Biological Signature of Life Stresses:
Allostatic load; Dynamic Range Compression

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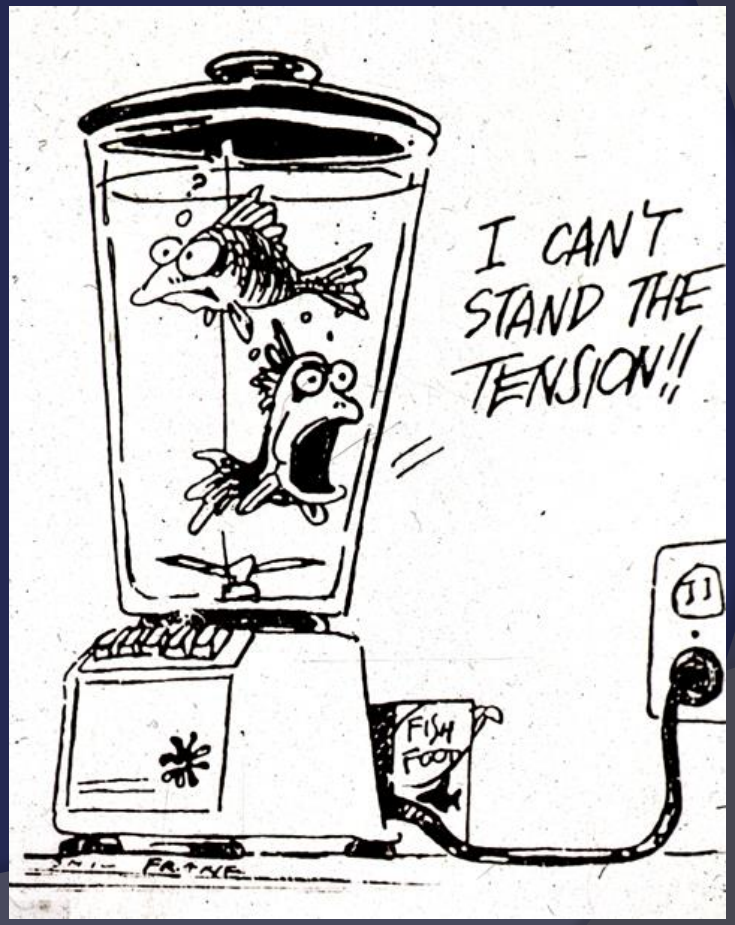
The Research Question

How do stresses over the life course get under our skin to affect biology, health, and how we age?

Life Stresses: Good, Bad, or Ugly ?

The Good: Induces an adaptive response which improves efficiency and is self-preserving

The Bad: Sustained or frequent ‘tension’ ultimately results in poor health, and in old age – loss of independence outcomes



The Good: Adaptive Stress Response
Allostasis

Adaptation of the internal physiological milieu in response to external challenges is critical to survival

Allostasis; Sterling and Eyer 1988

Adaptation capacity (allostatic reserve) is critical also to ecosystems, entire species, human communities, business enterprises

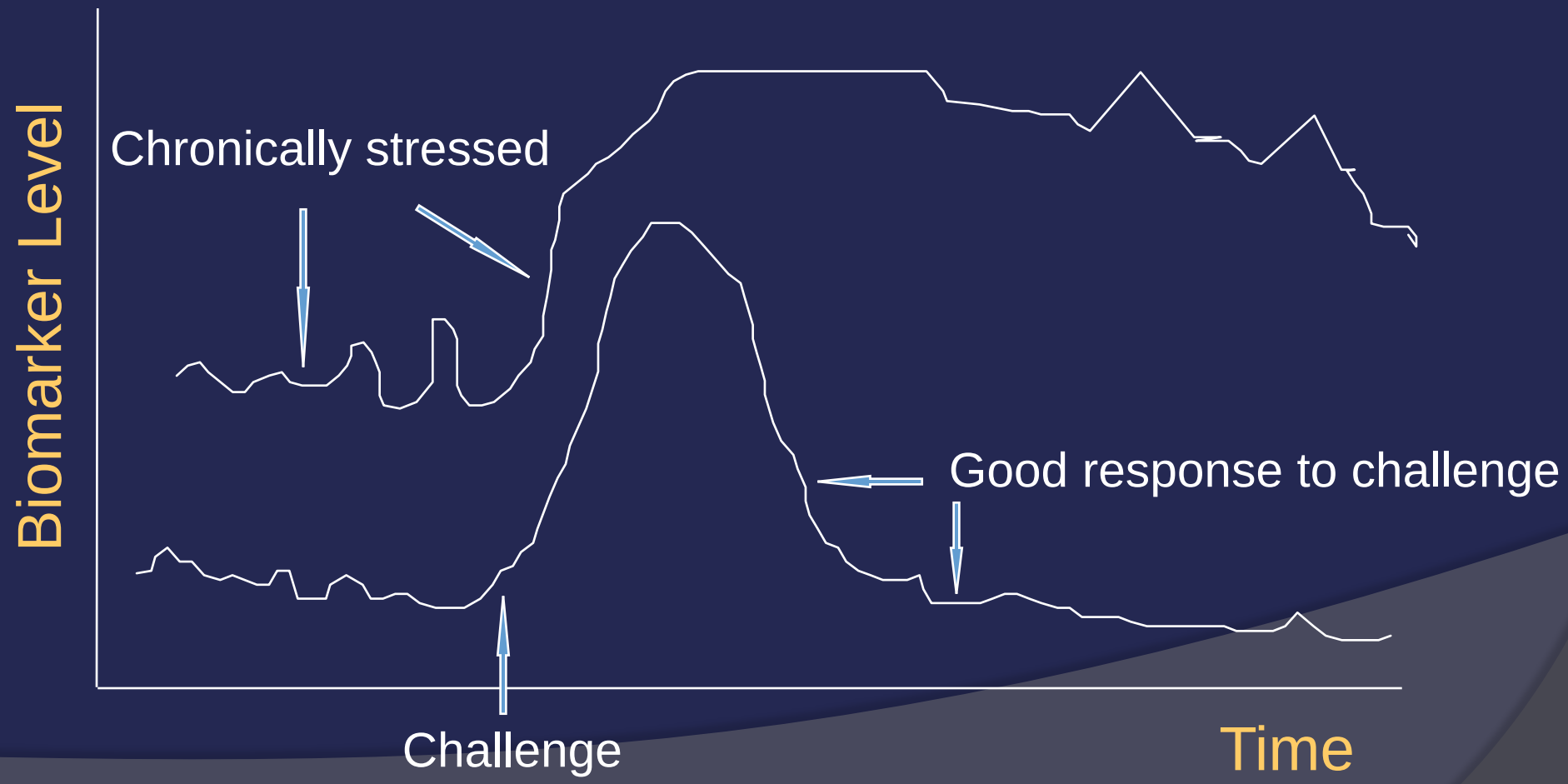
The Bad: Allostatic Load
Physiological Dysregulation as Consequence of Life Stresses

Frequent and repeated allostasis in the face of recurring stressors leads to dysregulated physiology in stress response systems

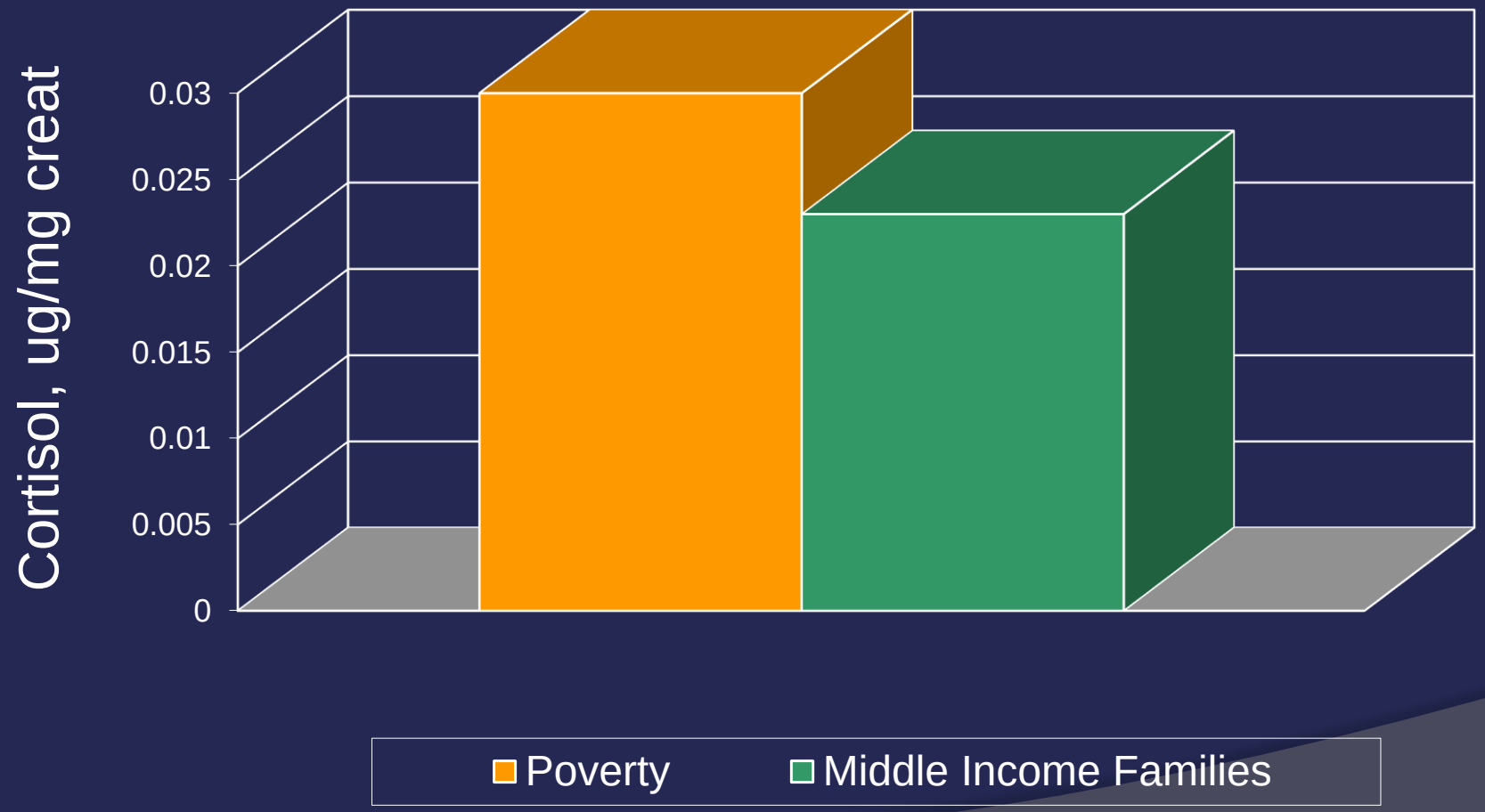
Allostatic Load; McEwen and Stellar 1993

Examples of dysregulation:
- Altered resting levels
- Altered reactivity
- Sluggish return to resting level

Dysregulation



Income level and Resting Overnight Cortisol
Children, ages 8-12



Evans & English, 2002

Allostatic load is more than altered resting states

- Reduction in reactivity to new challenges is also a consequence of too much stress

  - burn out or vital exhaustion

- Reduction in adaptation capacity is also a hallmark of aging, and seen in nearly every physiological system

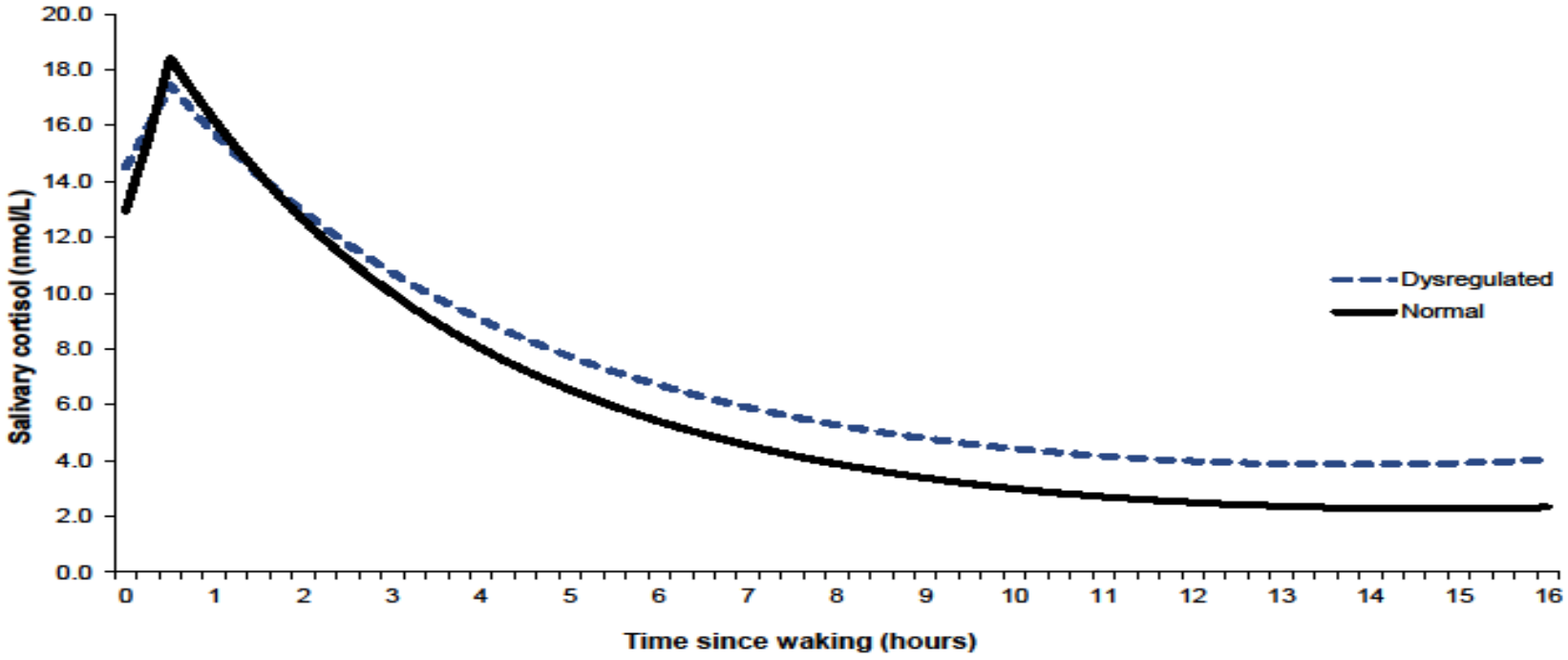
  - homeostenosis of aging

Cortisol Diurnal Rhythm – Spotlight on Homeostenosis

- Both, blunting of the cortisol morning peak and slowing of the rapid decline are seen in chronically stressed individuals
- The diurnal dynamic range (peak minus nadir) correlates strongly with dexamethasone suppression of the HPA axis (Dallman, ‘94)
- Compression of the diurnal dynamic range appears to be an indicator of HPA axis dysregulation.

Dallman et al., *Annals NYAS* 1994
Rosmond et al., *JCEM* 1998

Cortisol Diurnal Rhythm Dysregulation

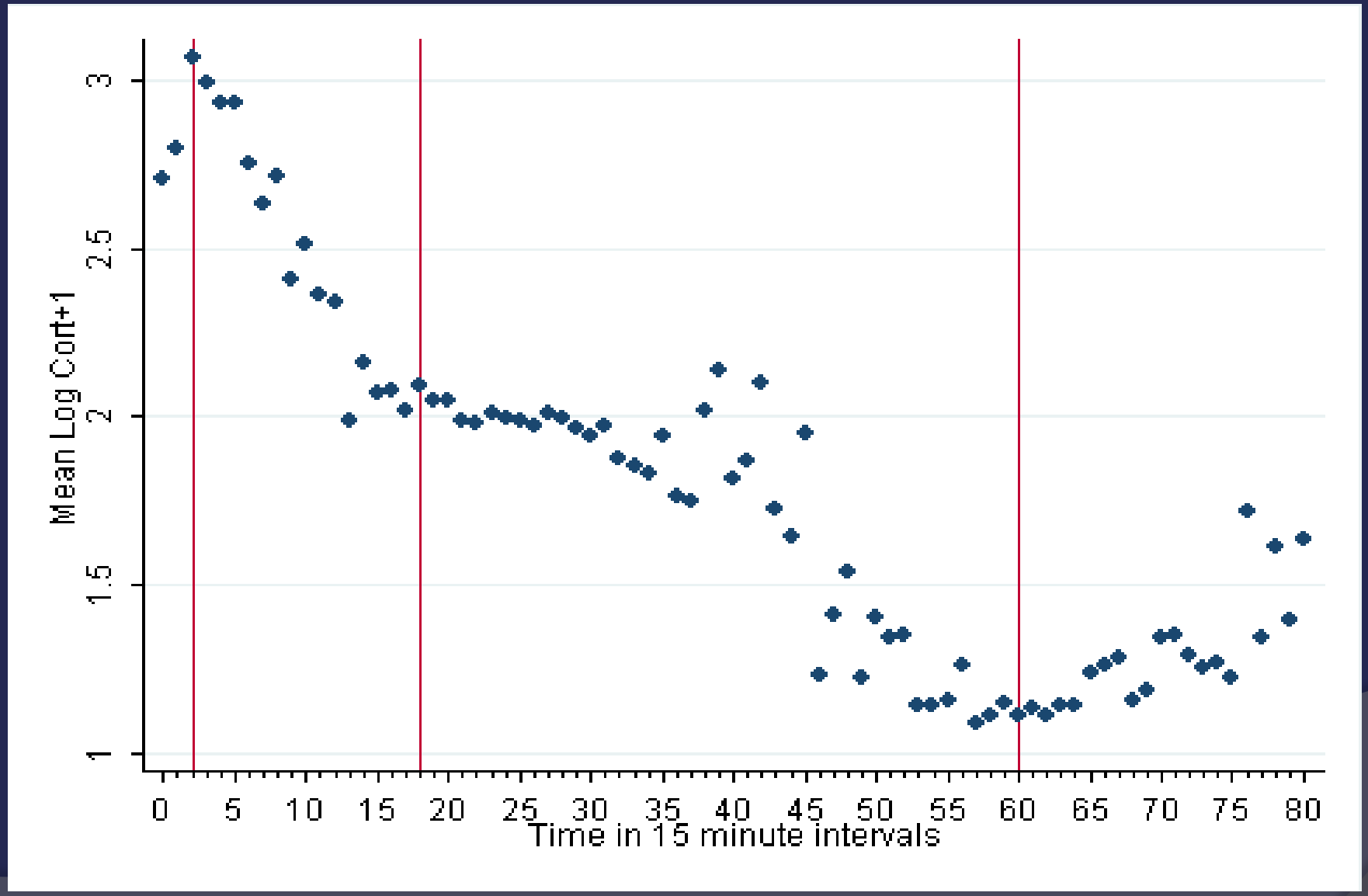


Midlife in the United States (MIDUS)
National Study of Daily Experiences

Wave II of MIDUS included a study of daily cortisol trajectories

- Salivary cortisol collected in 1,693 participants, ages 35-84y
- Collections on 4 days (including a weekend day); 6,318 days
- Sampled at 4 times in the day; total 24,388 samples
  - On waking
  - ~30 minutes after waking
  - Before lunch
  - At bedtime

Mean Cortisol Diurnal Ryhthm



Mutually Adjusted Effects on Diurnal Peak, Nadir, AUC

	Waking	Peak	Nadir	AUC
Mean:	2.63	2.98	1.12	29.0
Age: 60-74 y	+ 0.01	+ 0.08	+ 0.09	+ 1.29
75-84 y	+ 0.08	+ 0.17	+ 0.29	+ 3.90
Sex: Male	+ 0.11	+ 0.01	+ 0.09	+ 1.72
Race: Non-white	- 0.29	- 0.23	+ 0.19	+ 0.05
Educ: HS	- 0.08	- 0.08	+ 0.01	- 0.19
< HS	- 0.14	- 0.10	+ 0.06	- 0.21
Unit	log (nmol/L)	log (nmol/L)	log (nmol/L)	log (nmol/L)-hour

Findings
Two types of changes in cortisol diurnal rhythm

- Older people compared to younger, and men compared to women, start at a higher level of cortisol and stay higher the entire day
  - Peak, nadir and AUC (total exposure) are all higher

? Normal biology

- Less educated compared to higher educated, and non-whites compared to whites, start at a lower level and have a smaller peak but a higher nadir
  - Dispersion from nadir to peak is compressed
  - AUC is unaffected

? Dysregulation

Effects are adjusted for the other variables

Homeostenosis Hypotheses

- Compression of the diurnal cortisol dynamic range (the magnitude of the dispersion from nadir to peak) is a manifestation of allostatic load (dysregulation resulting from stresses over the life course)

- Cortisol's diurnal dynamic range is an index of the HPA axis' ability to respond robustly to new challenges. Smaller diurnal dynamic range indicates reduced ability to react.

Early life adversity
Effect on cortisol diurnal rhythm in adulthood

Early life adversity measured in MIDUS Wave I (recall)

- Childhood socio-economic adversity (range, 0-3)

  Low parental education + Family on welfare + Perceived status worse than others
- Childhood emotional adversity (range, 0-3)

  Parent death + parent divorce + physical or emotional abuse
- Childhood total adversity = Sum of above two measures

Cortisol diurnal rhythms from MIDUS Wave II (9-10 years later)

- Individual specific dynamic range and AUC created from mixed effects models
- Based on 4 samples per day over 4 consecutive days

Early life adversity and adult cortisol diurnal rhythm
Findings from MIDUS

Childhood adversity	**AUC** log (nmol/L)-hour		**Dynamic Range** log (nmol/L)	
Models:	**Adjusted for age, race, sex**	**+ control for adult SES***	**Adjusted for age, race, sex**	**+ control for adult SES***
Sample size:	N=1,696	N=1,612	N=1,696	N=1,612
SES Adversity (0-3)	-0.104	-0.097	**-0.0340**	-0.0253
Emotional adversity (0-6)	0.174	0.113	**-0.0388**	-0.0261
Total adversity (0-6)	0.032	0.009	**-0.0300**	**-0.0215**

* Controlled for Income poverty ratio and education level
Effects per unit of adversity scale

Inference

- Consistent with the hypothesis that stresses over the life course lead to compression of the cortisol dynamic range, we find that childhood adversity is associated with a smaller dynamic range but not with increased total exposure to cortisol

- Stress-related dysregulation manifests as compressed dynamic range not greater secretion of cortisol

But are there health implications of dynamic range compression?

Health Implications

- Flat diurnal cortisol rhythms have been linked to atherosclerosis (Toledo-Corral 2013) and lower cognitive function.
- A robust cortisol peak is critical to post-synaptic dendritic spine formation after learning in the brain cortex of mice (Liston 2013)
- A low nightly trough is needed to stabilize the new spines (needed for long-term retention of learned motor skills)

Liston et al., *Nature Neuroscience* 2013

HPA Axis and Cognition
Findings from MIDUS

	Episodic memory	Executive function
Diurnal cortisol rhythm		
AUC	-0.005	0.019
Dynamic range	0.055	0.052
Overnight cortisol		
Overnight level	0.047	0.021

Adjusted for age, sex, race, chronic conditions, education, smoking

Each SD increment in dynamic range has same effect as 2.5 years of aging

Inference

- Compression of the diurnal cortisol dynamic range may be the HPA axis signature of stresses over the life course

- Dynamic range compression appears to have greater import on health than increased secretion of cortisol (which is seen with aging, for instance)

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