Sleep, Circadian Rhythms and Metabolism

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Sleep Timing and Circadian Changes in Older Adults

- Reduced Circadian Amplitude
- Earlier Clock Hour for Circadian Melatonin Phase
- Shorter Sleep Duration
- Advanced Sleep Time and Waketime Than Desired
- Awakening at an Earlier Circadian Time Closer to Melatonin Midpoint

1) significance - Metabolic dysregulation and disease

- Prevalence of chronic metabolic disorders such as obesity and type 2 diabetes has increased rapidly over the past 30 years reaching world-wide epidemic proportions

Rate per 100 of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Age, United States, 1980-2011

CDC National Health Interview Survey
1) significance - Metabolic dysregulation and disease

• Prevalence of chronic metabolic disorders such as obesity and type 2 diabetes has increased rapidly over the past 30 years reaching world-wide epidemic proportions
• Obesity, diabetes and the metabolic syndrome have large economic and quality of life burdens
• Healthy People 2020 goals are to reduce the prevalence of obesity and diabetes
Overweight and obesity substantially raise the risk for

- Cardiovascular diseases
- Hypertension
- Hyperlipidemia
- Osteoarthritis
- Sleep apnea
- Depression
- Diabetes
- Cancer
- Urinary Incontinence
Diabetes substantially raises the risk for

- Heart disease and stroke
- Kidney damage
- Blindness
- Neuropathy
- Urinary Incontinence
- also evidence for Wernicke-Korsakoff syndrome - delirium
How sleep and circadian disruption may lead to metabolic disease

- Hypoxemia
- Sleep Apnea
- Obesity
- Sleep Deficiency
- Circular Misalignment

Disrupted central and peripheral rhythms/clock function

- Inflammation
- Oxidative Stress
- Impaired Glucose Tolerance
- Insulin Resistance

Type 2 Diabetes

- Insufficient Sleep
- Insomnia
- Short Sleep Duration
- Narcolepsy
- Periodic Limb Movement Disorder
- Shiftwork and Shiftwork disorder

2) State-of-the Art Knowledge

Do age related changes in sleep and circadian rhythms contribute to metabolic dysregulation and disease

• Sleep disorders – yes
• Short (and sometimes long) sleep duration – yes?
• Sleep architecture / fragmentation – yes?
• Sleep and circadian timing – yes
• Circadian misalignment/shift work - ?
1506 community dwelling 55-84 years old; phone survey

Obesity and diabetes were associated with sleep-related problems such as breathing pauses, snoring, daytime sleepiness, restless legs.
The association between sleep duration and obesity in older adults

SR Patel¹, T Blackwell², S Redline¹, S Ancoli-Israel³, JA Cauley⁴, TA Hillier⁵, CE Lewis⁶, ES Orwoll⁷, ML Stefanick², BC Taylor⁸, K Yaffe⁹ and KL Stone² for the Osteoporotic Fractures in Men and the Study of Osteoporotic Fractures Research Groups

Wrist actigraphy

5.2 (0.9 SD) nights in 3055 men (age: 67–96 years) participating in the Osteoporotic Fractures in Men Study (MrOS)

4.1 (0.8 SD) nights in 3052 women (age: 70–99 years) participating in the Study of Osteoporotic Fractures (SOF)

Subgroup of 2862 men and 455 women also underwent PSG for OSA
The bar chart shows the waist circumference (cm) by sleep duration for both men and women. The x-axis represents different sleep duration categories: < 5 hrs, 5 - < 7 hrs, 7 - < 8 hrs, and ≥ 8 hrs. The y-axis represents waist circumference in cm. The bars indicate that the waist circumference is generally higher for < 5 hrs sleep duration, with a noticeable difference between men and women. As sleep duration increases, the waist circumference decreases, with a slight overlap in the data for men and women in the 5 - < 7 hrs and 7 - < 8 hrs categories. The ≥ 8 hrs sleep duration category shows the lowest waist circumference for both genders.
ORIGINAL ARTICLE

The association between sleep patterns and obesity in older adults

SR Patel¹, AL Hayes², T Blackwell³, DS Evans³, S Ancoli-Israel⁴, YK Wing⁵ and KL Stone³ for the Osteoporotic Fractures in Men (MrOS) and the Study of Osteoporotic Fractures (SOF) Research Groups
3053 men (mean age 76.4 years) and 2985 women (mean age 83.5 years) mean 5.2 and 4.1 actigraphic sleep data days
Is Sleep Duration Associated With Obesity in Older Australian Adults?

Christopher A. Magee, PhD¹, Peter Caputi, PhD¹, and Don C. Iverson, PhD¹
<table>
<thead>
<tr>
<th>Sleep category</th>
<th>Overweight</th>
<th>Obese</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 hr</td>
<td>0.93</td>
<td>0.81-1.07</td>
<td>1.47*</td>
</tr>
<tr>
<td>6 hr</td>
<td>1.00</td>
<td>0.93-1.08</td>
<td>1.33*</td>
</tr>
<tr>
<td>7 hr</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>8 hr</td>
<td>0.97</td>
<td>0.92-1.02</td>
<td>1.05</td>
</tr>
<tr>
<td>≥9 hr</td>
<td>1.01</td>
<td>0.95-1.07</td>
<td>1.22*</td>
</tr>
</tbody>
</table>
A. 55 – 64 years \((n = 23,458; 51.8\%)\)

B. 65 – 74 years \((n = 13,848; 30.6\%)\)
C. 75 – 84 years \((n = 6,883; 15.2\%)\)

D. 85 – 95 years \((n = 1,136; 2.5\%)\)
N=1567, Massachusetts Male Aging Study without diabetes at baseline (1987–1989; aged 40-70) were followed until 2004 for development of diabetes

<table>
<thead>
<tr>
<th>Sleep duration</th>
<th>a. Age adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 h</td>
<td>2.60 (1.28–5.27)</td>
</tr>
<tr>
<td>6 h</td>
<td>1.93 (1.06–3.50)</td>
</tr>
<tr>
<td>7 h</td>
<td>1.00</td>
</tr>
<tr>
<td>8 h</td>
<td>1.40 (0.78–2.53)</td>
</tr>
<tr>
<td>&gt;8 h</td>
<td>3.63 (1.79–7.38)</td>
</tr>
</tbody>
</table>
Basic Research
Resetting of central and peripheral circadian oscillators in aged rats

Alec J. Davidson¹, Shin Yamazaki², Deanna M. Arble³, Michael Menaker, Gene D. Block *
Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock

Roman V. Kondratov, Anna A. Kondratova, Victoria Y. Gorbacheva, Olena V. Vykhovanets, and Marina P. Antoch

1Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA; 2Department of Molecular Genetics, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA

Mice deficient in the circadian transcription factor BMAL1

Reduced lifespan
Display various symptoms of premature aging
• Sarcopenia
• Cataracts
• Less subcutaneous fat
• Organ shrinkage
• Increased oxidative stress
• Diabetes (Marcheva et al Nature 2010)
Aging and sleep deprivation induce the unfolded protein response in the pancreas: implications for metabolism

1. Nirinjini Naidoo1,2,*, James G. Davis3,4, Jingxu Zhu2, Maya Yabumoto2, 2. Kristan Singletary2, Marishka Brown2, Raymond Galante2, Beamon Agarwal3,4,† and Joseph A. Baur3,4,*

Volume 13, Issue 1, pages 131–141, February 2014

• Adaptive arm of the unfolded protein response in pancreatic cells
  • Upregulated during SD in young mice
  • Reduced in older mice
• Maladaptive arm (pro-apoptotic) upregulated in older mice
3) knowledge gaps

• Mechanisms by which sleep deficiency and circadian disruption contribute to metabolic dysregulation and disease in older adults
  • Age related changes in sleep structure (e.g., slow wave sleep, sleep fragmentation), sleep duration, untreated sleep disorders
  • Age related changes in circadian timing, circadian amplitude, disrupted central and peripheral clocks
  • Vulnerable time for development of metabolic dis (young adult, middle-age, older age)
3) knowledge gaps

- Sex differences?
  - Menopause
  - Sleep disorders
  - Health behaviors

- Bi-directional effects (metabolic disorders impacting sleep and circadian)

- Sleep and circadian countermeasure/treatments to treat age related metabolic dysregulation
  - When is it optimal or too late to intervene to prevent versus manage disease
Do age related changes in sleep structure contribute to metabolic dysregulation?
Total growth hormone in older men reduced to 30% of levels in young men

Higher Plasma IGF-1 Levels Are Associated With Increased Delta Sleep in Healthy Older Men

Age-adjusted IGF levels in healthy senior men co-vary significantly with SWS
4) research opportunities

• Understanding mechanisms of how age related changes in sleep & circadian rhythms impact metabolic health & disease
  • How do central and peripheral clocks contribute to age-related changes in metabolic health?
    • Vary by organ? Reversible?
• Biomarkers
• Hormonal / sympathetic
  • hgh, IGF-1, appetitive hormones
  • Chronic sympathetic activation and reduced tissue responsiveness
• Nutrition intake / Energy expenditure/ resting metabolic rate
• Physical Activity (exercise, non-exercise, sedentary time)
• Sarcopenia
4) research opportunities

• Work hours
  • Metabolic dysregulation and disease in shift work (aging working population)

• Sex differences
  • Role of sex hormones (estrogen, testosterone, sex related sleep disorders, mech prior slide)

• Bi-directional effects
  • The effect of chronic metabolic disorders on sleep
  • The effect of sleep and circadian disruptions on worsening of chronic metabolic disorders

• Development of treatment strategies
How do age-related changes in sleep and circadian rhythms lead to metabolic disease?

N=3576, aged 71.6

<table>
<thead>
<tr>
<th>Sleep duration (hours per 24-h period)</th>
<th>≤5 (n = 350)</th>
<th>6 (n = 409)</th>
<th>7 (n = 532)</th>
<th>8 (n = 938)</th>
<th>9 (n = 591)</th>
<th>≥10 (n = 756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model adjusted for age and sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Obesity²</td>
<td>1.45 (1.09, 1.92)</td>
<td>1.18 (0.90, 1.55)</td>
<td>1</td>
<td>1.41 (1.12, 1.76)</td>
<td>1.14 (0.89, 1.47)</td>
<td>1.08 (0.85, 1.37)</td>
</tr>
<tr>
<td>Severe obesity³</td>
<td>2.36 (1.50, 3.74)</td>
<td>1.31 (0.80, 2.14)</td>
<td>1</td>
<td>1.86 (1.24, 2.78)</td>
<td>1.68 (1.08, 2.61)</td>
<td>1.28 (0.81, 2.00)</td>
</tr>
<tr>
<td>Abdominal obesity⁴</td>
<td>1.22 (0.89, 1.65)</td>
<td>1.01 (0.76, 1.35)</td>
<td>1</td>
<td>1.04 (0.82, 1.32)</td>
<td>1.09 (0.84, 1.41)</td>
<td>1.11 (0.87, 1.42)</td>
</tr>
<tr>
<td>Model with full adjustment⁵</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity²</td>
<td>1.33 (1.00, 1.77)</td>
<td>1.14 (0.86, 1.50)</td>
<td>1</td>
<td>1.39 (1.11, 1.75)</td>
<td>1.07 (0.82, 1.38)</td>
<td>0.96 (0.75, 1.23)</td>
</tr>
<tr>
<td>Severe obesity³</td>
<td>2.08 (1.31, 3.32)</td>
<td>1.29 (0.78, 2.12)</td>
<td>1</td>
<td>1.82 (1.21, 2.73)</td>
<td>1.57 (1.00, 2.47)</td>
<td>1.13 (0.71, 1.80)</td>
</tr>
<tr>
<td>Abdominal obesity⁴</td>
<td>1.14 (0.84, 1.56)</td>
<td>1.00 (0.75, 1.34)</td>
<td>1</td>
<td>1.04 (0.82, 1.32)</td>
<td>1.06 (0.82, 1.39)</td>
<td>1.06 (0.82, 1.36)</td>
</tr>
</tbody>
</table>
Is overweight/obesity associated with short sleep duration in older women?

Jean-Philippe Chaput¹, Christine Lord², Mylène Aubertin-Leheudre²,³, Isabelle J. Dionne²,³, Abdelouahed Khalil²,⁴ and Angelo Tremblay¹

Table 2 - Difference between means of investigated variables in relation with the number of sleeping hours in older women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;7 hours/day (n=19)</th>
<th>≥7 hours/day (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.0±3.0</td>
<td>60.8±5.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.0±9.7</td>
<td>72.8±12.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6±3.6</td>
<td>28.8±5.3</td>
</tr>
</tbody>
</table>

Risk to be overweight/obese (OR and 95% CI)

OR= odds ratio; 95% CI= 95% confidence interval.

Data on odds ratio: Children 3.45 (95% CI 2.45-4.79), Adults 1.69 (95% CI 1.12-2.53), Reference 1 (95% CI 0.92-1.09), Elders 0.91 (95% CI 0.78-1.07).

Data on odds ratio: Children from Chaput et al. (4) and data on adults are from Chaput et al. (14).
Impact of Carbohydrate-Rich Meals on Plasma Epinephrine Levels: Dysregulation with Aging

Plamen Penev, Karine Spiegel, Teresa Marcinkowski, and Eve Van Cauter
Successful 6-Month Endurance Training Does Not Alter Insulin-Like Growth Factor-I in Healthy Older Men and Women

Michael V. Vitiello,¹ Charles W. Wilkinson,¹,³ George R. Merriam,²,³ Karen E. Moe,¹ Patricia N. Prinz,¹,³ David D. Ralph,² Elizabeth A. Colasurdo,³ and Robert S. Schwartz²