Insomnia and Cardiometabolic Morbidity

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► Insomnia
► Polysomnography
► Hyperarousal
► Phenotypes
► Clinical Implications

NOSOLOGY

Clinical Psychology Review 2011;21(7):1037–59
INSOMNIA: SYMPTOM OR DIAGNOSIS?
Allan G. Horne
University of Oxford

Sleep Medicine 2004;5(S1):35-40
Is insomnia best categorized as a symptom or a disease?
Michel Billiard, Alixen Bousley

Sleep Medicine Centre, University Hospital of Lens, Lille, France
School of Psychology, University of Witswatersrand, Johannesburg, South Africa
PREVALENCE

Moderate to Severe Insomnia
¬ 8%

At least 1 Insomnia Symptom
¬ 40%

Female gender
Minority
Low SES, education
Socioeconomic-work burden

(Blot et al, J Psychosom Res 2002;53:589-92)

NOSOLOGY

Dysnomias
Insomnia Disorders
Insomnia related to Another Mental Disorder (organic)
Insomnia related to a Known Organic Factor
Primary Insomnia
Insomnia Not Otherwise Specified

Primary Insomnia

Insomnia due to a General Medical Condition
Insomnia due to Another Mental Disorder (nonorganic)
Insomnia related to a Known Organic Factor

Sleep Disorders Associated with Other Disorders

Primary Insomnia

ICSD-3 (2017)
ICD-11 (2018)
ICSD-2 (2005)
ICSD-1 (1992)
Insomnia in the general population is associated with:

- Significant differences in PSG variables such as:
  - Sleep latency (SL): ↑12 minutes
  - Wake after sleep onset (WASO): ↑10 minutes
  - Total sleep time (TST): ↓24 minutes
  - Sleep efficiency (SE): ↓5%

- Small and of little clinical significance
- Not necessarily related to self-reported severity

POLYSOMNOGRAPHY

In 1998, Vgontzas et al. first proposed that in chronic insomnia:

1. Physiologic hyperarousal is directly proportional to the degree of objective sleep disturbance, and
2. Objective sleep disturbance may be an index of the biological severity of the disorder.

HYPERAROUSAL

Pathophysiology:

Insomnia is a disorder of 24-h cognitive, emotional, and physiologic hyperarousal.
COGNITIVE-EMOTIONAL

Personality Patterns in Insomnia

Theoretical Implications


Biopsychosocial Correlates of Insomnia. II: Pattern Specificity and Consistency with the Minnesota Multiphasic Personality Inventory

Psychosomatic Medicine Vol. 45, No. 4 (August 1983)


Cognitive-Emotional Hyperarousal as a Premorbid Characteristic of Individuals Vulnerable to Insomnia


PHYSIOLOGIC

24-Hour Metabolic Rate in Insomniacs and Matched Normal Sleepers

N. H. Rosen and D. L. Arnaud

Psychosomatic Medicine 29:508-514 (1967)

Physiological Activation in Patients With Sleep State Misperception

M. H. Ross, J. E. Ross, and D. L. Arnaud, PhD

Psychosomatic Medicine 30:233-240 (1968)

Heart Rate Variability in Insomniacs and Matched Normal Sleepers

M. H. Ross, J. E. Ross, and D. L. Arnaud, PhD


Activity, Arousal, and the MSLT in Patients with Insomnia

Nathan, K. S., Dulany, J., and Feinman, D.


PHYSIOLOGIC

Neuromaging of NREM Sleep in Primary Insomnia: A To-99-HMPAO Single Photon Emission Computed Tomography Study

Buckner, J. L., Buckner, R. L., Buck, D. J., and Stoessel, D. J.


Functional Neuroimaging Evidence for Hyperarousal in Insomnia

Buxbaum, J. D., Buckner, R. L., and Stoessel, D. J.

PHYSIOLOGIC

Beta EEG activity and insomnia
Michael L. Perlis, Heli Merica, Michael T. Smith and Donna E. Giles

NREM Sleep EEG Frequency Spectral Correlates of Sleep Complaints in Primary Insomnia Subtypes

Beta EEG spectral analysis in primary insomnia: NREM period effects and sex differences


PHYSIOLOGIC

CHRONIC INSOMNIA AND ACTIVITY OF THE STRESS SYSTEM: A PRELIMINARY STUDY

ALEXANDROS N. VGONTZAS, CONSTANTINE TSIGOS, EDWARD O. WIJER, CONSTANTINE A. STRATAKIS, KEITH ZACHMAN, ANTHONY KALES, ANTONIO VELA-BUENO, and GEORGE P. CHRUSOS

PHYSIOLOGIC

Cortisol and DHEA-S levels

(Urgontzas et al., J Psychosom Res 1998;55:21-31)
Chronic Insomnia Is Associated with Nyctohemeral Activation of the Hypothalamic-Pituitary-Adrenal Axis: Clinical Implications

(From Vgontzas et al, J Clin Endocrinol Metab 2001;86:3787-94)

- Insomnia with Short Sleep Duration
- Insomnia with Longer Sleep Duration
PHENOTYPING

► From Biological Severity...
  • Biomarker(s)
  • Polysomnography ↔ Physiologic Hyperarousal
  • Clinically Significant Outcomes
  • Cardiometabolic and Neurocognitive Morbidity

► To Phenotypes
  • Biomarker(s)
  • Clinically Significant Outcomes
  • Natural Course
  • Differential Behavioral Profiles

► Clinical Implications:
  • Assessment
  • Diagnosis
  • Treatment

MORBIDITY

► Insomnia and Mental Health
  • Strongly and consistently associated
  • Insomnia (or symptoms) may:
    • be diagnostic criteria for,
    • precede the onset of,
    • contribute to the persistence of, or
    • be comorbid with mental health disorders

► Insomnia and Physical Health
  • Hypertension & CVD: modest or inconsistent results
  • Type 2 diabetes: insomnia symptoms
  • Mortality: negative results

HYPERTENSION

INSOMNIA AND HYPERTENSION
Insomnia with Objective Short Sleep Duration is Associated with a High Risk for Hypertension

Research: K. Sigurdsson, M.D., I. Qing, M.D., J. Lee, M.D., S. Lim, M.D., G. S. Ilunga, M.D., M. I. Strollo, M.D.
Department of Medicine and the Division of Sleep Medicine, University of Pennsylvania, Philadelphia, PA.


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HYPERTENSION

Hypertension

Insomnia With Objective Short Sleep Duration and Incident Hypertension: The Penn Water Cohort

J. Fernandez-Mendoza, Alexander D. Grunstein, L. Michel, Michelle L. Klerman, Arminia Yela, Benno, and Edward O. broccoli

Hypertension, 2012;60:929-935. doi: 10.1161/HYPERTENSIONAHA.112.15248

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HYPERTENSION

Phenotyping

Phenotyping

Phenotyping
HEART RATE

Heart rate in insomnia

Heart rate and heart rate variability in subjectively reported insomnia

RAE SPESCHELBERGER, LENA FUCHS, JOHANNES LADWIG, SIMON D. KYLE, CHRISTOPH MIESEN, ULRICH WODEHOLZER, HERND FEIGL, and DIETER RIEHANN

Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center, Freiburg, Germany and University of Giessen Sleep Center, Department of Psychosomatic Medicine, University of Giessen, Giessen, UK.

DIABETES

Insomnia With Objective Short Sleep Duration Is Associated With Type 2 Diabetes

A population-based study

ALEXANDER N. NAGLE, MD
JAYA J. KONERU, MD
MARCO RAFFATI, MD
EDWARD O. BIER, MD

Cross-Sectional Associations Between Measures of Sleep and Markers of Glucose Metabolism Among Subjects With and Without Diabetes

The Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study

INSOMNIA AND SHORT SLEEP

Changes in Insulin Secretion and Sensitivity in Short-Sleep Insomnia

Vasisht KP, MD, PharmD; Kessler LE, MD; Booth III JN, MS; Imperial JG, RN; Penev PD, MD, PhD

1Department of Medicine and 2General Clinical Research Center, University of Chicago, Chicago, IL 60637

INSOMNIA WITH SHORT SLEEP

Insomnia with Objective Short Sleep Duration is Associated with Deficits in Neuropsychological Performance: A General Population Study

NEUROCOGNITIVE

Information Processing Speed
Attention Processes
Executive Control of Attention

High-Order Processes
Low-Order Processes

Cognitive Flexibility
Working Memory

Adapted from Ríos-Lago et al, 2004
Does Physiological Hyperarousal Enhance Error Rates Among Insomnia Sufferers?

Edinger JD, PhD1,2; Means MK, PhD;2,3 Krystal AD, MD2

1National Jewish Health, Denver, CO and 2Duke University and 3VA Medical Centers, Durham, NC

SLEEP; accepted 2/21/2013

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Insomnia and daytime cognitive performance: A meta-analysis

Keesia Ferraro-Brooke, Simon Ruschitzka-Bromm, Patsy Ito, and Charles M. Mains

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Clinical Evidence

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MORTALITY

INSOMNIA, SLEEP DURATION AND MORTALITY
Insomnia with Short Sleep Duration and Mortality: The Penn State Cohort

Phenotyping

Phenotyping

MORTALITY IN MEN

MORTALITY IN MEN

Table 4—Mortality risk with insomnia and objective sleep duration by hypertension/diabetes status at baseline: men

<table>
<thead>
<tr>
<th>Baseline Hypertension or Diabetes Status</th>
<th>Odd Ratio 95% CI</th>
<th>Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6 h No Insomnia</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 6 h Insomnia</td>
<td>1.15 (0.93, 1.42)</td>
<td>0.59 (0.20, 1.63)</td>
</tr>
<tr>
<td>&lt; 6 h No Insomnia</td>
<td>0.98 (0.44, 2.19)</td>
<td>1.04 (0.01, 4.16)</td>
</tr>
<tr>
<td>&lt; 6 h Insomnia</td>
<td>1.45 (0.13, 16.14)</td>
<td>7.17 (1.76, 27.92)</td>
</tr>
</tbody>
</table>

Both models adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SBP, and sampling weight. The P-value for interaction between insomnia and sleep duration with hypertension/diabetes status was 0.15, which is not statistically significant.
Insomnia with Objective Short Sleep Duration had a higher risk of Persisting vs. Remitting over time:

<table>
<thead>
<tr>
<th>Outcome Level</th>
<th>Objective Short Sleep Duration</th>
<th>Mental Health Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Reference</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Fully Remitted</td>
<td>Normal Sleep</td>
<td>0.76 (0.30-1.91)</td>
</tr>
<tr>
<td>Partially Remitted</td>
<td>Normal Sleep</td>
<td>1.56 (0.84-2.90)</td>
</tr>
<tr>
<td>Persistent Insomnia</td>
<td>Normal Sleep</td>
<td>3.48 (1.63-7.34)**</td>
</tr>
<tr>
<td>Partially Remitted</td>
<td>Fully Remitted</td>
<td>2.55 (0.79-8.30)</td>
</tr>
<tr>
<td>Persistent Insomnia</td>
<td>Fully Remitted</td>
<td>4.54 (1.47-14.0)**</td>
</tr>
</tbody>
</table>

All data adjusted for all examined confounders; * p < 0.05; ** p < 0.01.
Shorter Sleep Duration in Poor Sleepers is a biologic marker of genetic predisposition to Insomnia

<table>
<thead>
<tr>
<th></th>
<th>Normal Sleepers w/ Incident Insomnia (n = 65)</th>
<th>Poor Sleepers w/ Incident Insomnia (n = 68)</th>
<th>Multivariable Logistic Regressiona (n = 65) (n = 68) OR (95%CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>51.4</td>
<td>86.0</td>
<td>5.08 (1.58-16.3) .005*</td>
</tr>
<tr>
<td>Age, years</td>
<td>45.5 (14.9)</td>
<td>45.4 (12.2)</td>
<td>---</td>
</tr>
<tr>
<td>Tobacco, cig./day</td>
<td>1.9 (6.7)</td>
<td>4.2 (8.8)</td>
<td>3.85 (1.14-12.9) .029*</td>
</tr>
<tr>
<td>Physical health, %</td>
<td>74.3</td>
<td>58.0</td>
<td>0.24 (0.08-0.72) .011*</td>
</tr>
<tr>
<td>Depression, %</td>
<td>17.1</td>
<td>28.6</td>
<td>3.85 (1.93-7.59) .002</td>
</tr>
<tr>
<td>Family History, %</td>
<td>5.0</td>
<td>28.9</td>
<td>---</td>
</tr>
<tr>
<td>SOL, min</td>
<td>32.6 (28.2)</td>
<td>28.8 (32.2)</td>
<td>0.99 (0.98-1.01) 5.16*</td>
</tr>
<tr>
<td>WASO, min</td>
<td>73.8 (50.0)</td>
<td>100.0 (63.5)</td>
<td>1.02 (1.01-1.03) .019*</td>
</tr>
<tr>
<td>TST, min</td>
<td>371.7 (58.0)</td>
<td>345.6 (75.0)</td>
<td>0.98 (0.97-0.99) .064*</td>
</tr>
</tbody>
</table>

(Fernandez-Mendoza et al, SLEEP 2013;35(5):689-697)

PHENOTYPING

Sleep Misperception and Chronic Insomnia in the General Population: Role of Objective Sleep Duration and Psychological Profiles

Fernandez-Mendoza, PhD, Victor L. Gamboa, MD, Edward B. Ehrlich, PhD, Marc Wastell, MD, Dina LeDividich, MD, Michael A. Schatzberg, MD, Allan R. Schretlen, MD, Nancy R. Harga, RD, and Alexander N. Vgontzas, MD

Psychosomatic Medicine 73:88-97 (2011)

SLEEP MISPERCEPTION

Discrepancy in subjective habitual sleep duration vs. objective sleep duration among study subgroups

SLEEP MISPERCEPTION

Discrepancy in subjective estimation upon awakening vs. objective sleep duration among study subgroups

Overestimation

Underestimation

PERSONALITY PROFILE

MMPI-2 scores of study subgroups based on objective sleep duration

SUBTYPING

NREM Sleep EEG Frequency Spectral Correlates of Sleep Complaints in Primary Insomnia Subtypes
TWO INSOMNIA PHENOTYPES

Insomnia with Normal Sleep Duration
- Lack of physiological hyperarousal (i.e., normal activity of both limbs of the stress system)
- Sleep Misperception
- More likely to Remit
- No significant Risk of Cardiometabolic Morbidity and Mortality

Insomnia with Short Sleep Duration
- Biological Vulnerability (e.g., genetic predisposition, higher sensitivity of sleep to activation of the arousal and stress systems)
- Physiological Hyperarousal (i.e., hyperactivity of both limbs of the stress system)
- Impaired Neurocognitive Functioning
- More likely to Persist
- Increased Risk of Cardiometabolic Morbidity and Mortality

CLINICAL IMPLICATIONS

Assessment and Diagnosis:
- Clinical history
  - Patient-reported measures
  - Objective, easy-to-use, and reliable sleep measures outside the sleep lab
- Nosology:
  - Diagnoses: biomarkers, behavioral profiles, and clinically significant outcomes
  - Clinical utility of 5% "paradoxical"?
- Clinical utility and reliability of these phenotypes:
  - Prospective clinical and treatment studies are mandatory
Treatment:

- These insomnia subtypes may respond differentially to treatment:

  - **Insomnia with Short Sleep Duration:**
    - Might benefit from treatments aimed at decreasing the hyperactivity of the stress system (e.g., medication) in combination with psychological treatment

  - **Insomnia with Normal Sleep Duration:**
    - First line, tailored psychological treatment (e.g., CBT-I), avoiding the use of medication

ACKNOWLEDGEMENTS

- **Sleep Research & Treatment Center**
  - Alexandros N. Vgontzas, MD (NIH R01 64415)
  - Edward O. Bixler, PhD (NIH R01 51931 & R01 40916)
  - Susan L. Calhoun, PhD
  - Ilia Kritikou, MD
  - Carrie Criley, BS, RPSGT
  - Patricia Cain, BS, RPSGT

- **Public Health Sciences**
  - Duaping Liao, MD, PhD
  - Michele L. Shaffer, PhD

- **Pennsylvania State University**
  - College of Medicine
  - Milton S. Hershey Medical Center

Many thanks for your attention