

De verlate slaapfase bij ADHD

Impuls – Jij en je brein
Noordwijkerhout, 6 april 2011
Dr. J.J.S. Kooij, psychiater



*Kenniscentrum
ADHD bij volwassenen*

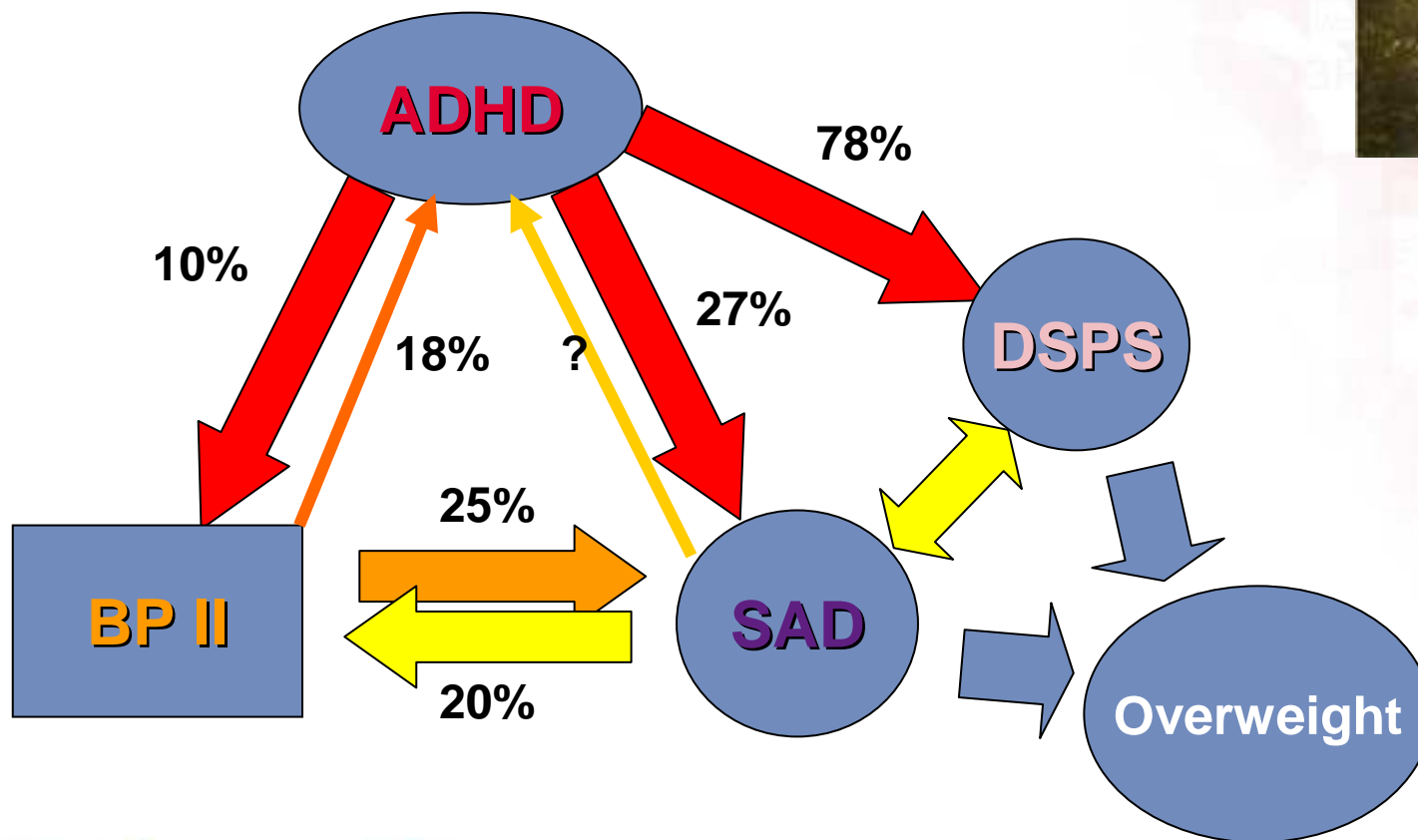


ADHD is highly comorbid with circadian based disorders

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%
- Obesity 30%
- Sleepproblems, DSPS pattern 80%

ADHD, sleep, circadian rhythm, mood and weight



ADHD & seasonal mood changes



- Adult ADHD co-occurs with lifetime depressive disorder in 55%
- Most of these (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

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 inattention, a planning problem, but may in fact reflect a fundamental problem of the biological clock

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 associated with eveningness
- Lack of sleep rhythm may lead to lack of rhythm in eating and activity patterns as well
- Eveningtypes, 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 winterdepression, and possibly also of Premenstrual Dysphoric Disorder than normal

ADHD and sleepproblems in children

Subjective measures:

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

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

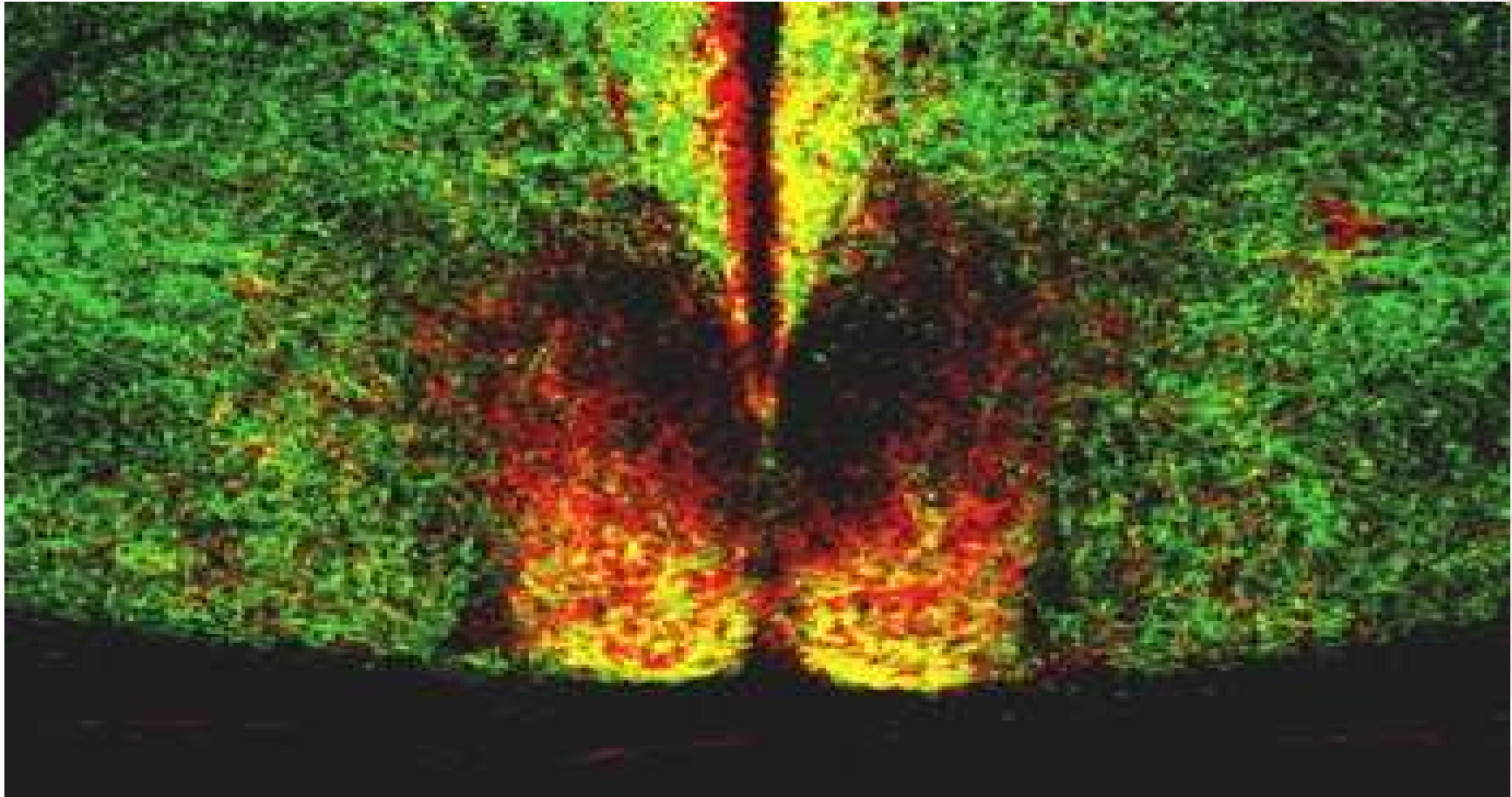
Sleep questionnaire in 120 adults with ADHD

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

Nucleus supra chiasmaticus (NSC): the biological clock



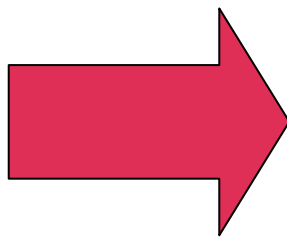
PSYQ
PSYCHO-MEDISCHE PROGRAMMAS

Hypothalamic nucleus, just above the chiasma opticum

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

Morning types are low in novelty seeking / impulsiveness



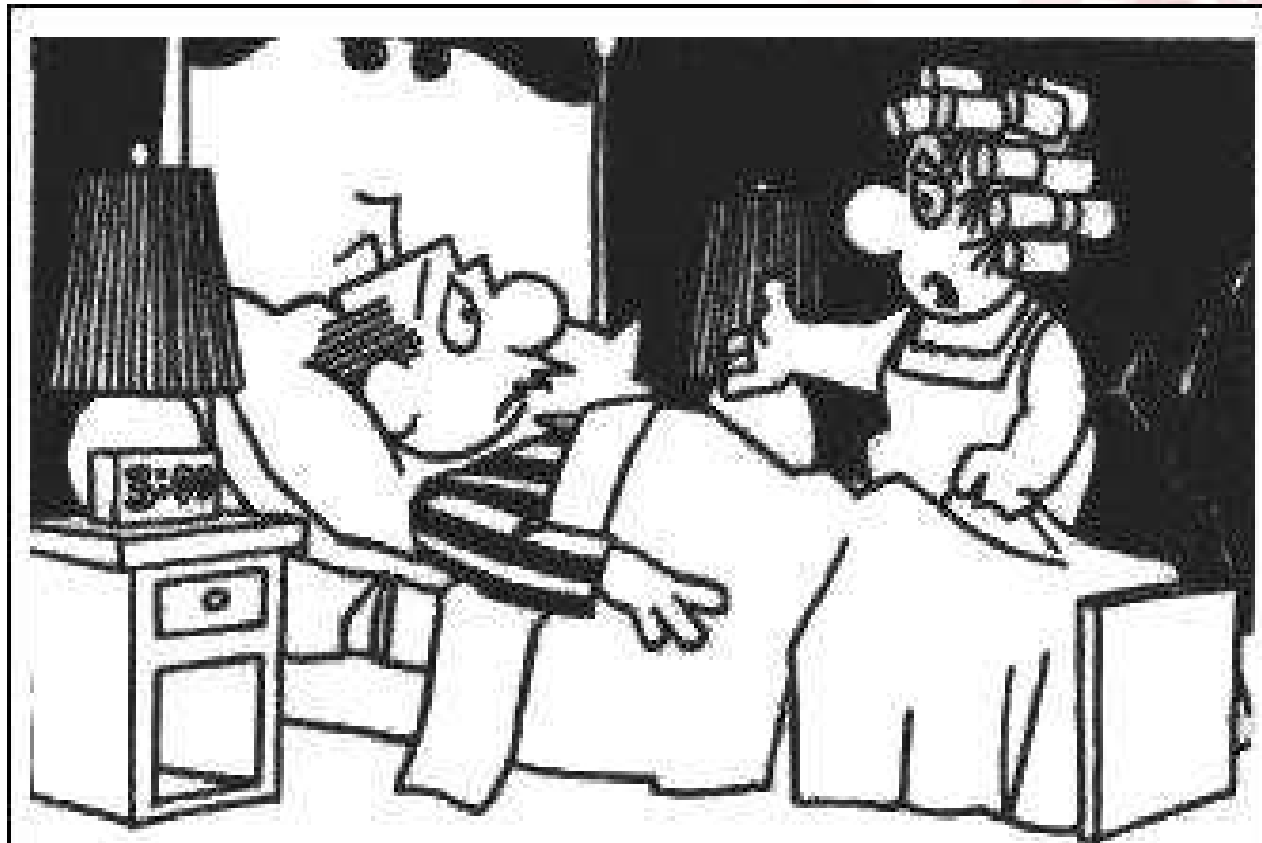
Evening types
the other way round

...

Link between impulsivity/ADHD and eveningness

Are most adults with ADHD eveningtypes?

- Eveningtypes are more active at night, prefer to go to bed late
- They get up late as well
- Eveningtypes may be late due to a delayed onset of melatonin
- If sleeping longer is not possible due to work or school obligations, a chronic sleepdebt 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?



"No wonder you have insomnia . . .
lying there awake all night."



Methods case-control study

Sleep Onset Insomnia in adult ADHD

Sleep Questionnaires

- Sleep problems and sleep diagnosis list
- Sleep log (1 wk)

Saliva samples: Dim Light Melatonin Onset (DLMO): 1 night at home, dim light conditions, 5 samples 21:00-01:00. DLMO = $> 3\text{pg/ml}$.

Saliva DNA sample

Actigraphy: 7 x 24 hrs

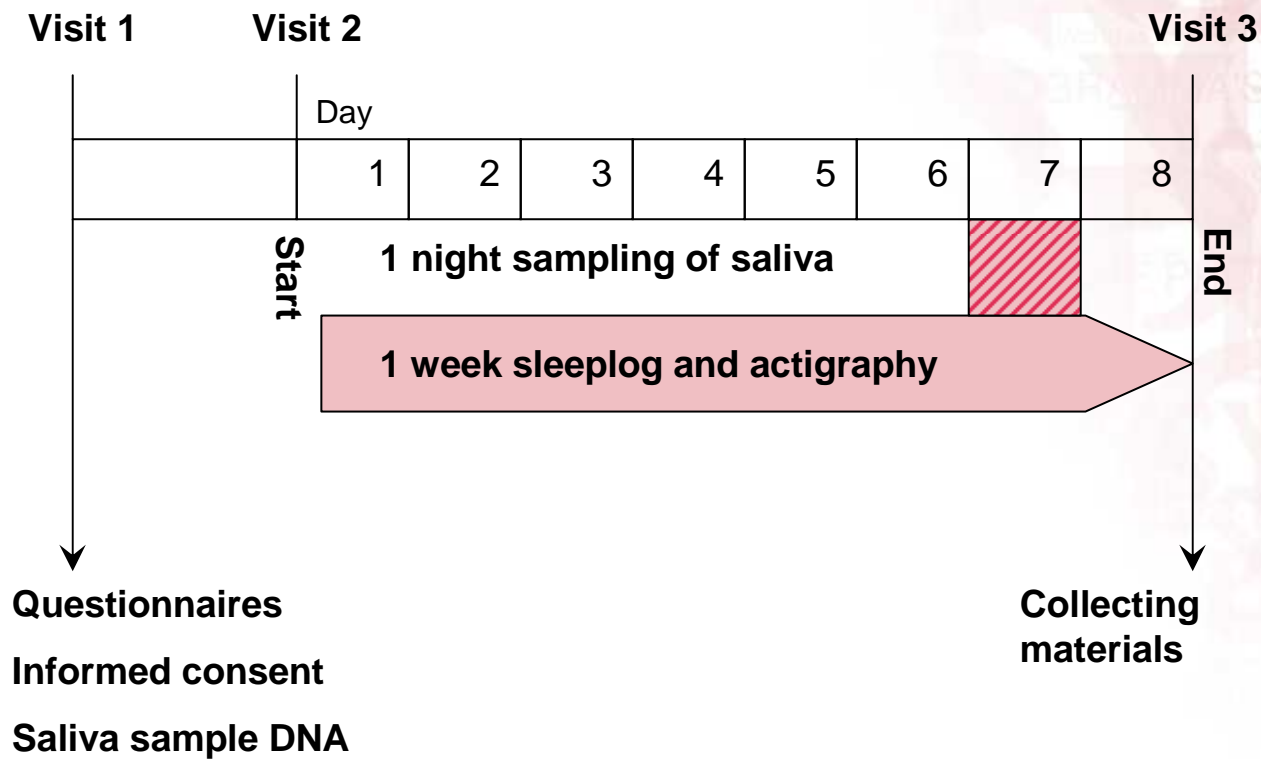
Definition Sleep Onset Insomnia (SOI)

- difficulty falling asleep at desired time ($> 23:30$) and/or sleep latency > 30 min
- at least 4 nights/week, duration > 6 months
- impairment

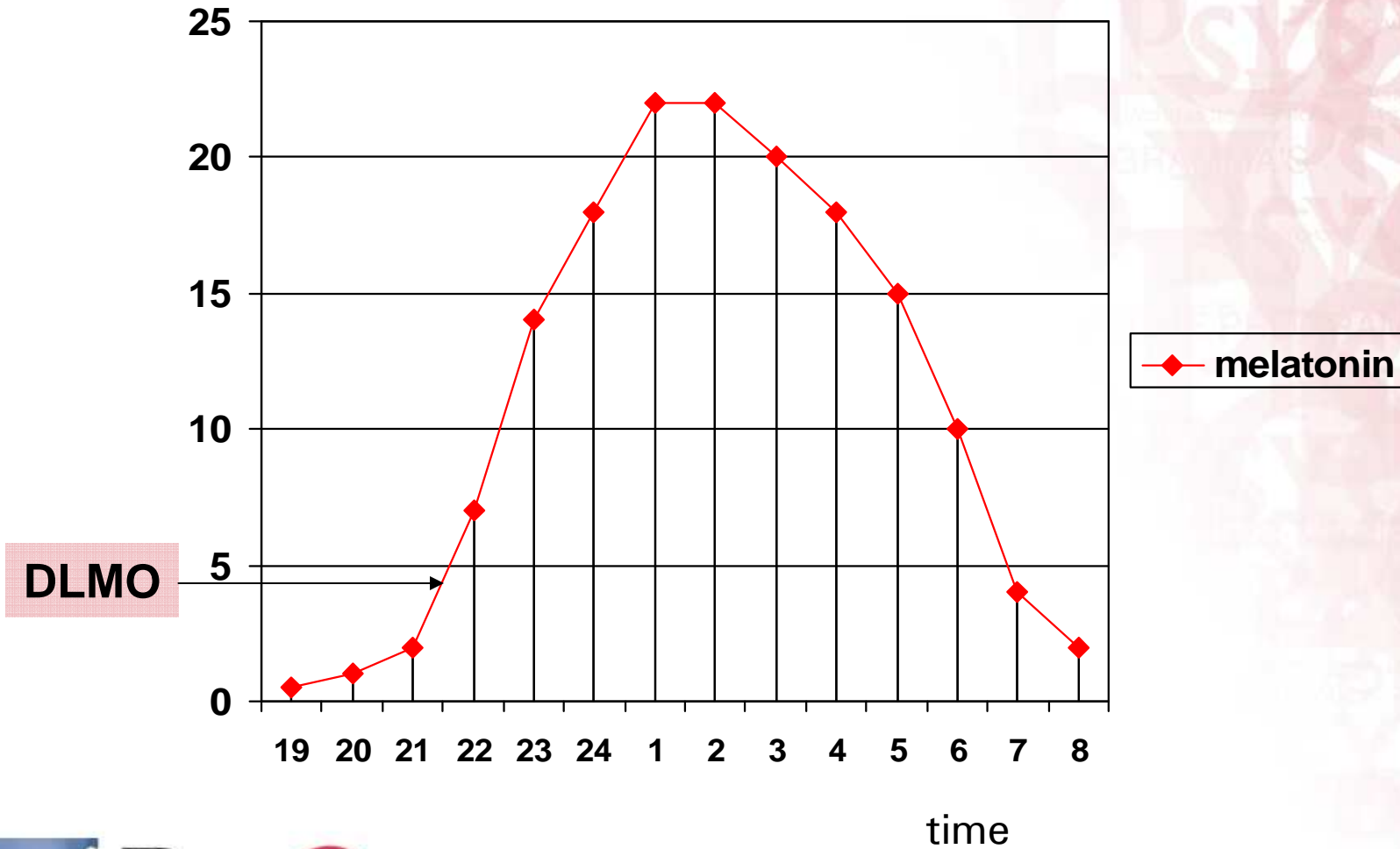


Van Veen 2010; Sweere 1999; van der Heijden 2005, 2006; Benloucif 2008, Klerman 2002, Nagtegaal 1998

Methods



Melatonin rhythm



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

Controls

Healthy controls actigraphy (n = 24)

and healthy controls DLMO (n = 28)

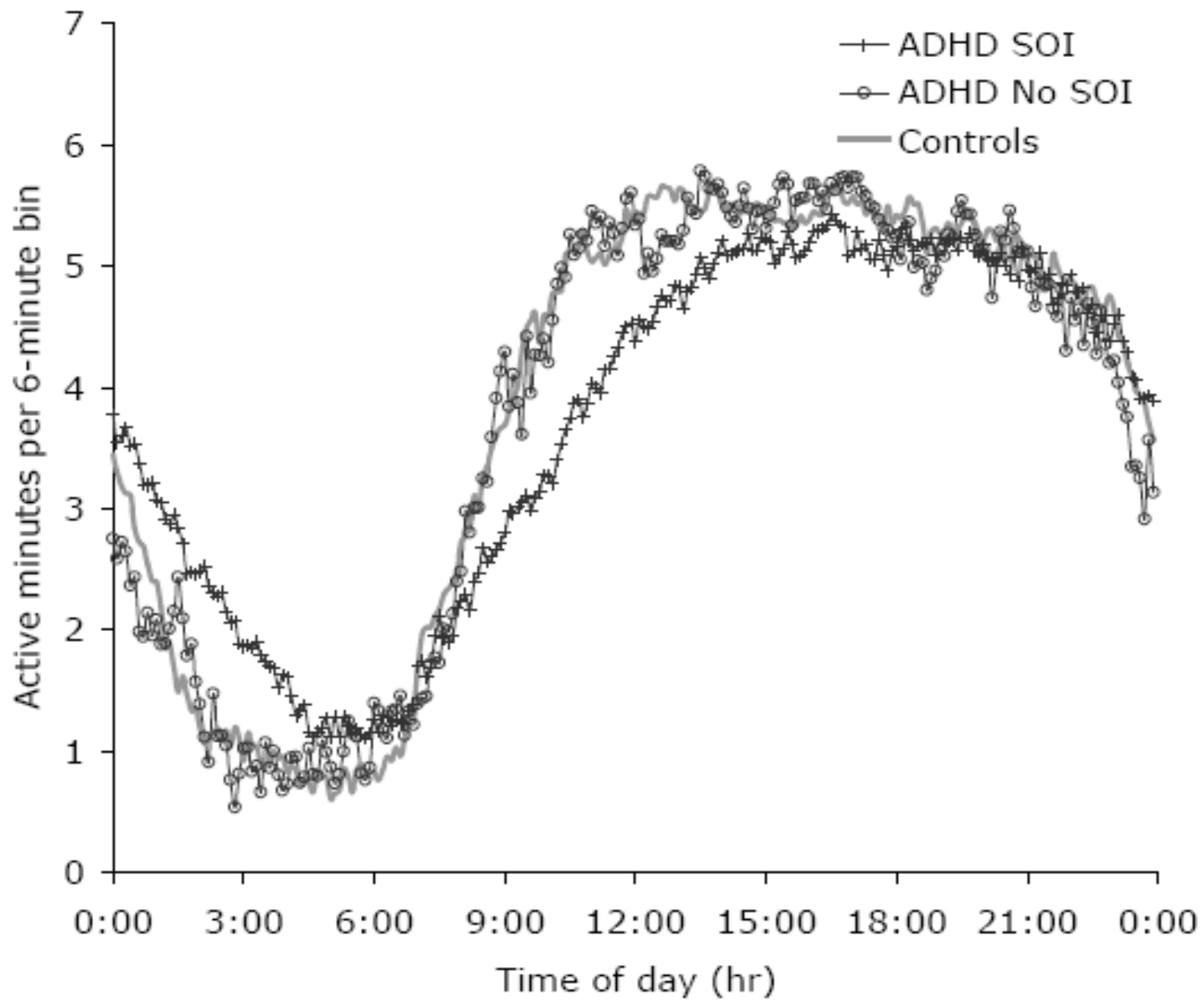
Age and gender matched

Results actigraphy I

	ADHD total	SOI	no-SOI	HC	<i>p</i> : ADHD vs HC	<i>p</i> : SOI vs HC
Sleep start (hr ± sd)	1:21 ± 1:26	1:42 ± 1:22	0:14 ± 1:04	0:49 ± 0:50	0.115	0.014
Sleep end (hr ± sd)	9:13 ± 1:37	9:27 ± 1:44	8:26 ± 0:48	8:27 ± 0:53	0.019	0.019
Sleep duration (mins ± sd)	418.9 ± 65.5	413.2 ± 69.2	438.2 ± 50.1	409.9 ± 41.4	0.501	0.926
Sleep eff. (% ± sd)	84.54 ± 5.87	84.45 ± 6.32	84.86 ± 4.29	87.88 ± 3.73	0.015	0.031

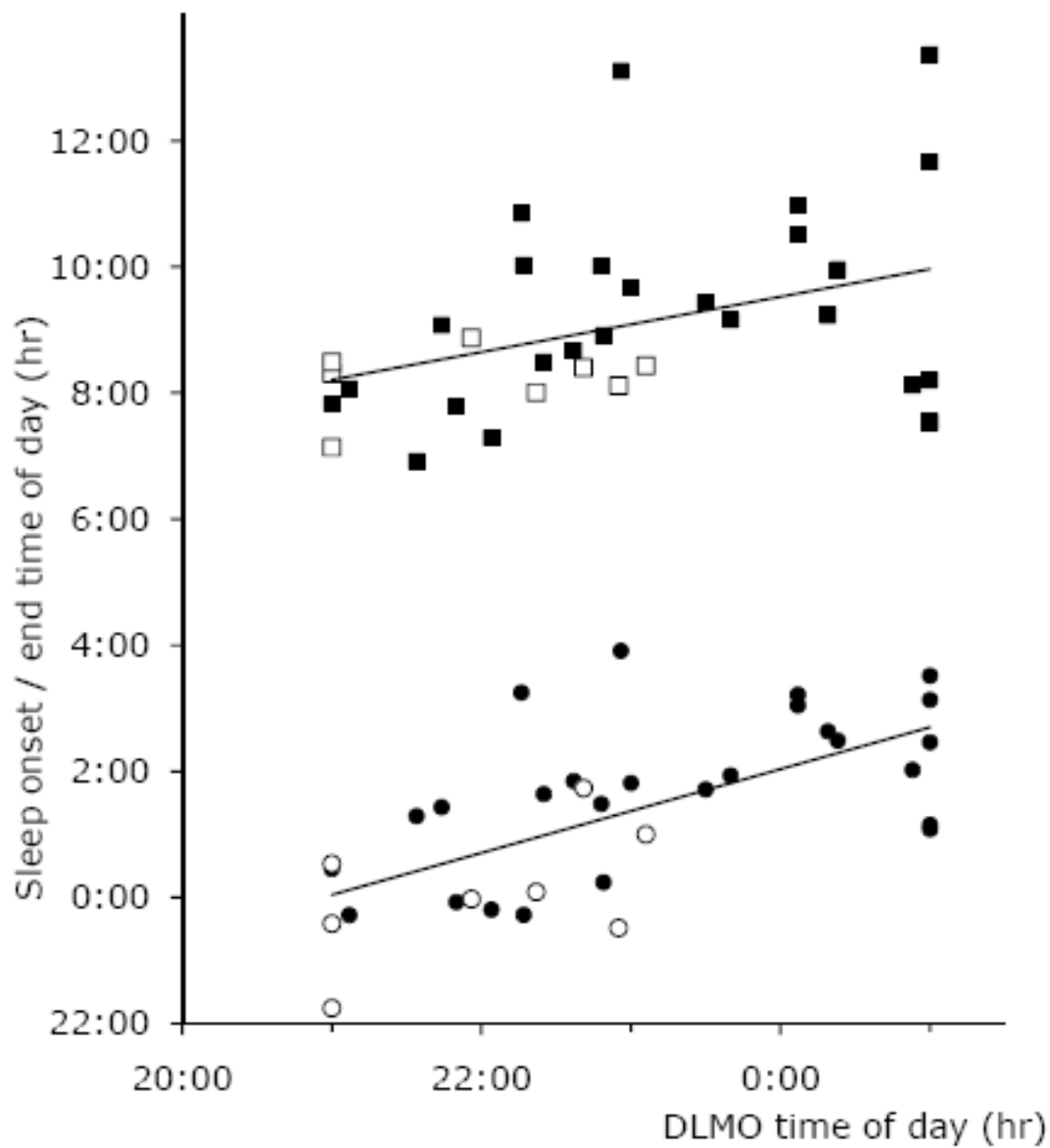
Results actigraphy II

	ADHD total	SOI	no-SOI	HC	<i>p</i> : ADHD vs HC	<i>p</i> : SOI vs HC
Sleep latency (mins)	17.71 ± 15.48	17.70 ± 16.05	17.74 ± 14.33	6.92 ± 4.78	0.002	0.004
IS (± sd)	0.74 ± 0.12	0.71 ± 0.13	0.83 ± 0.04	0.75 ± 0.09	0.476	0.103
IV (± sd)	0.41 ± 0.10	0.41 ± 0.11	0.41 ± 0.09	0.36 ± 0.06	0.039	0.053
AMP (± sd)	42.1 ± 5.1	41.1 ± 5.4	45.1 ± 2.5	46.1 ± 3.2	0.000	0.000



Results DLMO

	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
DLMO without assumptions (hr ± sd)	22:51 ± 1:20	22:55 ± 1:04	22:36 ± 0:28	21:34 ± 0:45	0.000	0.000



Pearson's correlations

DLMO – sleep onset

$r = 0,65$ ($p 0,0000$)

DLMO – sleep end

$r = 0,38$ ($p 0,0222$)

Conclusions

- **Adults with ADHD show a delayed rhythm compared to controls**
 - sleep start and end
 - Δ DLMO 83 minutes
- **Also delayed activity pattern during the day**
- **Smaller difference in activity level day and night**
- **78% of consecutive patients suffered from SOI**
- **ADHD subtypes separated by sleep problems**

But:

- Normal sleepduration
- Sleep rhythm adjusted to endogenous rhythm

Discussion

Possible mechanisms

- Weaker internal biotrhythm
- Different sensitivity to external Zeitgebers
- Prefrontal cortex
- Clockgenes

Treatment



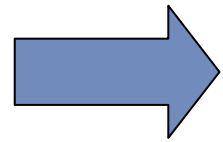
Delayed Circadian Rhythm in Adults with Attention-Deficit/Hyperactivity Disorder and Chronic Sleep Onset Insomnia

Biological Psychiatry 2010 Jun 1;67(11):1091-6

Maaïke M. Van Veen, J.J. Sandra Kooij, A. Marije Boonstra,
Marijke C.M. Gordijn, Eus. J.W. Van Someren



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
- Obesity is associated with diabetes, cardiovascular disease and cancer

Sleep loss causes loss of control over appetite

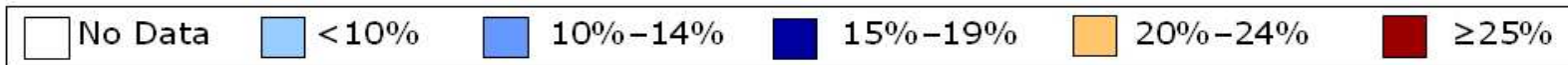
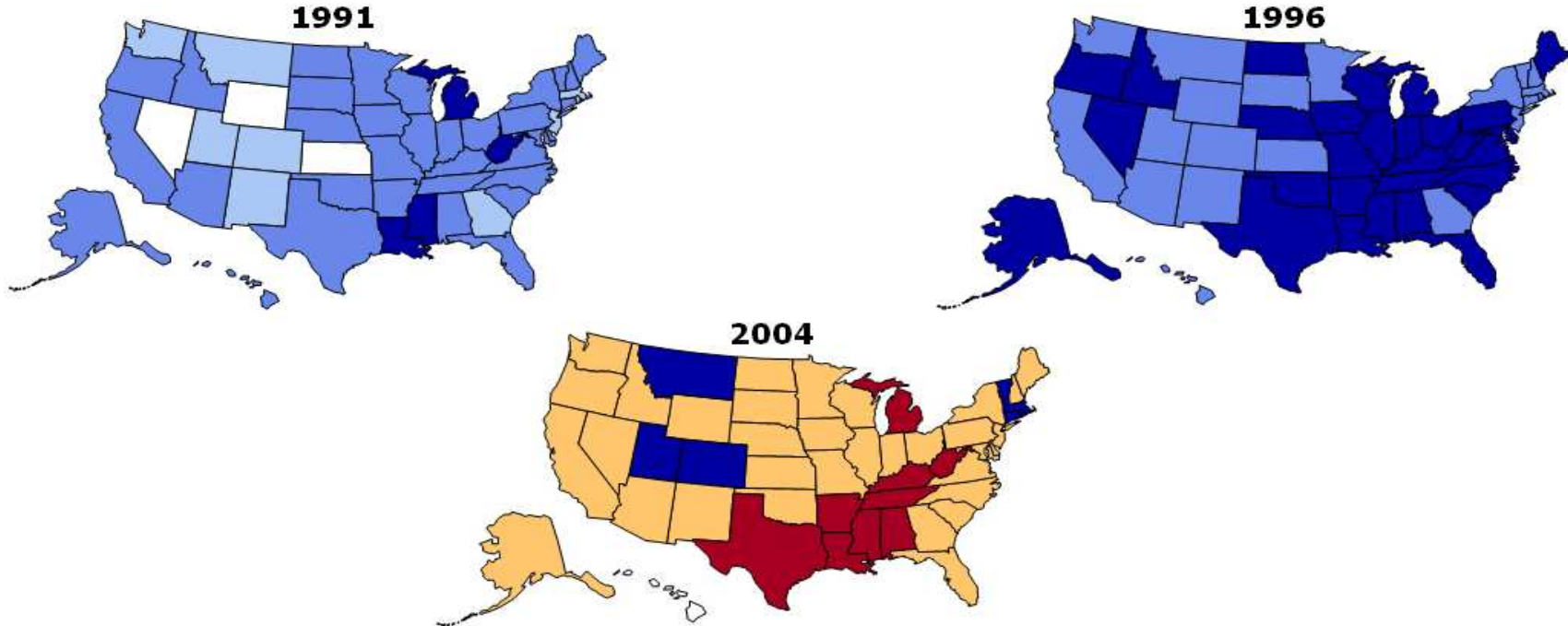
Leptin (satiety hormone) and ghrelin (hunger hormone)

- Leptin levels very sensitive to sleep duration
- Leptin levels much lower after sleep restriction
- Reducing sleep duration by 2 hours lowers the levels of this satiety ("fullness") signal
- During a sleep restriction study (n = 12), levels of leptin decreased by 18% and levels of ghrelin increased by 28%, leading to increased appetite and feelings of hunger
- Thirteen epidemiologic studies in adults and 8 in children have reported that sleep loss is associated with increased BMI
- Sleep loss was identified as a novel risk factor for insulin resistance and type 2 diabetes

Obesity Trends* Among U.S. Adults

BRFSS, 1991, 1996, 2004

(*BMI ≥ 30 , or about 30 lbs overweight for 5'4" person)

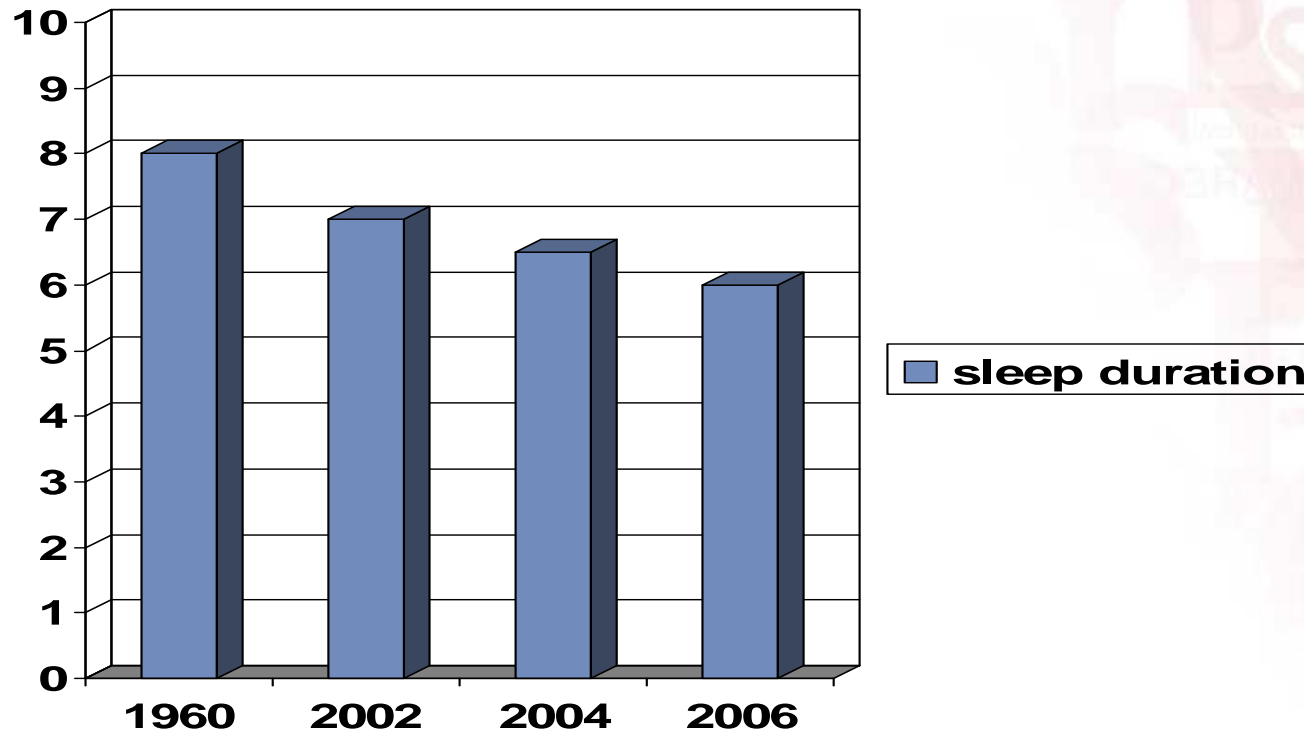


Source: Behavioral Risk Factor Surveillance System, CDC.



1960: 25% overweight and 11% BMI > 30 (obese)
 Now: 66% overweight and 33% obese

Sleep duration USA



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

Eating disorders and problems in adult ADHD (n = 120)

Eating disorders in ADHD

- **No Anorexia, and 9% bulimia nervosa**, except for the group with ADHD and childhood sexual abuse (18.5%): 33% had BN ($p = .003$)

Eating problems in the majority of patients:

- **Current or past binge eating most frequent eating problem (86.2%)** due to 'impulsive behavior or to get less restless'
- Frequency of binge eating: 40% several times a day, 40% at least once a week, the rest at least once a month
- Patients mentioned they forget to eat and do not plan their meals
- The group with binge eating problems was not diagnosed as bulimia nervosa or eating disorder NAO according to the CIDI, supposedly due to lack of inappropriate compensatory behaviors or to a lower frequency
- Patients with binge eating had a higher chance of large weight fluctuations over time (> 10 -20 kg) ($p = .002$)

Etiological links obesity and ADHD, so far

Shared etiology: reward deficiency syndrome (DA)

- DRD2, DRD3 and DRD4 genes associated with both

ADHD: poor planning and inhibitory control

- Immediate reward seeking: gambling, substance use, risk taking and bulimic behavior or binge eating
- Less internal feedback of feelings of appetite and hunger?
- Bulimic behavior may lead to obesity
- Inattention and impulsivity, but not hyperactivity are associated with obesity

Seasonal affective disorder is increased in ADHD (19-27%)

- Increased appetite, carbohydrate craving in winter may lead to increased weight

Stimulants effective for ADHD and increased appetite

- Stimulants improve disturbed eating behaviors, esp. binge eating and BN

ADHD ~ more eating disorders & bingeing

	Anorexia Nervosa	Bulimia Nervosa	Binge Eating Disorder	Binge Eating Behavior (lifetime)
Eating disorders In general population	1.2%	1 – 3%	5 %	?
Eating disorders in ADHD	?	8 - 12%	8.3%	86%
ADHD in eating disorders	10 - 17%	?		

Bulimic behaviors emerge in adulthood in women with ADHD

More ADHD in obese patients

ADHD in obese patients 27 - 34%
ADHD in extreme obesity (BMI > 40) 43 - 57%

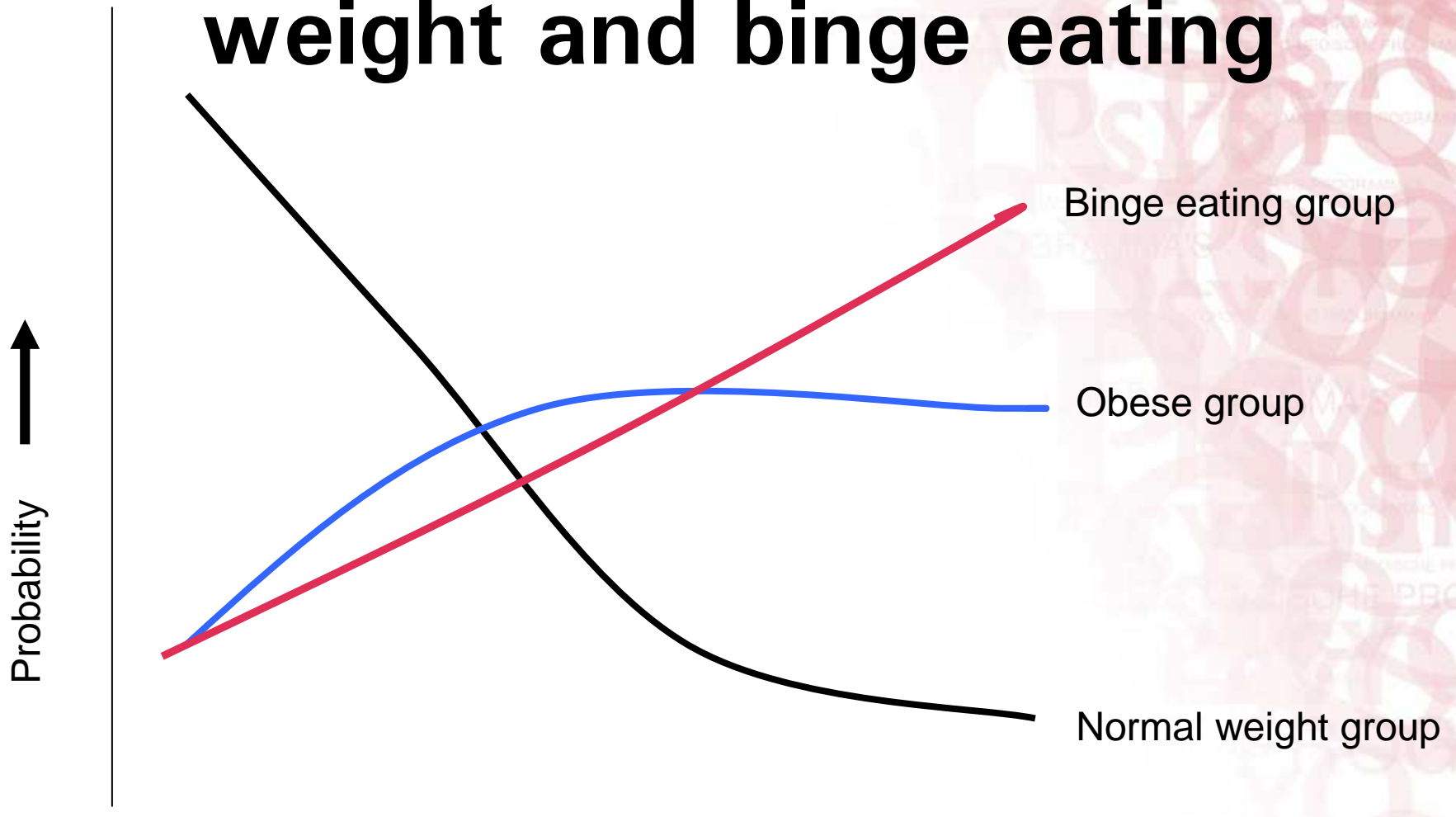
Obesity in ADHD

Higher BMIs in ADHD than controls in children and adults

29%)

34% of ADHD is overweight (controls and 30% is obese (vs 22%)
OR 1.58 overweight; OR 1.81 obesity

ADHD index predicts weight and binge eating



Circadian disturbance, ADHD and health

- ADHD may be 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

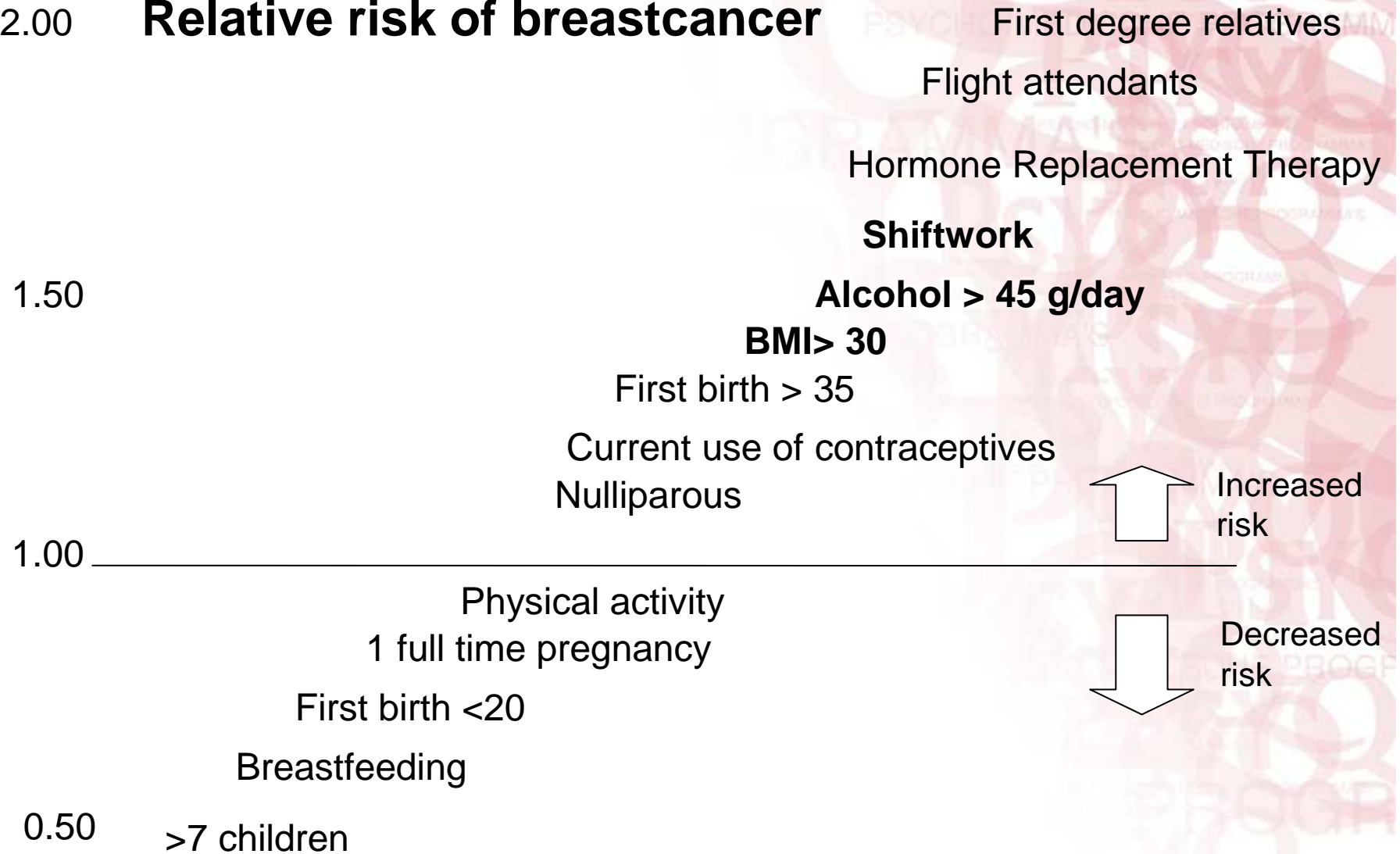


is ADHD a high riskgroup for cancer?

Schernhammer 2001,2005, Hansen 2001, Griefahn 2002, Stevens 2005, Blask 2005, Moser 2006



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?



ASESA study

First data from a survey among adults with ADHD and normal controls (students and parents), using the ASESA questionnaire, on Attention Problems, Sleep- and Eating Patterns, Mood, and General Health

ASESA: ADHD vs controls

Six parts (115 questions in total):

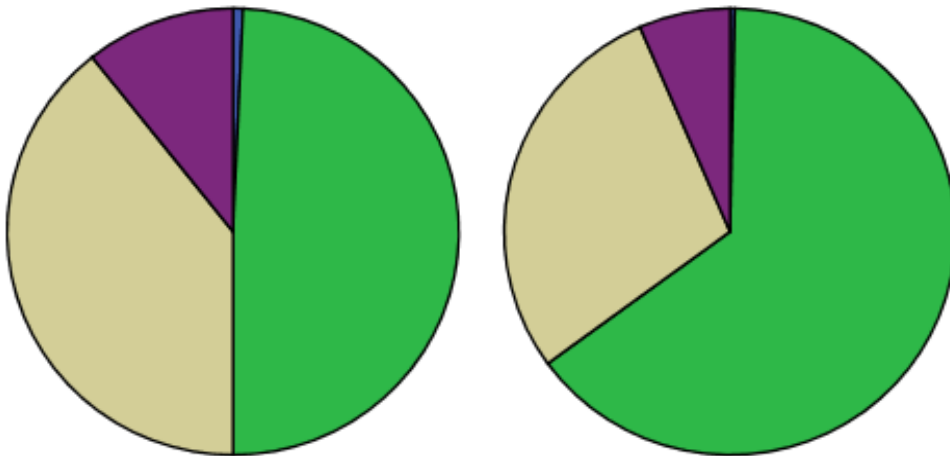
1. ADHD symptoms (ADHD RS)
2. Munich Chronotype Questionnaire
3. Current work situation (nightshifts)
4. Activity during evening and night
5. Mood and seasonal preference
6. Current and past health situation

ADHD more overweight than controls

BMI classification

Vier groepen: oud & jong
PsyQ>30 Leiden>30

BMI classification
■ underweight
■ normal weight
■ overweight
■ obese



ADHD skips more meals

Four groups * Vraag_26 Crosstabulation

			Vraag_26		Total
			No	Yes	
Four groups	PsyQ<30	Count	27	92	119
		% within Four groups	22,7%	77,3%	100,0%
	PsyQ>30	Count	53	94	147
		% within Four groups	36,1%	63,9%	100,0%
	Leiden<30	Count	174	139	313
		% within Four groups	55,6%	44,4%	100,0%
	Leiden>30	Count	224	83	307
		% within Four groups	73,0%	27,0%	100,0%
Total	Count	478	408	886	
	% within Four groups	54,0%	46,0%	100,0%	

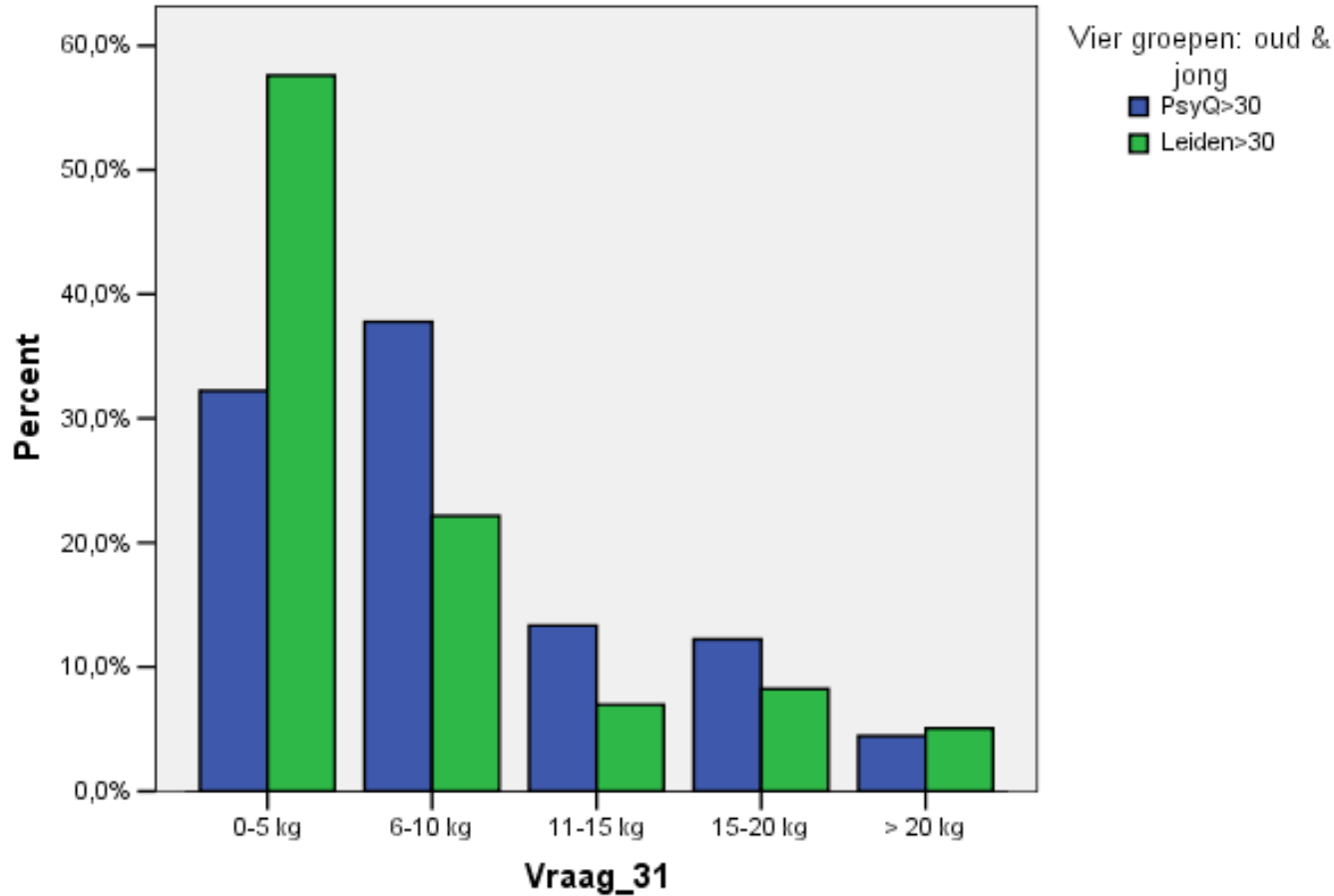
ADHD more binge eating

Four groups * Vraag_29 Crosstabulation

			Vraag_29		Total
			No	Yes	
Four groups	PsyQ<30	Count	50	69	119
		% within Four groups	42,0%	58,0%	100,0%
	PsyQ>30	Count	66	81	147
		% within Four groups	44,9%	55,1%	100,0%
	Leiden<30	Count	136	174	310
		% within Four groups	43,9%	56,1%	100,0%
	Leiden>30	Count	188	117	305
		% within Four groups	61,6%	38,4%	100,0%
Total	Count	440	441	881	
	% within Four groups	49,9%	50,1%	100,0%	

ADHD has more weight fluctuation

Weight fluctuation



ADHD is less healthy

Four groups * Vraag_32 Crosstabulation

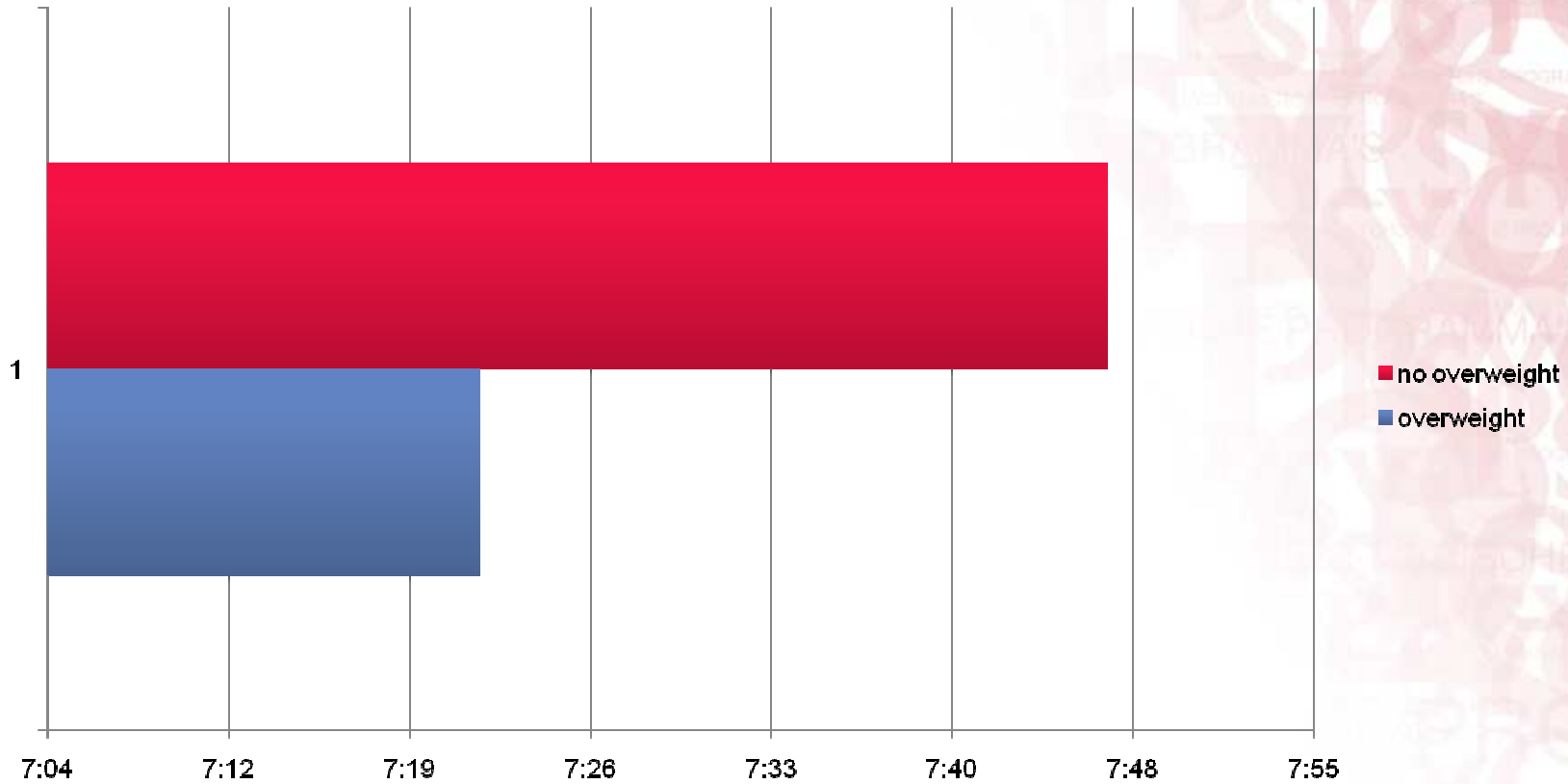
			Vraag_32		Total
			No	Yes	
Four groups	PsyQ<30	Count	16	103	119
		% within Four groups	13,4%	86,6%	100,0%
	PsyQ>30	Count	28	119	147
		% within Four groups	19,0%	81,0%	100,0%
	Leiden<30	Count	15	301	316
		% within Four groups	4,7%	95,3%	100,0%
	Leiden>30	Count	37	269	306
		% within Four groups	12,1%	87,9%	100,0%
Total	Count		96	792	888
	% within Four groups		10,8%	89,2%	100,0%

ADHD more physical disease in past

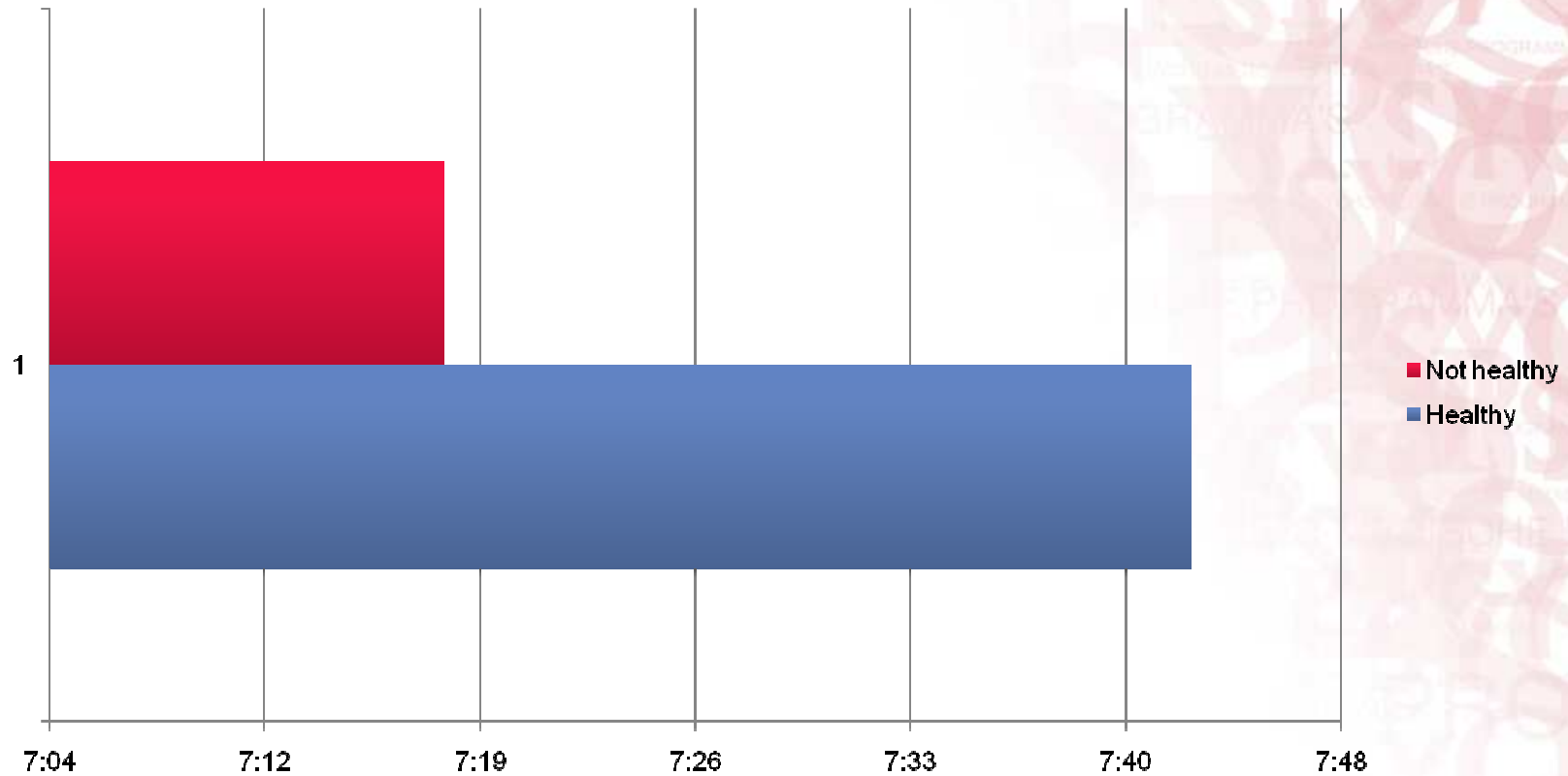
Four groups * Vraag_33 Crosstabulation

			Vraag_33			Total
			No	Yes	2	
Four groups	PsyQ<30	Count	88	31	0	119
		% within Four groups	73,9%	26,1%	,0%	100,0%
	PsyQ>30	Count	79	67	0	146
		% within Four groups	54,1%	45,9%	,0%	100,0%
	Leiden<30	Count	272	34	1	307
		% within Four groups	88,6%	11,1%	,3%	100,0%
	Leiden>30	Count	209	88	0	297
		% within Four groups	70,4%	29,6%	,0%	100,0%
Total	Count	648	220	1	869	
	% within Four groups	74,6%	25,3%	,1%	100,0%	

Shorter sleepduration ~ overweight



Shorter sleepduration ~ less healthy



Conclusions ASESA questionnaire

ADHD compared to controls:

- More evening types
- More skipping of meals and binge eating
- Shorter sleep related to higher BMI
- More evening activity & light @ night
- More health hazards

Circadian misalignment & cardiometabolic implications

Circadian misalignment study: 8 healthy subjects ate and slept 12 hours

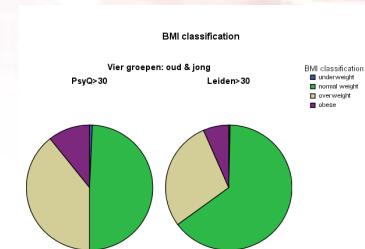
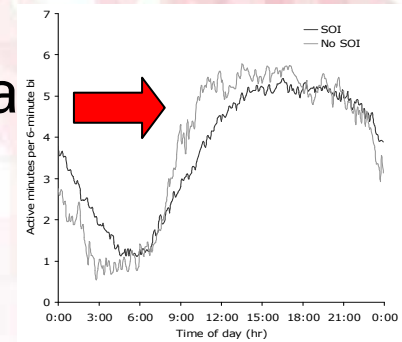
out of phase during 10 days:

- decreased leptin (-17%, $P < 0.001$)
- increased glucose (+6%, $P < 0.001$) despite increased insulin (+22%, $P = 0.006$),
- completely reversed the daily cortisol rhythm ($P < 0.001$)
- increased mean arterial pressure (+3%, $P = 0.001$)
- and reduced sleep efficiency (-20%, $P < 0.002$).
- In 3 of 8 subjects postprandial glucose responses typical of a prediabetic state developed

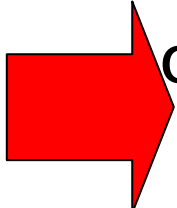
These adverse cardiometabolic events occur acutely with jet lag and chronically with shift work

What is the exact relationship between delayed sleep and obesity in ADHD?

- The majority of adults with ADHD have a sleep phase delay
- They live as if chronically in nightshifts and may have the same health risks
- ADHD patients are more often obese
- They also show a delayed activity pattern during 24 hours

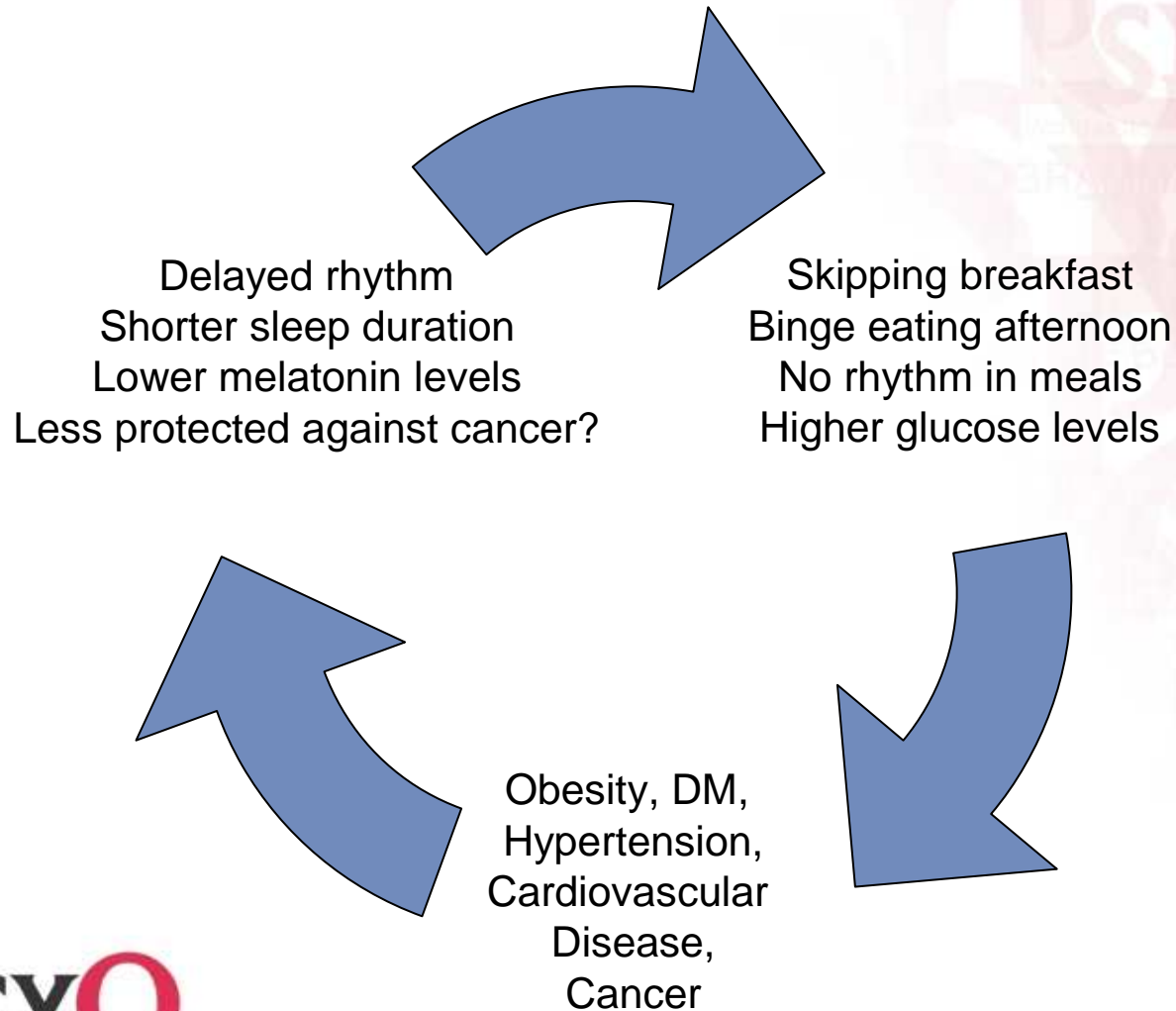


Relationship between delayed sleep and obesity in ADHD

 They may as well have a delayed rhythm of cortisol, temperature, insulin, appetite, leptin/ghrelin ratio's and other hormones due to short sleep duration

- The biological clock orchestrates all other biological rhythms; disturbances of the clock may be detrimental to several timed cardiometabolic processes

Obeying the clock benefits metabolism



Treatment perspectives?

Synchronisation of the biological clock:

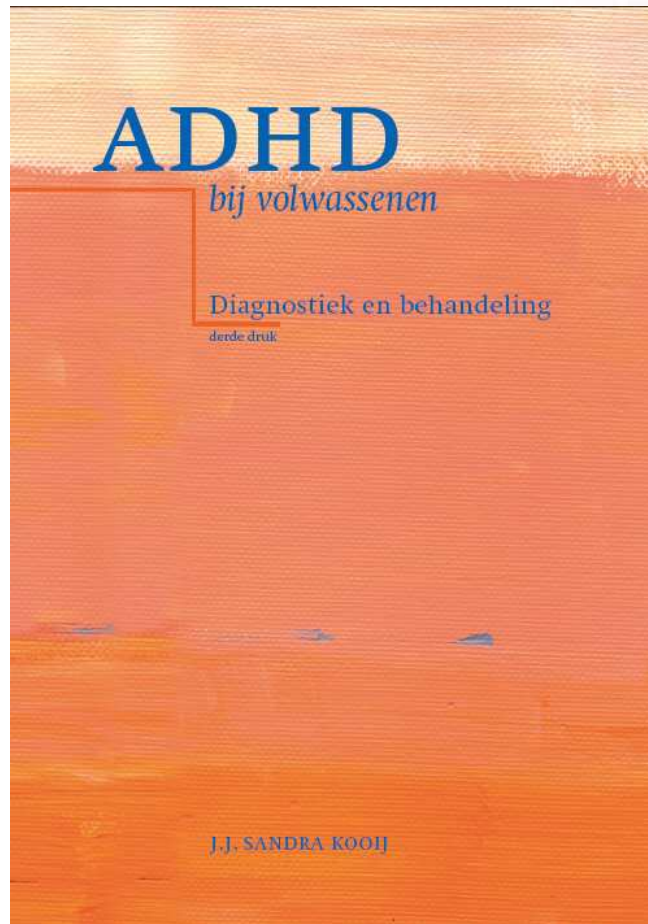
- Psychoeducation on the meaning of time, the light/dark cycle for sleep, appetite, metabolic entrainment, mood and health
- Sleephygiene (early to bed and early to rise ...)
- Lighttherapy in the morning (sleeprhytm, SAD)
- Melatonin at night (sleeprhytm)
- Light also for ADHD and overweight ??

Melatonin and light treatment

- To fall asleep: 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
- Early morning light with timer to wake up on time

DIAGNOSTIEK EN BEHANDELING VOOR PROFESSIONALS

3e gewijzigde druk, 2009



OVER MEDICATIE (incl. melatonine) voor volwassenen met ADHD

