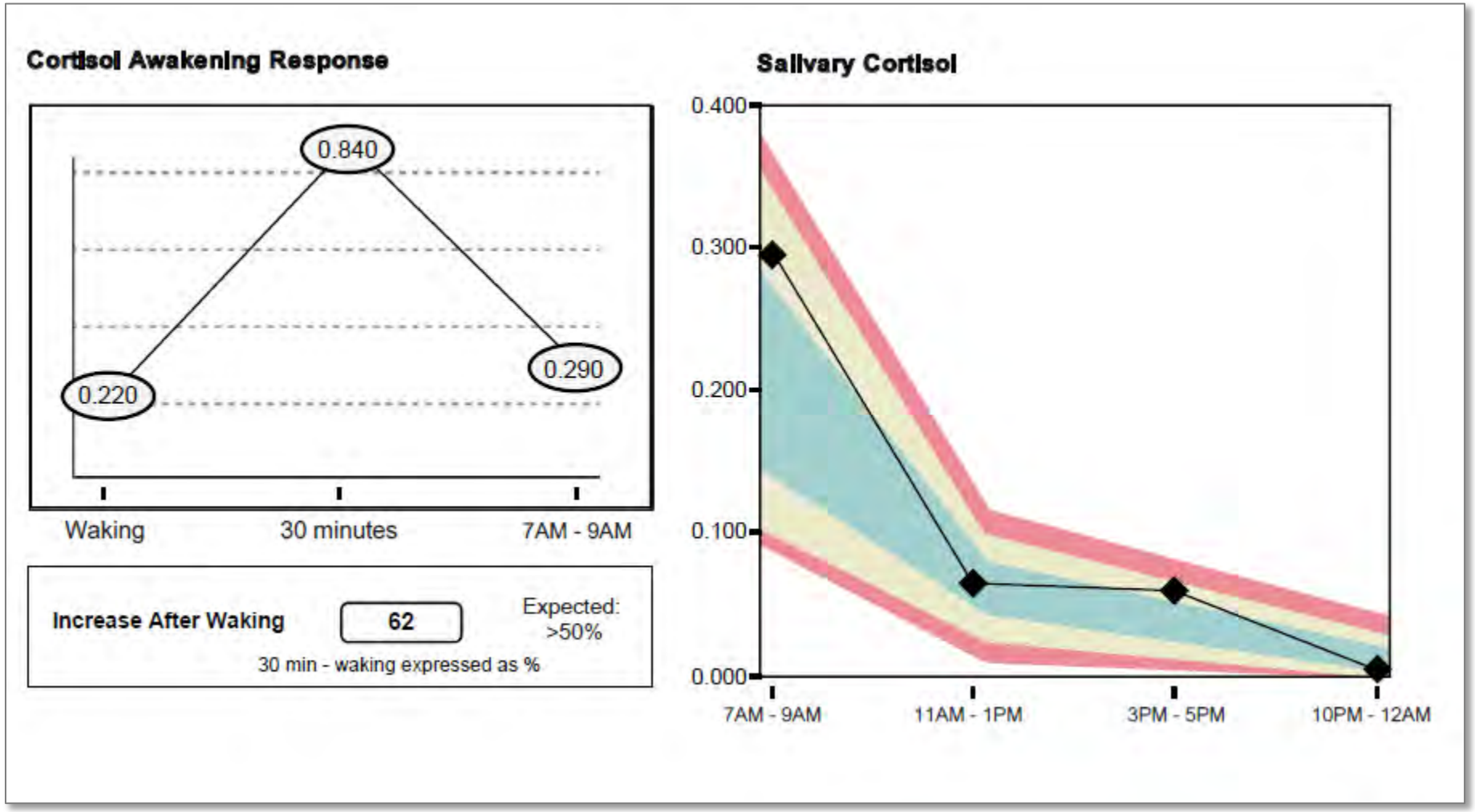

Cortisol Awakening Response
0.370
0.220
0.150
Waking
30 minutes
7AM - 9AM
Increase After Waking
15
Expected:
>50%
30 min - waking expressed as %
Salivary Cortisol
0.400
0.300
0.200
0.100
0.000
7AM - 9AM
11AM - 1PM
3PM - 5PM
10PM - 12AM

Initial Treatment

- **Diet/Nutrition**
  - 10 servings veg/2 fruits
  - 35g fiber
  - Zn and Se support foods
- **Nutraceuticals**
  - MVI
  - B Complex
  - Magnesium
  - Vitamin C
  - Methyl B12 IM
  - CoQ10
  - Glutathione support
- **Lifestyle Modification**
  - Yoga
  - HRV
  - Time for Self
  - Spiritual practice
  - Exercise

Repeat Salivary Adrenal Profile (3 months later)



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What would you do now?

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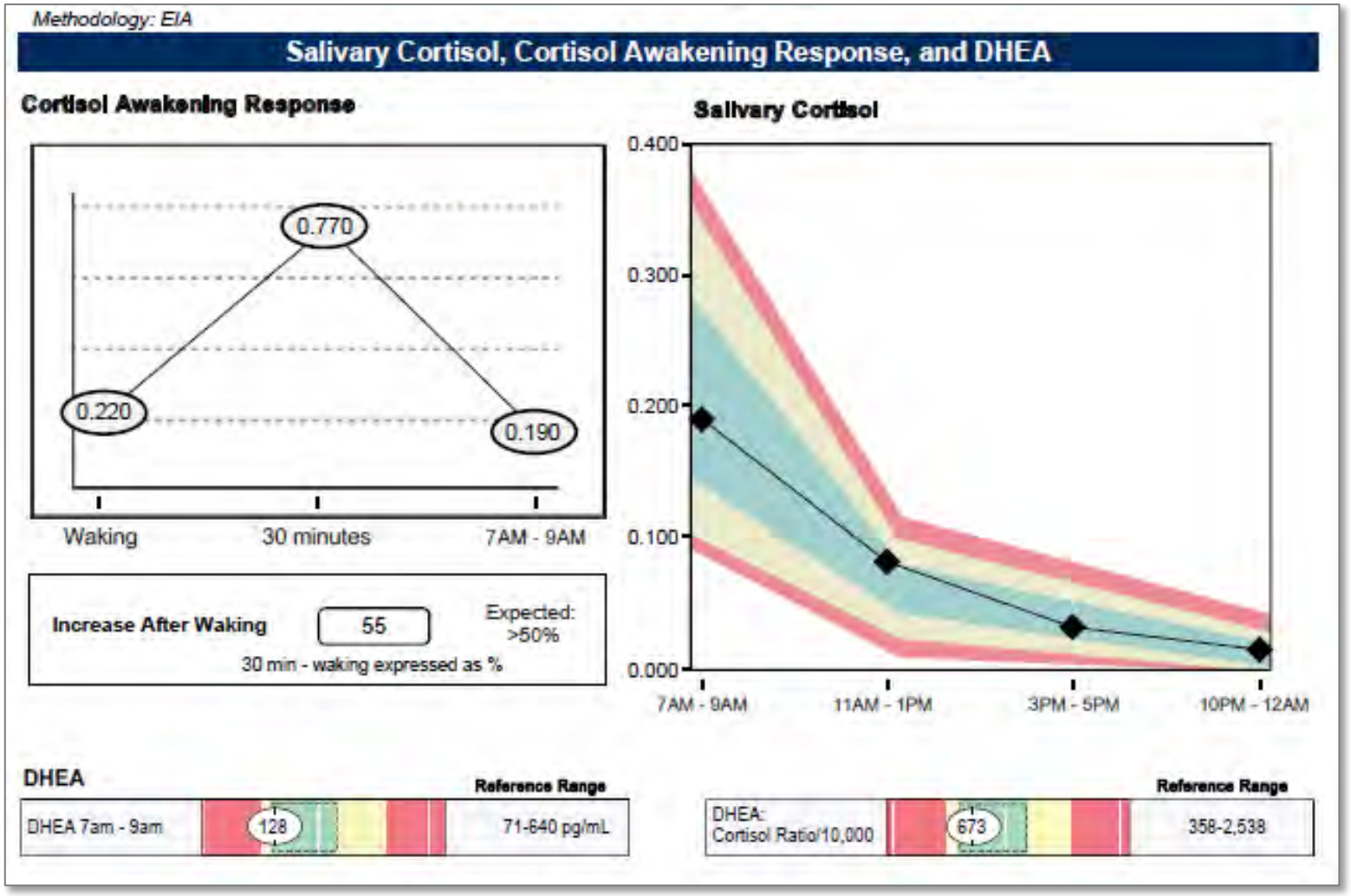
Repeat Salivary Adrenal Profile (8 months later)



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Lahnor Powell, ND, MPH
Moderator

Filomena Trindade, MD, MPH
Presenter

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- Review a profile that has already been completed on one of your patients

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Michelle Maddux, ND

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Are You Tired of Being Tired?

Filomena Trindade, MD, MPH, ABFM, ABOIM

April 25, 2018

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