



***ADHD & the circadian
rhythm in adults with ADHD***



Implications for sleep, mood and health

ADHD Netwerk oktober 2013

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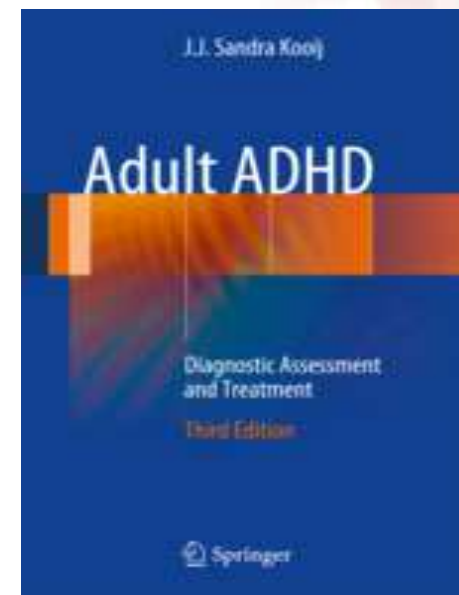
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**Kenniscentrum
ADHD bij volwassenen**

Financial Disclosures 2012-2013

- Dr. Sandra Kooij has disclosed she has received royalties from Springer Science and Business Media from her book: Adult ADHD: Diagnostic Assessment and Treatment



Learning Objectives

Upon completion of this educational activity,

participants should be able to:

- Recognize the delayed sleep phase in adults with ADHD.
- Explain the consequences for health in general of late and short sleep on the long term and how to treat the delayed sleep phase.

Adult ADHD is highly comorbid with circadian based disorders

75% has comorbidity (mean 3 disorders):

- Depression (60% SAD) 25-50%
- Anxiety 25%
- Substance Use Disorders 20-45%
- Personality Disorders 6-25%
- Eating Disorders (BN) 9%
- Binge eating 86%
- Obesity 30%
- Sleepproblems, DSPS pattern 75%

Kooij 2001 NTG;145(31):1498-501; Kooij 2004, Psychol Med;34(6):973-82, Kooij 2012, book Adult ADHD; van Veen 2010, Biol Psychiatry 67(11):1091-6; Biederman 1993, AJP;150(12):1792-8; Kessler 2006, AJP;163(4):716-23; Pagoto 2009, Obesity;17(3):539-44. Davis 2009, J Psychiatr Res;43(7):687-96. Kooij & Bijlenga, in press.

ADHD and sleepproblems in children

Subjective measures:

- Sleep onset latency / bedtime resistance
- Difficulty waking up
- Fragmented sleep
- Decreased sleep efficiency
- Excessive daytime sleepiness

Corkum 1998, JAACAP;37(6):637-46;Corkum 1999, JAACAP;38(10):1285-93; Corkum 2001, Sleep;24(3):303-12; Konofal 2007, Sleep Med;8(7-8):711-5; Philipsen 2006, Sleep Med Rev, 10(6):399-405; Gaultney 2005, Behav Sleep Med;3(1):32-43; Lecendreux 2000, J Child Psychol Psychiatry;41(6):803-12; Golan 2004, Sleep;27(2):261-6; Boonstra 2007, Sleep;30(4):433-42; Oosterloo 2006, Psychiatry Res;143(2-3):293-7; van der Heijden 2005, Chronobiol Int;22(3):559-70. Van der Heijden 2006, J Sleep Res;15(1):55-62 ; Sobanski 2008, Sleep;31(3):375-81; Sadeh 2006, Sleep Med Rev;10(6):381-98.

Objective measures (MSLT, actigraphy, PSG, DLMO):

- Excessive Daytime Sleepiness (EDS)
- Periodic limb movement disorder (PLMD) / Restless Leg Syndrome (RLS)
- Reduced % REM sleep
- Obstructive Sleep Apnea Syndrome (OSAS)
- Delayed Sleep Phase Syndrome (DSPS): DLMO 45 min delayed

Sleep questionnaire in 120 adults with ADHD

Difficulty ...

- going to bed on time: 78%
- falling asleep: 70%
- sleeping through: 50%
- getting up in the morning: 70%
- daytime sleepiness: 62%

This pattern lifetime in 60%, suggestive of
Eveningness or Delayed Sleep Phase Syndrome

Chronotypes: being a lark or an owl

- Morningtype: gets up early, active in morning (20-25%)
- Eveningtype: late to bed, active in evening (20-25%)
- In between: 50%
- Normal variation may differ +/- 2 hrs
- More variation disallows normal participation in society
- Clockgenes define chronotype and biological rhythm
- Zeitgebers: light through the eyes in the morning, and melatonin production in the brain at night synchronise us with the light/dark cycle of the world
- Artificial light may delay melatonin production at night (computer!)

Are most adults with ADHD evening types?

- Evening types are more active at night, prefer to go to bed late
- They get up late as well
- Evening types may be late due to a delayed onset of melatonin
- If sleeping longer is not possible due to work or school obligations, a chronic sleep debt can result
- Working in evening- or nightshifts may be adaptive
- Question: do adults with ADHD work more often in nightshifts?
- And if so, is that a problem?
- Morningness is associated with low impulsiveness / sensation seeking.
- Eveningness the other way round...

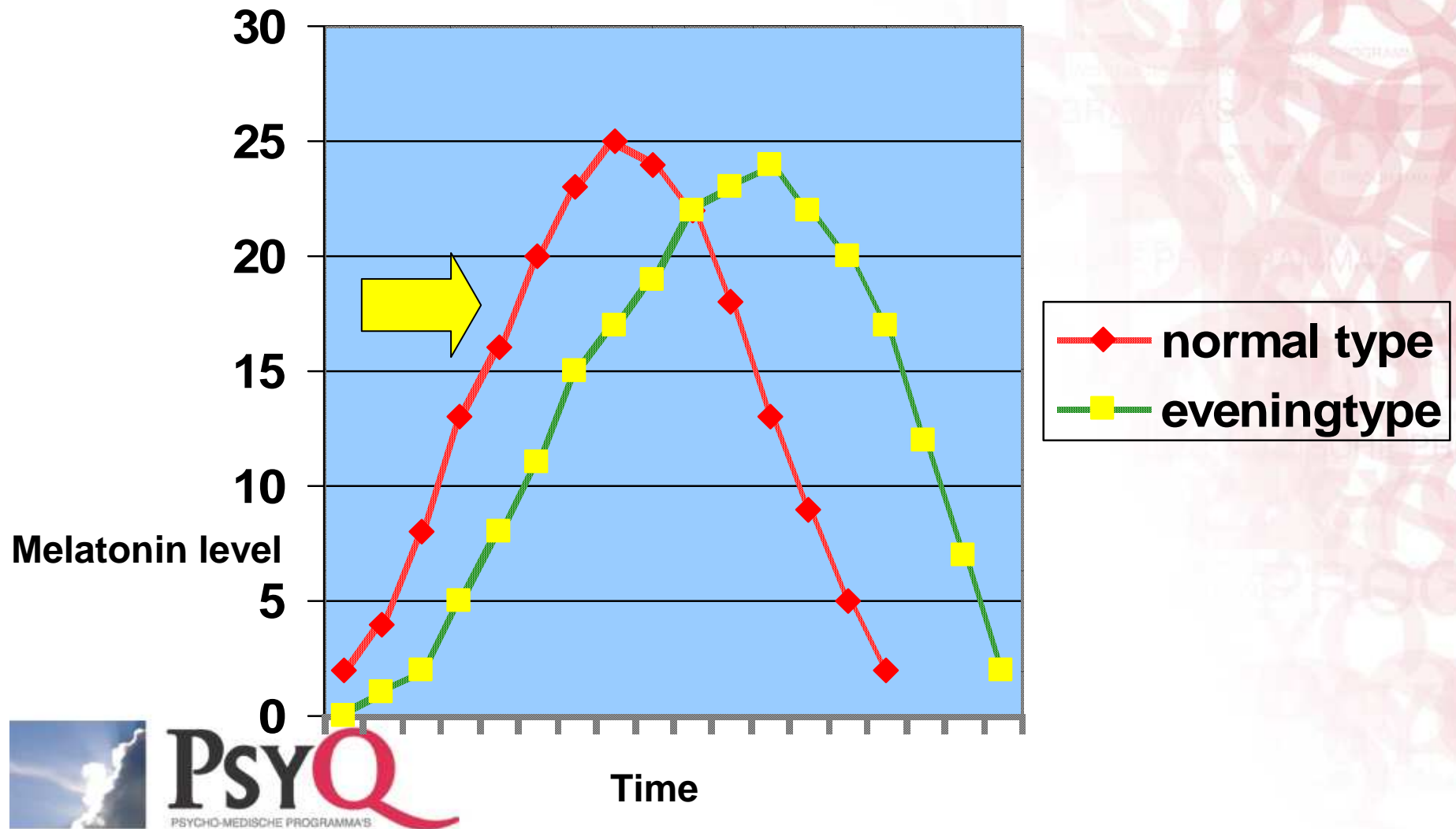
Barkley 1997, J Dev Behav Pediatr, 18(4):271-9. Caci 2004, Eur Psychiatry.; 19(2):79-84.
Levitan 2004, Biol Psychiatry; 56(9):665-9. Van Veen 2010, Biol Psychiatry 67(11): 1091-6;
Kooij 2012, book Adult ADHD

Delayed Sleep Phase Syndrome

DSPS is characterized by:

- (Very) late chronotype
- A chronic pattern of (very) late sleep and preference for late rise
- May result in daytime sleepiness and/or insomnia
- May be compensated for by an irregular sleep pattern
- Leads to dysfunctioning due to increased inattentiveness and/or social problems
- Main complaint is sleep onset insomnia

Sleep phase delay in ADHD



Characteristics of 40 consecutive ADHD patients

	Sleep Onset Insomnia (SOI)	No SOI
N	31 (78%)	9 (22%)
Male	17 (55%)	4 (44%)
Age, mean (SD)	28.2 (7.6)	30 (11.9)
ADHD, combined type	29 (94%)	5 (56%)
ADHD, inattentive type	2 (6%)	4 (44%)
Alcohol (U/wk)	6.76	5.67
Nicotine (Sig/day)	8.16	1.11
Sleep diagnosis	ns	ns

Dim Light Melatonin Onset (DLMO): delayed

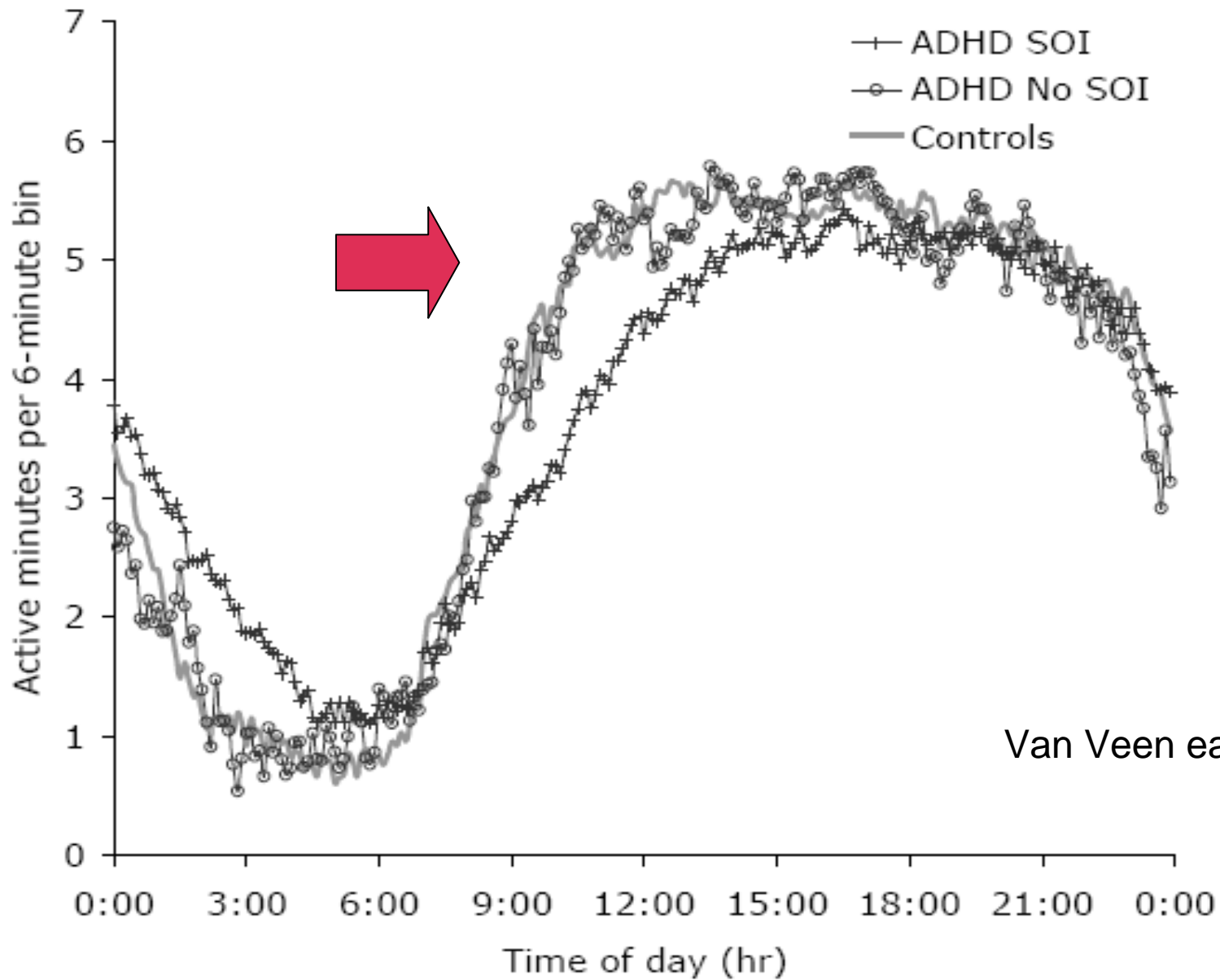
N = 40 adults with ADHD w/wo Sleep Onset Insomnia

versus healthy controls

	ADHD Total	SOI	no-SOI	HC	<i>p</i> : ADHD vs HC	<i>p</i> : SOI vs HC
DLMO (hr ± sd)	22:57 ± 1:20	23:15 ± 1:19	22:00 ± 0:54	21:34 ± 0:45	0.000	0.000

- 78% of consecutive ADHD patients had SOI
- DLMO: 105 min later in SOI vs HC
- After DLMO, it generally takes 2 hours to fall asleep

24 hour movement patterns ADHD + SOI compared to controls (actigraphy)



Van Veen ea 2010



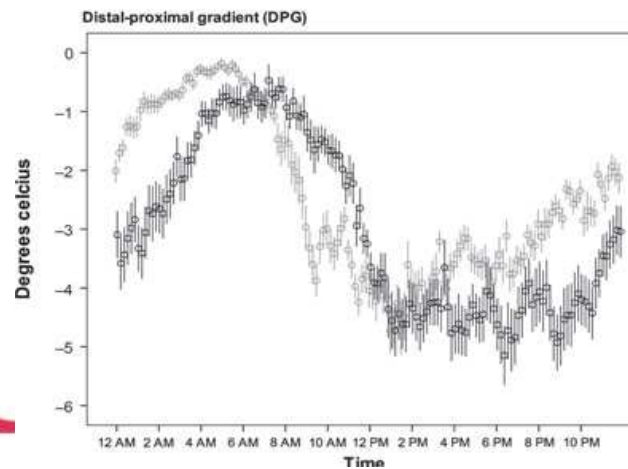
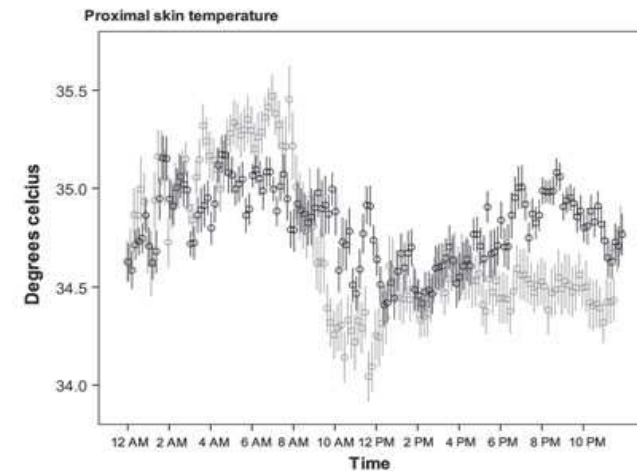
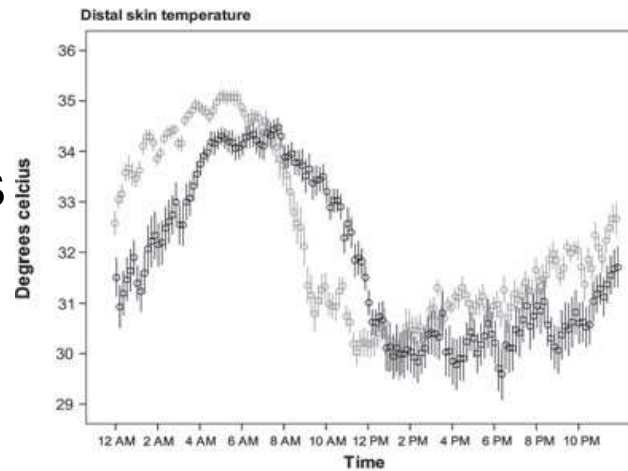
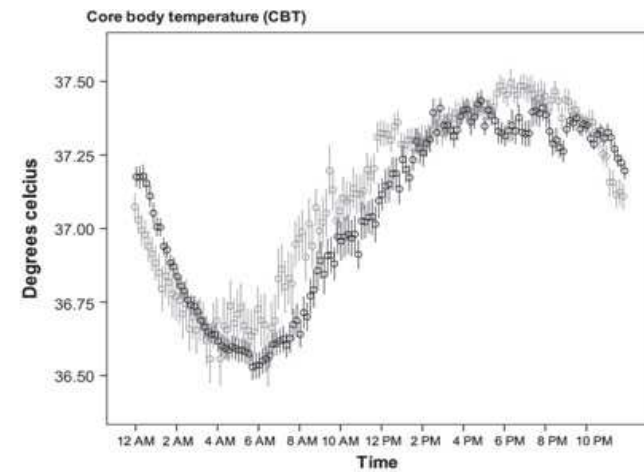
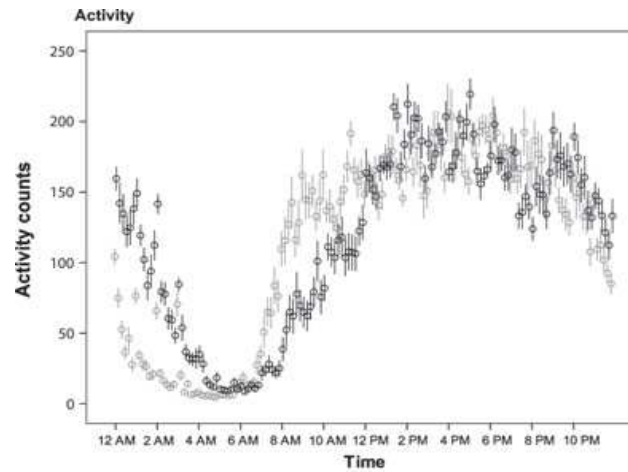
New study: core and skin temperature, DLMO and activity patterns

- N = 12 ADHD + DSPS (medication naïve) and 12 controls
- 5 consecutive days and nights

Results:

- More variable bedtimes in ADHD, but melatonin onset is the same every day in both groups
- DLMO 1.5 hours later in ADHD
- Sleep duration 1 hr shorter on days before workdays in ADHD
- Second delay, between DLMO and sleep onset was ≥ 1 hr longer in ADHD
- Melatonin, activity and temperature were all delayed to a similar degree in ADHD
- Overall temperatures were lower in ADHD
- Colder hands in ADHD, related to sleep onset difficulties

24 hr Activity, Core and Skin Temperature, in ADHD versus controls



Bijlenga, J Sleep Res 2013, Aug 16

ADHD patients lack any sense of time

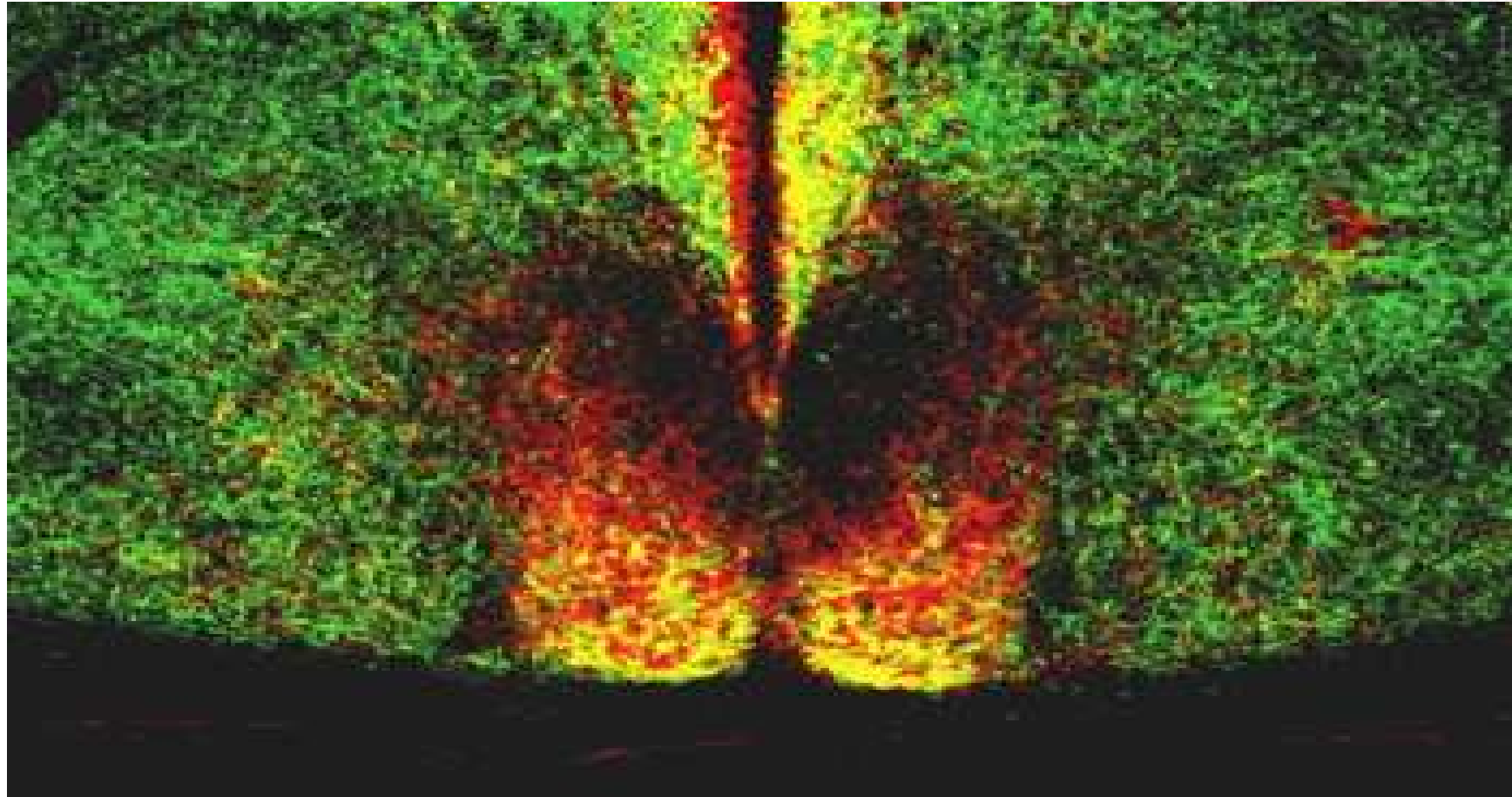


Clinical experience: adults with ADHD seem to lack any sense of time, as well as any rhythm in day/night

Their habitually being late has been regarded as part of their inattentiveness, a planning problem, but may in fact

reflect a fundamental problem of the biological clock

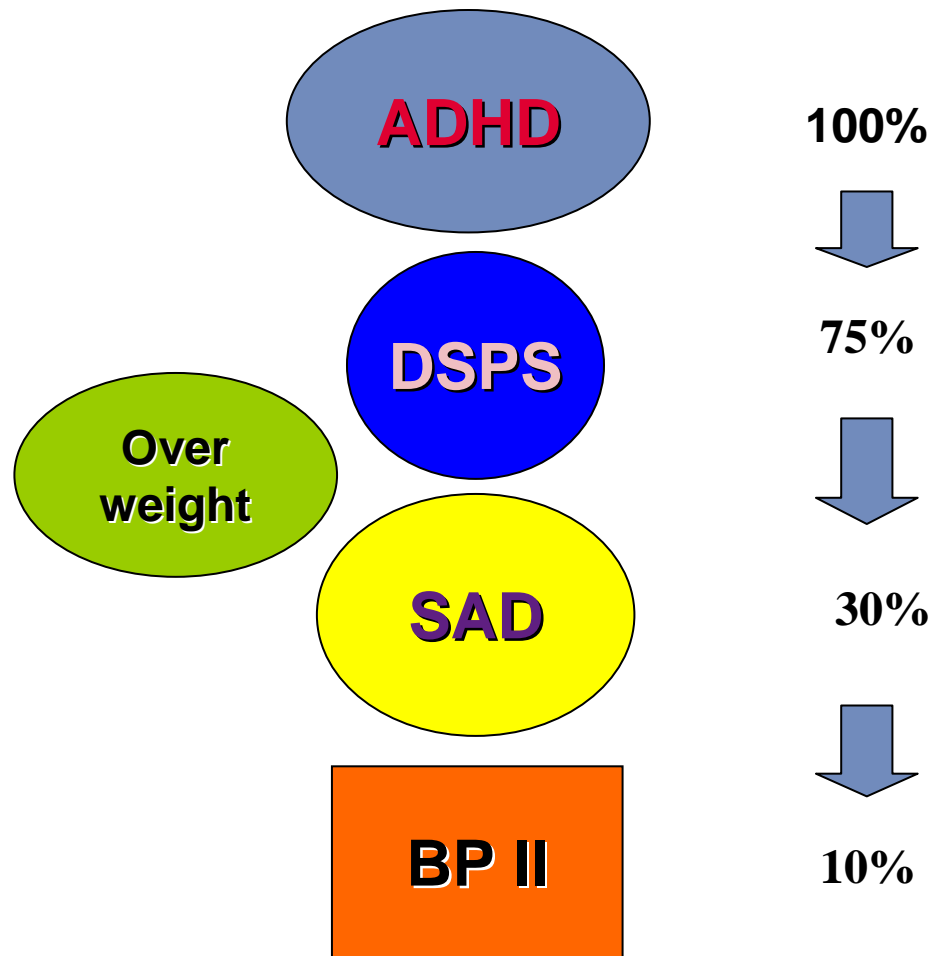
Nucleus supra chiasmaticus (NSC): the biological clock



PSYQ
PSYCHO-MEDISCHE PROGRAMMA'S

Hypothalamic nucleus, just above the chiasma opticum

ADHD, circadian rhythm, sleep, mood and season



Goikolea 2007, Psychol Med;37 (11):1595-9;
Amons 2006, J Affect Disord;91(2-3):251-5;
Lewy 2006, Proc Natl Acad Sci U S A;103(19):7414-9;
Van Veen 2010, Biol Psychiatry 67(11): 1091-6
Bijlenga 2013, J Att Disord; 17(3):261-75
Bijlenga 2013, J Sleep Res. Aug 16 epub

ADHD and disturbed rhythms

ADHD may not only be associated with circadian, but also with cyclical and seasonal disturbances, leading to problems with impulsiveness, eating, sleeping and mood:

- Impulsivity/novelty seeking has been associated with eveningness
- Lack of sleep rhythm may lead to lack of rhythm in eating and activity patterns as well
- Evening types, or those with a delayed sleep phase may prefer irregular work or work in night-shifts, thereby increasing the sleep phase delay, as well as obesity
- ADHD has a higher percentage of Seasonal Affective Disorder (SAD) or winter depression, and possibly also of Premenstrual Dysphoric Disorder than normal

Barkley 1997, J Dev Behav Pediatr,18(4):271-9;

Amons 2006, J Affect Disord;91(2-3):251-5

Caci 2004, Eur Psychiatry.;19(2):79-84.

Levitan 2004, Biol Psychiatry;56(9):665-9

Antunes 2010, Nutr Res Rev.(1):155-68.

ADHD & seasonal mood changes



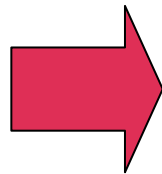
- Adult ADHD co-occurs with lifetime depressive disorder in 55%
- Most of them (60%) have Seasonal Affective Disorder (SAD) or winterdepression
- Open trial of Light therapy effective for SAD and ADHD, as well as for Delayed Sleep Phase
- SAD has a circadian phase delay in 70%
- Are SAD and ADHD related via circadian disturbances?
- Clockgenes associated with ADHD

Levitan 1999, Compr. Psychiatry, 40(4), 261-7;
Johansson 2003, Neuropsychopharmacol;28(4):734-9;
Amons 2006, J Affect Disord;91(2-3):251-5;
Rybak 2007, Compr Psychiatry;48(6):562-71;
Lewy 2006, Proc Natl Acad Sci U S A;103(19):7414-9;
Kissling 2008, Am J Med Genet B, Neuropsychiatr Genet;147(3):333-8.

Circadian disturbance, ADHD and health

- ADHD is associated with chronic DSPS
- ADHD patients often work in night shifts or are active at night
- May be gene-environment interaction: circadian preference based on (clock)genes and dopaminergic pathways

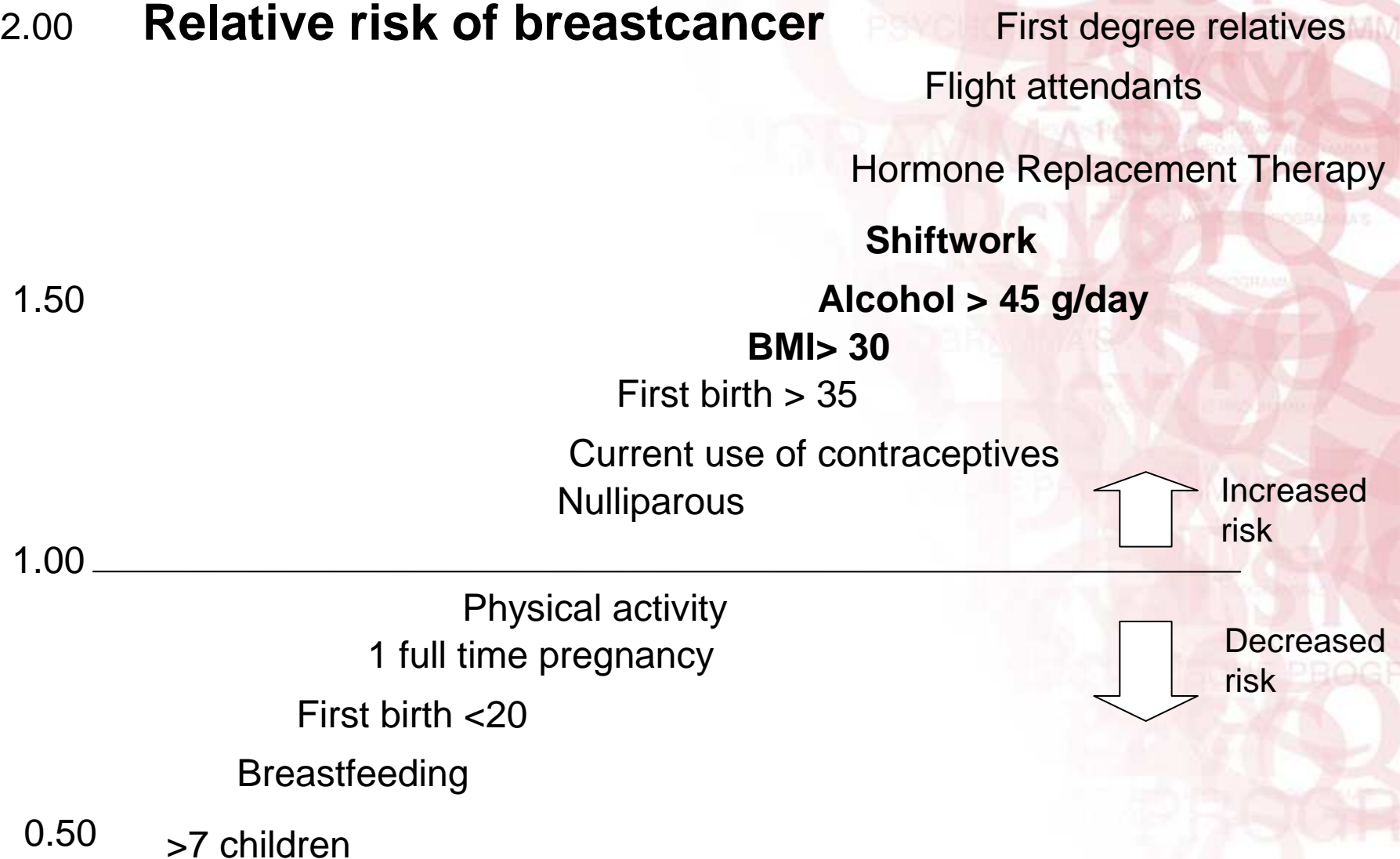
- But: chronic work (> 30 yrs) in night shifts is associated with higher risk of (breast)cancer
- Melatonin acts as a *circadian anti-cancer signal* at night
- Among others (light at night), chronic low melatonin levels may protect less well against development of cancer



is ADHD a high riskgroup for cancer?

Schernhammer 2001, J Natl Cancer Inst;93(20):1563-8;
Schernhammer 2005, Eur J Cancer;41(13):2023-32; Hansen 2001, J Natl Cancer Inst;93(20):1513-5; Blask 2005, Endocrine;27(2):179-88.
Moser 2006, Conf Proc IEEE Eng Med Biol Soc;1:424-8; Verkasalo 2005, Cancer Res;65(20):9595-600.

2.00 **Relative risk of breastcancer**



Does cancer risk cluster in ADHD?

Several lifestyle risk factors may cluster in ADHD individuals:

- Night shift work
- High BMI
- Alcohol/drug abuse
- Smoking
- Low melatonin levels?

Short sleep and cancer risk

- Shift work is considered carcinogenic in the long term (IARC 2007)
- Sleep loss by shiftwork is associated with higher incidence of breast- and prostate cancer
- Short sleep → short exposure to and/or low levels of melatonin
- Melatonin has anti-oxidative properties and protects against cancer growth
- Animal research shows inhibiting effects of melatonin on cancer growth and increased survival
- In humans, first studies with melatonin in cancer patients ongoing

Cancer risk and exposure to light@night

- Use of artificial light at night stops melatonin production through the eyes, feedback to pineal gland
- The light coming from TV, PC or Ipad also suppresses melatonin production and delays natural sleep onset easily by hours
- Light is the natural antidote to melatonin and wakes us up every day ...
- Timing of light may be crucial for health in general
- Women with total visual blindness have less cancer than sighted women

ASESA study

- To explore the sleep/wake patterns, psychiatric and somatic comorbidity, BMI and eating patterns in adults with ADHD (n = 202) compared to the general population (n = 189)

General characteristics

	ADHD, n = 202	Controls, n = 198	<i>p</i>
Women	47 %	65 %	<.001
Age: mean	34.9	33.0	.121
BMI: mean	24.8	23.2	<.001
BMI ≥ 30 (obese)	17 %	4 %	<.001
Unemployed	27 %	6 %	<.001
Smokes	52 %	18 %	<.001
> 14 U alcohol p/wk	17 %	7 %	.016

Self-reported Morbidities

(showing only significant differences)

	% ADHD, n = 202	% Controls, n = 198	<i>p</i>
Depressed mood	18	6	<.001
Stress/ burnout/ fatigue	5	1	<.001
Pulmonary problems	31	16	<.001
Cardiovascular problems	43	18	<.001
Gastro-intestinal problems	33	19	.001
Metabolic problems	12	6	.042
Immune system problems	7	3	.049
Skeletal problems	50	36	.005

Sleep characteristics

	<i>Age ≤ 30 yrs</i>			<i>Age > 30 yrs</i>		
	ADHD n = 83	Controls n = 106	<i>P</i>	ADHD n = 119	Controls n = 83	<i>p</i>
Bed time work days: mean	23:45	23:10	.002	23:33	23:00	.001
Bed time free days: mean	01:02	0:13	<.001	0:20	23:41	.002
Sleep length work days: mean	7:25	7:55	.029	7:01	7:42	<.001
Sleep-onset latency work days: mean	0:39	0:22	.002	0:34	0:12	<.001

Indication of DSPS: 26% in ADHD vs. 2% in controls (p<.001)

Summary

- More morbidities, complaints, and unhealthy lifestyle in ADHD
- More (extreme) evening chronotype in ADHD
- More sleep problems in ADHD: shorter sleep, longer sleep-onset latency, later mid-sleep, more variable bed times
- DSPTS relates to SAD and to health issues
- This is also apparent within the control group
- *Shorter sleep is related to a higher BMI*

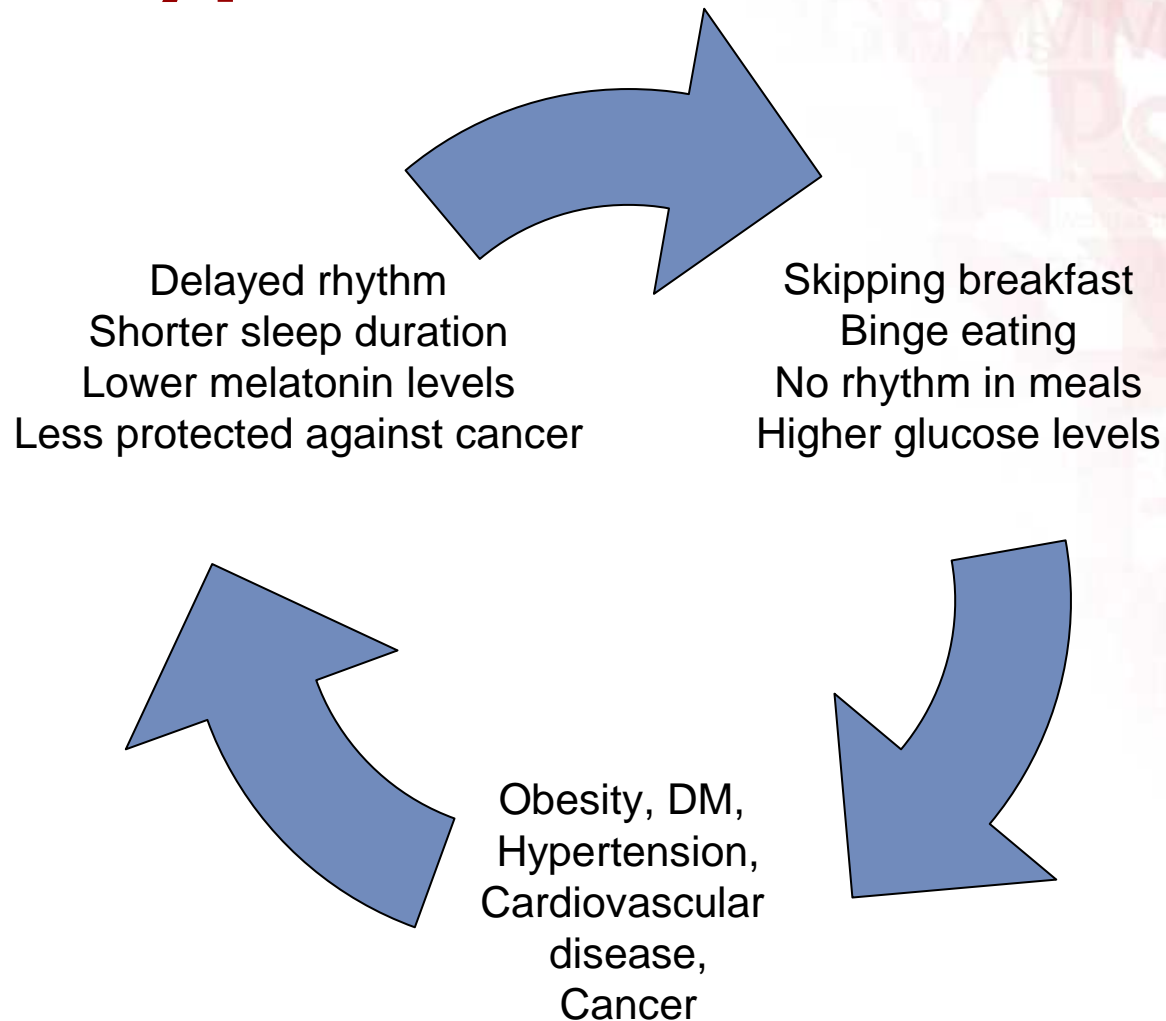
Next step: biomarkers in ADHD and DSPS

PHASE study: Phase shift in ADHD of
sleep

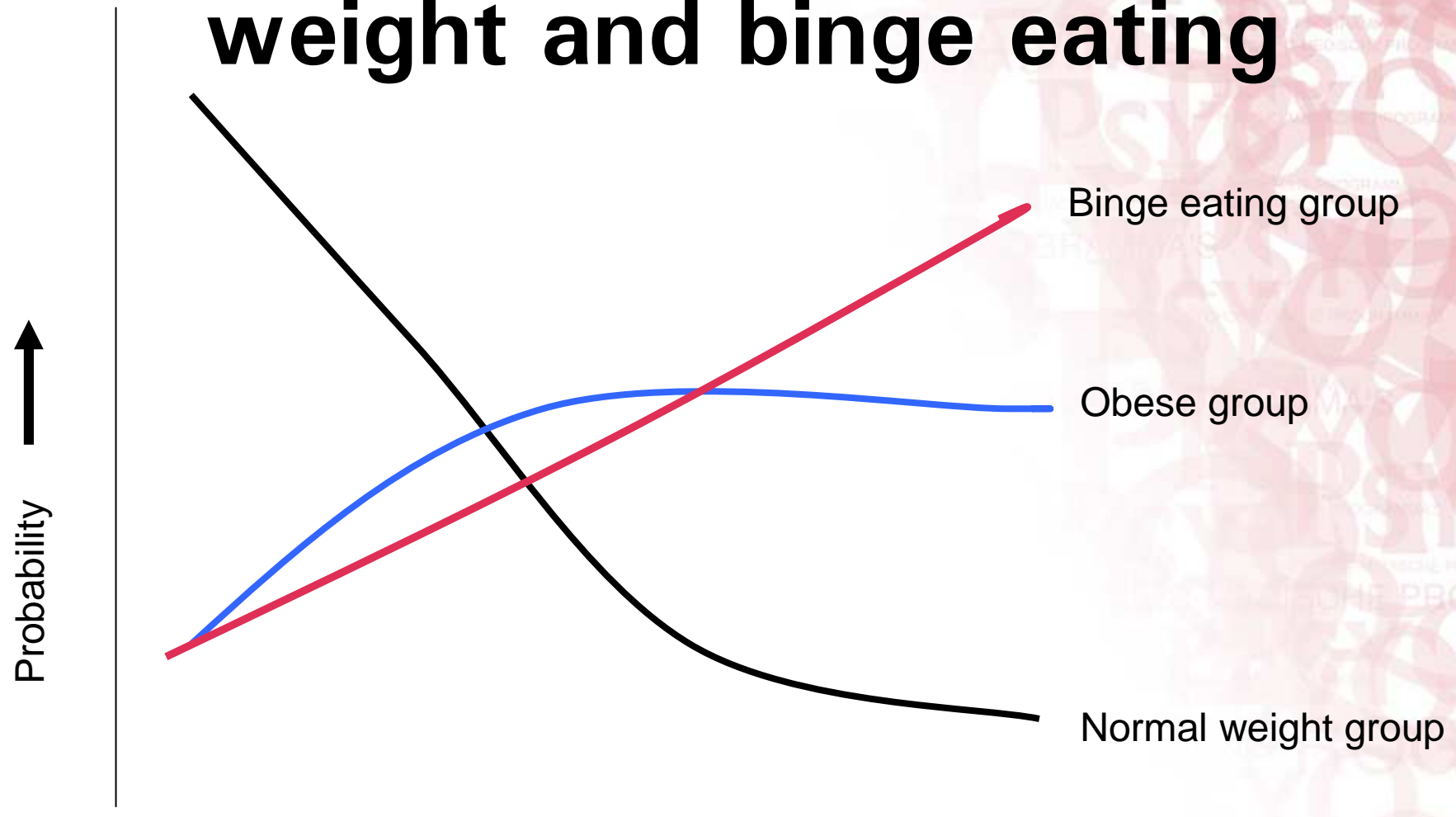
and appetite:

- 50 adults with ADHD and DSPS
- 3 wk treatment: Mel, Plac, Mel + LT
- Measurement at baseline, after 3 wks Tx and after 3 wks washout: DLMO, cortisol, leptin/ghrelin, glucose, insuline markers, inflammation markers, HRV

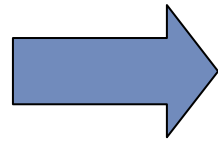
Hypothesized relations



ADHD index predicts weight and binge eating



Late sleep = short sleep



late meals

Possible impact of a delayed rhythm on weight and health:

- **Sleeping late** may lead to a short sleep duration
- **Short sleep** duration is associated with obesity
- Adults with ADHD tend to **skip breakfast**
- Breakfast skipping is associated with obesity
- ADHD patients suffer from eating problems in 80%, mostly **binge eating**
- Their **weight fluctuates** 10 - 20 kg's
- ADHD is associated with increased BMI
- Obesity is associated with diabetes, cardiovascular disease and cancer

Kooij 2012, book Adult ADHD;
Dubois 2009, Public Health Nutr;12(1):19-28;
Boere 2008, NTG;152(6):324-30;
Davis 2009, J Psychiatr Res;43(7):687-96;
Mota 2008, Ann.Hum.Biology;35(1)1-10;
Copinschi 2000, Novartis Found Symp;227:143-57
Spiegel 2005, J Appl Physiol;99(5):2008-19

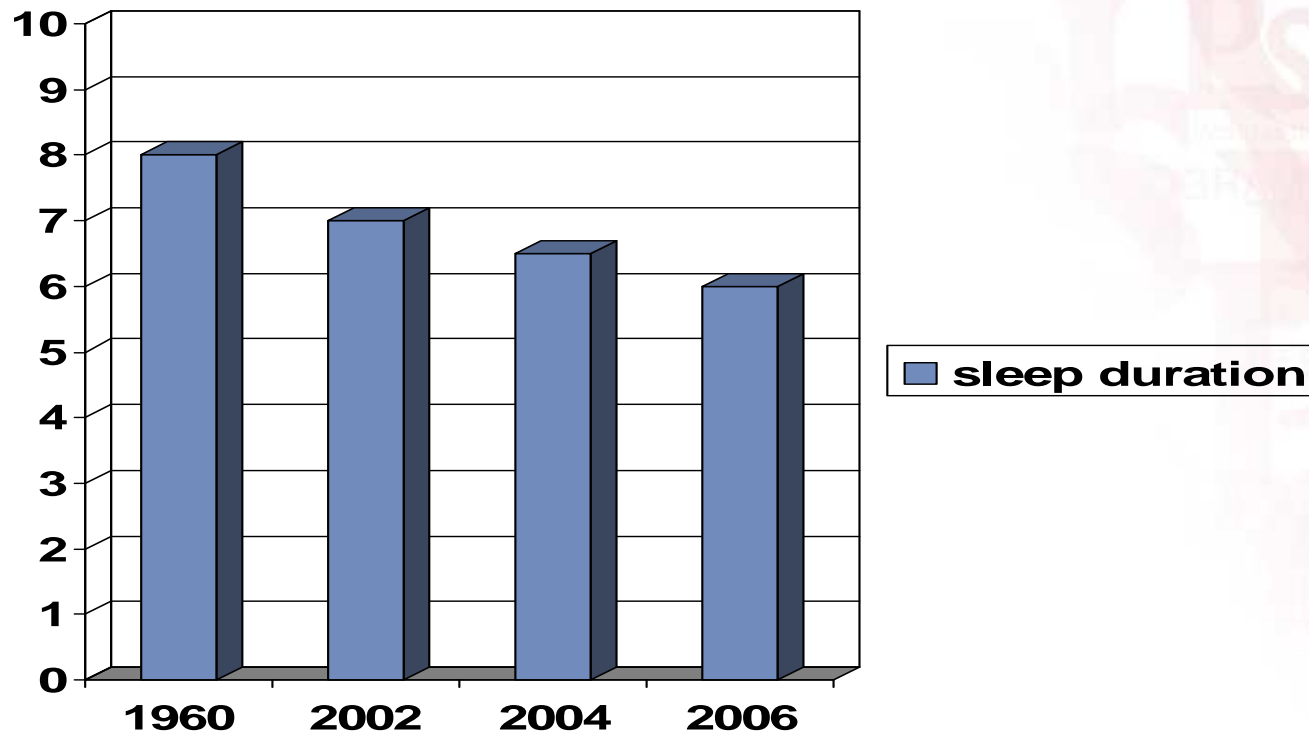
Sleep loss causes loss of control over appetite

Leptin (satiety hormone) and ghrelin (hunger hormone):

- Reducing sleep duration by 2 hours already lowers levels of leptin, the satiety ("fullness") signal
- Sleep restriction study (n = 12): leptin ↓ by 18% and ghrelin ↑ by 28%, leading to increased appetite and feelings of hunger
- 13 epidemiologic studies in adults and 8 in children: sleep loss is associated with increased BMI
- Sleep loss is a novel risk factor for insulin resistance and type 2 diabetes

Lauderdale 2006, Am J Epidemiol;164(1):5-16; Lauderdale 2009, Am J Epidemiol;170(7):805-13. Spiegel 2005, J Appl Physiol;99(5):2008-19; Copinschi 2005, Essent Psychopharmacol;6(6):341-7; Shea 2005, J Clin Endocrinol Metab;90(5):2537-44;

Sleep duration USA



As sleep time fell in USA, average weights rose
Whether and how sleep time and weight are connected is still unclear

Treatment of ADHD in obese patients

- N = 242 patients with severe therapy resistant obesity, ADHD in 32%!
- Comorbidity: depression, sleep apnea, binge eating
- 75% of the ADHD group got stimulant treatment
- Stimulants: effective for ADHD, and inhibit appetite
- Weight loss: 15 kg in stimulant treated group, while others increased 3 kg during treatment for obesity
- After follow up at 1.5 yrs, in which medication was continued, the results remained
- Patients: less restlessness, anxiety and tiredness, & needed less food to compensate for these feelings. Binge eating disappeared, better contact with feeling of hunger and satiety.
- Better able to plan and comply to the treatment for obesity.



Proposed treatment / prevention of obesity in ADHD

To reset the clock and increase sleep duration:

- Psycho education *on the meaning of time*, the light/dark cycle for sleep, appetite, metabolic entrainment, mood and health
- Sleep hygiene (early to bed and early to rise ...)
- No light@night, shower before going to bed, bedsocks
- Melatonin in evening*
- Light in morning

To reduce binge eating and weight gain:

- Treatment of comorbidity (depr/anx)
- Treatment of ADHD with stimulant
- Exercise, diet



*Melatonin has not been reviewed or approved by the FDA for the treatment of sleep disorders. Kooij, book Adult ADHD 2012

Melatonin treatment

- To fall sleep: 3 mg at 22:00 in order to sleep at 23:00
- To reset the clock: 0.1 mg - 0.5 mg between 16:00 and 19:00, *in steps of 1.5 hour/wk from the normal sleep time to the desired bedtime*
- Circadin 2 mg for those who wake up nevertheless at 03:00 am
- No light exposure of tablets of melatonin!

**Gewenste inslaaptijd – 8 uur =
uiteindelijke tijdstip inname 0.5 mg
melatonine**

Gewenste inslaaptijd	Tijdstip inname Mel
01:00	17:00
00:30	16:30
23:00-24:00	16:00

Light therapy in the morning

- Especially in winter more sleep phase delay
- More difficult to get up on time
- Inducing strong early morning light artificially, usually does work as sunlight in summer
- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light box of 500 W, or Light therapy device 10.000 lux and timer 30 min before wake up time
- Wake Up Light uses only 75 W and does not wake all patients with delayed sleep phase
- Warning: 500 W light becomes hot and contains UVA + B



New: is the eye implicated as well in ADHD?

- Webbased questionnaire in $n = 495$, 47% with ADHD (symptoms)
- ADHD had in 68% *photophobia* vs 28% of controls
- ADHD wore sign. more hours/day *sunglasses in every season*, because of photophobia
- By wearing sunglasses, less entrainment by light during the day, possibly delaying sleep phase further
- No relationship with chronotype or season of birth



Next: looking into the eye of ADHD

- Children with ADHD have in 70-80% visual acuity difficulties, that may respond to stimulant treatment
- Adults with ADHD have difficulties with depth and blue-spectrum colour perception, visual search and processing, and peripheral vision
- Photophobia may point to deficiencies in the pupillary response to light

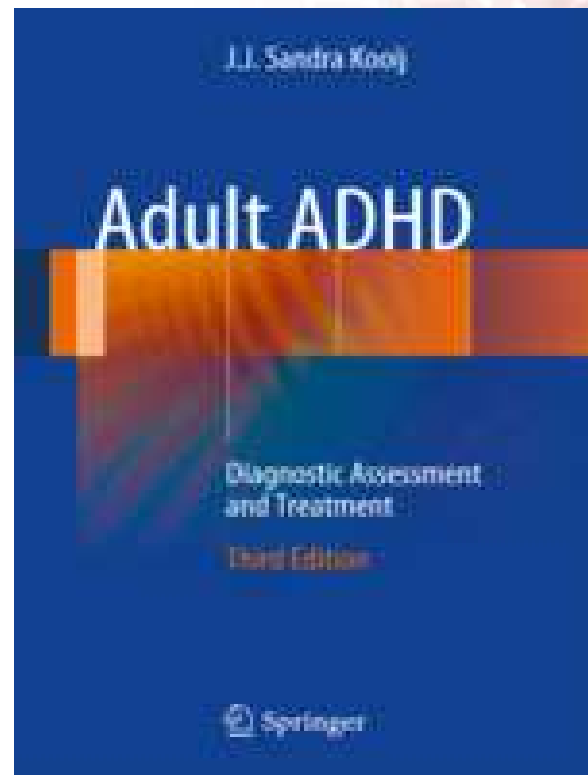
Adult ADHD

Diagnostic Assessment and Treatment

Including DIVA 2.0

JJS Kooij, 3rd edition
2012

www.springer.com
Search for 'Adult ADHD'



Thanks to the circadian rhythm study group:

- Denise Bijlenga
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- Annet Bron