Endocrine & Metabolic Aspects: Obstructive Sleep Apnoea

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Endocrine considerations

- Endocrine disorders and OSA
  Acromegaly, Hypothyroidism etc
- OSA and Endocrine Disturbances
  Pituitary-Gonad Axis
- Cause and effect relation not known
  Obesity, Diabetes, metabolic syndrome

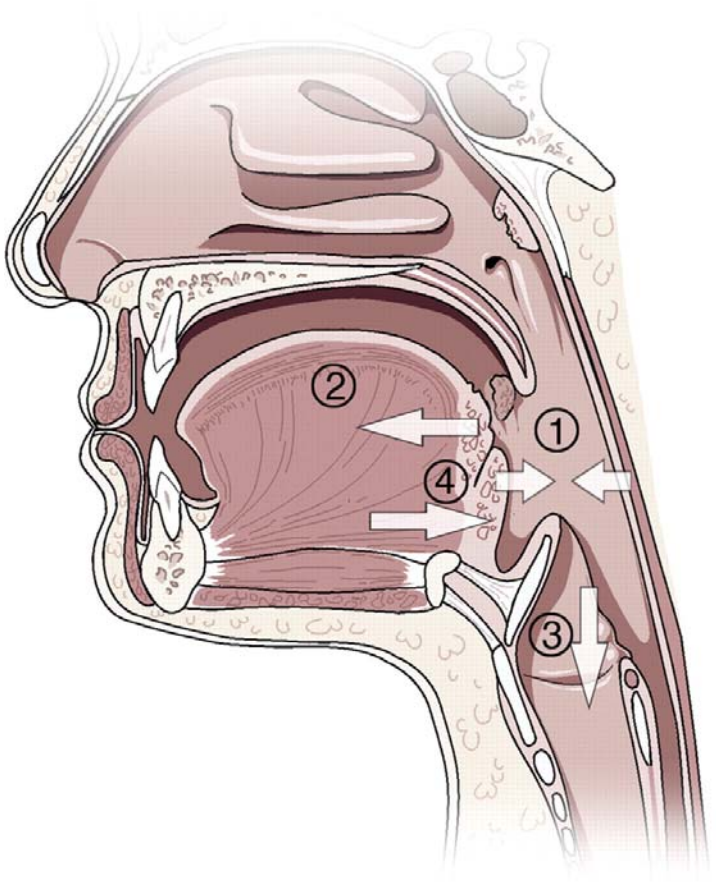
Upper Airway structures & OSA

- Brain stem regulates breathing during sleep by sending inputs to respiratory muscles
- These centers are sensitivity
  Fall in PO_2 inhibits respiration
  increase in PCO_2

  Set of 10 striated muscles in Pharynx controlled by brainstem. These muscles have mechanoreceptors and dilatory effect on to prevent UA collapse in normal

  These mechanism are not full proof and up to 5 apnea episodes up can be seen in normal subjects

Sagittal representation of the pharynx.



Attal P , and Chanson P JCEM 2010;95:483-495

Role of testosterone in pathogenesis of OSA

Supporting points

1. Testosterone Provokes and Estrogen protects
2. Testosterone replacement in males can trigger OSA
3. PCOD have higher AHI matched controls (44 % vs 6%)

Point Against:

There are reports also that androgen blockade did not modify the sleep disturbances

Nocturnal melatonin plasma levels in patients with OSA: the effect of CPAP.

Nocturnal Peak of Melatonin at 2.00 am in normal
Primarily due to circadian rhythm
Promotes sleep and decrease wakefulness

OSA: Peak at 6.00 am with level lower than normal

Levels not increased on the night of CPAP treatment

Hernández C, Eur Respir J. 2007 Sep;30(3):496-500.

Androgen and OSA

Hypogonadism:

Common males and can lead to Erectile dysfunction

It is independent of increasing age or obesity

CPAP therapy improves total testosterone

Females with higher AHI have lower serum estradiol & progesterone indicating poor ovarian function

The Association of Testosterone Levels with Overall Sleep Quality, Sleep Architecture, and Sleep-Disordered Breathing

TABLE 3. BMI-adjusted association between total testosterone and sleep outcomes

	Total testosterone levels in quartiles (ng/dl)				
	Quartile 1, 5–330 ng/dl (n = 328)	Quartile 2, > 330–414 ng/dl (n = 327)	Quartile 3, > 414–513.4 ng/dl (n = 329)	Quartile 4, > 513.4–1345 ng/dl (n = 328)	*P* for trend
	Adjusted mean (95% CI)				
Total sleep time (h)	6.48 (6.35–6.61)	6.50 (6.38–6.63)	6.45 (6.32–6.58)	6.47 (6.34–6.60)	0.76
Sleep efficiency (%)	82.2 (81.2–83.2)	84.0 (83.0–85.0)[a]	83.0 (82.0–84.0)	83.8 (82.8–84.9)[a]	0.10
Wake after sleep onset (min)	81.5 (77.1–85.9)	71.0 (66.7–75.3)[a]	76.5 (72.2–80.8)	73.4 (69.0–77.8)[a]	0.07
Time in stage 3/4 sleep, %	11.9 (10.9–12.9)	11.1 (10.1–12.1)	11.5 (10.6–12.5)	11.4 (10.3–12.4)	0.62
Time in REM sleep, %	19.0 (18.2–19.7)	20.0 (19.3–20.7)	19.8 (19.0–20.5)	19.5 (18.8–20.2)	0.45
AHI	16.1 (14.6–17.6)	16.1 (14.6–17.6)	16.9 (15.4–18.4)	15.9 (14.3–17.4)	0.97
Arousal index	23.4 (22.2–24.7)	22.1 (20.9–23.3)	22.9 (21.7–24.1)	23.1 (21.9–24.3)	0.97
		Odds ratios (95% CI)			
≥1% sleep time O_2 desaturated < 90%	1.0	1.01 (0.73–1.41)	0.88 (0.63–1.23)	0.84 (0.60–1.18)	0.23
AHI 15+	1.0	.80 (0.58–1.11)	1.15 (0.83–1.60)	0.98 (0.70–1.37)	0.58

Models adjusted for age, race, site, and BMI. CI, Confidence interval.

[a] $P < 0.05$, compared with the lowest quartile.

Conner et al JCEM 2008

OSA and Hypothalamic-Pituitary-Adrenal and Thyroid axis

- No clear involvement of Hypothal-PIT-Adrenal impairment.
- Except exaggerated response of ACTH to CRH not explained by obesity alone.
- No dysfunction in Hypothalamic-Pituitary-Thyr oid axis
- Increased BMP due to increased pre and after load on heart can give polyuria

Endocrine Hypertension

- Risk of HT icreased by 3 fold when AHI of> 15
- Drug resistant hypertension

- Mechanism implicated
- Sympathetic activity
- Increased renin angiotensin-aldosterone activity.
- Hypoxemia induced O2 species, free radicals, endothelial dysfunction & atherosclerosis

- RCT of CPAP showed lowering of HT, improved Left ventricular systolic function, Ventricular premature contractions and reduced sympathetic activity in patients with heart failure
  (Bradley TD, Lancet 2009 373: 82-93)

Obesity and OSA

- **Prevalence**
- OSA is a complication of obesity- and reverse
- 10% increase in wt leads to 32% increase in AHI.
- 55-100% candidates for bariatric surgery have OSA

- **Fat Distribution**
- Besides BMI, fat distribution is important.
- Neck & waist circumference
- Narrowed UA and reduced tidal volume with increasing girth and therefore stretching of UA during inspiration is less

Obesity and OSA

- Metabolic syndrome independent of obesity is 9 times more common in OSA

- Mechanism implicated

- IL-6 & TNG-alpha aggravates CV risk independent of obesity
- Hypoxemia induced O2/free radicals, endothelial dysfunction
- Increase adipose tissue in OSA patients,

- Adipose tissues generated hormones: adipocytokines
- Over/under-expression of many adipokines reported in OSA.
- Leptin,
- Adiponectin,
- Visfatin,
- Vaspin,
- Apelin,
- Chemerin
- Omentin (sensitizes insulin action but increased in OSA) .

Treatment of Obesity and OSA

-
- Meta analysis: AHI of 54.7/hr to 15.8 after bariatric surgery.

- Peri-operative deaths > with OSA.
- OSA may recur due to lesser weight reduction around neck.

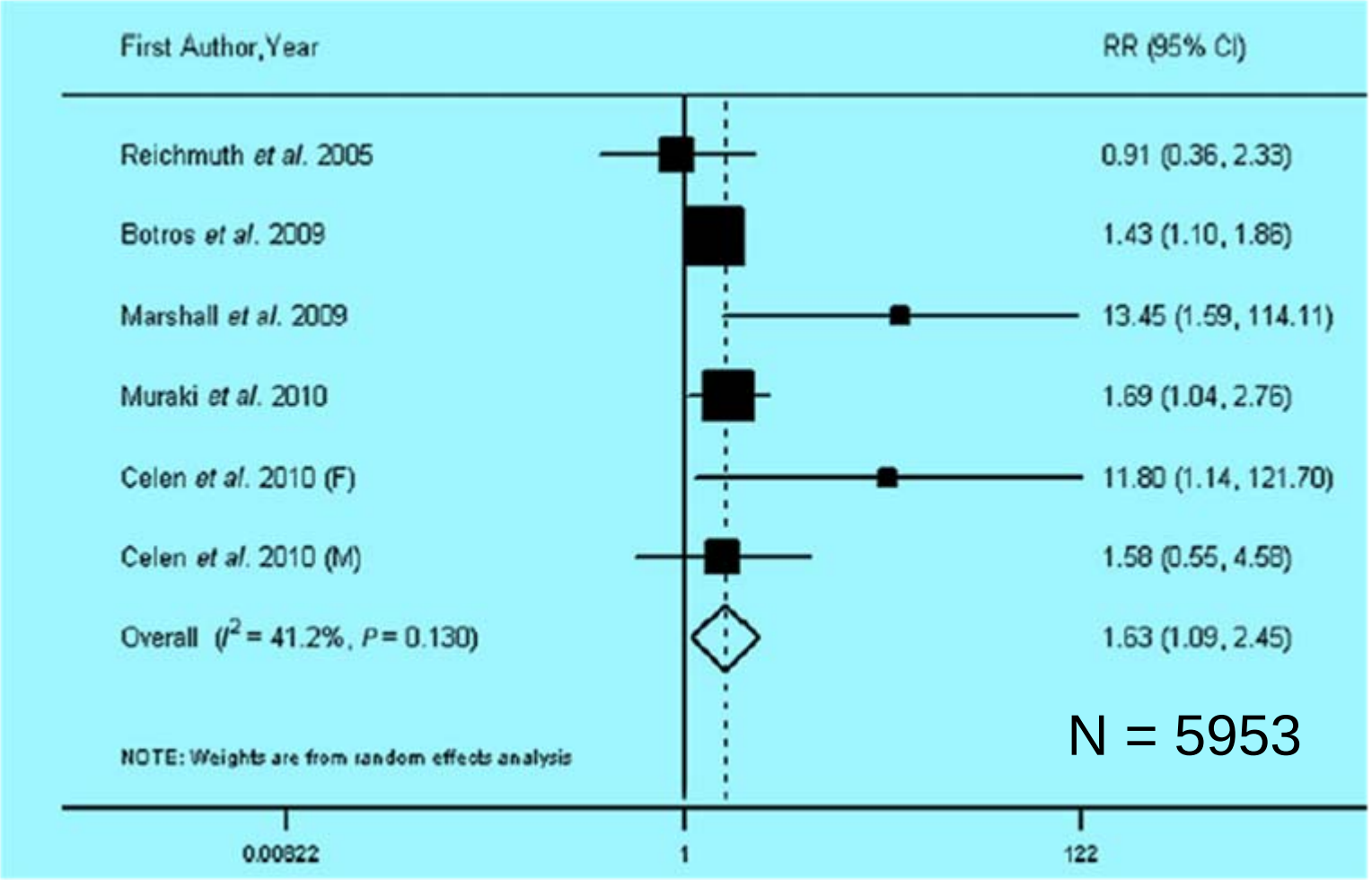
Diabetes and OSA

- Type 2 DM
- Type 1 DM
- Metabolic syndrome including Fatty liver
- Complications of DM
- Relation with glycemic control
- Effect of treatment on glycemic control

T2DM & OSA

Wang et al 2013; Respirology

Obstructive sleep apnoea and the risk of type 2 diabetes: A meta-analysis of prospective cohort studies



N = 5953

Meta analysis: Risk of T2DM in mild OSA

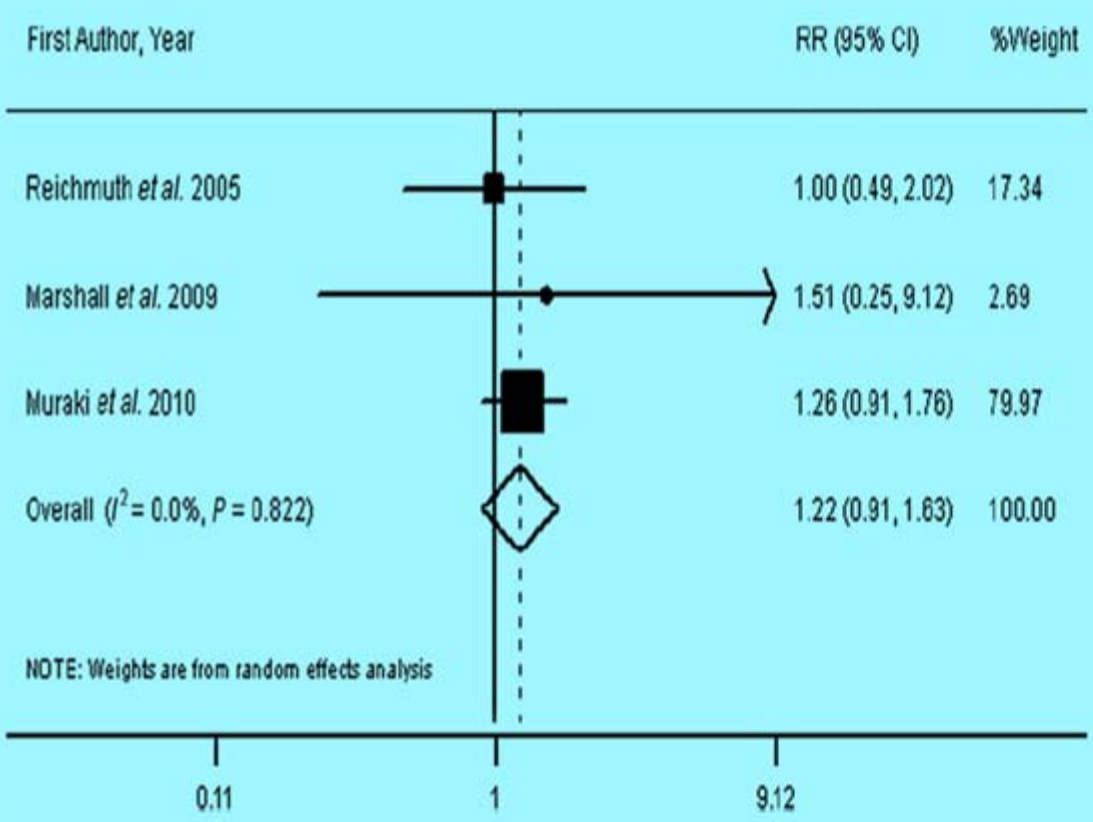


Figure 3 Association between mild obstructive sleep apnoea and the risk of type 2 diabetes, as identified in prospective cohort studies. CI, confidence interval; RR, relative risk.

Diabetologia (2011) 54:1967–1976
DOI 10.1007/s00125-011-2184-7

ARTICLE

Disturbed subjective sleep characteristics in adult patients with long-standing type 1 diabetes mellitus

M. van Dijk · E. Donga · J. G. van Dijk ·

Results Of the patients with type 1 diabetes, 35% had subjective poor sleep quality compared with 20% of the control participants (p=0.021). A higher proportion of the patients with type 1 diabetes were at increased risk for obstructive sleep apnoea (OSA) (17.2% vs 5.1%, p=0.012). There was no significant association between individual sleep characteristics and HbA_{1c} values. On logistic regression analysis, the HADS depression score, presence of peripheral polyneuropathy, habitual snoring and other sleep disturbances (e.g. hypoglycaemia) were independently associated with poor sleep quality.

T2DM with OSA: CVS & chronic complications

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2013; 29: 227–234.
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/dmrr.2387

RESEARCH ARTICLE

Sleep apnoea syndrome and 10-year cardiovascular risk in females with type 2 diabetes: relationship with insulin secretion and insulin resistance

Michel P. Hermans[1*]

| **Abstract**

Table 1. Patients' characteristics

	OSAS[−]	OSAS[+]	p
n	280	25	~
Age (years)	66 (12)	65 (9)	0.6848
Diabetes duration (years)	15 (9)	15 (8)	1.0000
Family history of diabetes (%)	56	44	0.2978
Family history of premature CHD (%)	15	13	0.3290
Education (%)	69:31	88:12	0.0645
Exercise level (none/light/moderate; %)	76/20/4	100/0/0	0.0021
Smoking (never/former/current; %)	74/18/8	68/20/12	0.4885
Ethanol (U week^{-1})	6 (11)	5 (10)	0.6613
Menopause (%)	84	92	0.3925
BMI (kg m^{-2})	29.7 (6.1)	38.7 (6.5)	<0.0001
Fat mass (%)	40.7 (6.5)	46.4 (5.2)	<0.0001
Neck circumference (cm)	37 (3)	41 (4)	<0.0001
Predicted neck circumference (%)	94 (8)	102 (9)	<0.0001
Waist circumference (cm)	99 (14)	119 (12)	<0.0001
Waist/hip	0.92 (0.08)	0.98 (0.10)	0.0072
Conicity index (m^2 kg^{-1})	1.32 (0.10)	1.39 (0.06)	<0.0001
Waist/height	0.62 (0.09)	0.75 (0.08)	<0.0001
Visceral fat (0–30 score)	10 (3)	13 (3)	<0.0001
Skeletal muscle (%)	25 (3)	23 (3)	0.0008
Fat mass/skeletal mass	1.66 (0.42)	2.08 (0.49)	<0.0001

Hermans et al 2013

Table 2. Cardiometabolic profile

	OSAS[−]	OSAS[+]	p
n	280	25	~
Epworth score	6 (4)	9 (5)	0.0072
Epworth score >9 (%)	14	43	0.0007
HOMA S (%)	59 (44)	37 (20)	<0.0001
HOMA B (%)	67 (50)	59 (28)	0.2150
Hyperbolic product [B × S] (%)	30.0 (18.8)	19.8 (12.3)	0.0006
[B × S] loss rate (% yr^{-1})	1.22 (0.41)	1.39 (0.31)	0.0442
Fasting plasma insulin (pmol L^{-1})	110 (73)	147 (83)	0.0170
Metabolic syndrome (%)	85	100	0.0327
Metabolic syndrome score (0/5 to 5/5)	3.69 (1.13)	4.36 (0.64)	<0.0001
Hepatic steatosis (%)	65	92	0.0063
Hypertension (%)	83	96	0.1468
Systolic BP (mmHg)	139 (20)	136 (24)	0.4805
Diastolic BP (mmHg)	78 (10)	76 (12)	0.3470
UKPDS 10-year risk[a]			
CAD (%)	12 (10)	18 (11)	0.0136
Fatal CAD (%)	9 (9)	13 (10)	0.0671
Stroke (%)	10 (15)	8 (7)	0.3011
Fatal stroke (%)	2 (3)	1 (1)	0.1503

Hermans et al 2013

Table 3. Laboratory values

	OSAS[–]	OSAS[+]	p
n	280	25	~
HbA_{1c} (mmol mol^{-1})	62 (13)	69 (12)	0.0099
eGFR [a] (mL min^{-1} 1.73 m^2)	79 (28)	74 (26)	0.3904
eCrCl [b] (mL min^{-1} 1.73 m^2)	86 (39)	109 (42)	0.0053
Albuminuria (μg mg $creatinine^{-1}$)	49 (94)	95 (163)	0.1766
Cholesterol (mg dL^{-1})	182 (41)	175 (45)	0.4178
LDL-C (mg dL^{-1})	99 (36)	92 (29)	0.3455
Non-HDL-C (mg dL^{-1})	130 (40)	132 (45)	0.8128
HDL-C (mg dL^{-1})	53 (15)	43 (13)	0.0014
apoA-I (mg dL^{-1})	165 (29)	147 (29)	0.0032
$apoB_{100}$ (mg dL^{-1})	90 (26)	105 (34)	0.0410
$apoB_{100}$/apoA-I	0.53 (0.18)	0.68 (0.24)	0.0052
Triglycerides (mg dL^{-1})	155 (93)	185 (111)	0.1295
Atherogenic dyslipidaemia (%)	35	48	0.1999
log(TG)/HDL-C	0.044 (0.016)	0.058 (0.025)	0.0109
LDL-C/$apoB_{100}$	1.07 (0.30)	0.95 (0.18)	0.0050
hsCRP (mg dL^{-1})	0.44 (0.53)	0.92 (1.10)	0.0406
Fibrinogen (mg dL^{-1})	337 (76)	380 (100)	0.0459
Uric acid (mg dL^{-1})	5.2 (1.6)	5.9 (2.0)	0.0412
Testosterone (nmol L^{-1})	0.93 (0.54)	0.91 (0.57)	0.8599
Free testosterone (nmol L^{-1})	0.014 (0.008)	0.024 (0.024)	0.0491
SHBG (nmol L^{-1})	49 (30)	35 (31)	0.0265

Hermans et al 2013

Obstructive Sleep Apnea and Diabetic Neuropathy

A Novel Association in Patients with Type 2 Diabetes

Abd A. Tahrani[1,2], Asad Ali[3,4], Neil T. Raymond[5], Safia Begum[3], Kiran Dubb[1], Shanaz Mughal[3], Biju Jose[3], Milan K. Piya[5,6], Anthony H. Barnett[1,2,3], and Martin J. Stevens[1,2]

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 186 2012

T2DM with OSA: chronic microvascular complications

TABLE 1. PARTICIPANT CHARACTERISTICS IN RELATION TO OBSTRUCTIVE SLEEP APNEA STATUS

	OSA− (*n* = 83)	OSA+ (*n* = 151)	*P* Value
Male	34 (41%)	101 (67%)	<0.001
White	32 (39%)	97 (64%)	<0.001
Age, yr	54.7 (11.9)	58.5 (11.3)	0.02
Diabetes duration, yr	9 (5–15)	11 (7–17)	0.02
Body mass index, kg/m^2	30.2 (27.3–35.0)	34.4 (30.9–39.5)	<0.001
Waist circumference, cm	105.5 (96.0–115.0)	116.0 (107.5–125.5)	<0.001
Hip, cm	106.0 (98.0–117.0)	114.0 (105.0–125.0)	<0.001
Waist/hip ratio	0.97 (0.93–1.02)	1.01 (0.96–1.05)	0.002
Neck circumference, cm	38.0 (36.5–41.3)	43.0 (39.0–46.0)	<0.001
Height, cm	163.5 (8.3)	167.8 (10.0)	0.001
Systolic blood pressure, mm Hg	125.5 (115.0–135.5.0)	130.0 (123.5–140.0)	0.002
Diastolic blood pressure, mm Hg	78.50 (71.0–85.00)	78.00 (71.00–84.50)	0.88
HbA1c, %	7.7 (7.0–8.7)	8.3 (7.3–9.3)	0.05
Total cholesterol, mmol/L	3.7 (3.4–4.5)	3.7 (3.3–4.3)	0.57
Triglycerides, mmol/L	1.5 (1.0–2.1)	1.8 (1.3–2.5)	0.03
HDL, mmol/L	1.2 (0.9–1.4)	1.1 (0.9–1.2)	0.02
Estimated GFR, ml/min/1.73 m^2	92.92 (25.16)	82.41 (26.41)	0.003
TSH	1.6 (1.0–2.2)	1.7 (1.2–2.4)	0.32
Epworth sleepiness score	5.0 (2.0–12.0)	8.0 (4.0–13.0)	0.003
Smoking (current or ex-smoker)	32 (39%)	62 (41%)	0.71
Alcohol (drinks alcohol)	12 (15%)	12 (35%)	0.001
Oral antidiabetes treatment	81 (98%)	137 (91%)	0.05
Insulin	34 (41%)	91 (60%)	0.005
Insulin dose, units	61 (35–88)	80 (56–118)	0.007
ACE inhibitors	40 (48%)	69 (46%)	0.71
Antihypertensive agents	61 (74%)	129 (85%)	0.03
Lipid-lowering treatment	71 (86%)	125 (83%)	0.58
Stroke or TIA	60 (7%)	18 (12%)	0.28
Ischemic heart disease	14 (17%)	33 (22%)	0.40
PVD	1 (1%)	10 (7%)	0.06
Albuminuria	20 (24%)	65 (43%)	0.007
Sight-threatening retinopathy	17 (21%)	72 (48%)	<0.001

Mechanism of Diabetes & Metabloic syndrome in OSA

Experimental studies

Intermittent hypoxia in animals leads to
sympathetic activation,
reduced insulin sensitivity
Oxidative stress,
lipid peroxidation,
upregulation of nuclear factor kB
Hypoxia inducible fcator 1 are the main determinants.

Spiegel et al Nat Rev Endorinol 5: 253-261

Treatment of OSA and Diabetes

- RCT with CPAP/Sham Rx for 3 months in patients with T2DM and OSA had no effect on HbA1c and insulin resistance.

  West et al , Thorax 2007; 62:969-974.

- Systematic evaluation of OSA in T2DM is recommended in view of increased risk of T2DM

PCOD and OSA

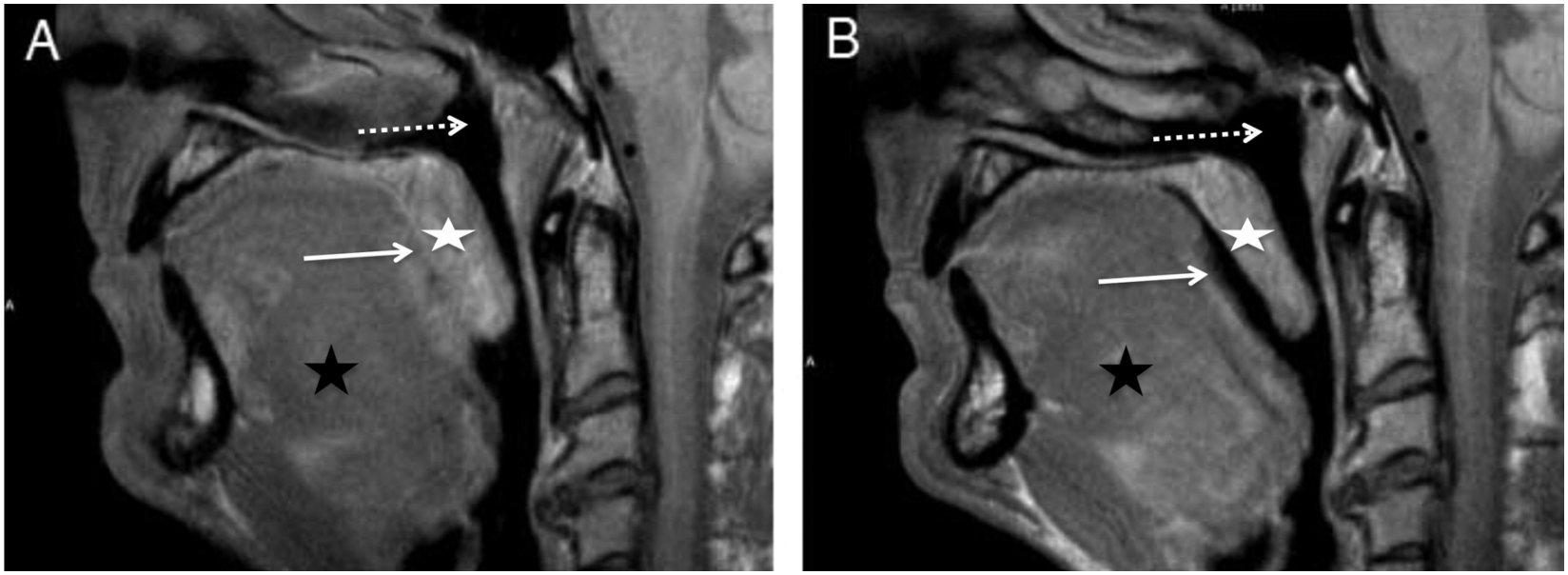
- Patients with PCOD have higher AHI values than age and BMI matched controls (44 % vs 6%)
- OSAS and insulin resistance based on HOMA index more common in PCOD with > AHI on polysomnography
- Similarly PCOD with OSA were found to have more impaired glucose intolerance than those without PCOS

Acromegaly & OSA

- 70% of patients with active acromegaly have OSA

- **Mechanism**
- Facial skeletal: Opening of the angle leads to back protrusion of the tongue &UA obstruction
- Enlarged Tongue
- Pharynx tissue thickness, edema & narrowing
- Odema is because of Sodium retaining effect of GH
- Obesity and Hypothyroidism are additional factors
- Myopathy of sternohyoid muscle dilator

Sagittal T1-weighted MRI sequences of the neck before (A) and after (B) effective treatment of acromegaly in a male patient with OSA. The treatment of acromegaly allowed a clear decrease in thickness of the tongue (black star), soft palate (white star), and...



Attal P , and Chanson P JCEM 2010;95:483-495

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Acromegaly and OSA

- Effective treatment improves OSA to a substantial extent
- But may persist in 40% of the patients cured of acromegaly. Therefore patients need t reassessed after surgery for treatment

GH deficiency, therapy and OSA

- GH deficiency can also lead to OSA
- Up to 60% adult patients with panhypopituitary receiving all replacement hormones except GH have OSA.
- GH therapy improved SWS and shift from OSA to hypopnea.
- May worsen OSA following GH replacement: depends on BMI

Hypothyroidism and OSA

- OSA is present 25-35% patients with hypothyroidism Hypothyroidism in up to 10% patients with OSA

- **Causes**
- Pharynx narrowing with soft tissue infiltration by mucoploysaccharides & protein as in skin
- Central apnea
- Neuropathy giving altered function of dilator muscle
- Macroglossea
- Goiter

Hypothyroidism RX & OSA

- Treatment reverses OSA in most patients with Hypothyroidism especially if there is no obesity
- Hence, attempt should be made to screen and treat hypothyroidism before CPAP therapy

Summary

- Testosterone, Melatonin, Obesity, adipokines may have role
- Hypogonadism can be seen in both males and females
- Increased CRH cotisol response to ACTH but with resistance
- OSA prevalence in Acromegaly is high and partially reversible
- Hypothyroidism is a reversible cause of OSA and need to be looked in all patients before CPAP treatment

Summary

- HT, Metabolic syndrome, T2DM, are increased
- T1 DM also can have metabolic syndrome
- Micro vascular & macrovascular complication are increased
- Effect of treatment CPAP on HbA1c: sufficient data not Available
- **DM patients need to be assessed for OSA**

Thank You

Sleep-Endocrinology

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Circadian Rhythm and Sleep

- There is endogenous rhythm which optimally synchronizes with body physiology (rest/activity or biological day/night)
- Suprachiasmatic nuclei: Master circadian clock, Bilateral, in Ant. hypothalamus near 3rd ventrical
- Its neuron has autorythmicity of ~ 25-24 hr.
- But it requires constant entrainment

Entrainment of Circadian clock

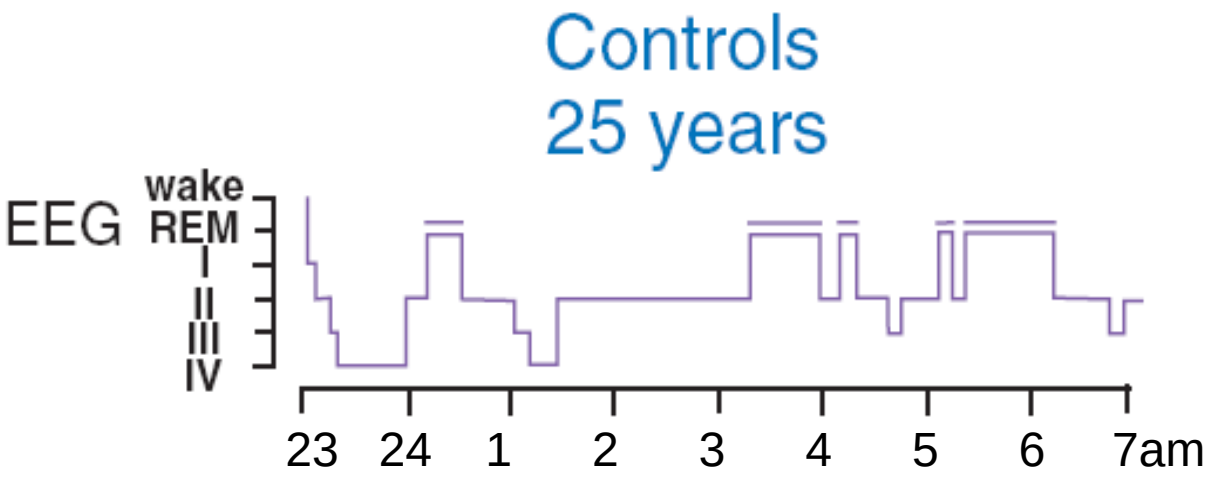
- **Retinohyopthalamic tract**: Projections to the SCN
- Photopigment in rods, cones & retinal ganglion cells are sensors
- Light is the most potent time cue to the master circadian oscillator.
- Body temperature, exercise, feeding can modify this to some extent

Entrainment of Circadian clock

- **SCN projections to the**
- **Hypothalamus: determines** circadian rhythm of hormones
- **Cerebral cortex: Arousal**
- **Pineal gland:** Multisynaptic pathway to PVN---IML column of upper thoracic spinal cord---- cervical ganglion -----pineal
- **Autonomic nervous system:** Maximum epinephrine secretion between 6.0 am to 9.0 am is independent of behavior.
- Explains the peak time for the MI/Stroke in the morning.
- Can be relevant for development of novel therapeutic strategy

General aspects of sleep

- Sleep is important & humans spends at least 1/3 of life in this activity. Reduction of motor output & consciousness.
- Sleep has cycles of NREM and REM. Phase 2 -4 of NREM correlates with slow wave EEG activity & sleep intensity



Sleep & Endocrinology

- Thus, in simplistic term both sleep & hormone changes are part of circadian system determined by SCN.
- There is some pattern in hormonal changes with sleep Difficult to say hormones modifies sleep or sleep modifies hormone.
- **Forced protocol:** Subjects sitting in dim light, relaxed, reclining, equal calories snacks distributed equally in 24 hour which allows study of circadian component
- Repeated Hormonal sampling and EEG are inherent part of this forced protocol

Sleep & Hormones

- GHRH-GH
- CRH-Cortisol
- Melatonin
- Others
- Ghrelin
- Somatostatin
- Sex hormones Testosterone and osteorgen and DHEAS
- Neuropeptides
- Increased BMP in night: poluria

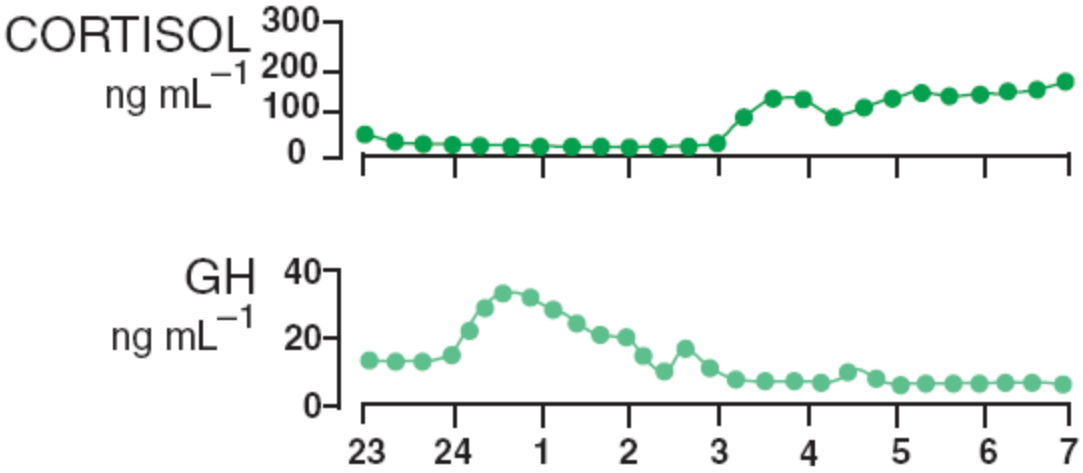
Sleep and Hormones

- 1st half of Sleep
- GHRH-GH Predominates

- 2nd half
- CRH-Cortisol predominates
- Morning normal 08.00 hr plasma cortisol higher than evening

Sleep & Hormone

1st half of Sleep GH and 2nd half Cortisol



Sexual dimorphism
Males show a single peak
Females multiple peak during sleep (Bioadaptation)

Sleep & Hypothalamic-Growth Hormone axis

- GH-Rise after sleep irrespective of sleep time
- GH releasing hormone (GHRH) is the best endogenous substance with sleep promoting activity
- After central and systemic & central administration of GHRH, SWS activity is increased in animals.
- I.V & intranasal boluses of GHRH during first few hr of sleep in normal young and elderly males lead to

Increased GH secretion and SWS

Decreased cortisol and ACTH levels

Prolonged first NREM & reduced awakenings

Sleep & Hypothalamic-Growth Hormone axis

However, in females there was sexual dimorphism and opposite changes were with increased ACTH and cortisol in females.

This indicate that that there is reciprocal anatgonism between GHRH and CRH in males and

Synergism between these two hormones in females

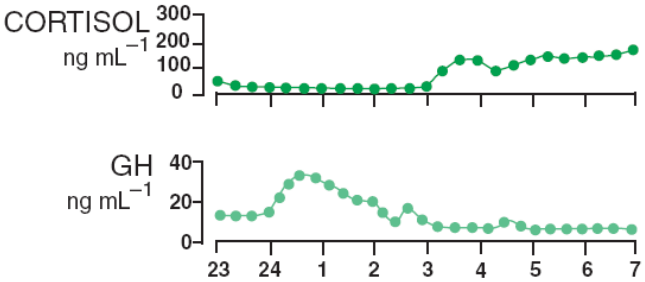
This might explain the increased prevalence of depression and Cushing's in females

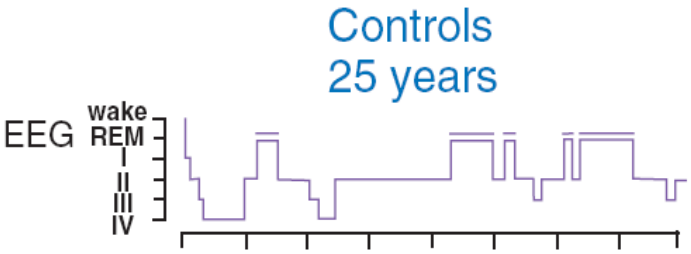
Sleep, GH analogues & Somatostatin

- **Ghrelin:** An endogenous ligand of GH scretagogues receptor.
- Released from stomach to increase the appetite
- In young males effects of IV Ghrelin & synthetic scertagogues and GHRH are similar with increased GH and enhanced SWS
- Unlike GHRH, ACTH and cortisol secretion is increased

- **Somatostatin:**
- In young/elderly males SWS is reduced after IV somatostatin & SC octreotide.
- Sleep is more impaired in elderly at a lesser dose
- After arginine (a somatostatin antagonist) SWS is increased

Sleep & CRH-ACTH-Cortisol Axis





CRH

Pulsatile IV CRH in young males (4 x50 ug) led to **increased cortisol** during first half of night,

GH surge bunted & **decreased SWS**

Changes were more with ageing including wakefulness

Sleep & CRH-ACTH-Cortisol Axis

- In stressed rats after CRH antagonist (Astressin)
- RMES sleep decreased
- This preclinical work indicates CRH promotes wakefulness

- RX of patients with CRH receptor antagonist
  NBI 30775 induced normalization of sleep changes in EEG

  A 4 wk trial of the compound in depressed patients led to increased SWS with decrease in REM density & awakenings

  Thus CRH-I receptor I antagonist is a possible way to counteract sleep changes

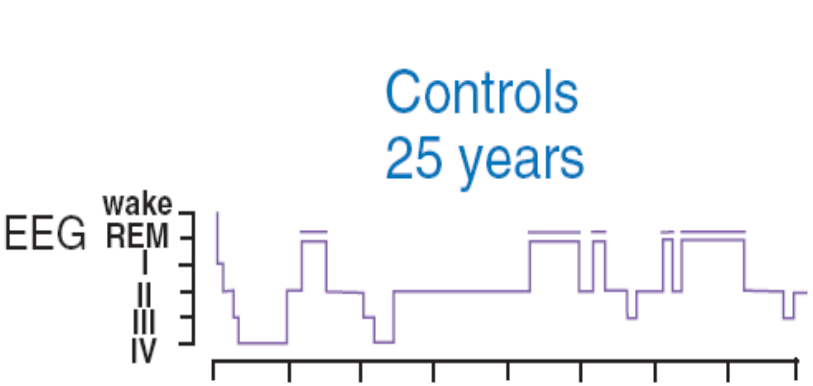
Sleep & CRH-ACTH-Cortisol Axis

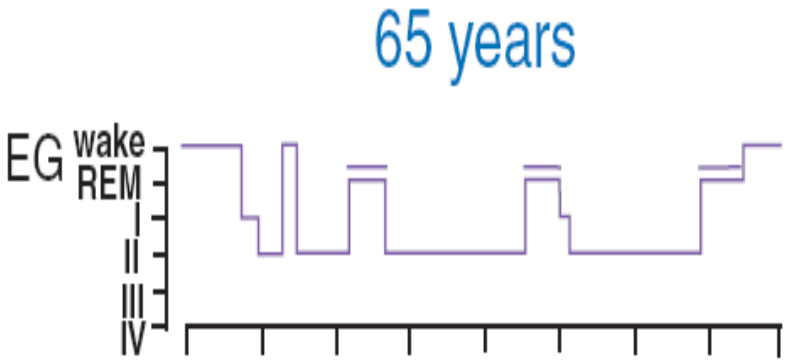
- **ACTH**
- Administration of synthetic ACTH analogue to volunteers led to general CNS activation but REMS, GH & cortisol remain unchanged
- It seems unlikely that it has an effect on Sleep disturbances

Sleep & CRH-ACTH-Cortisol Axis

- **Steroids**
- Continuous/hrly cortisol infusion from 11.00 pm-7.0 am led to increased SWS and decreased REM in young/elder
- Thus CRH mediated decrese in sleep density is unlikely to be because of cortisol
- Long term methylprednisolone in females with multiple sclerosis: REM latency was shortened and SWS density shifted to late phases of sleep. These changes are similar to that of depression

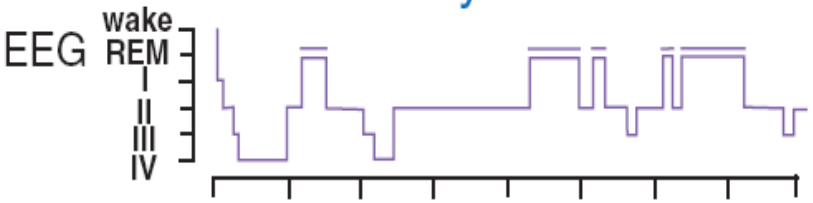
Sleep & Aging & Depression



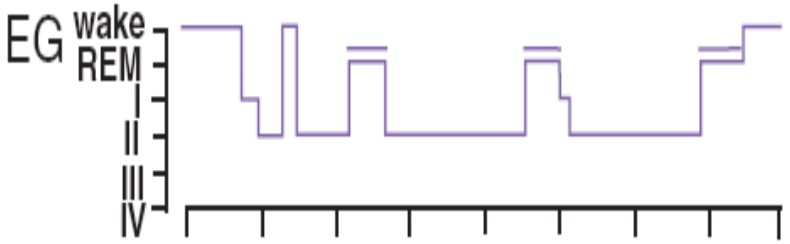


Sleep & Aging & Depression

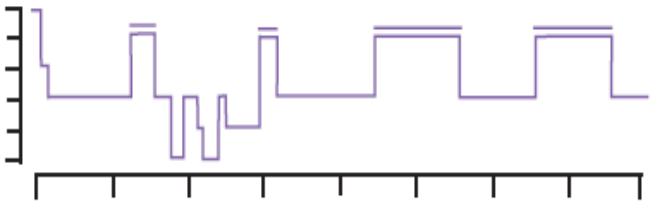
Controls
25 years



65 years

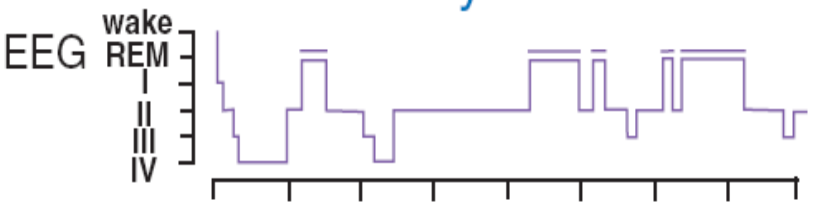


Patients with depression
25 years

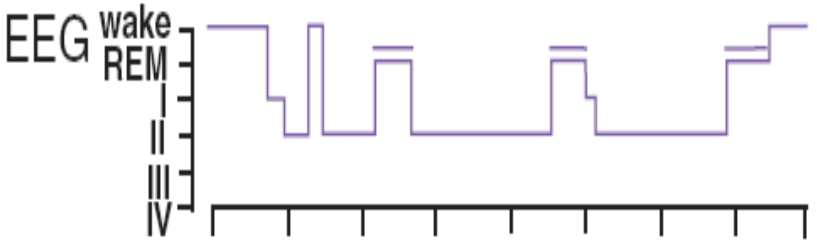


Sleep, Aging & Depression

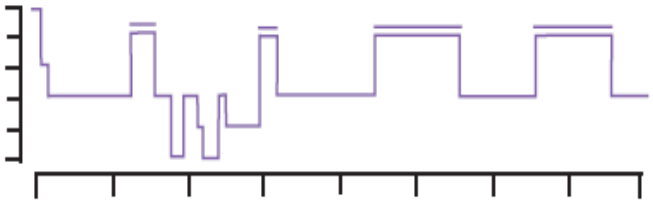
Controls
25 years



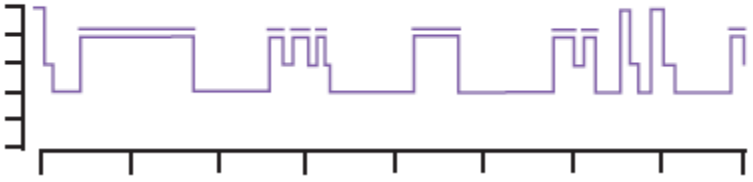
65 years



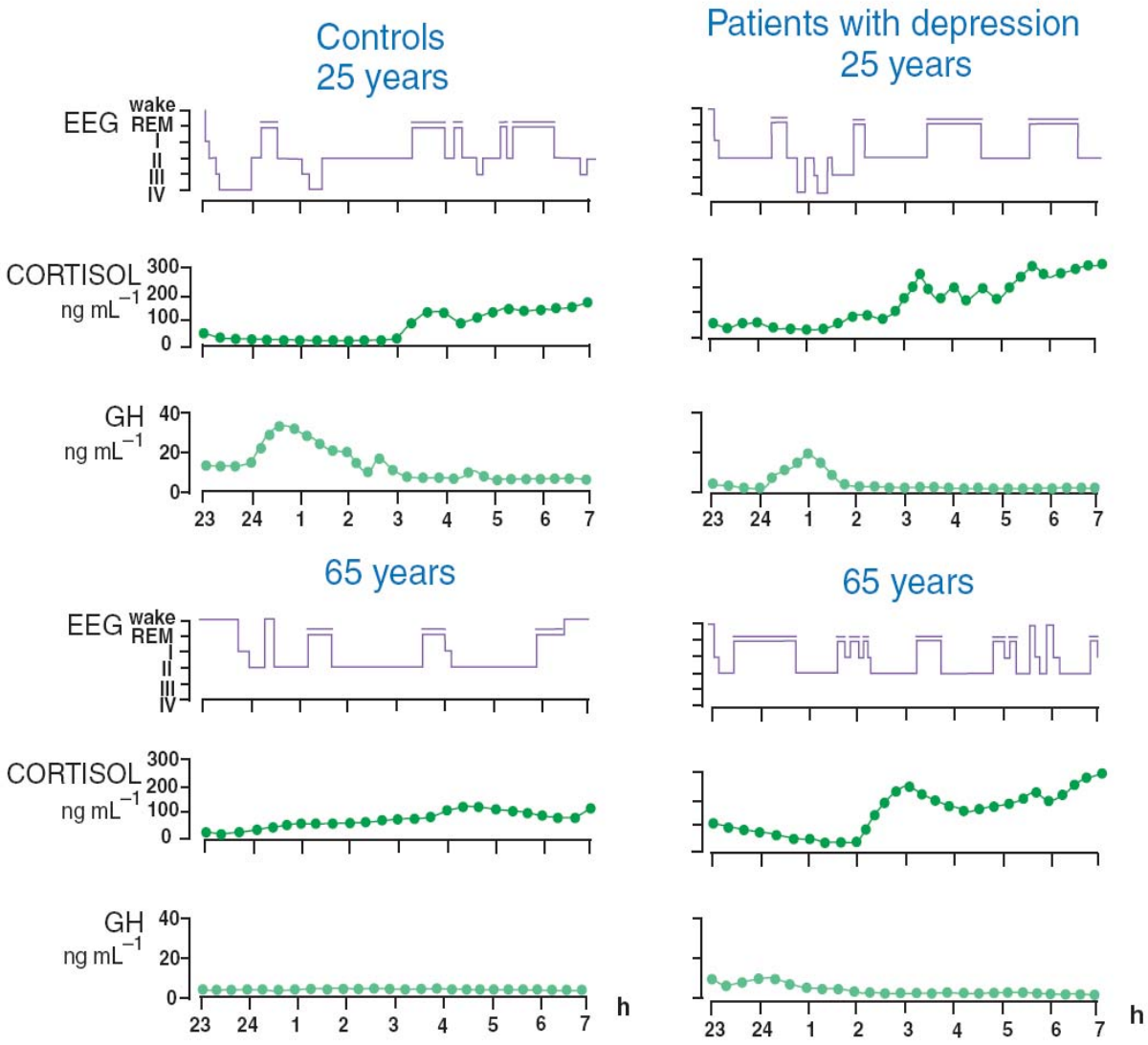
Patients with depression
25 years



65 years



Sleep, Depression, Aging & Hormone



Sleep, Depression, Aging & Hormone

Disorders of sleep due the misalignment in sleep cycle with circadian rhythm as in night shift workers

Jet lag due to time differences in two countries

Patients with depression and senior citizens with sleep disturbances

Cushing's disease and patients requiring subchronic steroids as in Multiple sclerosis

Common drugs like betablockers are known to increase wake time

Adverse consequences of Misalignment in Day and night sleep

OPEN ACCESS Freely available online

PLoS MEDICINE

Rotating Night Shift Work and Risk of Type 2 Diabetes: Two Prospective Cohort Studies in Women

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Abstract

Background: Rotating night shift work disrupts circadian rhythms and has been associated with obesity, metabolic syndrome, and glucose dysregulation. However, its association with type 2 diabetes remains unclear. Therefore, we aimed to evaluate this association in two cohorts of US women.

Methods and Findings: We followed 69,269 women aged 42–67 in Nurses' Health Study I (NHS I, 1988–2008), and 107,915 women aged 25–42 in NHS II (1989–2007) without diabetes, cardiovascular disease, and cancer at baseline. Participants were asked how long they had worked rotating night shifts (defined as at least three nights/month in addition to days and evenings in that month) at baseline. This information was updated every 2–4 years in NHS II. Self-reported type 2 diabetes was confirmed by a validated supplementary questionnaire. We documented 6,165 (NHS I) and 3,961 (NHS II) incident type 2 diabetes cases during the 18–20 years of follow-up. In the Cox proportional models adjusted for diabetes risk factors, duration of shift work was monotonically associated with an increased risk of type 2 diabetes in both cohorts. Compared with women who reported no shift work, the pooled hazard ratios (95% confidence intervals) for participants with 1–2, 3–9, 10–19, and ≥20 years of shift work were 1.05 (1.00–1.11), 1.20 (1.14–1.26), 1.40 (1.30–1.51), and 1.58 (1.43–1.74, *p*-value for trend <0.001), respectively. Further adjustment for updated body mass index attenuated the association, and the pooled hazard ratios were 1.03 (0.98–1.08), 1.06 (1.01–1.11), 1.10 (1.02–1.18), and 1.24 (1.13–1.37, *p*-value for trend <0.001).

Conclusions: Our results suggest that an extended period of rotating night shift work is associated with a modestly increased risk of type 2 diabetes in women, which appears to be partly mediated through body weight. Proper screening and intervention strategies in rotating night shift workers are needed for prevention of diabetes.

Shift work, and sub fertility among Swedish midwives.
Ahlborg G et al Int J Epidemiol. 1996;25:783–790.

Molecules with potential role in Disorders of Sleep

Nocturnal Peak of Melatonin at 2.00 am in normal
Primarily a circadian rhythm and very little change in day
Promotes sleep and decrease wakefulness

Use of Melatonin particularly sustained release might be of help to Night shift workers

GHRH for obvious reasons is not a viablr option but GH scretagoglues need evaluation

CRG anatgonist (astressin) and CRG receptor antagonist

Thank You

Different phase of Airway obstruction

- **Phase I:** Increased collapse of airway, turbulent flow & fluttering of soft palate leading to snoring
- **Pahse II:** Increased airway resistance, respiratory efforts & short arousals noticed in sleep analyses
- **Phase III:** Apnoea/Hyponea episodes > 5/hr
  Apnea = Interruption of breathing > 10 sec
  Hypopnea = (a) fall in inspiratory flow to 50% for 10 sec
  (b) 4% fall in O2 saturation

Diagnostic Procedures for OSA

- Gold standard : polysomography in sleep Laboratory
- History of snoring, disturbances in sleep
- Nocturnal oximetry during sleep
- Assessment of airway by optic procedure
- Video-endoscopy under sedation
- Measurement of pharyngeal pressure in sleep

Neurocognitive consequences of OSA

- Neurocognitive
  Day time sleep slow reactions, oor memory, irritability and quality of life, road accidents

CVS- consequences

- HT risk increased by 3 fold in AHI of> 15
- Drug resistant hypertension.
- Higher sympathetic tone & plasma aldosterone

- Higher CVS mortality. Cardiac pre & after load increased due to –ve intrathoracic pressure during breathing with narrow UA.

- Hypoxemia induced reactive O2 species, free radicals, endothelial dysfunction & atheraosclerosis

CVS-Consequences of OSA

- OSA is an independent risk for arrhythmia, heart failure & stroke in epidemiological studies.

- RCT of CPAP showed lowering of HT, improved Left ventricular systolic function, Ventricular premature contractions and reduced sympathetic activity in patients with heart failure

(Bradley TD, Lancet 2009 373: 82-93)