Insomnia Symptoms and Epigenetic Age Acceleration In WHI

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Steve Horvath, Ph.D.
HOW WELL I SLEEP

AT WORK

WATCHING A MOVIE

DRIVING

LAYING IN MY OWN BED AT NIGHT
Insomnia symptoms and mortality

Yanping Li et al. Circulation. 2014;129:737-746
Sleep Problems

Diabetes

Cognitive declines

Hypertension

Cancer

Cardiovascular Disease

- Akbaraly et al., 2014; Jennings et al., 2007; Troxel et al., 2010, Vgontzas et al., 2003; Irwin et al., 2013; Motivala, 2013; Laugsand, 2012, 2013; Irwin et al., 2015; Cappucio 2010; Li et al., 2015; Sands-Lincoln et al., 2013
AGING BIOLOGY IS AT THE CORE OF DISEASE
Aging occurs with the accumulation of damage

- In thermodynamic systems (such as organisms), as there is consumption of energy there is an increase in entropy – or a gradual decline into disorder/deterioration.

- Neighborhood = Body
- House = Cell
- The cells produce garbage
- Garbage trucks clean up

- Removal of garbage necessary to maintain health
• Cost of living - RESULT IS ACCUMULATION OF DAMAGE
• “Loss of molecular fidelity” = Failure of function

• In the brain = neurons die, plaque/amyloid B
• In the organs = cells die, fibrous tissue, organ failure
• In cardiovascular = arterial stiffening, cell death
  — necrosis/fatty plaque — clogged arteries
Hallmarks of Aging at the Cellular and Subcellular Level

Primary hallmarks
Causes of damage

Antagonistic hallmarks
Responses to damage

Integrative hallmarks
Culprits of the phenotype

- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis
- Deregulated nutrient sensing
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication
Telomere Length: One marker of biological aging

Insomnia and Telomere Length in Older Adults

Judith E. Carroll, PhD; Stephanie Esquivel, BS; Alyssa Goldberg, MD; Teresa E. Seeman, PhD; Rita B. Effros, PhD; Jeffrey Dock, PhD; Richard Olmstead, PhD; Elizabeth C. Breen, PhD; Michael R. Irwin, MD

Telomere Length: One marker of biological aging
Senescent Cells – The Senescent Associated Secretory Phenotype (SASP)

Rodier F, and Campisi J J Cell Biol 2011;192:547-556

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Baker et al., 2011
NATURE

Senescent cells removed
Senescent cells not removed
Partial Sleep Deprivation

Day 1: Acclimation
Full night sleep
No measures

Day 2: Baseline
Full night of sleep

Day 3: Partial Sleep Deprivation

Day 4: Recovery
Full night of sleep
Figure 1. Senescence associated secretory phenotype (SASP) Increases after partial sleep deprivation (PSD)

Carroll, Cole, et al., 2016, *Brain, Behavior, and Immunity*
Figure 2. DNA damage response (DDR) increases after partial sleep deprivation (PSD) and remains elevated at recovery

Carroll, Cole, et al., 2016, *Brain, Behavior, and Immunity*
Figure 3. Differences in expression of p16^{INK4a} (CDKN2A) from baseline to partial sleep deprivation (PSD) and recovery.

Error bars represent standard error of estimated marginal mean. Carroll, Cole, et al., 2016, Brain, Behavior, and Immunity
Age Related Disease and Death

Aging Phenotype

Sleep Deprived
• Horvath 2013 Genome Biology Developed a measure of epigenetic clock using data from 7,844 samples

• Chronological age correlates with epigenetic age, $r = .97$

• **Older epigenetic age predicts early onset of chronic disease, physical & cognitive declines, cancer and earlier death** (Levine 2015; Marioni 2015; Zhang 2016)

• Younger epigenetic age is related to longevity (Horvath 2015)
• Are sleep disturbances associated with the epigenetic clock marker of accelerated aging?
Study Design

- Postmenopausal Women: N=2,078
- Women’s Health Initiative Study
- Age M(SD)=64.5(7.1)
- WHIIRS
- **Insomnia symptoms**: restlessness, difficulty falling asleep, waking at night, trouble getting back to sleep, and early awakenings
- **Sleep duration** (short-sleep <6hrs; long-sleep >8hrs)
Epigenetic Age

- **Estimated from DNA methylation array data** using a weighted average of select CpGs, which is then transformed to DNAm age using a calibration function.

- **Extrinsic Epigenetic Age Acceleration (EEAA):**
  - 71 CpGs (Hannum, 2013) and weights from Naïve T cells, Late differentiated T cells, B cells
  - [http://labs.genetics.ucla.edu/Horvath/dnamage/](http://labs.genetics.ucla.edu/Horvath/dnamage/)
  - This yields a value that represents the deviation from chronological age

- NHLBI 60442456 BAA23
Immune senescence

- Blood cell proportions derived from epigenetic clock software [https://labs.genetics.ucla.edu/horvath/dnamage/](https://labs.genetics.ucla.edu/horvath/dnamage/)

- Naïve T cell (CD8+CD45RA+CCR7+)

- Late differentiated T cells (CD8+CD28-CD45RA-)
### Sleep Descriptive Statistics

<table>
<thead>
<tr>
<th>Sleep Duration</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>&lt; 6 hours</td>
<td>271 (13.1%)</td>
</tr>
<tr>
<td>6 hours</td>
<td>626 (30.1%)</td>
</tr>
<tr>
<td>7-8 hours</td>
<td>1096 (52.7%)</td>
</tr>
<tr>
<td>&gt; 8 hours</td>
<td>85 (4.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHI Insomnia Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Sleep Disturbances (0-10)</td>
</tr>
<tr>
<td>Sleep Disturbance (&gt;10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any Insomnia Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Insomnia Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1-2</td>
</tr>
<tr>
<td>3-4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>
Table 1. Linear effect model coefficient (B) and standard error (SE) of each sleep characteristic predicting Extrinsic Epigenetic Age (EEAA). *Each independent predictor is entered in a separate model with EEAA as the dependent variable. Model 1 adjusts for race (Black vs. non-Black; Hispanic vs. non-Hispanic), education (category), BMI (category), and snore (yes=1). Model 2 adjusts for comorbid chronic conditions: diabetes, hypertension, and CVD.

<table>
<thead>
<tr>
<th>Independent Predictor</th>
<th>B(SE)</th>
<th>P value</th>
<th>B(SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Sleep (&lt; 6 hours)</td>
<td>-.005(.44)</td>
<td>.99</td>
<td>-.08(.44)</td>
<td>.86</td>
</tr>
<tr>
<td>Normal Sleep (7-8 hours; Reference)</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Long Sleep (&gt; 8 hours)</td>
<td>-.75(.70)</td>
<td>.29</td>
<td>-.73(.71)</td>
<td>.31</td>
</tr>
<tr>
<td>Sleep Disturbance (WHIIRS &gt;10 vs 10 or less)</td>
<td>.61(.35)</td>
<td>.09</td>
<td>.64(.36)</td>
<td>.08</td>
</tr>
<tr>
<td>Wake at night</td>
<td>1.00(.35)</td>
<td>.004</td>
<td>.92(.35)</td>
<td>.008</td>
</tr>
<tr>
<td>Restless</td>
<td>.12(.38)</td>
<td>.74</td>
<td>.11(.38)</td>
<td>.78</td>
</tr>
<tr>
<td>Trouble Falling Asleep</td>
<td>.11(.32)</td>
<td>.74</td>
<td>.07(.32)</td>
<td>.82</td>
</tr>
<tr>
<td>Waking too early</td>
<td>.20(.29)</td>
<td>.51</td>
<td>.19(.29)</td>
<td>.52</td>
</tr>
<tr>
<td>Trouble going back to sleep</td>
<td>.20(.31)</td>
<td>.50</td>
<td>.18(.31)</td>
<td>.57</td>
</tr>
<tr>
<td>Any Insomnia Symptom (Yes vs. No)</td>
<td>1.02(.37)</td>
<td>.005</td>
<td>.85(.36)</td>
<td>.02</td>
</tr>
</tbody>
</table>
Increasing number of WHIIRS insomnia symptoms associated with difference in epigenetic age (P=0.007)

Relative Years of Epigenetic Age Acceleration by Insomnia Symptoms

Number of Insomnia Symptoms

- 0 Symptoms (Ref)
- 1-2 Symptoms
- 3-4 Symptoms
- 5 Symptoms

Years of Epigenetic Age Acceleration
## Immunosenescence: Correlations with Late Differentiated: CD8+CD28-CD45RA-

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Sleep Duration (&lt;6 hrs)</td>
<td>.0</td>
<td>.29</td>
</tr>
<tr>
<td>Long Sleep Duration (9-10 hrs)</td>
<td>.04</td>
<td>.22</td>
</tr>
<tr>
<td>WHIIRS Sleep disturbance (&gt;10)</td>
<td>.06</td>
<td>.005</td>
</tr>
<tr>
<td>Trouble Falling Asleep</td>
<td>.07</td>
<td>.003</td>
</tr>
<tr>
<td>Waking at Night</td>
<td>.05</td>
<td>.02</td>
</tr>
<tr>
<td>Waking too early</td>
<td>.03</td>
<td>.17</td>
</tr>
<tr>
<td>Trouble going back to sleep</td>
<td>.05</td>
<td>.03</td>
</tr>
<tr>
<td>Snore</td>
<td>.02</td>
<td>.41</td>
</tr>
<tr>
<td>Restless Sleep</td>
<td>.01</td>
<td>.65</td>
</tr>
<tr>
<td>Any Insomnia Symptom</td>
<td>.08</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Short/Long Sleep

- Short/long sleep unrelated to epigenetic age.
- Short sleep associated with fewer naïve T cells (P<.005).
- Short/Long sleep unrelated to late differentiated T cells.
Summary

• Insomnia symptoms were related to accelerated epigenetic age.

• There were more “older” T cells and fewer naïve “young” T cells in those with more insomnia symptoms.

• This data supports a growing literature showing indications of accelerated biological aging among those with sleep disturbances particularly in the immune system.
Archival Report

Epigenetic Aging and Immune Senescence in Women With Insomnia Symptoms: Findings From the Women’s Health Initiative Study

Judith E. Carroll, Michael R. Irwin, Morgan Levine, Teresa E. Seeman, Devin Absher, Themistocles Assimes, and Steve Horvath

Work published January 2017

Media coverage: Time.com; Huffington Post; CBS News; Telegraph UK; WebMD; Oprah.com
Age Related Disease and Death

Aging Phenotype

Age Related Disease and Death
Acknowledgements: Team Science

Collaborators:
- Steve Horvath, PhD
- Morgan Levine, Ph.D.
- Devin Absher, Ph.D.
- Themistocles Assimes, Ph.D.
- Michael Irwin, MD
- Teresa Seeman, PhD

- The Cousins Center for Psychoneuroimmunology, UCLA

Clinical Coordinating Center: Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women’s Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

NIH/NIA K01 AG044462 (Carroll); NIH/NHLBI 60442456 BAA23 (Assimes, Absher, Horvath); National Institutes of Health NIH/NIA 5R01AG042511–02 (Horvath and Levine); NIH/NIA R01 AG034588 and R01 AG026364, NIH/NCI R01 CA160245, NIH/NIDA R01 DA032922, NIH/NHLBI R01 HL095799-01 (Irwin), P30 AG017265, R24AG037898 (Seeman).

HHSN268201100046C, HHSN268201600003C, HHSN268201600002C, HHSN268201600004C, HHSN268201600001C, and HHSN271201100004C.