Dreams of Better Vision:

How Sleep Impacts Ocular Health and Systemic Function

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Financial Disclosures

- Investigator
  - Lexitas
  - Claris Bio
  - Trinity Life Sciences
- Consultant
  - Optase
  - Dompe
  - Tarsus
- Founder, advisor, minority shareholder
  - SunSnap Kids

All relevant relationships have been mitigated

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3 parts:

1) Sleep, melatonin, blue light, ipRGCs, refractive error
2) Sleep and ocular surface disease
3) Sleep, posterior pole pathology, and systemic disease

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Sleep, melatonin, blue light, ipRGCs, refractive error

Thanks to Dr. Lisa Ostrin for her contributions

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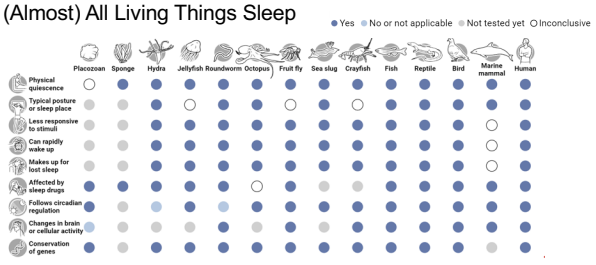
(Almost) All Living Things Sleep



Desai, Science, 2021

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What is Sleep?

- Naturally recurring state of mind and body
- Altered consciousness
- Inhibition of sensory activity
- Inhibition of nearly all voluntary muscles

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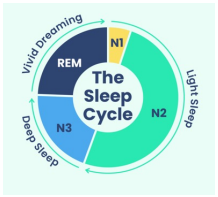
Sleep Stages

- One sleep cycle is three non-rapid and one rapid eye movement stages
- One night consists of four to six sleep cycles per night
- Sleep stages allow the brain and body to recuperate
- Duration of stages can vary based on age, sleep patterns, alcohol, and sleep disorders
- Improved sleep hygiene can encourage healthy transitions through the sleep stages



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What is Rapid Eye Movement Sleep?

- Eyes are closed but move rapidly
- Heart rate and breathing increase
- REM periods increase from 10 to 60 minutes across the night
- Can have intense dreams, brain is more active

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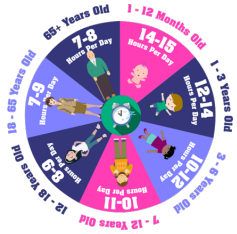
How Much Sleep is Needed?

- Infants (< 1): 14-15 hours
- Toddlers and preschoolers (3-6): 10-13 hours
- Children and teens (7-18): 8-11 hours
- Adults (18-64): 7-9 hours
- Elderly (65+): 7-8 hours



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Humans Tend to Fight Sleep

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Why Sleep?

- Metabolism
- Growth, renewal, and repair
- Brain function
- Immunity
- Heart health
- Emotional and mental health

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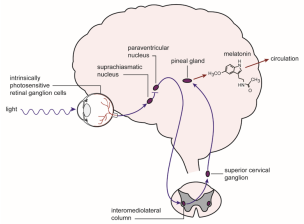
Light – Eye – Sleep Relationship

- Light is the strongest Zeitgeber for circadian rhythms
- Light is detected and carried to brain centers by the intrinsically photosensitive retinal ganglion cells
- Darkness cues the release of melatonin



Ostrin L. Clinical Exp Opt. 2019

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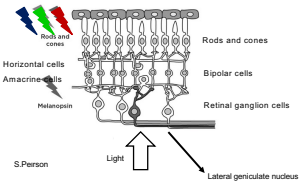
Retinal Ganglion Cells



- RGCs are found in the inner retina
- RGCs receive input from rod and cone pathways through bipolar cells
- RGC axons exit the eye as the optic nerve
- The majority of RGCs project to the LGN and visual cortex and are involved in image formation

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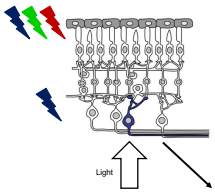
Intrinsically Photosensitive Retinal Ganglion Cells



Suprachiasmatic nucleus
Superior colliculus
Olivary pretectal nucleus

- Direct ipRGC activation through melanopsin is the intrinsic pathway
- Synaptic input from the rod and cone pathways is the extrinsic pathway
- ipRGCs synapse with dopaminergic amacrine cells

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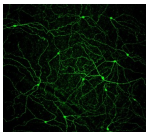
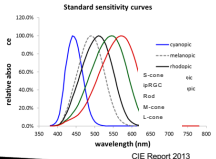
Intrinsically Photosensitive Retinal Ganglion Cells

- Approximately 1-3% of RGCs are intrinsically photosensitive
- Most sensitive to short wavelength light (blue, 482 nm)
- ipRGCs are directly stimulated by light through the photopigment melanopsin



Ostrin, et al. 2018



CIE Report 2013

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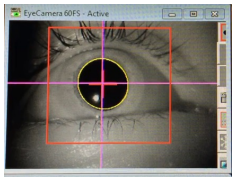
Intrinsically Photosensitive Retinal Ganglion Cells

- Primarily involved in non-image forming visual processing
  - Irradiance detection
  - Pupil size control
  - Circadian rhythm entrainment



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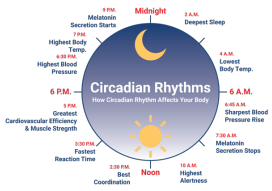
Circadian Rhythm

- Fluctuations in physiological processes over approximately 24 hours
- Mediated by light input and endogenous clocks
- ipRGCs are irradiance detectors in the inner retina that entrain circadian rhythm



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Systemic circadian rhythm
- Sleep/wake patterns
- Blood pressure and heart rate
- Body temperature
- Metabolism
- Hormone release

Ocular circadian rhythm
- Choroidal thickness
- Axial length
- Intraocular pressure
- Photoreceptor disc shedding
- Neurotransmitter synthesis and release

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Da Vinci L, 1490

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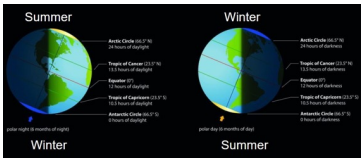
Seasonal Changes in Day Length

- Photoperiod – day length
- Shortened day lengths in winter in northern countries are associated with seasonal affective disorder (SAD)



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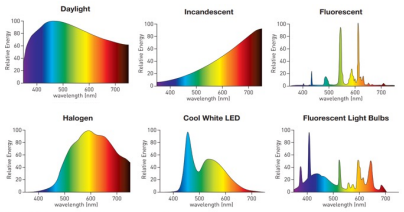
Spectral Composition of Light

- Natural light
  - Sunlight
  - Fire
- Artificial light
  - Indoor lighting
    - *Fluorescent*
    - *Incandescent*
    - *LED*
  - Electronic devices
    - *Tablets*
    - *Phones*
    - *Computers*
    - *Televisions*



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Poor Sleep Hygiene

- Poor sleep hygiene can disrupt sleep patterns by creating an environment and routine that hinders the body's natural ability to fall asleep and stay asleep
- Contributing factors
  - Irregular sleep schedules
  - Exposure to electronic screens before bedtime
  - Consuming stimulants close to bed time

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Shift Work

- Shift work
  - Accounts for 20-25% of the workforce (Caruso, 2014)
  - Requires artificial light during the night and irregular sleep patterns
  - Recurrent phase reversal causes constant disruption of the circadian rhythm
- Associated health problems with night shift work
  - Sleep disorders, sleepiness, physical and mental fatigue, poor memory, decreased cognitive function (Vanttola et al., 2020)
  - Shift work is associated with metabolic syndrome, myocardial infarction, ischemic stroke and premature death
- Systematic review and meta-analysis of 21 studies showed that a single dose of 2000-5000 lux for <1 hour, particularly in the blue range of the spectrum can help regulate the negative circadian effects (Lam and Chung, 2021)

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Travel Across Time Zones

- 200 million passengers take international flights in or out of the US each year
- Jet lag leads to an acute circadian disruption – internal clocks are desynchronized with the environment
- Some parts of the brain and the periphery take days or weeks to reset
- Effects of jet lag include
  - Sleep disruption
  - Daytime sleepiness
  - Impaired thinking
  - Hampered physical function
  - Emotional difficulties
  - Stomach problems

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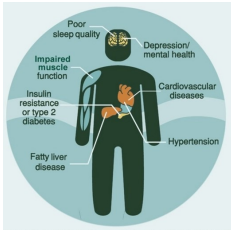
Systemic Effects of Circadian Disruption

- Cognitive dysfunction
- Heart disease
- Asthma
- Altered gut microbiome
- Neurodegenerative diseases
- Cancer
- Immune response and macrophage behavior



Integrative and Functional Nutrition Academy, 2021

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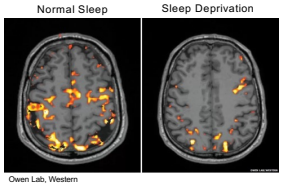
Cognitive Function



Owen Lab, Western

- Short term effects
  - Difficulty concentrating
  - Decline in mood
  - Impaired memory
  - Fatigue
- Long term effects
  - Poor academic/work performance
  - Cognitive decline
  - Heightened risk of dementia

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Heart Health

- Circadian rhythms are important regulators of cardiovascular physiology and disease
- When circadian rhythms in rodents are out of sync it leads to
  - Cardiomyopathy
  - cardiac fibrosis
  - systolic dysfunction
  - can lead to cardiovascular death
- Circadian disruption is associated obesity and diabetes, which further affect heart health

https://www.nhlbi.nih.gov/

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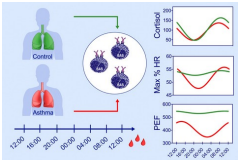
Asthma

- Inflammatory pathways have been observed to vary with the time of day
- In asthma, airway diameter is directly controlled by circadian rhythms (Spengler et al., 2019)
- Circadian disruption through mechanisms such as light at night can exacerbate asthma and allergic conditions



Spadaro et al., 2020

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Cancer

- Natural light helps regulate hormones
- Artificial light at night causes disruption
  - Increases the risk of hormone-dependent cancers
  - Changes
    - hormone production and release
    - hormone receptor affinities
    - weakens immune system
    - general stressor and endocrine disruptor
- Circadian disruption from blue light at night has been linked to:
  - Breast cancer (Rybnikova 2018)
  - Prostate cancer (Haim 2013)
  - Colorectal cancer (Schernhammer 2001)

NPR

MIT News

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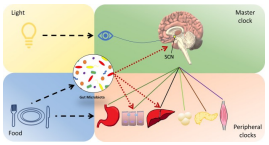
Gut Microbiome



Matenchuk et al., 2020

- Gut microbiota shown to undergo diurnal rhythms in humans
  - *Parabacteroides*, *Lachnospira*, *Bulleida*, *Roseburia*, *Veillonella*, *Haemophilus*, *Adlercreutzia*, *Eggerthella*, *Anaerotruncus*, *Oscillospira*, *Ruminococcus*, *Holdemania*, *Desulfovibrio*, *Escherichia*, and unspecified genera of families *S24-7* and *Enterobacteriaceae* (Matenchuk et al., 2020)
- Gut microbiota undergoes energy metabolism, DNA repair, and cell growth during the dark phase (Thaiss et al., 2014)

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Weight gain

- Poor sleep is associated with obesity
- Affects the hypothalamus which regulates appetite and energy expenditure
- Reduced sleep effects:
  - endocrine alterations (glucose)
  - decreased glucose tolerance
  - decreased insulin sensitivity
  - increased evening concentrations of cortisol
  - increased levels of ghrelin
  - decreased levels of leptin
  - increased hunger and appetite

Montgomery Advisor

Taheri S. The link between short sleep duration and obesity: We should recommend more sleep to prevent obesity. *Arch Dis Child* 2006;91:881–884.
Beccuti G, Pannain S. Sleep and obesity. Curr Opin Clin Nutr Metab Care. 2011 Jul;14(4):402-12. doi: 10.1097/MCO.0b013e3283479109. PMID: 21659802; PMCID: PMC3632337

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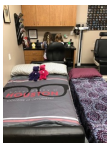
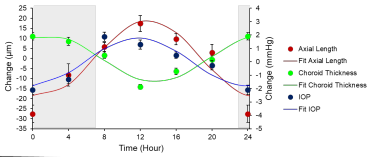
Ocular Circadian Rhythms

- Corneal thickness, epithelial shedding
- Choroidal thickness, axial length
- Intraocular pressure, perfusion pressure
- Photoreceptor disc shedding, neurotransmitter synthesis and release





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Ostrin et al., 2019

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Ocular Effects of Circadian Disruption

- Cornea: epithelial shedding in the morning
  - recurrent corneal erosions
- Conjunctiva: thicker in the early morning immediately after waking (Read 2016),
  - scleral lens implications
- Meibomian glands: yielding liquid secretions, neutrophils (Blackie 2010, Reyes 2018)

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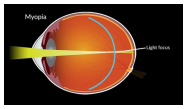
Circadian Rhythms and Refractive Error

- Light input and circadian rhythm may play a role in myopia development
  - Brief periods of light at night affects eye growth in chicks (Nickla and Totonelly, 2016)
  - Constant light or constant dark induces refractive changes (Li et al. 1995, Gottlieb et al. 1987)
- Time of day of defocus important in experimental myopia (Nickla et al. 2017)
  - Myopic defocus in the evening is more effective at inhibiting eye growth than in the morning



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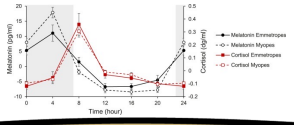
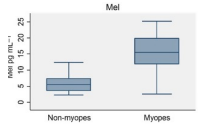
Myopia, Melatonin, and Sleep

- Sleep duration, quality, and bedtime
  - Emmetropes and myopes demonstrate differences in sleep duration and sleep quality (Gong et al, 2014, Jee et al, 2016)
  - Late bedtime (after 9:30 pm) increased the risk of myopia (Liu et al. 2020)
  - Myopia is associated with decreased sleep quality (Abbott et al. 2018)
- Morning melatonin varies with refractive error (Kearney et al. 2017, Kumar et al. 2021)





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Burfield et al. 2019

Kearney et al. 2017

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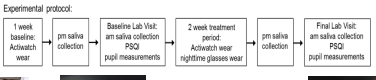
Effects of Nighttime Blue Blocking Lenses

- 22 adult subjects recruited to wear blue blocking glasses at nighttime for 2 weeks
- One subject was excluded due to non-compliance
- Average age of 26.7
- 10 females and 11 males



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Ostrin, Abbott, Queener, 2019

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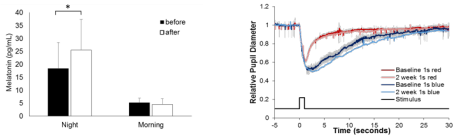
Results

- After wearing blue blocking glasses at nighttime for 2 weeks:
  - Nighttime melatonin increased 58%
  - ipRGC pupil responses were altered
  - Objectively measured sleep duration increased by 24 minutes
  - Subjectively measured sleep quality improved



Ostrin, Abbott, Queener, OPO 2017

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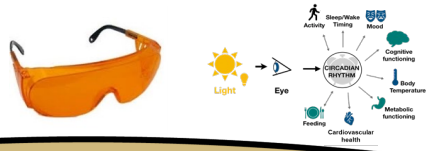
Conclusions

- Blue light exposure during the day is important for regulating circadian rhythm
- Blue light exposure at night leads to circadian disruption, which can have widespread physiological ramifications
- It is beneficial to decrease blue light exposure (by turning off artificial lights at night or wearing blue blocking lenses that block ALL short wavelengths)



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Sleep and ocular surface disease

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Case Report – Initial Visit

76 year-old white female presents with constant dryness and irritation
Lives in nursing home
POH: CE/IOL
PMH: mild dementia and mild HTN
Meds: Aricept, hydrochlorothiazide
Ocular meds: Patanol 0.2% 1-2x per day

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Case Report – Initial Visit

- VAsc
  - OD: 20/25-2
  - OS: 20/30
- Emmetropic after CE/IOL
- SLE: 2+ diffuse PEK, minimal MGD
- Posterior pole: unremarkable
- Plan: PFATs QID, FML BID for 2 weeks, Restasis BID
- RTC 2 months

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Case Report – 2nd visit

- No improvement in corneal epitheliopathy or symptoms
- Never received any drops
- Plan
  - Re-printed prescriptions
  - Daughter to give prescriptions directly to nurse at facility

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Case Report – 3rd visit

- Patient thrilled with how her eyes feel. No dryness or irritation.
- VAsc
  - OD: 20/20
  - OS: 20/20
- Resolved corneal epitheliopathy

- So the plan worked? Right?

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Case Report – 3rd visit

- The only problem was…

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Case Report – 3rd visit

- The only problem was… Patient never received any eyedrops

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Case Report – 3rd visit

- The only problem was… Patient never received any eyedrops

- I'm confused.
- Daughter is confused.
- Patient is thrilled.

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Case Report – what changed?

- Began asking questions
- Patient was more alert, energetic, and in better spirit
- Daughter said she had been sleeping sleeping better lately
- 5 hours ---> 8 hours per night

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Case Report – what changed?

- Began asking questions
- Patient was more alert, energetic, and in better spirit
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- 5 hours ---> 8 hours per night

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Patients with dry eye disease have poor sleep

High prevalence of sleep and mood disorders in dry eye patients: survey of 1,000 eye clinic visitors

Dry eye and sleep quality: a large community-based study in Hangzhou
Xiaoning Yu[1,2,3,†], Huilan Guo[2,3,4,†], Xin Liu[1,2,3], Guowei Wang[2,3,4], Yan Min[5], Shih-Hua Sarah Chen[5], Summer S. Han[6], Robert T. Chang[7], Xueyin Zhao[2,3,4], Ann Hsing[5], Shankuan Zhu[2,3,4,*] and Ke Yao[1,*]

The association of sleep quality with dry eye disease: the Osaka study

The relationship between dry eye and sleep quality
Morten Schjerven Magno[a,b], Tor Paaske Utheim[a], Harold Snieder[c], Christopher J. Hammond[d,e], Jelle Vehof[b,c,d,*]

Sleep Disorders are a Prevalent and Serious Comorbidity in Dry Eye
Masahiko Ayaki,[1,2] Kazuo Tsubota,[1] Motoko Kawashima,[1] Taishiro Kishimoto,[3] Masaru Mimura,[3] and Kazuno Negishi[1]

Sleep and mood disorders in dry eye disease and allied irritating ocular diseases
Masahiko Ayaki[1,3], Motoko Kawashima[1], Kazuno Negishi[1], Taishiro Kishimoto[2], Masaru Mimura[2] & Kazuo Tsubota[1]

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Patients with sleep disorders are more likely to have dry eye disease

Evaluation of Ocular Surface Health in Patients with Obstructive Sleep Apnea Syndrome
Emine Esra Karaca,[1,*] Hanife Tuba Akçam,[2] Feyzahan Uzun,[3] Şengül Özdek,[4] and Tansu Ulukavak Çiftçi[5]

The association of dry eye symptom severity and comorbid insomnia in US veterans
Anat Galor, MD, MSPH[1,2], Benjamin E Seiden, BS[1], Jasmine J. Park, BS[1], William Feuer, MS[2], Allison L. McClellan, OD[1], Elizabeth R. Felix, PhD[1,3], Roy C. Levitt, MD[1,4,5,6], Constantine Sarantopoulos, MD, PhD[1,4], and Douglas M. Wallace, MD[1,7]

Ocular surface assessment and morphological alterations in meibomian glands with meibography in obstructive sleep apnea Syndrome

Prevalence and Predictors of Ocular Complications in Obstructive Sleep Apnea Patients: A Cross-sectional Case-control Study
Nesreen E. Morsy, Badawi E Amani, Ahmad A Magda, Awadalla J Nabil, Seithikurippu R. Pandi-Perumal, Ahmed S. BaHammam, David Warren Spence, Per O. Lundmark and Nevin FW Zaki

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Relationship between dry eye and sleep quality

- 71,761 participants in Netherlands
- Pittsburg Sleep Quality Index
  - 19 questions about quality, latency, duration, efficiency, disturbances, mediations, and daytime dysfunction
- Women's Health Study dry eye questionnaire
  - How often do your eyes feel dry?
  - How often do your eyes feel irritated?
  - Have you every been diagnosed with dry eye?

Morten Schjerven Magno, Tor Paaske Utheim, Harold Snieder, Christopher J. Hammond, Jelle Vehof. The relationship between dry eye and sleep quality. The Ocular Surface. Volume 20. 2021. Pages 13-19. ISSN 1542-0124,

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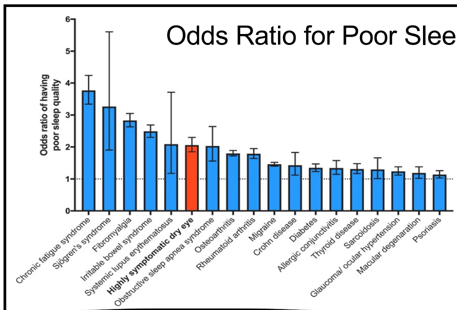
Relationship between dry eye and sleep quality

- 8.9% had dry eye disease (WHS)
- In the dry eye group, 36.4% had poor sleep (24.8% of controls)
- 44.9% of patients with dry eye symptoms "often" or "constantly" had poor sleep
- All components of sleep quality were affected in subjects with dry eye
  - After correcting for comorbidities
- Participants with poor sleep were 50% more likely to have dry eye

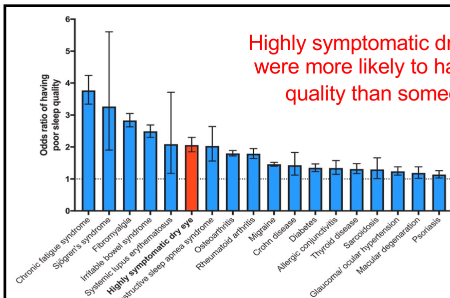
52

Odds Ratio for Poor Sleep Quality by Condition



53

Highly symptomatic dry eye patients were more likely to have poor sleep quality than someone with OSA!



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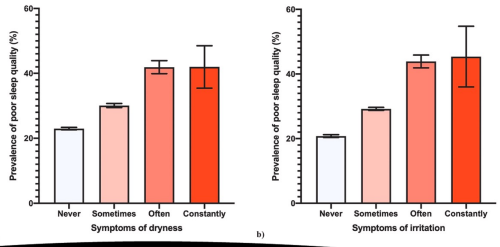
Worse DED Symptoms = Worse Sleep Quality



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Conclusions

- Sleep quality is reduced in dry eye patients of all demographics
- After correction for comorbidities, dry eye symptoms were strongly associated with poor sleep quality
- People with dry eye symptoms were 1.5x more likely to have poor sleep
- Participants with poor sleep quality were 50% more likely to have dry eye

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Conclusions

- Sleep quality is reduced in dry eye patients of all demographics
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Conclusions

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Sjogren's Syndrome Patients Have Worse Sleep

- Wang et al found a 81.7% prevalence of sleep disorders amongst patients with primary Sjogren's Syndrome
- 52.7% of Sjogren's patients suffering from moderate or severe sleep disorders
- 2017 systemic review concluded that SS patients with daytime fatigue should be screened for sleep disorders

1) Cui Y, Li J, Li L, et al. Prevalence, correlates, and impact of sleep disturbance in Chinese patients with primary Sjögren's syndrome. *Int J Rheum Dis*. 2020;**23**(3):367–373. doi: 10.1111/1756-185X.13678
2) Hackett KL, Gatts ZM, Ellis J, et al. An investigation into the prevalence of sleep disorders in primary Sjögren's syndrome: a systematic review of the literature. *Rheumatology*. 2017;**56**(4):570–580. doi: 10.1093/rheumatology/kew443
3) Wang YF, Fan Z, Cheng YB, Jin YB, Huo Y, He J. [Investigation of sleep disturbance and related factors in patients with primary Sjögren's syndrome]. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2020;**52**(6):1083–1088. Chinese. doi: 10.19723/j.issn.1671-167X.2020.06.012

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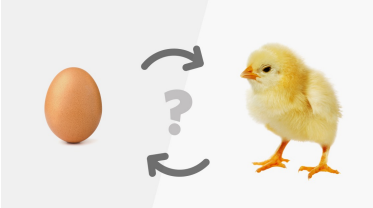
Does poor sleep cause dry eye
or does dry eye cause poor sleep?



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After 1 Night of Sleep Deprivation in Humans

- ↑ Tear osmolarity
- ↓ TBUT
- ↓ Lacrimal gland secretions

Y.B. Lee, J.W. Koh, J.Y. Hyon, W.R. Wee, J.J. Kim, Y.J. Shin. Sleep deprivation reduces tear secretion and impairs the tear film. Invest Ophthalmol Vis Sci, 55 (6) (2014), pp. 3525-3531

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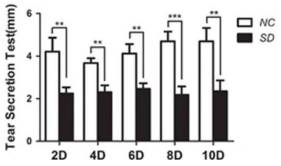
Sleep Deprivation in Mice

- 50% reduction in aqueous tear secretions after 2 days of sleep deprivation



S. Li, K. Ning, J. Zhou, Y. Guo, H.Zhang, Y. Zhu, *et al.* Sleep deprivation disrupts the lacrimal system and induces dry eye disease. Exp Mol Med, 50 (3) (2018)

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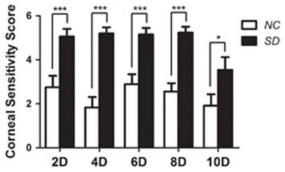
Sleep Deprivation in Mice

- Significant increase in corneal sensitivity



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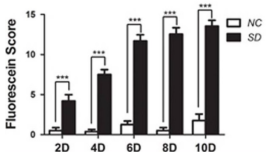
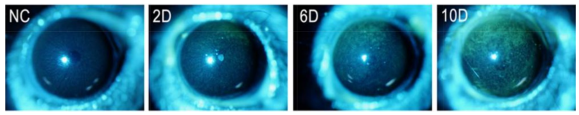
Sleep Deprivation in Mice

- Increase in corneal staining





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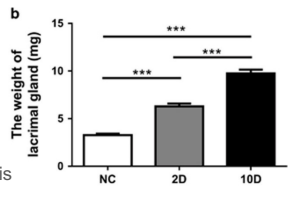
Sleep Deprivation in Mice

- Lacrimal gland (LG) hypertrophy
  - Altered lipid metabolism
- Decreased dopamine and acetylcholine in LG tissue
- Altered tear film amino acids
  - Altered gene expression in LG
- Increased corneal epithelial apoptosis



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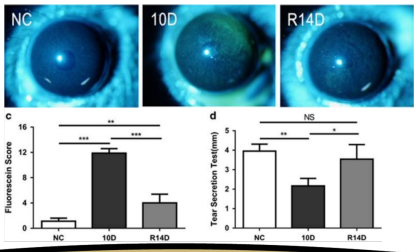
Reversibility of Ocular Surface Changes



Decreased corneal staining after 14 days of rest

Increased tear secretions after 14 days of rest

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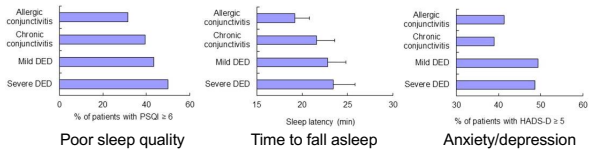
Sleep and Other Ocular Surface Diseases

- Patients with DED have worse sleep quality than patients with allergic conjunctivitis or chronic conjunctivitis
- Patients with DED have worse sleep latency and higher anxiety/depression



Poor sleep quality | Time to fall asleep | Anxiety/depression

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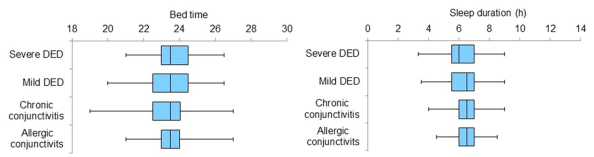
M. Ayaki, M. Kawashima, K. Negishi, T. Kishimoto, M. Mimura, K. Tsubo. **Sleep and mood disorders in dry eye disease and allied irritating ocular diseases.** Sci Rep, 6 (2016), p. 22480

68

Sleep and Other Ocular Surface Diseases

- Compared to allergic conjunctivitis or chronic conjunctivitis patients, DED patients have lower sleep duration and later bedtime



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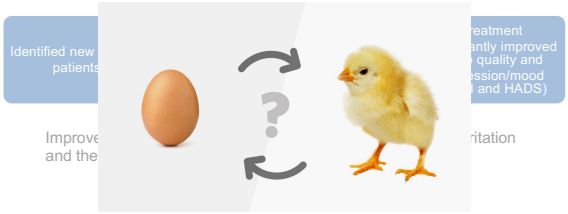
69

Treating Dry Eye Improves Sleep Quality!



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M. Ayaki, I. Toda, N. Tachi, K. Negishi, K. Tsubota. Preliminary report of improved sleep quality in patients with dry eye disease after initiation of topical therapy. Neuropsychiatric Dis Treat, 12 (2016), pp. 329-337

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Treating Dry Eye Improves Sleep Quality!

Identified new dry eye patients → Initiated treatment consisting of hyaluronate, mucin secretagogue, and steroid → Treatment significantly improved sleep quality and depression/mood (PSQI and HADS)

Improvement in sleep attributed to alleviated ocular surface irritation and the mental relief of a formal diagnosis and treatment

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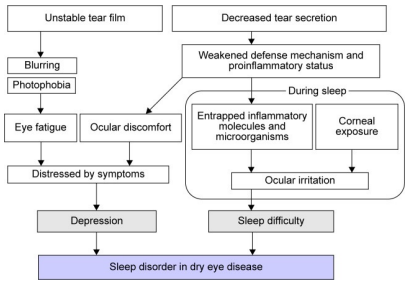
M. Ayaki, I. Toda, N. Tachi, K. Negishi, K. Tsubota. Preliminary report of improved sleep quality in patients with dry eye disease after initiation of topical therapy. Neuropsychiatric Dis Treat, 12 (2016), pp. 329-337

71

Hypothesis of relationship between DED and Sleep



Credit Ayaki et al

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How does sleep position affect DED?

Side or face: increased lissamine green staining and higher OSDI scores
Back: less lissamine green staining and lower OSDI scores

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Alevi D, Perry HD, Wedel A, Rosenberg E, Alevi L, Donnenfeld ED. Effect of Sleep Position on the Ocular Surface. Cornea. 2017 May;36(5):567-571. doi: 10.1097/ICO.0000000000001167. PMID: 28257381

73

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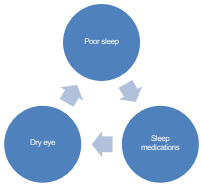
Sleep Medications and Dry Eye Disease

- Sleep medications often work like tricyclic antidepressants
  - Decrease lacrimal gland secretions
- Common sleep medications include:
  - Doxepin (Silenor, Zonalon, Prudoxin)
  - Eszopiclone (Lunesta)
  - Suvorexant (Belsomra)
  - Triazolam (Halcion)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien)
  - Trazodone (Desyrel)
  - Remelteon (Rozerem)



- Both poor sleep and taking sleep medications may cause dry eye

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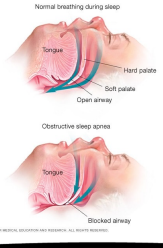
Obstructive Sleep Apnea and Ocular Surface



Individuals with OSA
- 66.7% have associated dry eye disease
- 54.17% have floppy eyelid syndrome
- *Dry eye is worse with CPAP/BIPAP
- Increased meibomian gland dropout
- Lower TBUT

*not always true

1) Shah, Priya V., et al. "The correlation between non-invasive ventilation use and the development of dry eye disease." Cureus 13.9 (2021).
2) Mulhafiz, Ersin MD*; Ölçen, Merhamet MD*; Erten, Remzi MD*; Bozkurt, Erdinç MD*. Evaluation of Meibomian Glands in Obstructive Sleep Apnea-Hypopnea Syndrome. Cornea 39(6):p 685-690, June 2020.

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OSA and Floppy Eyelid Syndrome

- Bilateral, asymmetric
- Marked laxity of eyelids
  - Decreased elastin
  - Collagen changes to eyelids
- Friction related OSD
  - Palpebral conjunctiva irritation
  - Ocular surface irritation

- The prevalence of OSA in patients with floppy eyelid syndrome ranged from 96% to 100% in the 2 retrospective case reviews performed by McNab.

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Positive Airway Pressure and Floppy Eyelids

- Acar M et al assessed effects of positive airway pressure (PAP) on the ocular surface over months

FES Stage	CFS	TBUT	Schirmer's	OSDI

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Acar M, Firat H, Yucesoge M, Ardic S. Long-term effects of PAP on ocular surface in obstructive sleep apnea syndrome. Can J Ophthalmol. 2014 Apr;49(2):217-221

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✓ FES Stage ✓ CFS ✓ TBUT ✓ Schirmer's ✓ OSDI

Sue Anschutz-Rodgers Eye Center | uchealth | Acar M, Firat H, Yuceege M, Ardic S. Long-term effects of PAP on ocular surface in obstructive sleep apnea syndrome. *Can J Ophthalmol*. 2014 Apr;49(2):217-221

79

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✓ FES Stage ✓ CFS ✓ TBUT ✓ Schirmer's ✓ OSDI

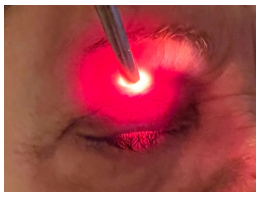
- Long-term PAP therapy may improve the clinical picture of FES

Sue Anschutz-Rodgers Eye Center | uchealth | Acar M, Firat H, Yuceege M, Ardic S. Long-term effects of PAP on ocular surface in obstructive sleep apnea syndrome. *Can J Ophthalmol*. 2014 Apr;49(2):217-221

80

Purpose of sleep for the ocular surface

- Eyelids create a mechanical barrier during sleep
- REM promote aqueous humor flow which increases nutrient supply to the cornea
- REM distributes tears over the ocular surface during sleep



Sue Anschutz-Rodgers Eye Center | uchealth | 1) Guillon, S. (2019) Rationale for 24-hour management of dry eye disease: A review. *Cornea: Lens and Anterior Eye* 42: 147–154. 2) Epstein, A.B. (2021) Optometric Physician e-journal. Review of Optometry Vol. 21, No.2

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Incomplete Lid Seal / Incomplete Lid Closure

- Affects ~5% of the population
- 80% of MGD patients report "eyelids sticking to the eyes" in the mornings
- Occurs in cases of FES
- Worsened by CPAP air flow
- Treatments
  - MGD treatment
  - Ung, moisture goggles, saran wrap, eyelid reconstruction

Korb-Blackie Light Test

Sue Anschutz-Rodgers Eye Center | uchealth | 1) Guillon, S. (2019) Rationale for 24-hour management of dry eye disease: A review. *Cornea: Lens and Anterior Eye* 42: 147–154. 2) Epstein, A.B. (2021) Optometric Physician e-journal. Review of Optometry Vol. 21, No.2

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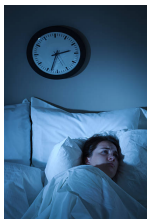

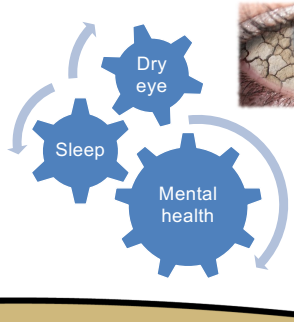

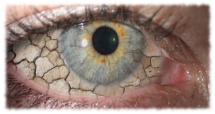

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Mougeot et al. Pro-inflammatory cytokines associated with clinical severity of dry eye disease of patients with depression. *Advances in Medical Sciences*. Volume 62, Issue 2, 2017. Pages 339-344.

Wan W, Wu Y, Chen Y, Gong L, Li M, Chen X, Yan M, Xiao Z, Sun X. Dry eye disease in patients with depressive and anxiety disorders in Shanghai. *Cornea*. 2012 Jun;31(6):646-52.

Dry Eye

Pro-inflammatory cytokines (IL-6, IL-17 and TNF-α) were present in high levels in the tears of patients with depression

In Shanghai, 60% of residents in a psychiatric facility were found to have dry eye disease

Sleep

Anxiety

Meta-analysis showed the prevalence of anxiety and depression is approximately threefold higher is dry eye patients

Subjects with DED are more likely to experience short sleep duration, physiological stress, and depressed mood

Depression

Wan, K., Chen, L. & Young, A. Depression and anxiety in dry eye disease: a systematic review and meta-analysis. *Eye* 30, 1558–1567 (2016).

An Y, Kim H. Sleep disorders, mental health, and dry eye disease in South Korea. *Sci Rep*. 2022 Jun 30;12(1):11046.

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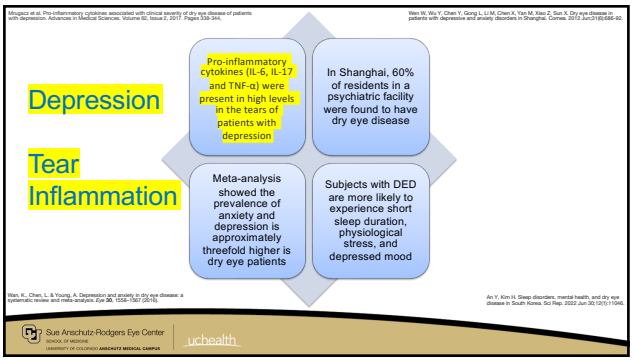

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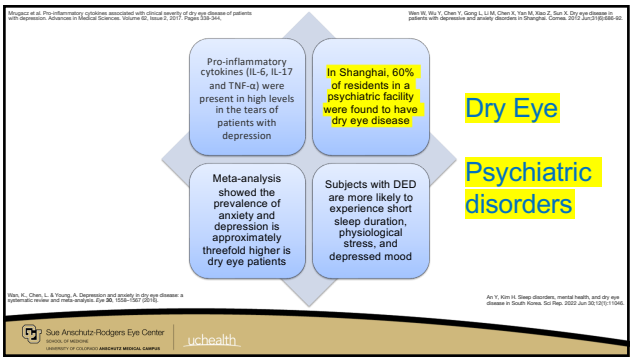

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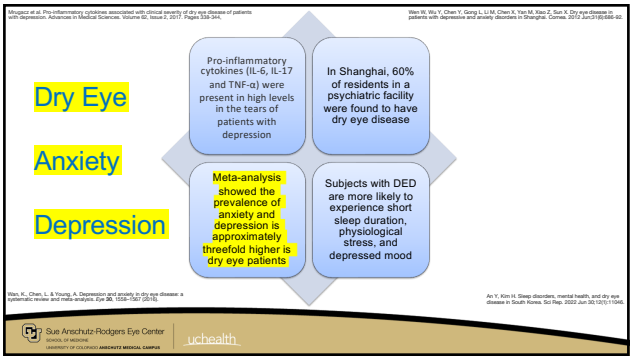

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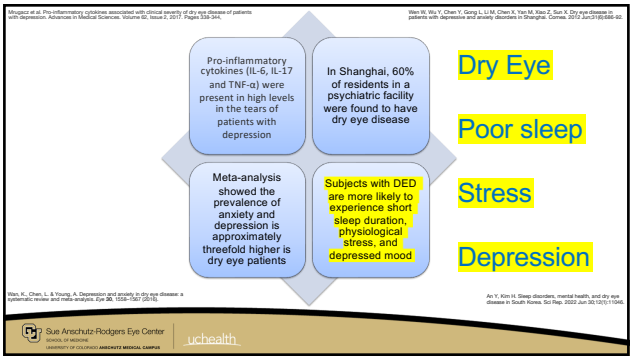

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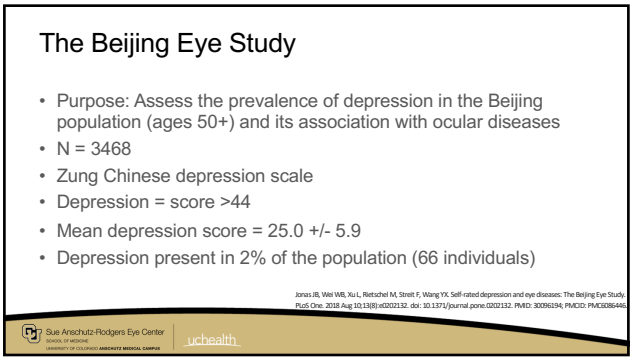

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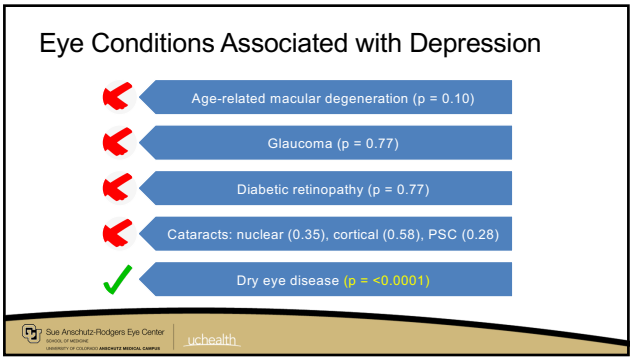

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The Beijing Eye Study – Results

- Dry eye was the only common ocular condition associated with depression
- Dry eye was linked more with depression than low visual acuity
- Although this study had more extreme results, it aligns with a meta-analysis of 28 studies by Zheng et al which found dry eye is more frequently associated with depression than any other eye condition
- Theory: patients with with depression/anxiety can experience sensitization which increases pain perception making them more susceptible to pain from dry eye disease

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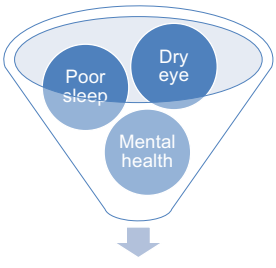

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Posterior ocular health and systemic disease

Thanks to Dr. Sherrol Reynolds for her contributions

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Posterior conditions associated with poor sleep

- Glaucoma
- Papilledema
- Diabetic retinopathy
- Central serous chorioretinopathy
- Non-arteritic anterior ischemic optic neuropathy
- AMD

Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310–8.
D'Souza H, Kapoor KG. Retinal vascular manifestations of obstructive sleep apnea. Curr Opin Ophthalmol. 2020 Nov;31(6):508-513.

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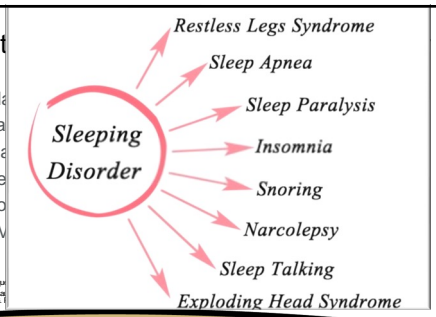
Post sleep



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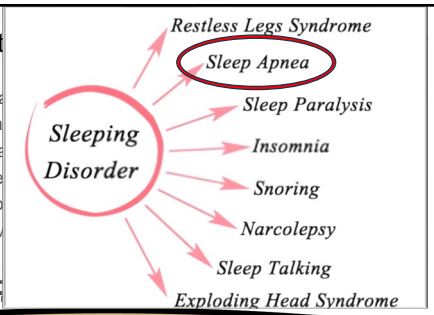
Post sleep



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OSA

- Characterized by episodic upper airway collapse
  - Periodic reductions or cessations in ventilation
  - Subsequent hypoxia
  - Hypercapnia
  - Arousals from sleep
- Symptoms
  - Daytime fatigue
  - Morning headaches
  - Snoring, choking, or gasping during sleep
- Prevalence has increased by as much as 55% in certain age groups in two decades
- Associated with increase systemic disease which impact posterior ocular health

Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310–8.
D'Souza H, Kapoor KG. Retinal vascular manifestations of obstructive sleep apnea. Curr Opin Ophthalmol. 2020 Nov;31(6):508-513.

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OSA Risk Factors

- Older age
- Male
  - Affects 15-30% of males and 10-15% of females
- Obesity
  - OSA affects about 75% of individuals with a BMI greater than 40 kg/m2
  - 58% of moderate-to-severe OSA cases are attributable to a BMI greater than or equal to 25
- Upper airway anatomical abnormalities
- Smoking
- Family history

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OSA Eye Associations

- Anterior segment
  - Floppy eyelid syndrome
  - Keratoconus
- Posterior segment
  - Glaucoma
  - Non-arteritic anterior ischemic optic neuropathy
  - Papilledema
  - Central serous chorioretinopathy
  - AMD
  - Diabetic retinopathy and macular edema
  - Retinal artery and vein occlusions

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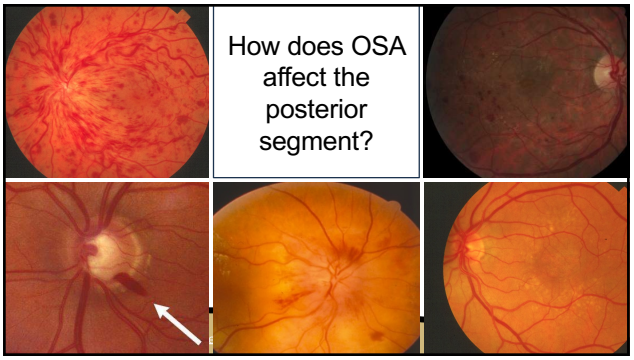

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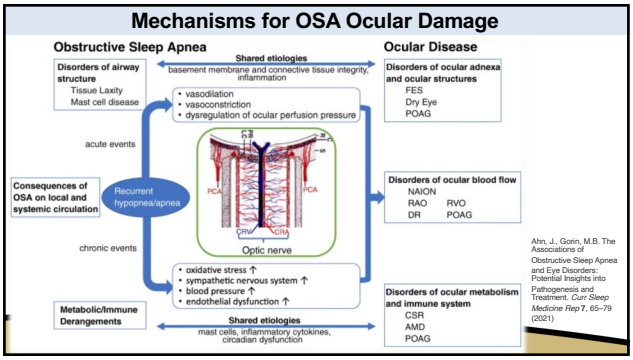

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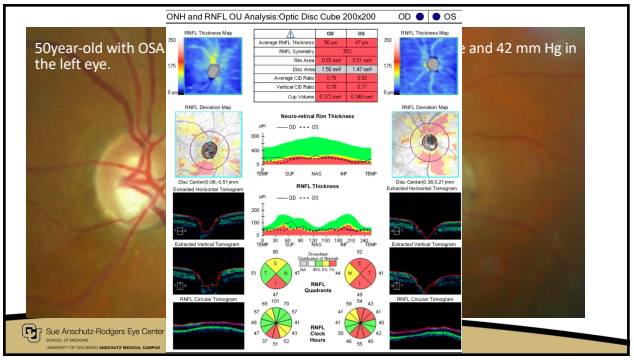

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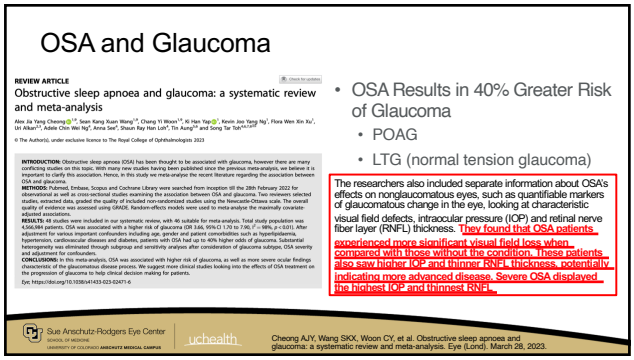

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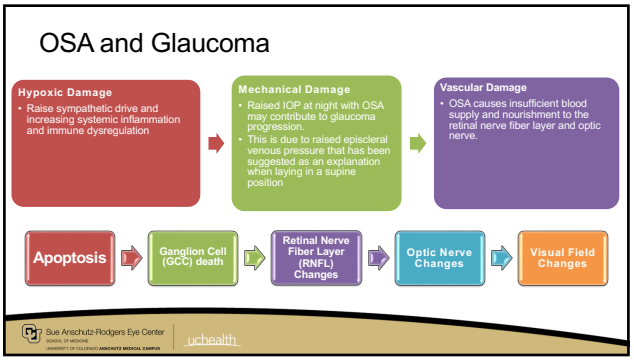

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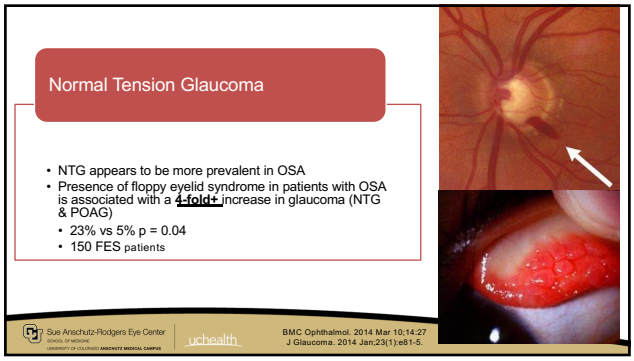

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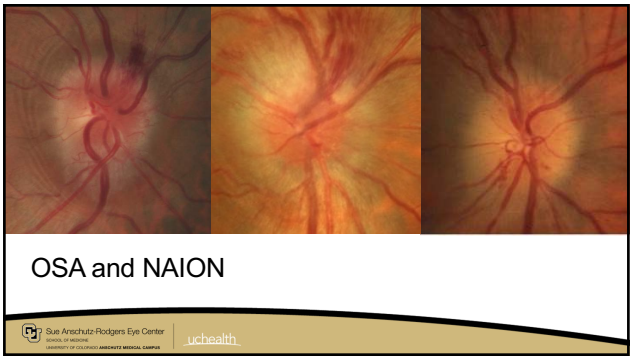

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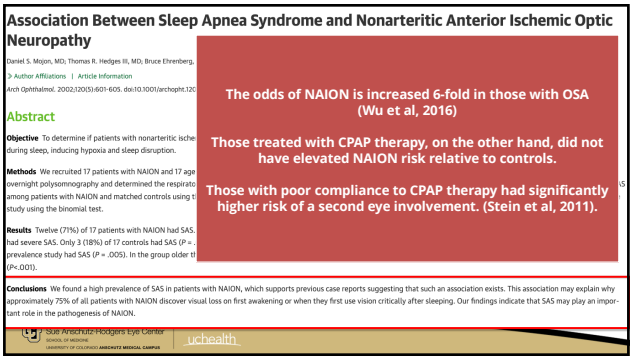

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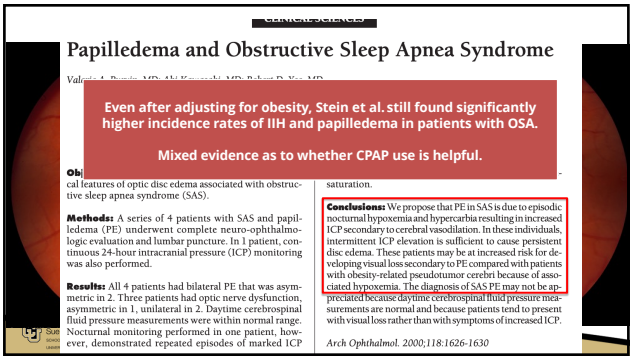

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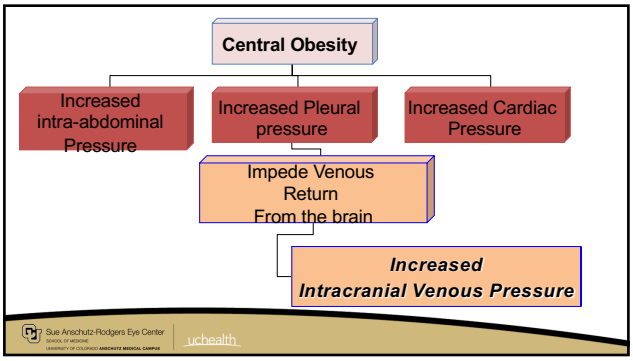

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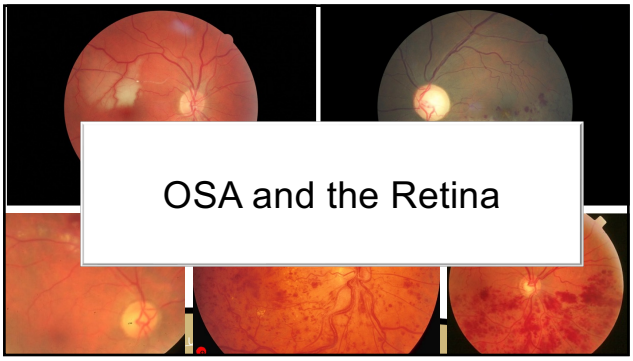

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OSA Health Impact

Type 2 Diabetes
Leading cause
of blindness
in working age
adults (20-74 year of age)

Cognitive Decline/ Stroke

Kidney Disease

HTN/
Hypercholesterolemia

Cardiovascular
Disease/ MI

Peripheral nerve
pain/damage

Other conditions:
Chronic Lung diseases
Hypothyroidism
Gastrointestinal conditions
Parkinson disease

Vannan Kandi Vijayan (2012) Morbidities associated with obstructive sleep apnea, Expert Review of Respiratory Medicine, 6:5, 557-566,

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OSA and Diabetes

- Short sleep (< 5.5 hours) **triples** the likelihood of T2DM in observational studies after all controls.
- Severe obstructive sleep apnea increased incident diabetes 71% over 13 years independently of adiposity.
- Both short (<5.5 hrs) and long (> 9 hrs) sleep duration are significantly associated with adiposity & insulin resistance.

Diabetes Res Clin Pract. 2018 May;139:195-202

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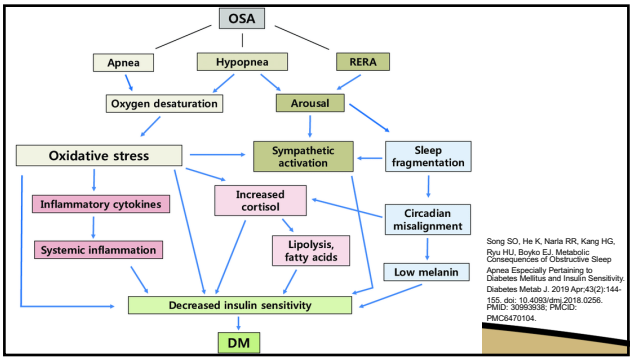

Song SO, He K, Narla RR, Kang HG, Ryu HU, Boyko EJ. Metabolic Consequences of Obstructive Sleep Apnea Especially Pertaining to Diabetes Mellitus and Insulin Sensitivity. Diabetes Metab J. 2019 Apr;43(2):144-155. doi: 10.4093/dmj.2018.0256. PMID: 30993938; PMCID: PMC6470104.

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OSA and Diabetes

- During REM sleep, the number of hypoxic events per sleep hour is linked with diabetic retinopathy severity
- A better predictor of retinopathy is # of sleep events during which SpO2 decreases by at least 4%
- Upregulation of CLOCK genes increases retinal VEGF expression, leading to retinal neovascularization especially under OSA induced hypoxic conditions

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OSA and Diabetes

- DR rates were 2-2.5X higher in patients with untreated/under-treated OSA
- OSA is associated with 5-fold increase in the odds of progressing to severe NPDR and PDR
- Patients with CSME have better visual outcomes when treated with a CPAP

Am J Respir Crit Care Med. 2017 Oct 1;196(7):892-900. Retina. 2014 Dec;34(12):2423-30. Respiration. 2012;84(4):275-82

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THE EYE AS A WINDOW FOR EARLY DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

Objective measures on OCTA may allow more effective management of this common condition.

PLEX® Elite Montage

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OSA and Hypertension & HTR

OSA leads to systemic hypertension as decreased pulmonary stretch, hypoxia, and hypercapnia lead to sympathetic activation, decreased baroreceptor sensitivity, and activation of the renin–angiotensin aldosterone system

Liu Q, Lahey JM, Karlen R, Stewart JM. Laboratory evaluation of hypercoagulable states in patients with central retinal vein occlusion who are less than 56 years of age. Retina (Philadelphia, Pa) 2018; 38:1175–1179.

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The prevalence of severe OSA among patients with a newly diagnosed RVO was 96% in a study of 27 patients, leading to a recommendation that all patients with newly diagnosed RVO should be referred for polysomnography

Felfeli T, Alan R, Al Adel F, et al. Screening for obstructive sleep apnea amongst patients with retinal vein occlusion. Can J Ophthalmol 2020; 55:310–316

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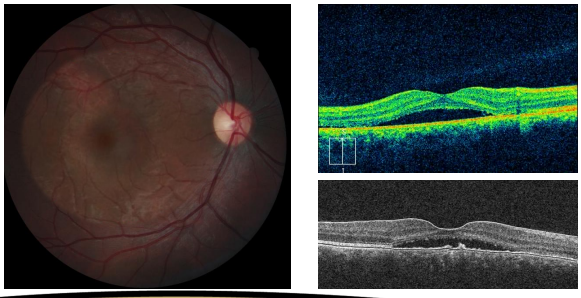

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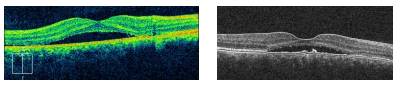
OSA and Central Serous Chorioretinopathy

- OSA is considered as a risk factor for developing CSCR
  - significantly elevates circulating levels of epinephrine and cortisol
  - autonomic dysregulation
- Poor sleep quality (even without OSA) has also been shown to be a risk factor for development of CSCR



Wu CY, Riangwiwat T, Rattanawong P, et al. Association of obstructive sleep apnea with central serous chorioretinopathy and choroidal thickness: a systematic review and meta-analysis. Retina 2018; 38:1642–1651
Ji Y, Li M, Zhang X, et al. Poor sleep quality is the risk factor for central serous chorioretinopathy. J Ophthalmol Hindawi 2018; 2018

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AMD – Risk Factors


Smoking


UV Light

Metabolic Syndrome


Blue eyes


Unhealthy diet

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OSA and AMD

- Retinal oxygen consumption is highest in the darkness
  - Requires 50% more oxygen in the due to the need to maintain the dark current
- OSA likely increases hypoxia in the outer retina


All About Vision

Yu D-Y, Cringle SJ. Outer retinal anoxia during dark adaptation is not a general property of mammalian retinas. Comp Biochem Physiol A Mol Integr Physiol 2002;132:47–52.

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Associations between age-related macular degeneration and sleep dysfunction: A systematic review

Josh Tjunrong Sia MBBS, Ester P. X. Lee MSc, Chui Ming Gemmy Cheung FRCOphth, Eva K. Fenwick PhD, Augustinus Laude FRCSEd(Ophth), Kam Chun Ho PhD, Beau J. Fenner MD, PhD ... See all authors

First published: 17 August 2022 | https://doi.org/10.1111/ceo.14146 | Citations: 3

Ryan E. K. Man and Raymond P. Najjar contributed equally and are to be considered co-last authors.

2 case–control studies
3 longitudinal cohort studies
1 cross-sectional study)

- AMD was associated with increased rates of sleep apnea and poorer reported sleep quality (4 studies)
- Patients with sleep apnea or insomnia were at higher risk of developing AMD (5 studies)

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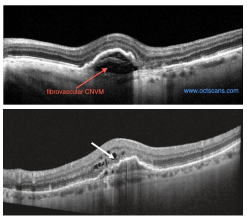
OSA and AMD

- Short sleep duration increases the risk of nvAMD
  - In a case control study of AMD pts with self-reported short sleep the relative risk of CNVM was:
    - 3.29 for 7-8 hourrs of sleep
    - 2.25, for 6-7 hours of sleep
    - 1.39 for > 8 hours of sleep
- Poor response to anti-VEGF treatment in untreated OSA
- Better visual outcomes with CPAP+Avastin than Avastin alone



Ophthalmic Epidemiol. 2016;23. Retina. 2016 Apr;36(4):791-7. (1):20-6.

Yu D-Y, Cringle SJ. Outer retinal anoxia during dark adaptation is not a general property of mammalian retinas. Comp Biochem Physiol A Mol Integr Physiol 2002;132:47–52.

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Clinical Pearls

- Ask your patients about sleep!
- Counsel about sleep!
- Discuss blue light in patients with poor sleep
- Ask about timing of dry eye
  - Check for incomplete lid seal or incomplete lid closure
- Check for floppy eyelid syndrome and ask about OSA
- Know that poor sleep, DED, and depression/anxiety likely exacerbate one another and contribute to the overall burden of disease
- Know the risk factors for OSA and the potential ocular consequences
- Refer for polysomnography and sleep studies when you are suspicious for OSA

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Listen to your body!

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My family of 3



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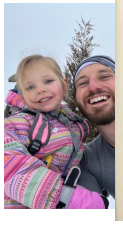
My family of ~~3~~….5!

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Thank you!

Any questions?


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OSA Summary

- OSA is severely underdiagnosed
  - 60% of patients who report sleep apnea symptoms remaining undiagnosed
  - Only 15% of those who are symptomatic receive diagnosis and treatment
- OSA causes hypoxia, sympathetic overactivation, and hormonal dysregulation that can lead to a number of posterior ocular health conditions
- Each of these conditions can lead to permanent vision loss or blindness.
- Treatment of these conditions without addressing underlying OSA leads to ineffective or suboptimal treatment and significant cost

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Kapur V, Strohl KP, Redline S, et al. Underdiagnosis of sleep apnea syndrome in U.S. communities. Sleep Breath 2002; 6:49–54

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