The Science of Stress and Stress Reduction

Ana Maria Lopez, MD, MPH, MACP
Professor and Vice Chair, Medical Oncology
Chief of Cancer Services, Jefferson Health New Jersey, SKCC, NCI Designated
Thomas Jefferson University
Stress by any other name....

smithsonianmag.com; apa.org
Stress symptoms

• Feeling overwhelmed
• Feeling out of control
• Difficulty relaxing
• Can’t quiet mind, can’t focus
• Worrying, forgetful, disorganized
• Pessimism, low self-esteem, lonely, worthless, depressed
• Fatigue, headaches, TMJ, GI sx, poor sleep, frequent colds, anhedonia

_May be in response to an actual event or an anticipated event_
Common

- In US, 25% reported high stress
- 50% report a major stressful event in the prior year
- Nearly half report more stress than last year

Objectives

• Improve our understanding of the physiology of stress
• Outline evidence-based interventions
  • What can we do?
  • What can our patients do?
Science of stress

• What is stress?
Stress is not

• Only about how you feel

• It is not strictly psychological

• It has real impact and physical health
Stress

• Source can vary: environment, physical, emotional, psychological
• Release of stress hormones: adrenaline, noradrenaline, cortisol—“fight or flight” response
• Can be positive for that moment: help us focus, motivated, alert
• Adverse outcomes with sustained exposure
  • Sustained stress response: wear and tear on body, mind, and spirit
Mind and Body

- Interconnection between psychological stress (feelings) and physical health
  - Impact of brain-body pathways

So stress has metrics!

• The brain/the self interprets what is stressful
  • Self-rated scales
So stress has biological metrics!

- Stress can be identified through physiological changes: biomarkers
  - Hypothalamic-Pituitary-Adrenal axis: free cortisol, ACTH
  - Activation of the locus coeruleus–norepinephrine–sympathetic nervous system pathway: blood pressure, skin temp, RR, HR, HRV
  - Immune system: cytokines
  - Genes: epigenetic changes, telomere shortening
  - Metabolic activity fluctuations
  - Muscle activity: muscle activity contraction


Example: what does stress look like?

• Begins above your shoulders
• Amygdala: processes environmental data and communicates with hypothalamus to turn on the sympathetic system:
  • Increases heart rate
  • Constricts some blood vessels and dilates others
  • Slows intestines and inhibits digestive secretions
  • Cortisol is released
    • Disturbed circadian rhythms
    • Sleep-wake cycle is disturbed
    • Memory disruption
    • Brain fog
Stress physiology

Cardiac:

• Increased epinephrine and norepinephrine: heart rate, vasoconstriction, electrodermal activity, catecholamine release, and blood pressure.
• Increased cortisol and thyroxine: exacerbates inflammation and arterial plaque
  • If persist: damage blood vessels and arteries.
• Increased risk for HTN, MI, CVA.

Stress physiology

Respiratory:
• Increase respiratory rate (get more O2 to tissues)
• May result in quick, shallow breathing
• Hyperventilation
  • patients with asthma, anxiety, panic attacks may feel the stress more
Stress physiology

Musculoskeletal system:
• Muscles tense up to protect self from injury and pain
• Repeated muscle tension:
  • aches and pains
  • e.g. tense shoulders/neck
    • tension headaches and migraines
Stress physiology

Gastrointestinal system:

- Hypothalamus stimulates adrenals to release epinephrine and norepinephrine: impacts digestive process
  - Reflux
  - Stomach ache
  - Bloating, nausea, diarrhea, constipation
  - Change in ability to absorb nutrients

- “stress eating”: eat more, eat less, eat differently-more sugar, more fat
Stress physiology

Endocrine:

• Metabolic changes.

• Release of stress hormones triggers the liver to produce more glucose-energy to deal with stress.
  • If stress response persists, metabolic disruption.
Stress physiology

Reproductive system:

• Decrease hormonal production-
  • Women
    • Impact fertility: impacts implantation
    • Impact menstrual cycle
  • Men
    • decrease sperm production
Stress Physiology

• Neurological:
  • Epilepsy
  • Parkinson’s disease
  • Multiple sclerosis

Stress and the immune system

• Cortisol release
  • Immunosuppression
  • Increased inflammatory pathways
  • Increased infections
  • Increased chronic inflammatory conditions
Stress and emotional well-being

- Stress hormones contribute to hyperarousal
  - Poor sleep
    - Chronic health problems, obesity
  - Poor concentration, attention
  - Adversely impacts memory, learning

Stress and emotional well-being

- Fatigue, mood swings, irritability, easily frustrated
- Catastrophizing: constantly thinking negative thoughts
- Addiction/self medication: substance disorder, eating disorder
- PTSD

Impact of stress on the brain

• Post-traumatic stress and fear conditioning: impact mediated by cortisol
  • Decline in prefrontal cortex
  • Increased size of portions of the amygdala
  • Hippocampal atrophy
    • Damages cognitive function
    • Interferes in the process of creating memories
  • Impacts:
    • Behavior
    • Ability to form a stable, realistic, and cohesive sense of self

Stress Physiology

Stress and the brain

• Stress particularly impacts prefrontal cortex
• Cognitive function: memory altered by stress
• May affect speed, attention, and executive function
• May become more evident when compounded by age
  • Highly stressed elders: caregivers of patient with dementia

Job stress

• High demand
• Small sphere of control: low decision-making power
• Increase risk for cardiovascular disease
  • Type “D” personalities: chronic distress

INTENSIVE LIFESTYLE CHANGES MAY AFFECT THE PROGRESSION OF PROSTATE CANCER

DEAN ORNISH, GERDI WEIDNER, WILLIAM R. FAIR, RUTH MARLIN, ELAINE B. PETFENGILL, CAREN J. RAISIN, STACEY DUNN-EMKE, LILA CRUTCHFIELD, F. NICHOLAS JACOBS, R. JAMES BARNARD, WILLIAM J. ARONSON, PATRICIA MCCORMAC, DAMIEN J. MCKNIGHT, JORDAN D. FEIN, ANN M. DNISTRIAN, JEANMAIRE WEINSTEIN, TUNG H. NGO, NANCY R. MENDELL, PETER R. CARROLL
Prostate Cancer

• Impact of lifestyle changes on early prostate cancer (UCSF)
• Who: men with early prostate cancer who chose observation, Gleason <7, PSA 4-10 ng/ml randomized to control or lifestyle intervention group
Assessment: Biological Endpoints

• PSA: baseline and at 1y (MSKCC)
• Testosterone
• Clinically relevant tissue culture: LNCaP cells
  • androgen sensitive prostate cancer cells from a human metastatic PC lesion
  • change in LNCaP cell growth is a standard test used for evaluating the effects of conventional treatments on prostate cancer in the laboratory
    • Expose LNCaP cells to patient serum exposed to therapeutic intervention/control to assess response
Study Population

• 181 eligible
• 73 declined: not willing to be randomized and either follow or not follow lifestyle changes or declined periodic testing
• 15 actually had Gleason scores $>7$ ng/ml
• 93 enrolled:
  • 44 intervention, 3 withdrew—too difficult to follow
  • 49 control
<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>44</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>65 ± 7</td>
<td>67 ± 8</td>
<td>0.25</td>
</tr>
<tr>
<td>% Married/cohabitating</td>
<td>66</td>
<td>76</td>
<td>0.31</td>
</tr>
<tr>
<td>% Employment:</td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Full/part time</td>
<td>54</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>46</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Mean PSA ± SD (ng/ml)</td>
<td>6.32 ± 1.72</td>
<td>6.28 ± 1.66</td>
<td>0.92</td>
</tr>
<tr>
<td>Mean cholesterol ± SD (mg/dl)</td>
<td>204 ± 42</td>
<td>203 ± 39</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean low density protein ± SD (mg/dl)</td>
<td>129 ± 36</td>
<td>127 ± 33</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean high density protein ± SD (mg/dl)</td>
<td>48 ± 11</td>
<td>50 ± 13</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean triglycerides ± SD (mg/dl)</td>
<td>133 ± 77</td>
<td>135 ± 88</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean Ln-CRP ± SD</td>
<td>−0.0310 ± 1.1</td>
<td>0.2767 ± 0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean wt ± SD (kg)</td>
<td>80 ± 13.6</td>
<td>80 ± 11.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean LNCaP apoptosis ± SD (% FBS)</td>
<td>48.16 ± 22.1</td>
<td>44.33 ± 33.0</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean testosterone ± SD (ng/dl)</td>
<td>414 ± 860</td>
<td>387 ± 100</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean Gleason ± SD (Sum)</td>
<td>5.7 ± 0.5</td>
<td>5.7 ± 0.7</td>
<td>0.80</td>
</tr>
</tbody>
</table>

To convert cholesterol, LDL and HDL to mmol multiply by 0.0259, to convert triglycerides to mmol multiply by 0.0113 and to convert testosterone to nmol multiply by 0.0347.
Study Intervention

• A nurse case manager contacted patients by telephone once weekly for the first 3 months and once monthly thereafter.

• A registered dietitian was available for nutrition education and counseling.

• All therapeutic decisions, including whether to undergo conventional treatment during the study course, were deferred to the personal physician of each patient.

• Control group patients were asked to follow the advice of their physicians regarding lifestyle changes.
Lifestyle Intervention

• Vegan diet: 1 daily serving of tofu, fortified soy protein powdered beverage, predominantly fruits, vegetables, whole grains (complex carbohydrates), legumes and soy products, low in simple carbohydrates and with approximately 10% of calories from fat.
  • In earlier studies most patients were able to adhere to this diet for at least 5 years
• Supplements: fish oil (3 gm daily), vitamin E (400 IU daily), selenium (200 mcg daily) and vitamin C (2 gm daily)
• Physical activity: moderate aerobic exercise (walking 30 minutes 6 days weekly)
• Stress management techniques (gentle yoga based stretching, breathing, meditation, imagery and progressive relaxation for a total of 60 minutes daily)
• 1-hour support group once weekly to enhance adherence to the intervention
Lifestyle Changes
Differences in lifestyle change scores between groups (p < 0.001)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Baseline ± SE</th>
<th>Mean 12 Mos ± SE</th>
<th>Mean Baseline-12-Mo Change ± SE</th>
<th>F (df)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dietary fat (% calories from fat):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>28.9 ± 1.8</td>
<td>11.2 ± 0.4</td>
<td>-17.7 ± 1.4</td>
<td>130.7 (1.81)</td>
</tr>
<tr>
<td>Control</td>
<td>26.2 ± 1.2</td>
<td>25.3 ± 8.8</td>
<td>-0.9 ± 1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Dietary cholesterol (mg/day):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>230.4 ± 21.6</td>
<td>7.5 ± 1.9</td>
<td>-222.9 ± 21.8</td>
<td>98.3 (1.81)</td>
</tr>
<tr>
<td>Control</td>
<td>218.0 ± 19.2</td>
<td>182.1 ± 19.3</td>
<td>-35.9 ± 16.0</td>
<td></td>
</tr>
<tr>
<td><strong>Exercise (days/wk):</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Experimental</td>
<td>3.1 ± 0.4</td>
<td>4.8 ± 0.3</td>
<td>1.7 ± 0.4</td>
<td>14.7 (1.80)</td>
</tr>
<tr>
<td>Control</td>
<td>3.3 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>0.0 ± 0.4</td>
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<tr>
<td><strong>Exercise (mins/wk):</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Experimental</td>
<td>120.8 ± 18.8</td>
<td>262.9 ± 38.8</td>
<td>142.1 ± 32.7</td>
<td>11.4 (1.80)</td>
</tr>
<tr>
<td>Control</td>
<td>186.1 ± 27.6</td>
<td>160.6 ± 21.3</td>
<td>-25.5 ± 26.8</td>
<td></td>
</tr>
<tr>
<td><strong>Stress management (days/wk):</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Experimental</td>
<td>2.1 ± 0.4</td>
<td>5.7 ± 0.3</td>
<td>3.6 ± 0.4</td>
<td>46.2 (1.80)</td>
</tr>
<tr>
<td>Control</td>
<td>2.0 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td>0.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Stress management (mins/wk):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>39.6 ± 11.0</td>
<td>315.7 ± 20.9</td>
<td>276.0 ± 20.9</td>
<td>102.5 (1.80)</td>
</tr>
<tr>
<td>Control</td>
<td>71.3 ± 22.1</td>
<td>75.7 ± 19.1</td>
<td>4.4 ± 18.0</td>
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</tr>
<tr>
<td><strong>% Overall lifestyle index:</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Experimental</td>
<td>41.4 ± 3.8</td>
<td>94.8 ± 3.8</td>
<td>53.4 ± 4.2</td>
<td>115.2 (1.80)</td>
</tr>
<tr>
<td>Control</td>
<td>45.4 ± 2.9</td>
<td>45.1 ± 3.5</td>
<td>-0.3 ± 3.0</td>
<td></td>
</tr>
</tbody>
</table>
Results
<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Baseline ± SD</th>
<th>Mean 12 Mos ± SD</th>
<th>Mean Baseline-12-Mo Change ± SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA (ng/ml):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>6.23 ± 1.7</td>
<td>5.98 ± 1.7</td>
<td>-0.25 ± 1.2</td>
<td>0.016</td>
</tr>
<tr>
<td>Control</td>
<td>6.36 ± 1.7</td>
<td>6.74 ± 2.1</td>
<td>0.38 ± 1.3</td>
<td></td>
</tr>
<tr>
<td><strong>Total cholesterol (mg/dl):</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>205.0 ± 42</td>
<td>172.6 ± 34</td>
<td>-32 ± 39.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>200.6 ± 39</td>
<td>202.8 ± 37</td>
<td>2 ± 25.7</td>
<td></td>
</tr>
<tr>
<td><strong>Low density protein (mg/dl):</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>130.9 ± 35</td>
<td>101.2 ± 25</td>
<td>-30 ± 31.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>125.2 ± 33</td>
<td>124.1 ± 30</td>
<td>-1 ± 25.2</td>
<td></td>
</tr>
<tr>
<td><strong>High density protein (mg/dl):</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>47.3 ± 10</td>
<td>41.9 ± 12</td>
<td>-5 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>48.3 ± 12</td>
<td>49.3 ± 12</td>
<td>1 ± 6.8</td>
<td></td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dl):</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Experimental</td>
<td>133.0 ± 78</td>
<td>138.0 ± 96</td>
<td>5 ± 65.4</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>137.1 ± 91</td>
<td>150.9 ± 93</td>
<td>14 ± 77.5</td>
<td></td>
</tr>
<tr>
<td><strong>LNCaP growth (% FBS):</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>105.50 ± 19.0</td>
<td>35.56 ± 9.2</td>
<td>-69.94 ± 19.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>91.40 ± 19.2</td>
<td>82.34 ± 36.8</td>
<td>-9.06 ± 42.8</td>
<td></td>
</tr>
<tr>
<td><strong>LNCaP apoptosis (% FBS):</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>Experimental</td>
<td>48.16 ± 22.1</td>
<td>125.38 ± 127.0</td>
<td>77.23 ± 120.6</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>45.16 ± 33.7</td>
<td>90.18 ± 128.0</td>
<td>45.02 ± 112.7</td>
<td></td>
</tr>
<tr>
<td><strong>Ln-CRP (mg/l):</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Experimental</td>
<td>-0.0310 ± 1.1</td>
<td>-0.2782 ± 1.0</td>
<td>-0.2472 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.2767 ± 0.8</td>
<td>0.2121 ± 0.9</td>
<td>-0.0646 ± 0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Testosterone (ng/dl):</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Experimental</td>
<td>414.2 ± 86</td>
<td>443.3 ± 117</td>
<td>29 ± 96</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>387.0 ± 100</td>
<td>435.0 ± 155</td>
<td>48.0 ± 123</td>
<td></td>
</tr>
<tr>
<td><strong>Wt (kg):</strong></td>
<td>80 ± 13.8</td>
<td>76 ± 10.0</td>
<td>-4.5 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>80 ± 11.4</td>
<td>80 ± 11.4</td>
<td>0 ± 3.9</td>
<td></td>
</tr>
</tbody>
</table>
Results

• Lifestyle intervention:
  • No evidence of progressive disease or PSA increase
  • PSA decreased 4%
  • Growth of LNCaP prostate cancer cells (American Type Culture Collection, Manassas, Virginia)
    • Inhibited almost 8 times more by serum from the experimental than from the control group (70% vs 9%, p <0.001).
    • Changes in serum PSA and also in LNCaP cell growth were significantly associated with the degree of change in diet and lifestyle.

• Control:
  • PSA increased 6%, p=0.016
  • 4 experienced increase in PSA, 2 disease progression: entered standard therapy
Conclusion

• Intensive lifestyle changes may affect the progression of early, low grade prostate cancer in men. Further studies and longer term follow-up are warranted.
**Question**

- *Experimental serum seemed to contain something that differentially inhibited cell line growth but so what. Just because these serums were different does not mean that they were good. They might have also killed normal cells.*

- Although it is true that chemotherapy and radiation may kill normal as well cancerous cells, we are not aware of any evidence that fruits vegetables, whole grains, legumes and soy products kill normal cells. Indeed, (this) evidence suggests that substances present in these foods, such as lycopene, flavonoids, sulphoraphanes, omega-3 fatty acids, isoflavones, polyphenols, lignans and other substances, are protective of normal cells.
  - The significant correlation between degree of changes in diet and lifestyle and degree of change in PSA and LNCaP cell growth adds to the strength of evidence.
Follow-up
Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study

Prof Dean Ornish, MD, Jue Lin, PhD, Prof June M Chan, PhD, Elissa Epel, PhD, Colleen Kemp, RN, Prof Gerdi Weidner, PhD, Ruth Marlin, MD, Steven J Frenda, MA, Mark Jesus M Magbanua, PhD, Jennifer Daubemier, PhD, Ivette Estay, PhD, Nancy K Hills, PhD, Nita Chainani-Wu, DMD, Prof Peter R Carroll, MD, Prof Elizabeth H Blackburn, PhD

Published Online: 17 September 2013
Telomere shortness in human beings is a prognostic marker of aging, disease, and premature morbidity.
Methods

• Follow-up study in men with biopsy-proven low-risk prostate cancer and had chosen to undergo active surveillance.

• Eligible participants were enrolled from previous studies.
  • Intervention: comprehensive lifestyle changes--diet, activity, stress management, and social support
  • Control: active surveillance.

• Biological correlates: blood samples at 5 years and compared relative telomere length and telomerase enzymatic activity per viable cell with those at baseline, and assessed their relation to the degree of lifestyle changes.
Results

• Relative telomere length increased from baseline in the lifestyle intervention group, but decreased in the control group (p=0.03).

• Adherence to lifestyle changes was significantly associated with relative telomere length after adjustment for age and the length of follow-up (p=0.005).

• At 5 years, telomerase activity had decreased from baseline by 0.25 (−2.25 to 2.23) units in the lifestyle intervention group, and by 1.08 (−3.25 to 1.86) units in the control group (p=0.64), and was not associated with adherence to lifestyle changes (relative risk 0.93, 95% CI 0.72–1.20, p=0.57).
Conclusion

• Comprehensive lifestyle intervention was associated with increases in relative telomere length after 5 years of follow-up compared with controls
Commentary

• This report undoubtedly will excite the aficionados and devotees of lifestyle changes for cancer but it should also give pause to the skeptics.

• For those of us taking care of patients with prostate cancer it will reinforce the use of lifestyle changes in management.

• For those of us living life, it will enhance interest in lifestyle medicine
  • Increase in data re: the impact of nutrition, physical activity, and stress reduction on favorable health outcomes
Question

• Even if scientific evidence is still meager, complementary medicine approaches have strong appeal in practicing the medical art since they give the patient an active role in his care and promote an attitude of optimism and hope.
Where to start?

• Identify your pressure points
Teach happiness

• What activities boost positive affect
  • Seek them
  • Practice them
  • Enjoy them

• Reducing your stress levels can not only make you feel better right now, but may also protect your health long-term.
Five Take Aways

• Identify what's causing stress
• Support and build strong relationships
• Step away from anger
• Rest
• Seek others
Thank you!

anamaria.lopez@Jefferson.edu