Outline

1. How the immune system affects sleep
2. How sleep affects the immune system
Why should an allergist worry about sleep?

Chronic urticaria, allergic rhinitis, atopic dermatitis, and asthma are all associated with fragmented sleep and short sleep duration.

35% to 40% of the adult U.S. population report sleeping less than the usually recommended 7 to 8 hours on weekday nights, and about 15% report sleeping less than 6 hours regularly.


“Get plenty of rest, or you will get sick.”
The Acute Phase Response

Sequence

1. A foreign antigen is detected
2. Pathogen-associated molecular patterns (PAMPs) interact with Pathogen recognition receptors (PRRs), including Toll-like receptors and NOD receptors
3. PAMP/PRR interaction leads to cytokine production, importantly IL-1β, IL-6, and TNF-α
4. These cytokines and others lead to activation of other parts of the innate immune system, and induction of the adaptive immune system
The Acute Phase Response (APR)

- Complex activation of many cell types and organs, production of cytokines
- Physiologic changes (fever, increased vascular permeability)
- Metabolic changes (insulin resistance)
- Behavioral changes (anorexia, social withdrawal, sleepiness)

Altered sleep is part of the APR to inflammation

“Tired because you are sick”

A little neuroanatomy

- The system functions to stabilize the brain in one of three states:
  - Wake
  - Non-REM sleep
  - REM-sleep
IL-1β induces and increases non-REM sleep and suppresses REM sleep

- IL-1β released from glial cells and neurons.
- Peaks levels at sleep onset
- Levels increase during sleep deprivation

NFκB + +


TNF-α induces and increases non-REM sleep and suppresses REM sleep

- Inhibition of TNF-α inhibits non-REM sleep.
  - IL-4, IL-10, and IL-13 inhibit spontaneous sleep (by inhibiting TNF-α?)
  - In humans, TNF-α blood levels correlate with deep sleep
- OSA patients with sleepiness have elevated TNF-α plasma levels
- TNF-α is elevated in chronic fatigue, chronic insomnia, rheumatoid arthritis, AIDS, and pre-eclampsia patients
- Reduced fatigue with anti-TNF medications (adalimumab, etanercept, etc.)

NFκB + +

Neuronal activity and enhanced Sleep Related Substances (SRS) activity

- What is it about neuronal activity or wakefulness that causes the enhanced SRS activity?
- Adenosine triphosphate (ATP) is released as a product of presynaptic neuronal activity:
  - Some ATP is converted to adenosine and some acts on glial cells to release TNF and IL-1.
- TNF and IL-1 activate NFkB, NFkB enhances the adenosine receptor (A1AR) making cells more susceptible to adenosine.

Effects of other cytokines

Table 2. NREM2 response in cytokines and growth factors

<table>
<thead>
<tr>
<th>Cytokine/Growth Factor</th>
<th>Effect on NREM2</th>
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<tbody>
<tr>
<td>Interleukin-1 alpha</td>
<td>↑</td>
<td>362</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonist</td>
<td>↓</td>
<td>363</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>↑</td>
<td>364, 365</td>
</tr>
<tr>
<td>Interleukin-4</td>
<td>↑</td>
<td>366</td>
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<tr>
<td>Interleukin-6</td>
<td>↑</td>
<td>367, 368</td>
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<tr>
<td>Interleukin-10</td>
<td>↑</td>
<td>200, 369</td>
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<tr>
<td>Interleukin-13</td>
<td>↑</td>
<td>370</td>
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<tr>
<td>Interleukin-15</td>
<td>↑</td>
<td>365</td>
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<tr>
<td>Transforming growth factor beta</td>
<td>↑</td>
<td>372</td>
</tr>
<tr>
<td>Acidic fibroblast growth factor</td>
<td>↑</td>
<td>373, 374, 375</td>
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<td>Nerve growth factor</td>
<td>↑</td>
<td>273</td>
</tr>
<tr>
<td>Brain-derived neurotrophic factor</td>
<td>↑</td>
<td>279</td>
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<tr>
<td>Glia-derived neurotrophic factor</td>
<td>↑</td>
<td>283</td>
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<tr>
<td>Interferon alpha</td>
<td>↑, ↓</td>
<td>364, 376, 377, 378, 379, 380</td>
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<tr>
<td>Interferon gamma</td>
<td>↑</td>
<td>381</td>
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<tr>
<td>Tumor necrosis factor beta</td>
<td>↑</td>
<td>382</td>
</tr>
<tr>
<td>Transforming growth factor beta</td>
<td>↑</td>
<td>370</td>
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<tr>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>↑</td>
<td>383</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor</td>
<td>↑</td>
<td>384</td>
</tr>
<tr>
<td>Insulin-like growth factor</td>
<td>↑</td>
<td>166, 167</td>
</tr>
<tr>
<td>Soluble TNF receptor</td>
<td>↓</td>
<td>249</td>
</tr>
<tr>
<td>Soluble IL-1 receptor</td>
<td>↓</td>
<td>281</td>
</tr>
</tbody>
</table>

IL-1 beta and TNF alpha are omitted from this list; they are reviewed extensively in the text. ↑ Indicates increase; ↓ decrease; and ↔ no change in duration of NREM2.

Sleep Deprivation and the Immune System

Sleep Deprivation Research
Sleep habits and Susceptibility to Rhinovirus

- 153 subjects experimentally exposed to rhinovirus
- Self-report of sleep duration and sleep efficiency for the following 14 days
  - Sleep Efficiency = sleep time/time in bed x 100
- Subjects with less than 7 hours of sleep prior to infection were more likely to develop a cold than those with 8 or more hours of sleep
  - OR 2.94 (1.18–7.30)
- Sleep efficiency of <92% prior to infection were 5.50 times as likely to develop cold symptoms than those with >98% sleep efficiency

Response to Hepatitis A vaccine

- 20 subjects, 10 with normal sleep and 10 with total sleep restriction for 36 hours after Hep A vaccination
- Hep A titers measured every 4-6 hours for the first two days of the study, then daily for days 5–14, and on day 28
- Early sleep restriction appears to inhibit the emergence of the primary adaptive immune response
- Lower GH and prolactin levels in the sleep restricted subjects, both of which augment T-cell function


Can sleep influence immunologic memory?

- 27 male subjects, Hepatitis A vaccine 3-dose series
- Sleep and Wake groups
  - Wake group was sleep-deprived for 36 hours following each vaccination
  - Ag-specific Th cell response measured
- The increase in CD40L+ HAV-specific Th cells was increased in the sleep group compared to the wake group
- HAV-specific IgG1 was significantly higher in the sleep group
- IgG2, 3, and 4 did not differ between sleep and wake groups


Sleep acts like an adjuvant to enhance Th cell and Antibody response to vaccination

1. Long-term Th Cell response to vaccination is impaired with one night of missing sleep
2. Ag-specific IgG production is impaired only acutely

What is it about sleep that improves vaccine response?

- Time spent in slow-wave sleep had the highest correlation with Th cell response at 18-20 weeks and at 52 weeks post-vaccination
- Growth hormone/prolactin increases, and cortisol suppression during slow-wave sleep


Shift Work and Illness

- Shift workers are sleep-deprived. Always.
- Large population study
  - Increased respiratory and gastrointestinal illnesses in those with the most shift changes

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Day Work</th>
<th>Three-shift Work</th>
<th>Five-shift Work</th>
<th>Irregular Shift Work</th>
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<tbody>
<tr>
<td>N (number of organizations)</td>
<td>5,809 (45)</td>
<td>878 (19)</td>
<td>1,058 (11)</td>
<td>420 (25)</td>
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<tr>
<td>Common cold %</td>
<td>53.0</td>
<td>57.5*</td>
<td>51.0</td>
<td>55.5</td>
</tr>
<tr>
<td>Flu-like illness %</td>
<td>22.4</td>
<td>31.2***</td>
<td>22.1</td>
<td>30.5***</td>
</tr>
<tr>
<td>Gastroenteritis %</td>
<td>11.8</td>
<td>18.2***</td>
<td>15.4**</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Significant difference with day work: *P < 0.05, **P < 0.01, ***P < 0.001.

# Inflammatory Mediator Studies

<table>
<thead>
<tr>
<th>First author, year of publication, duration of total sleep deprivation (TSD), sample size</th>
<th>Immune changes</th>
<th>Inflammatory changes</th>
<th>After 8 h-recovery sleep</th>
<th>Sleep countermeasures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pohlmüller, 1976; 77 h TSD, n = 8</td>
<td>↓ Neutrophil phagocytic activity</td>
<td>Interferons by in-vitro-stimulated lymphocyte</td>
<td>Not reported</td>
<td>?</td>
</tr>
<tr>
<td>Dingess, 1994; 64 h TSD, n = 10</td>
<td>↑ Leukocyte neutrophil, monocyte counts and natural killer activity</td>
<td>Leukocyte, neutrophil and monocyte counts &gt; baseline</td>
<td>Leukocyte, neutrophil and monocyte counts &gt; baseline</td>
<td>?</td>
</tr>
<tr>
<td>Born, 1997; 64 h TSD, n = 20</td>
<td>↑ Lymphocyte and monocyte counts and natural killer cells</td>
<td>Lymphocyte and monocyte counts — baseline, natural killer cells &lt; baseline</td>
<td>Lymphocyte and monocyte counts — baseline, natural killer cells &lt; baseline</td>
<td>?</td>
</tr>
<tr>
<td>Shearer; 2001; 88 h TSD, n = 21</td>
<td>↑ IL-6, TNF-α, IL-8, CRP</td>
<td>2 × 2 h nap (14:45–16:45 h; 02:45–04:45 h) during TSD</td>
<td>2 × 2 h nap (14:45–16:45 h; 02:45–04:45 h) during TSD</td>
<td>↓ IL-6, TNF-α, IL-8</td>
</tr>
<tr>
<td>Frey, 2007; 40 h TSD, n = 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayer-Ebert; 2007; 88 h TSD, n = 10</td>
<td>↑ IL-6, CRP, ↑ IL-8, IL-1β</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vgontzas, 2007; 40 h TSD, n = 41</td>
<td>↑ IL-6</td>
<td>Not reported</td>
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<tr>
<td>Saezet; 2010; 40 h TSD, n = 12</td>
<td></td>
<td>↑ IL-6, ↑ Norepinephrine</td>
<td></td>
<td></td>
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</tbody>
</table>

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# Inflammatory Mediator Studies

<table>
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<tr>
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<th>Inflammatory changes</th>
<th>After 8 h-recovery sleep</th>
<th>Sleep countermeasures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vgontzas, 2007; 4 nights of 6 h-sleep (02:30–04:30 h), n = 23</td>
<td>↑ Leukocyte and monocyte counts</td>
<td>IL-6, TNF-α only in d</td>
<td>Not reported</td>
<td>?</td>
</tr>
<tr>
<td>Irwin, 2006; 2010; 1 night of 4 h-sleep (03:00–07:00 h), n = 20</td>
<td></td>
<td>IL-6, TNF-α gene expression and protein by in vitro-stimulated monocytes</td>
<td>Not reported</td>
<td>?</td>
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<tr>
<td>Haack, 2007; 10 nights of 4 h-sleep (23:00–05:00 h), n = 18</td>
<td></td>
<td>IL-6, unchanged CRP</td>
<td>Not reported</td>
<td>?</td>
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<tr>
<td>Kerkhof, 2007; 3 nights of 4 h-sleep (01:00–05:00 h), n = 10</td>
<td>↑ Leukocyte and mononuclear cells</td>
<td>CRP</td>
<td>Not reported</td>
<td>?</td>
</tr>
<tr>
<td>Mayer-Ebert; 2007; 10 nights of 4.2 h-sleep (01:00–05:00 h), n = 10</td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
<td>?</td>
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<tr>
<td>Bougelis, 2009; 1 night of 4 h-sleep (01:00–05:00 h), n = 8</td>
<td>↓ Leukocyte and neutrophil counts</td>
<td>CRP, ↑ IL-6, IL-17 and IL-1β gene expression by in vitro-stimulated PBMC</td>
<td>CRP and IL-17 &gt; baseline</td>
<td>?</td>
</tr>
<tr>
<td>van Leeuwen, 2009; 5 nights of 4 h-sleep (00:00–07:00 h), n = 13</td>
<td></td>
<td>↑ CRP, ↑ IL-6, ↑ Myeloperoxidase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irwin, 2010; 1 night of 4 h-sleep (03:00–07:00 h), n = 20</td>
<td>↑ Leukocyte and mononuclear cells</td>
<td>↑ Myeloperoxidase, leukocyte and monocyte counts &gt; baseline</td>
<td>Not reported</td>
<td>?</td>
</tr>
<tr>
<td>Faraut, 2011; 1 night of 2 h-sleep (02:00–04:00 h), n = 12</td>
<td></td>
<td>↑ Myeloperoxidase, Leukocyte and neutrophil counts &gt; baseline</td>
<td>Not reported</td>
<td>?</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zouzmi-Boudjellaa, submitted; 5 nights of 5 h-sleep (01:00–05:00 h), n = 9</td>
<td></td>
<td>↑ Mox-LDL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chronic Sleep Debt is a Pro-inflammatory Condition

**Leukocytes**
- Increased WBC / Leukocytosis
- Monocytes and lymphocytes increased number and density
- Neutrophils increased number, but decreased effect
  - Decreased phagocytosis
  - Ineffective pathogen clearance
  - NK cell dysregulation

**Proinflammatory cytokines**
- Increased production of IL-1β, TNF-α, IL-6
- Increased production of interferon

**Sleep Debt and the Immune Response**
- Sleep debt – relative immunocompromised state
  - Diminished immune response
  - Blunted stress hormone response
  - Altered glucose metabolism
Bidirectional interactions between the immune system and sleep


Summary

- The immune and endocrine systems, especially IL-1, TNF, GHRH, and prolactin, are involved in physiologic sleep regulation
- The acute phase response increases NREM sleep and suppresses REM sleep
- Sleep loss is a pro-inflammatory state that impairs acquired immunity and increases vulnerability to infection
Thank you!
The effects of Atopy on Sleep

Fatima Khan, MD, FACAAL
Ann & Robert H. Lurie
Children’s Hospital of Chicago
Allergy/Immunology
November 6, 2021

Allergic Conditions affecting sleep

• Atopic dermatitis (AD)
• Asthma
• Allergic rhinitis (AR)
• Food allergies
• Pediatric obstructive sleep apnea (OSAS)
Review of sleep architecture

- Sleep architecture undergoes significant changes from newborn to adulthood
- Critical for body/brain maturation and development
- Consists of 4 main stages:
  - Stage 1 (light sleep) 2-5% sleep
  - Stage 2 (deeper sleep) 45-55%
  - Stage 3 slow wave/delta sleep (deep sleep) ~25%
  - REM 20-25%

Pediatric sleep

- Term infants sleep 16-18 hours/day
  - Circadian rhythm not yet developed
  - 2 stages (REM, NREM), enter sleep through REM
  - each cycle 50-60min only
  - 50% of their time spent in REM sleep
- During childhood duration of sleep cycles increases (90-110min)
  - Older children enter into sleep through NREM
- Mid-adolescence sleep resembles adult pattern
- Slow wave sleep (stg 3) decreases with age and puberty

Th1 vs Th2 balancing act

Cytokine circadian rhythm

- First half of sleep increased IL-12 and T helper cells (Th1) by end of night Th2 predominates
- Sleep disturbance affects Th1/Th2 balance
- Allergies mediated by Th2 pathway stimulates release of IL-4, IL-5, IL-13 cytokines which directly and indirectly affect sleep architecture
  - These cytokines cause increased time to REM and therefore decreased total REM duration
  - Increased sleep arousals
  - Stimulate target cells (eosinophils, mast cells, basophils)

Atopic dermatitis and sleep

- Sleep disruption occurs in both pediatric and adult AD patients
- Sleep disruption increases during acute AD flares
- Increased scratching during NREM further disrupting sleep cycle
- AD patients are awake 53 min longer than non-AD peers
- Overall, difficulty falling and staying asleep, increased waking
- Decreased melatonin levels also found in AD patients further negatively impacting sleep
- Greater association between AD and OSA in adults

Asthma and Sleep

- Much has been published on this topic
- Those with nocturnal asthma symptoms have greater sleep fragmentation
- 35% of adults with asthma also have OSA
- ~30% of children with controlled asthma also have OSA
- 63% of children with uncontrolled asthma have OSA
- Overall, decreased sleep duration and difficulty falling asleep despite adequate asthma control in children


Food allergy and Sleep

- Poor sleep quality in both mothers and children with FA due to anxiety
- Sleep quality assessed using Childhood sleep habit questionnaire (CSHQ) and Pittsburgh sleep quality index (PSQI)

Allergic rhinitis and sleep

- 88% of AR have sleep disturbance
- 75% report overall poor sleep quality
- 75% can’t fall asleep
- 64% wake up frequently through the night
- Cough also contributes to sleep disruption
  - Via histamine stimulation of afferent nerve
  - PND causing pharyngeal irritation


AR and nasal valve

https://medlineplus.gov/ency/imagepages/9657.htm

Reproduced with permission from Springer
Textbook of Allergy and Sleep. 2019. Springer
Adenotonsillar hypertrophy

- Found in both atopic children and those with habitual snoring
- Inflammatory cytokines increase during sleep as cortisol levels decline increase nasal congestion
- Mast cells recruited into tonsils
- Zicari et al found increased leukotrienes and LT receptors in patients with sleep disordered breathing
- Vibration from chronic snoring increases inflammatory mediators → OSAS
- Leads to chronic anatomic changes (“adenoid facies”)
- Evaluated via lateral neck film or rhinoscopy

Snoring & Obstructive Sleep Apnea

- 80% of children with OSAS are atopic
- Habitual snoring also induces airway inflammation
- Children with AR, asthma and AD are at greatest risk for OSAS
- Need high index of suspicion, inquire about sleep

References:
Jai Youl Ro. JACI. 2017;139(2). AB165.

Pediatric obstructive sleep apnea syndrome (OSAS)

- Due to partial or complete upper airway obstruction
- Can affect up to 5% of children 2-8 years of age
- Risk of cardiovascular, neurocognitive, metabolic comorbidities if untreated
- H&P
- Polysomnography gold standard for diagnosis
- Apnea-hypopnea index (AHI) used to gauge severity
- Treatment approach based on severity

Li et al. JACIP. 2016;4:852-61.

Pertinent History and Physical findings

- Important to assess mouth breathing not just snoring/apneic events
- Detailed sleep history (bedtime, wake time, sleep hygiene)
- Nocturnal enuresis (?)
- Daytime somnolence primarily in older children
- School performance, behavior changes (ADHD, aggression)
- High arched palate, retrognathia, narrow face/nose, tonsillar enlargement, dental crowding/crossbite (orthodontics)
- Allergic shiners, nasal mucosal edema/pallor
- Obesity, poor growth
- HTN
- + sleep questionnaire

Li et al. JACIP. 2016;4:852-61.
Treatment

• Behavioral modifications
  – Create good sleep habits
  – “Sleep hygiene” calm, quiet, bedroom environment
  – Daily routine more calming, less stimulating towards evening
  – Allergen avoidance measures

• Medications
  – Chronotherapy (AR/asthma/AD meds)
  – LTRA can decrease adenotonsillar hypertrophy
  – Nasal steroids +LTRA greater benefit, improved AHI
  – Melatonin

• Weight loss
• Positive airway pressure

Treatments

• Surgery
  – Adenotonsillectomy is 90% curative
  – Improvement of anatomic facial changes post-operatively
  – Significant improvements in apnea-hypopnea index (AHI)

Summary

- Chronic sleep disruption, regardless of cause leads to Th1/Th2 imbalance
- Inflammation due to physical factors (snoring, obesity) or allergies leads to development of OSAS
- Bidirectional relationship between allergic disease and overall effect on sleep

Thank you!
The Importance of Sleep Apnea for an Allergist

Timothy Craig, FAACAI, FAAAAI, FACP, FACOI
Professor of Medicine and Pediatrics
Distinguished Educator
AAAAI Board of Directors
Section Chief
Director Alpha-1-Antitrypsin Deficiency Center
Director of International Angioedema Center (ACARE)
Vietnam Education Foundation Scholar
Honorary Board of Directors, Lam Dong Medical College

Conflicts of Interest:

<table>
<thead>
<tr>
<th>Company</th>
<th>Research</th>
<th>Consultant</th>
<th>Speaker</th>
<th>Travel</th>
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<td>Kalvista</td>
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</table>
Objectives:

• 1. To understand how important Sleep Disordered Breathing is for the Allergist.
• 2. To review the meta-analyses on Sleep Disordered Breathing and how they apply to our patients
• 3. To improve care and outcomes of patients with allergic disease and Sleep Disordered Breathing.

All the slides are based on meta-analysis
Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
• 3. Does treatment of rhinitis improve Sleep Disordered Breathing?
• 4. Does treatment improve Apnea Hypopnea Index?
• 5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
• 6. What are the consequences of untreated Sleep disordered breathing

The BIG Question is, if allergic rhinitis increases sleep apnea, can correcting it reduce risk of the poor outcomes associated with sleep apnea
Questions:

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• 6. What are the consequences of untreated Sleep disordered breathing
Prevalence of AR in SDB and OSA in Children

Children:

- 40% of SDB children had Allergic Rhinitis.
- 45% of OSA children had Allergic Rhinitis.
Prevalence of AR in SDB and OSA in Adults

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Adults</th>
<th>OR (95% CI)</th>
<th>Events</th>
<th>Events</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SDB</td>
<td></td>
<td>0.15 (0.04, 0.53)</td>
<td>13</td>
<td>26.7</td>
</tr>
<tr>
<td>2</td>
<td>OSA</td>
<td></td>
<td>0.48 (0.36, 0.65)</td>
<td>26</td>
<td>38.1</td>
</tr>
</tbody>
</table>

Adults:

- 22% of SDB adults had Allergic Rhinitis.
- 35% of OSA adults had Allergic Rhinitis.

Comparing AR in those with and without SDB and OSA in Children

Children with SDB are more likely to have AR; however, this was not the case with OSA.
Comparing AR in those with and without SDB and OSA in Adults

In ADULTS, AR was not increased in those with either SDB or OSA as compared to those without SDB and OSA, and in addition BMI, neck circumference, ESS and AHI were not different between those with AR and those without.

Questions:

1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
   Yes, in children, AR is more prevalent in those with sleep disordered breathing, but in adults with obstructive sleep apnea, allergic rhinitis is not more prevalent than in those without obstructive sleep apnea

2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?

3. Does treatment of rhinitis improve Sleep Disordered Breathing?

4. Does treatment improve Apnea Hypopnea Index?

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• 3. Does treatment improve Apnea Hypopnea Index?
• 4. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
• 5. What are the consequences of untreated Sleep disordered breathing

RESEARCH ARTICLE

The association between allergic rhinitis and sleep: A systematic review and meta-analysis of observational studies

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There was no difference in sleep duration between AR and control group.
People with AR compared to controls had poorer sleep and less sleep efficiency, but no effect on Apnea Hypopnea Index (AHI).

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of studies</th>
<th>Sample size</th>
<th>No. of AR cases</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum PSQI score</td>
<td>2</td>
<td>1,194</td>
<td>582</td>
<td>0.68 (0.20, 1.15)</td>
</tr>
<tr>
<td>PSQI-Daytime dysfunction</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>0.01 (0.77, 0.80)</td>
</tr>
<tr>
<td>PSQI-Habitual sleep efficiency</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>0.03 (0.26, 0.32)</td>
</tr>
<tr>
<td>PSQI-Sleep disturbance</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>0.20 (0.13, 0.27)</td>
</tr>
<tr>
<td>PSQI-Sleep latency</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>0.29 (0.13, 0.45)</td>
</tr>
<tr>
<td>PSQI-Sleep quality</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>0.19 (0.40, 0.78)</td>
</tr>
<tr>
<td>PSQI-Use of sleep medications</td>
<td>2</td>
<td>370</td>
<td>184</td>
<td>-0.07 (-0.16, 0.01)</td>
</tr>
<tr>
<td>ESS score</td>
<td>3</td>
<td>1,449</td>
<td>489</td>
<td>1.53 (0.23, 3.30)</td>
</tr>
<tr>
<td>PSG-AHI</td>
<td>5</td>
<td>883</td>
<td>314</td>
<td>0.91 (-2.79, 4.61)</td>
</tr>
<tr>
<td>Oxyhemoglobin saturation (%)</td>
<td>2</td>
<td>247</td>
<td>94</td>
<td>0.99 (-0.99, 2.97)</td>
</tr>
<tr>
<td>PSG-Sleep efficiency</td>
<td>4</td>
<td>771</td>
<td>277</td>
<td>-3.95 (-7.00, -0.45)</td>
</tr>
<tr>
<td>Sleep stage 1 (%)</td>
<td>2</td>
<td>472</td>
<td>114</td>
<td>-4.88 (-16.46, 6.70)</td>
</tr>
<tr>
<td>Sleep stage 2 (%)</td>
<td>2</td>
<td>472</td>
<td>114</td>
<td>-0.63 (-3.24, 1.99)</td>
</tr>
<tr>
<td>Sleep stage 3/4 (%)</td>
<td>2</td>
<td>472</td>
<td>114</td>
<td>0.38 (-2.98, 3.73)</td>
</tr>
<tr>
<td>Sleep stage REM (%)</td>
<td>4</td>
<td>755</td>
<td>216</td>
<td>-1.29 (-3.04, 0.26)</td>
</tr>
</tbody>
</table>

Those with AR had other substantial effects on their sleep when compared to normal.

Allergic rhinitis was associated with:
- insomnia
- restless sleep
- enuresis
- snoring
- sleep disordered breathing
- obstructive sleep apnea
- daytime dysfunction
- difficulty waking up
- daytime sleepiness
- AM headaches
- use of sleeping pills
Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
   No, it appears people with AR have poorer sleep, but the severity of obstructive sleep apnea was not different than controls.
• 3. Does treatment of rhinitis improve Sleep Disordered Breathing?
• 4. Does treatment improve Apnea Hypopnea Index?
• 5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
• 6. What are the consequences of untreated Sleep disordered breathing
Objective. To determine the impact of treatment for patients with nasal obstruction secondary to allergic rhinitis (AR) and nasal septal deviation (NSD) on sleep quality.

Impact of Treatment for Nasal Cavity Disorders on Sleep Quality: Systematic Review and Meta-analysis

Jacob Fried, MD¹, Erick Yuen¹, Kathy Zhang¹, Andraia Li¹, Nicholas R. Rowan, MD², Rodney J. Schlosser, MD¹, Shaun A. Nguyen, MD¹, and David A. Gudis, MD³

Treatments for the allergic rhinitis cohort were any therapy for allergic rhinitis from antihistamines, to topical therapies and even montelukast and alternative therapies.
Rhinitis Quality of Life total score improves with therapies and this includes almost any therapy.

Rhinitis Quality of Life Sleep Score improves with rhinitis treatments.
Epworth Sleepiness Score and Pittsburgh Sleep Quality Index both improve with therapy.

There was not a change in objective metrics of sleep.

Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index changes with nasal septum correction.
Nasal Obstruction Symptom Evaluation (NOSE) and Apnea Hypopnea Index post deviated septum correction improve

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Post Treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>Pre Treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 NOSE</td>
<td>2.2</td>
<td>2.6</td>
<td>64</td>
<td>13.5</td>
<td>2.7</td>
<td>64</td>
<td>-11.30</td>
<td>[-12.22, -10.38]</td>
<td></td>
</tr>
<tr>
<td>Stapleton 2014</td>
<td>17.5</td>
<td>13.8</td>
<td>61</td>
<td>68.2</td>
<td>19.7</td>
<td>61</td>
<td>-33.3%</td>
<td>[-64.74, -4.66]</td>
<td></td>
</tr>
<tr>
<td>Valsamides 2019</td>
<td>27.7</td>
<td>27</td>
<td>60</td>
<td>76.1</td>
<td>20</td>
<td>60</td>
<td>32.9%</td>
<td>[-80.40, -56.90, -39.90]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>185</td>
<td></td>
<td>185</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>-36.64</td>
<td>[-87.51, -5.78]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 734.50; Chi^2 = 228.87, df = 2 (P = 0.00001); P^2 = 99%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 2.33 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 3.1.2 AHI          | 16.1                | 12.3 | 21    | 19.1               | 11.8 | 21    | 3.3%   | -3.00 [-10.29, 4.28]              |                                   |
| Kim 2004           | 6.5                 | 2.9  | 90    | 11.6               | 5.8  | 90    | 96.7%  | -5.10 [-6.44, -3.76]              |                                   |
| Mandour 2019       | 111                 |     | 111   | 100.0%             |     |       | -3.03  | [-6.35, -3.71]                   |                                   |
| Subtotal (95% CI)  | 111                 |     | 111   | 100.0%             |     |       |        |                                    |                                   |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.31, df = 1 (P = 0.58), P^2 = 0% |
| Test for overall effect Z = 7.40 (P < 0.00001) |

Questions:

1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
3. Does treatment of rhinitis improve Sleep Disordered Breathing?
4. Does treatment improve Apnea Hypopnea Index?
   - Yes, with deviated septum repair, but not other treatments; however, all treatments improved subjective data
5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
6. What are the consequences of untreated Sleep disordered breathing
Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
• 2. Does treatment of rhinitis improve Sleep Disordered Breathing?
• 3. Does treatment improve Apnea Hypopnea Index?
• Why again? To study nasal steroids and topical decongestants!
• 4. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
• 5. What are the consequences of untreated Sleep disordered breathing

Topical nasal treatment efficacy on adult obstructive sleep apnea severity: a systematic review and meta-analysis

Topical decongestants (first 2 studies) and topical corticosteroids (last 2 studies) do not affect the AHI
Again, topical decongestants did not affect the AHI

![Table showing data on AHI and mean difference]

**Figure 4.** Meta-analysis conducted on An et al, Clarenbach et al, and Wijesuriya et al to analyze TNT (oxymetazoline, xylometazoline, and phenylephrine, respectively) efficacy on improving OSA severity (AHI) when compared with placebo treatment. AHI = apnea-hypopnea index; CI = confidence interval; IV = inverse variance; OSA = obstructive sleep apnea; TNT = topical nasal treatment.

![Table showing data on baseline and nasal decongestants]

**Figure 5.** Meta-analysis on Braver et al and Clarenbach et al analyzing the efficacy of TNTs (oxymetazoline and xylometazoline, respectively) on OSA severity (AHI) when compared with baseline. AHI = apnea-hypopnea index; CI = confidence interval; OSA = obstructive sleep apnea; TNT = topical nasal treatment; IV = inverse variance.

In conclusion, based on the limited evidence, topical nasal sprays do not significantly impact AHI in adult patients with OSA, but they may improve MinSaO₂, ODI, RDI, and subjective quality-of-life measures in this population. Allergic patients may have more improvement in OSA measures with use of TNTs when compared with nonallergic patients. Future studies of larger sample sizes are indicated to more accurately determine the efficacy of these treatments.
Questions:

1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
3. Does treatment of rhinitis improve Sleep Disordered Breathing?
4. Does treatment improve Apnea Hypopnea Index?
   Again subjective measures improve, but neither nasal steroids or decongestants improve AHI
5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
6. What are the consequences of untreated Sleep disordered breathing?
Longitudinal Cardiovascular Outcomes of Sleep Disordered Breathing in Children: A Meta-Analysis and Systematic Review

Zarmina Ehsan, MD; Stacey L. Ishman, MD; Thomas R. Kimball, MD; Nanhua Zhang, PhD; Yunshe Zou, PhD; Raouf S. Amin, MD

*Division of Pulmonary and Sleep Medicine, Children’s Mercy Hospital, Kansas City, MO; Division of Pediatric Otolaryngology–Head and Neck Surgery, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Division of Cardiology, Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Department of Biostatistics & Epidemiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Division of Pulmonary and Sleep Medicine, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

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Figure 1: Flowchart for the identification of studies used in the systematic review and meta-analysis of the long-term cardiovascular outcomes of sleep disordered breathing (SDB) in children.
Multiple cardiac measurements failed to demonstrate significant abnormalities before and after correction of SDB

CRP was not different during and after correction of SDB
Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
• 3. Does treatment of rhinitis improve Sleep Disordered Breathing?
• 4. Does treatment improve Apnea Hypopnea Index?
• 5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
  Yes, it appears early correction prevent cardiovascular disease
• 6. What are the consequences of untreated Sleep disordered breathing
Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis

Emily S Heilbrunn,¹ Paddy Ssentongo,¹,² Vernon M Chinchilli,¹ John Oh,³ Anna E Ssentongo ⁴,³


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. JBI, Joanna Briggs Institute; OSA, obstructive sleep apnoea; EBP, Evidence-Based Practice.
Moderate and Severe Obstructed Sleep Apnea results in risk of all-cause sudden death

Cardiovascular mortality is increased in OSA
CONCLUSION

Individuals with OSA have nearly a twofold higher risk of sudden death and cardiovascular mortality. Treatments and interventions related to decreasing this risk and other adverse outcomes are necessary to optimise survival and QOL.

Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
• 3. Does treatment of rhinitis improve Sleep Disordered Breathing?
• 4. Does treatment improve Apnea Hypopnea Index?
• 5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
• 6. What are the consequences of untreated Sleep disordered breathing Cardiac remodeling with increase risk of sudden death
Questions:

• 1. In Sleep Disordered Breathing (SDB) populations are people with allergic rhinitis more prevalent?
  Yes for sure

• 2. Do patients with Allergic Rhinitis have a greater Apnea Hypopnea Index (AHI)?
  They have much poorer sleep, but AHI is not different from controls

• 3. Does treatment of rhinitis improve Sleep Disordered Breathing?
  It improves quality of sleep, but does not improve AHI

• 4. Does treatment improve Apnea Hypopnea Index?
  Neither topical steroids or decongestants improve the AHI

• 5. Can treatment early on in life prevent the consequences of Sleep Disordered Breathing?
  For sure

• 6. What are the consequences of untreated Sleep disordered breathing?
  Cardiac remodeling with increase risk of sudden death

Summary

The BIG Question is, if allergic rhinitis increases sleep apnea, can correcting it reduce risk of the poor outcomes associated with sleep apnea.

Correction of nasal obstruction, including deviated nasal septum, nasal polyps, adenoid hypertrophy is essential to correct early in life. To me the data for rhinitis is less clear, but none the less subjective improvement in sleep occurs.
Thank you from Penn State University