Sleep, obesity and Diabetes Mellitus

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Disclosures

Conflict of Interest Disclosures

Type of Potential Conflict	Details of Potential Conflict
Grant/ Research Support	Research funding support from Eli Lilly and Sanofi Aventis Research support from RGC & HHSRF
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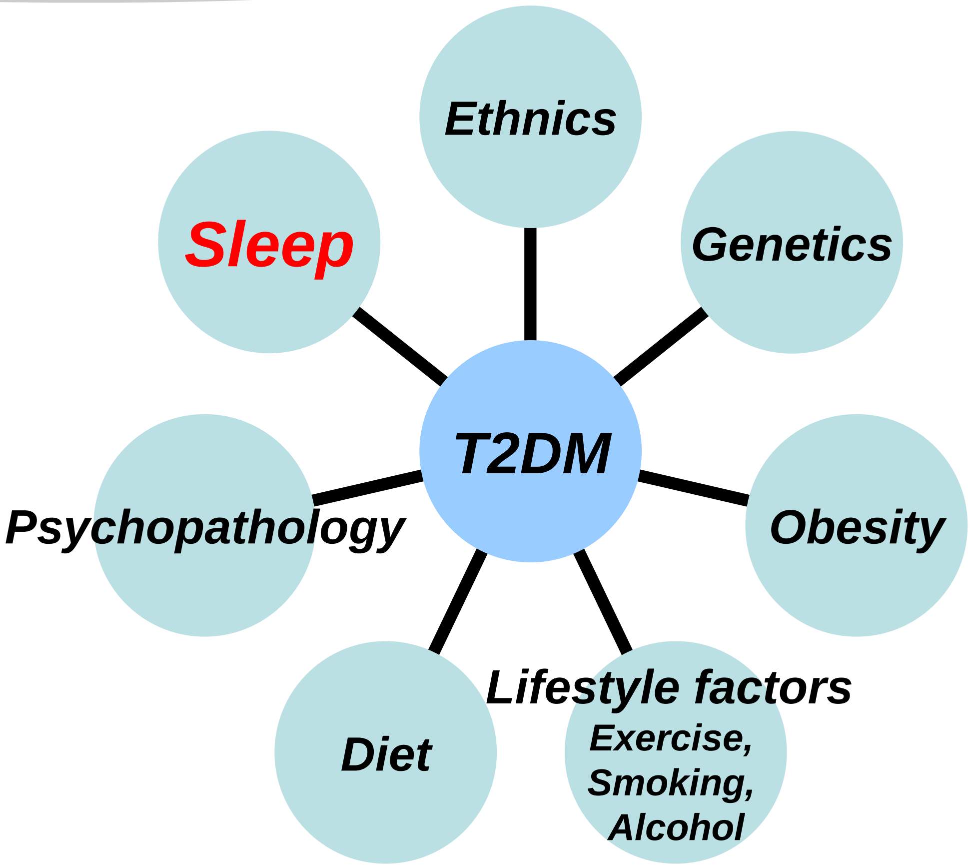
Others	No stock/ share from pharmaceutical industry

Outline

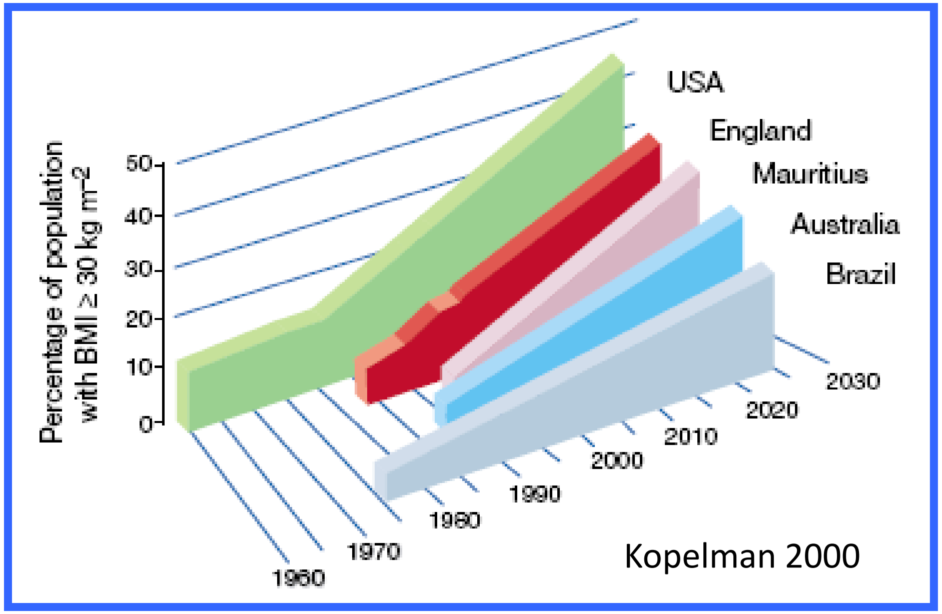
- Global Epidemics –
  - DM (Type 2), Obesity & Sleep problems
- Sleep and diabetes risk, illustrations by
  - Seep duration
  - sleep disturbances
  - sleep disorders
  - Circadian rhythm and sleep regularity
- Globalization and urbanization – East vs West
- From Adult to children – future Pandemics

Factors contributing to diabetes



Globalization

The epidemics of diabetes, obesity & sleep deprivation



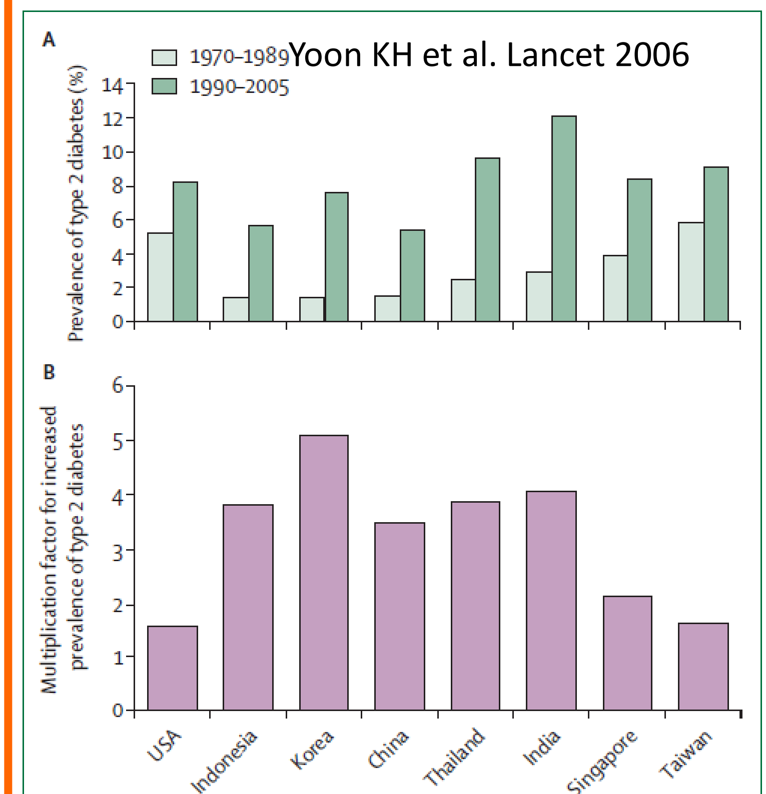
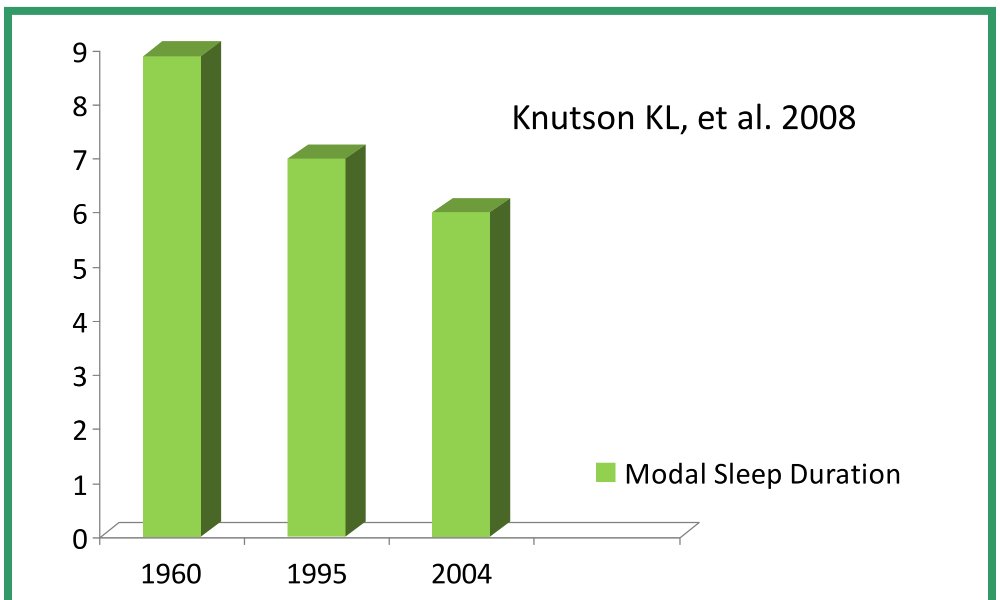


Figure 1: Comparison of prevalence rates of diabetes in selected countries between 1970–1989 and 1990–2005



Early report

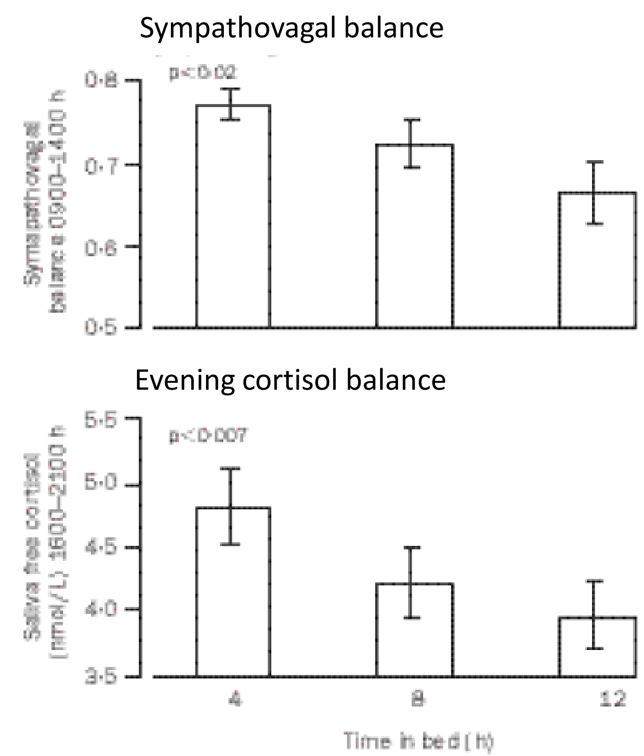
Impact of sleep debt on metabolic and endocrine function

Karine Spiegel, Rachel Leproult, Eve Van Cauter

Pre-test
8hr sleep
(3 nights)

Sleep-debt
4hr sleep
(6 nights)

Recovery phase
12hr sleep
(7 nights)



Laboratory study:

11 healthy, young & lean subjects

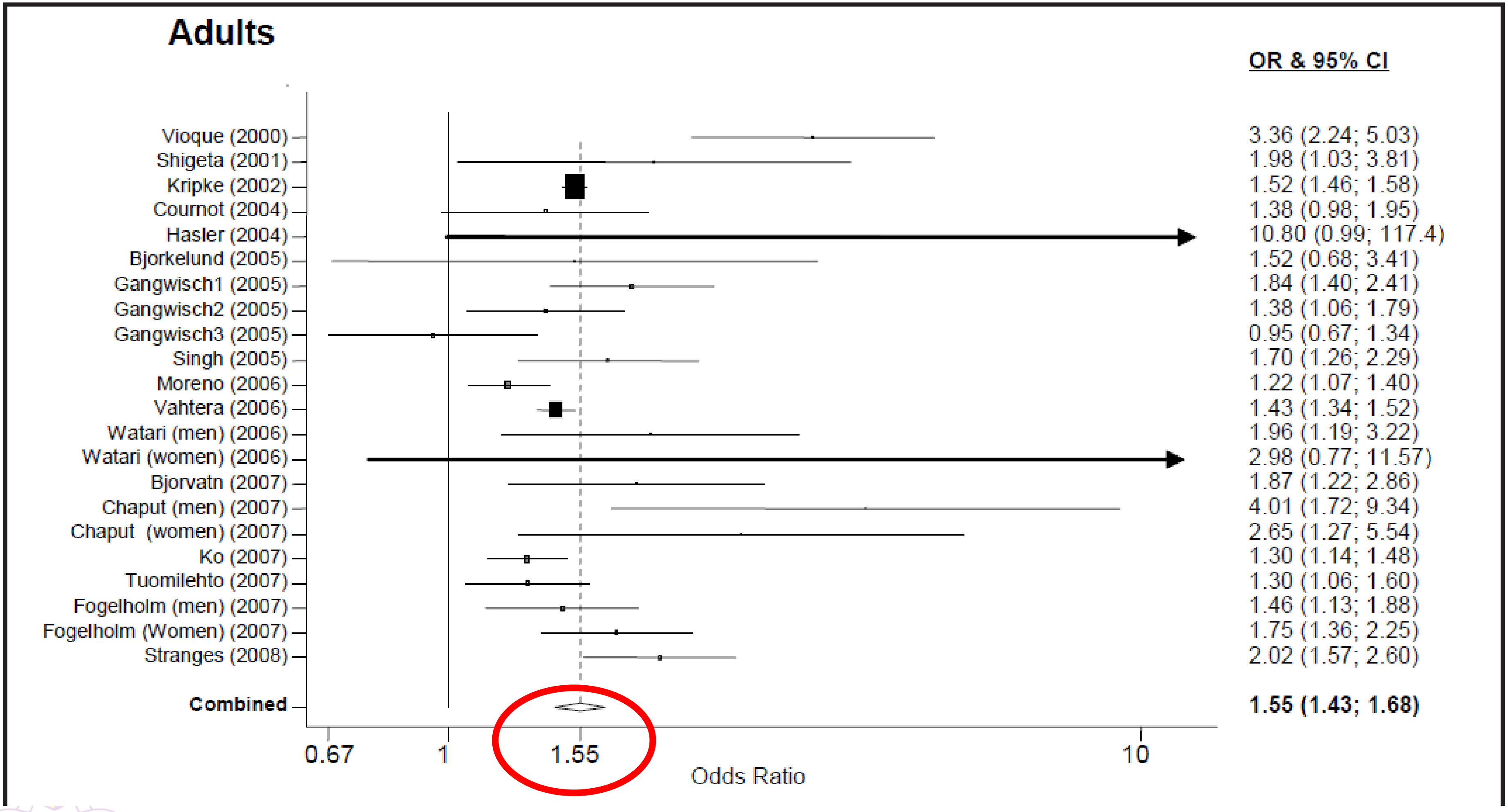
Spiegel et al. Lancet 1999

Sleep duration, Sleep disturbances & DM risk

EPIDEMIOLOGY: LONGITUDINAL DATA ON SLEEP, OBESITY & DM

Adult data:
short sleep duration & obesity

Cappuccio FP et al. Sleep 2008



Epidemiological data on sleep & DM risk

Cardiovascular and Metabolic Risk
ORIGINAL ARTICLE

Sleep Duration as a Risk Factor for the Development of Type 2 Diabetes

H. Klar Yaggi, MD, MPH[1,2]
Andre B. Araujo, PhD[3]
John B. McKinlay, PhD[3]

ORIGINAL INVESTIGATION

Association of Sleep Time With Diabetes Mellitus and Impaired Glucose Tolerance

Daniel J. Gottlieb, MD, MPH; Naresh M. Punjabi, MD, PhD; Ann B. Newman, MD, MPH; Helaine E. Resnick, PhD; Susan Redline, MD, MPH; Carol M. Baldwin, RN, PhD; F. Javier Nieto, MD, PhD

ORIGINA

Role of Sleep Duration and Quality in the Risk and Severity of Type 2 Diabetes Mellitus

Kristen L. Knutson, PhD; Armand M. Ryden, MD; Bryce A. Mander, BA; Eve Van Cauter, PhD

SLEEP DURATION AND DIABETES

Sleep Duration as a Risk Factor for Diabetes Incidence

James E. Gangwisch, PhD[1]; Steven B. Heymsfield, MD[2]; Bernadette Boden-Albala, DrPH[3]; Ruud M. Buijs, PhD[4]
DPhil[6]; Andrew G. Rundle, DrPH[7]; Gary K. Zammit, PhD[8]; Dolores Malaspina, MD[9]

Insomnia With Objective Short Sleep Duration Is Associated With Type 2 Diabetes

A population-based study

Alexandros N. Vgontzas, MD[1]
Duanping Liao, MD, PhD[2]
Slobodanka Pejovic, MD[1]
Susan Calhoun, PhD[1]
Maria Karataraki, PsyCHD[1]
Edward O. Bixler, PhD[1]

heart rate variability, is
niacs who meet both s
jective polysomnograph

A Prospective Study of Self-Reported Sleep Duration and Incident Diabetes in Women

Najib T. Ayas, MD[1,2]
David P. White, MD[1,2]
Wael K. Al-Delaimy, MD, PhD[3]
JoAnn E. Manson, MD, DrPH[2,4,5,6]
Meir J. Stampfer, MD, DrPH[3,4,6]
Frank E. Speizer, MD[2,6]
Sanjay Patel, MD[1,2]
Frank B. Hu, MD, PhD[3,4,6]

SLEEP DISRUPTION IN TYPE II DIABETES

Factors Predicting Sleep Disruption in Type II Diabetes

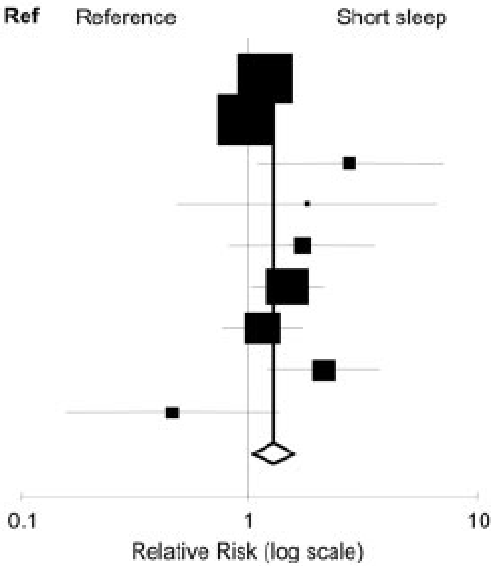
Nicole Lamond BSc (Hons), Marika Tiggemann* PhD, and Drew Dawson PhD

Meta-analysis of prospective studies on sleep duration & DM risk (Adult)

Cappuccio FP. et al Diabetes Care 2010

A Short duration of sleep and incidence of type 2 diabetes

Author (ref)	Year	Country	Sample size	Incident Cases	Prevalence of short sleep	Short Sleep v Ref	Relative Risk (95% CI)
Ayas[8]	2003	USA	70,026	1,969	4.3%	≤5h v 8h	1.19 (0.97 to 1.44)
Björkelund[10]	2005	Sweden	1,462	126	6.8%	<6h v >6h	0.97 (0.83 to 1.14)
Mallon (men)[11]	2005	Sweden	550	50	6.9%	≤5h v 6-8h	2.80 (1.09 to 7.18)
Mallon (women)[11]	2005	Sweden	620	38	7.1%	≤5h v 6-8h	1.80 (0.49 to 6.71)
Yaggi[12]	2006	USA	1,564	90	9.4%	≤5h v 7h	1.72 (0.81 to 3.61)
Gangwisch[13]	2007	USA	8,992	430	8.9%	≤5h v 7h	1.48 (1.04 to 2.11)
Hayashino[15]	2007	Japan	6,509	230	n/a	<6h v 6-7h	1.15 (0.76 to 1.74)
Beihl (white)[14]	2009	USA	662	107	66%	≤7h v 8h	2.16 (1.22 to 3.81)
Beihl (black)[14]	2009	USA	238	39	84%	≤7h v 8h	0.47 (0.16 to 1.37)
Combined effect (random model): p=0.024			**90,623**	**3,079**			**1.28 (1.03 to 1.60)**



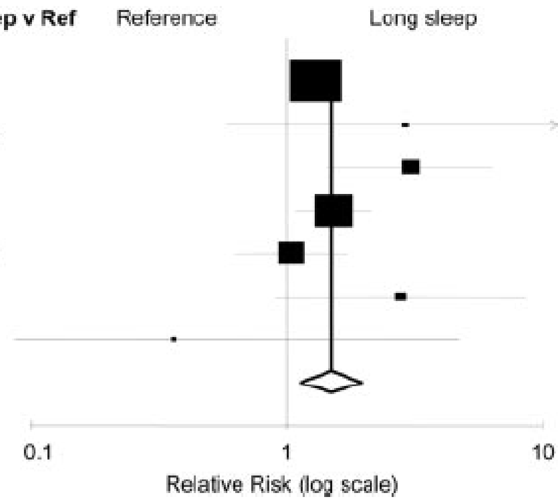
Heterogeneity: I^2=58% (11 to 80); Q=18.9, p=0.015
Publication bias: Egger's test p=0.14

Meta-analysis of prospective studies on sleep duration & DM risk (Adult)

Cappuccio FP. et al Diabetes Care 2010

B Long duration of sleep and incidence of type 2 diabetes

Author (ref)	Year	Country	Sample size	Incident cases	Prevalence of long sleep	Long sleep v Ref	Relative Risk (95% CI)
Ayas[8]	2003	USA	70,026	1,969	4.5%	≥9h v 8h	1.28 (1.04 to 1.59)
Mallon (women)[11]	2005	Sweden	620	38	2.7%	≥9h v 6-8h	2.89 (0.58 to 14.4)
Yaggi[12]	2006	USA	1,564	90	6.5%	>8h v 7h	3.03 (1.44 to 6.39)
Gangwisch[13]	2007	USA	8,992	430	8.7%	≥9h v 7h	1.52 (1.07 to 2.17)
Hayashino[15]	2007	Japan	6,509	230	n/a	>8h v 6-7h	1.03 (0.62 to 1.72)
Beihl (white)[14]	2009	USA	662	107	4.1%	≥9h v 8h	2.77 (0.89 to 8.64)
Beihl (black)[14]	2009	USA	238	39	3.4%	≥9h v 8h	0.36 (0.03 to 4.70)
Combined effect (random model): p=0.005			**88,611**	**2,903**			**1.48 (1.13 to 1.96)**



Heterogeneity: I^2=37% (0 to 74); Q=9.6, p=0.14
Publication bias: Egger's test p=0.42

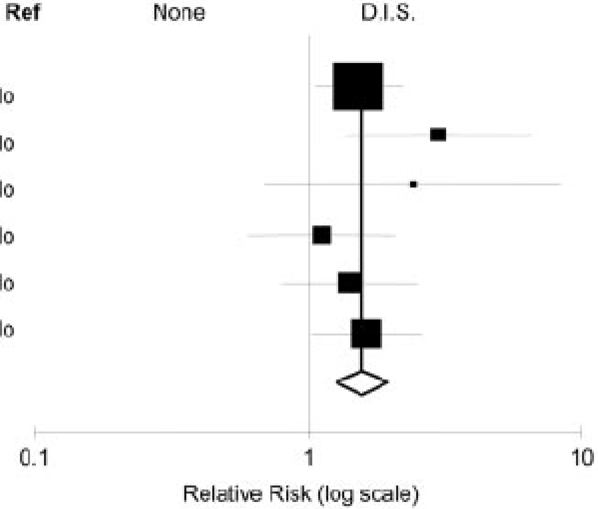
Meta-analysis of prospective studies on insomnia & DM risk (Adult)

Cappuccio FP. Et al Diabetes Care 2010

A Difficulty in initiating sleep and incidence of type 2 diabetes

Author (ref)	Year	Country	Sample size	Incident cases	Prevalence of D.I.S.	D.I.S. v Ref	Relative Risk (95% CI)
Nilsson[9]	2004	Sweden	6,599	281	9.3%	Yes v No	1.52 (1.05 to 2.21)
Kawakami[16]	2004	Japan	2,265	38	n/a	Yes v No	2.97 (1.36 to 6.51)
Mallon (men)[11]	2005	Sweden	550	50	4.4%	Yes v No	2.41 (0.69 to 8.45)
Meisinger (men)[17]	2005	Germany	4,140	119	7.2%	Yes v No	1.11 (0.59 to 2.07)
Meisinger (women)[17]	2005	Germany	4,129	69	13.7%	Yes v No	1.42 (0.80 to 2.51)
Hayashino[15]	2007	Japan	6,509	230	8.0%	Yes v No	1.62 (1.01 to 2.59)
Combined effect (random model): p<0.0001			**24,192**	**787**			**1.57 (1.25 to 1.97)**

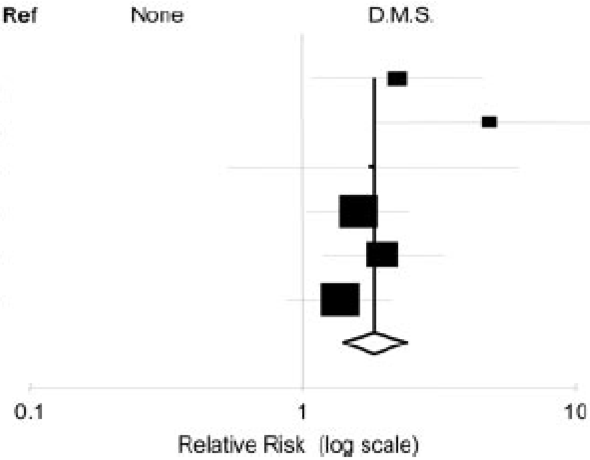
Heterogeneity: I^2=0% (0 to 75); Q=4.37, p=0.50
Publication bias: Egger's test p=0.37



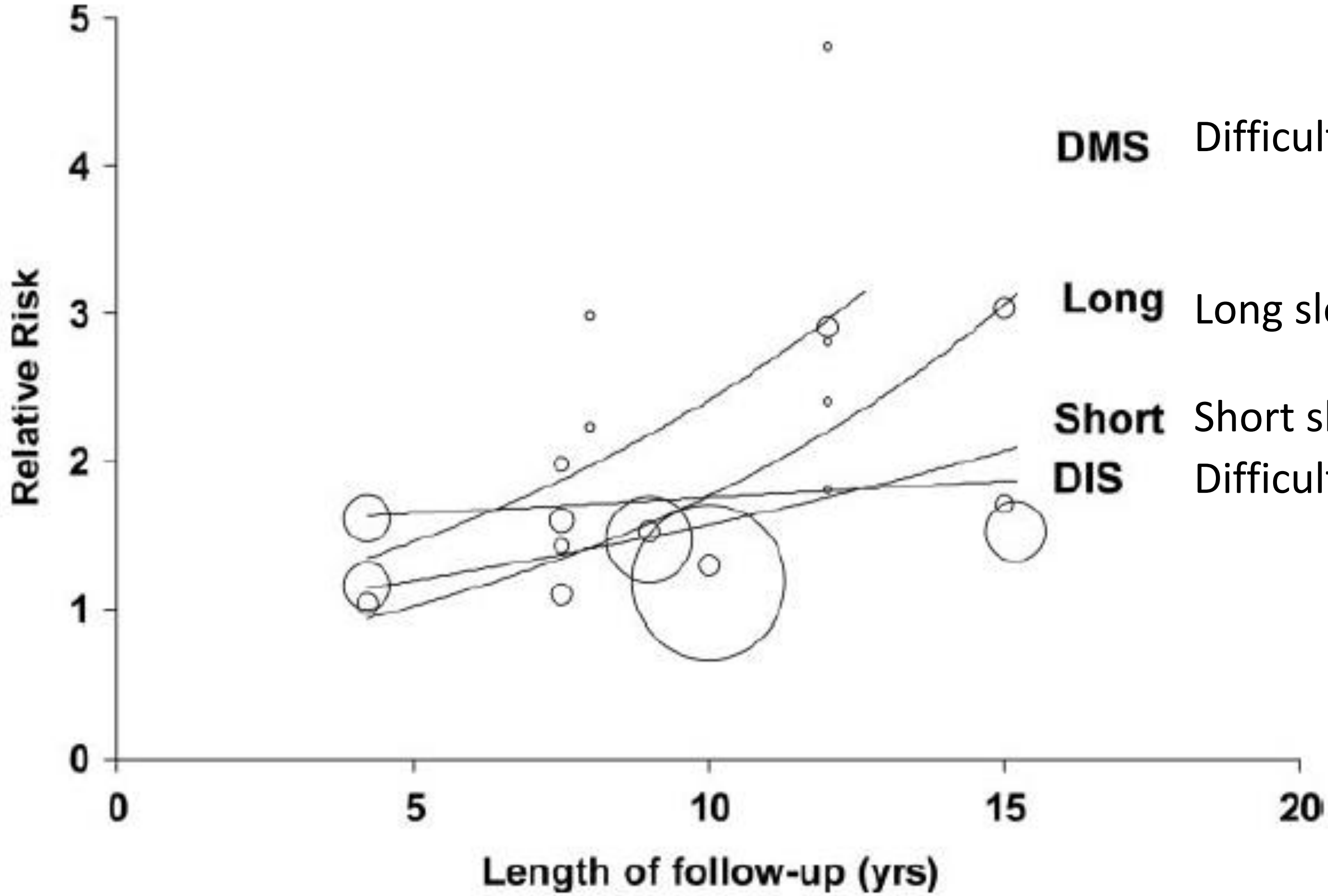
B Difficulty in maintaining sleep and incidence of type 2 diabetes

Author (ref)	Year	Country	Sample size	Incident cases	Prevalence of D.M.S.	D.M.S. v Ref	Relative Risk (95% CI)
Kawakami[16]	2004	Japan	2,265	38	n/a	Yes v No	2.23 (1.08 to 4.60)
Mallon (men)[11]	2005	Sweden	550	50	8.4%	Yes v No	4.81 (1.88 to 12.3)
Mallon (women)[11]	2005	Sweden	620	38	11.9%	Yes v No	1.80 (0.52 to 6.20)
Meisinger (men)[17]	2005	Germany	4,140	119	14.4%	Yes v No	1.60 (1.04 to 2.46)
Meisinger (women)[17]	2005	Germany	4,129	69	19.0%	Yes v No	1.97 (1.19 to 3.29)
Hayashino[15]	2007	Japan	6,509	230	n/a	Yes v No	1.36 (0.87 to 2.14)
Combined effect (random model): p<0.0001			**18,213**	**544**			**1.84 (1.39 to 2.43)**

Heterogeneity: I^2=22% (0 to 66); Q=6.38, p=0.27
Publication bias: Egger's test p=0.15



Risk of DM increased with duration of FU



DMS Difficulty in maintaining sleep

Long Long sleep duration

Short Short sleep duration

DIS Difficulty in initiating sleep

Cappuccio FP. Et al Diabetes Care 2010

Points to note when interpreting the epidemiological data of sleep duration & DM

1. Most prospective studies did not have serial measurements during the follow-up period
   - Is there any difference in risk between those having transient and persistent short/ long sleep duration?
2. Measurement tools:
   - Based on self reported questionnaires
   - Mostly Lack of objective sleep measurement
3. Confounding factors:
   - Most studies adjusted common factors such as BMI, alcohol
   - BUT other important confounding variables were not measured: OSAS, Depression

A study of the joint effect of insomnia & sleep duration on diabetes

- N=1741, randomly selected
- Measurements: overnight PSG, fasting glucose, self reported questionnaires
- Results adjusted for AHI, Dx of depression

→interaction of insomnia and short sleep duration in predisposing risk of DM

- Limitation: cross-sectional study

Sleep difficulty and duration	Adjusted OR (95% CI)*
Normal sleeping	
>6 h	1.00
5–6 h	1.45 (0.91–2.30)
<5 h	1.10 (0.68–1.79)
Poor sleep	
>6 h	1.52 (0.87–2.65)
5–6 h	1.55 (0.80–3.01)
<5 h	1.06 (0.53–2.15)
Insomnia	
>6 h	1.10 (0.40–3.03)
5–6 h	2.07 (0.68–6.37)
<5 h	2.95 (1.24–7.03)

Interaction between insomnia and sleep duration is not statistically significant, $P = 0.75$. *Adjusted for age, race, sex, BMI, sampling weight, smoking, alcohol consumption, depression symptoms, and SDB.

Vgontzas A et al. Diabetes Care 2009

Sleep duration & DM in rural population of lean body built

- > 1400 adults in rural China
- Relatively lean Chinese (mean BMI: men- 21.7, women 22.0; % of total fat: men- 7.7, female 14.6)
- Findings:
  - Sleep duration <7 hrs associated with higher HOMA in women, adjusted for BMI & total fat

Liu R et al. Sleep Medicine in press

Magnitude of sleep debt / sleep disturbances on DM control

Magnitude of effect of sleep curtailment

- In patients without diabetic complication
  - A perceived sleep debt of 3 hours per night predict an increase in HbA1c of 1.1%
- Among patients with at least 1 complication
  - A 5-point increase in PSQI (sleep quality) predicted an increase in HbA1c of 1.9%
- Effects comparable to those of widely use oral anti-diabetic agents

Knutson KL, et al. Arch Intern Med 2006

Short sleep duration & HbA1c

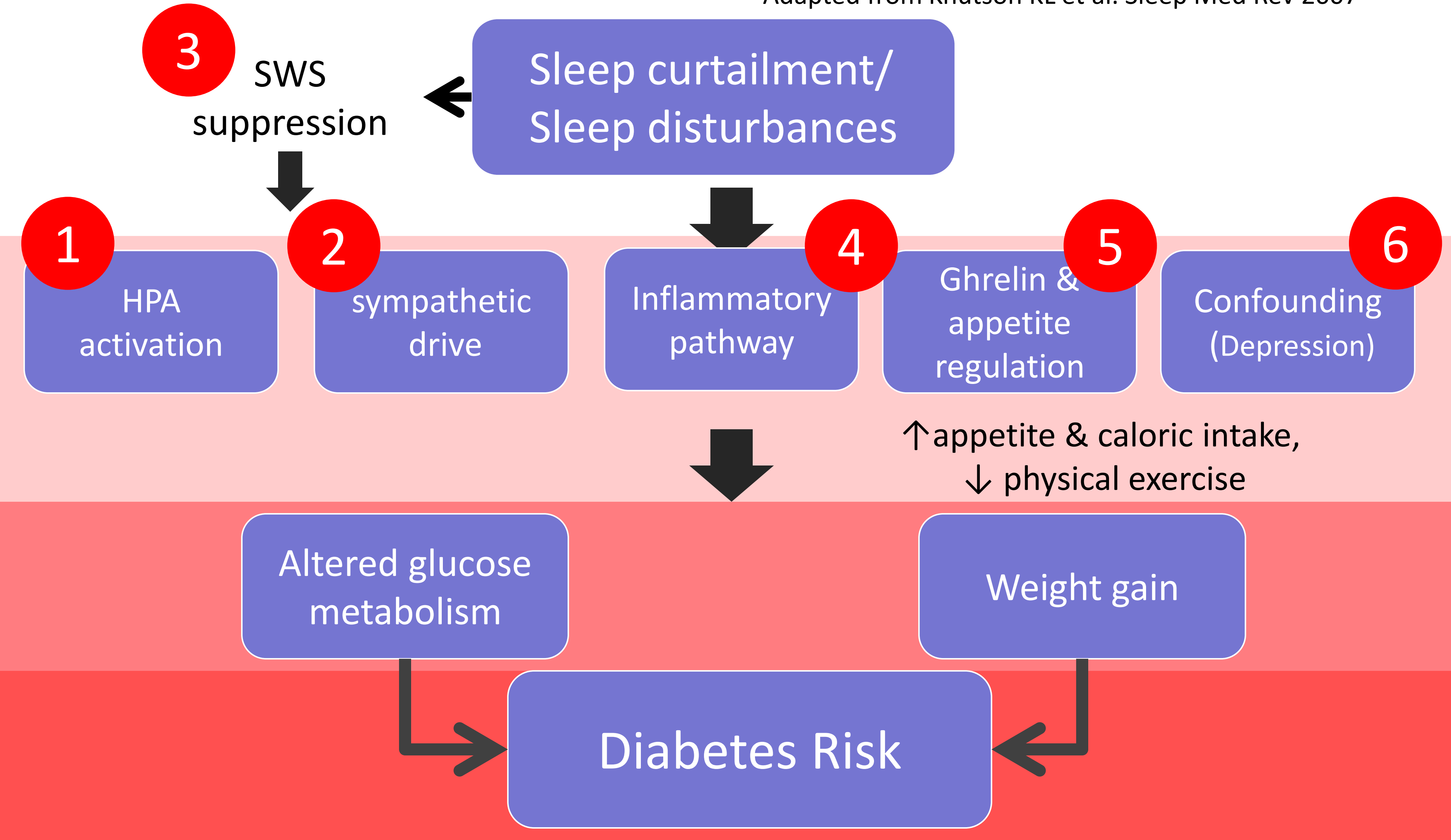
- 394 DM patients in HK
- Mean age: 54 years old, 59% men
- 17.5% had sleep duration< 7hr during weekdays
- sleep duration< 7hr during weekdays was associated with an increased HbA1c (regression coefficient=0.45, p=0.007) with adjustment for age and gender

Kong A & Wing et al. Submitted

POSSIBLE MECHANISMS MEDIATING THE EFFECT OF SLEEP CURTAILMENT/ DISTURBANCES ON OBESITY & DM RISK

Possible mechanisms mediating sleep duration/disturbances & diabetes risk

Adapted from Knutson KL et al. Sleep Med Rev 2007



1 & 2. ↑ Sympathetic drive & cortisol

Early report

Impact of sleep debt on metabolic and endocrine function

Karine Spiegel, Rachel Leproult, Eve Van Cauter

Pre-test
8hr sleep
(3 nights)

→

Sleep-debt
4hr sleep
(6 nights)

→

Recovery phase
12hr sleep
(7 nights)

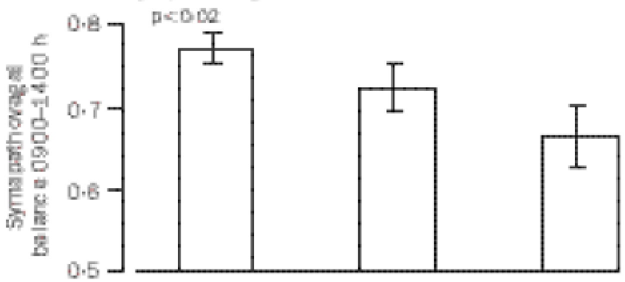
Laboratory study:

11 healthy subjects

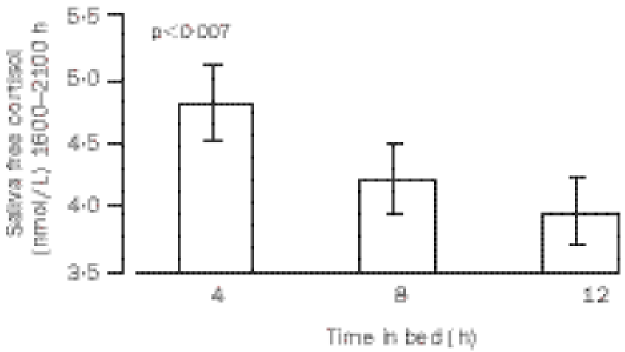
Findings:

- By ivGTT, glucose tolerance was lower in sleep-debt condition
- Insulin resistance was higher in sleep deprived conditions, and progressively increased with partial sleep loss
- Sleep deprivation is associated with higher sympathetic activities and higher evening cortisol

Sympathovagal balance



Evening cortisol balance



Spiegel et al. Lancet 1999

Relationship of Sleep Quantity and Quality with 24-Hour Urinary Catecholamines and Salivary Awakening Cortisol in Healthy Middle-Aged Adults

Jihui Zhang, MD, PhD[1]; Ronald C.W. Ma, MD, FRCP[2]; Alice P.S. Kong, FRCP, FHKAM (Physician)[2]; Wing Yee So, MD, FRCP[2]; Albert M. Li, MD, FHKAM (Paed)[3]; Sui Ping Lam, MRCPsych, FHKAM (Psych)[1]; Shirley Xin Li, MA[1]; Mandy W.M. Yu, MPH, RPSGT[1]; Chung Shun Ho, PhD[4]; Michael H.M. Chan, FRCPA[4]; Bin Zhang, MD, PhD[5]; Yun Kwok Wing, FRCPsych, FHKAM (Psych)[1]

[1]*Department of Psychiatry,* [2]*Department of Medicine and Therapeutics,* [3]*Department of Pediatrics,* [4]*Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong SAR, China;* [5]*Guangdong Academy of Medical Science, Guangdong General Hospital, Guangdong Institute of Mental H*

Healthy middle age sleepers from community (N=114) FU for 3 yrs

Assessment:

Sleep log & 3-days actigraphy

Results:

High stability of sleep/wake pattern (r=0.6-0.79)

Objective sleep efficiency < 85% had a higher 24-hr urinary norepinephrine

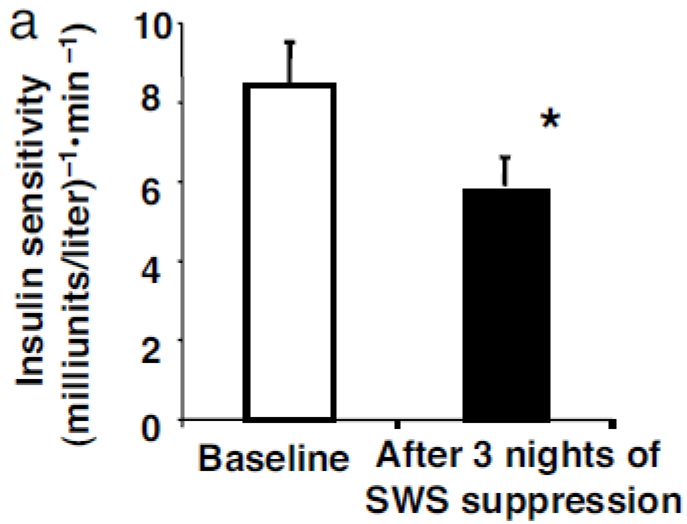
urinary epinephrine & norepinephrine also had correlation with waist/hip ratio (0.29- 0.30, p<0.01)

Implications:

Poor sleep quality (no subjective complaints) had higher sympathetic activity

3. Effect of modulation of slow wave sleep on insulin sensitivity

- Function of slow wave sleep:
  - Decrease brain glucose utilization
  - Stimulation of growth hormone release
  - Inhibition of corticotropic activity
  - Decrease sympathetic nervous system
- SWS suppression (without disruption to other sleep stages/ shorten sleep duration)



Tasali E et al. PNAS 2008

4. Inflammatory pathway

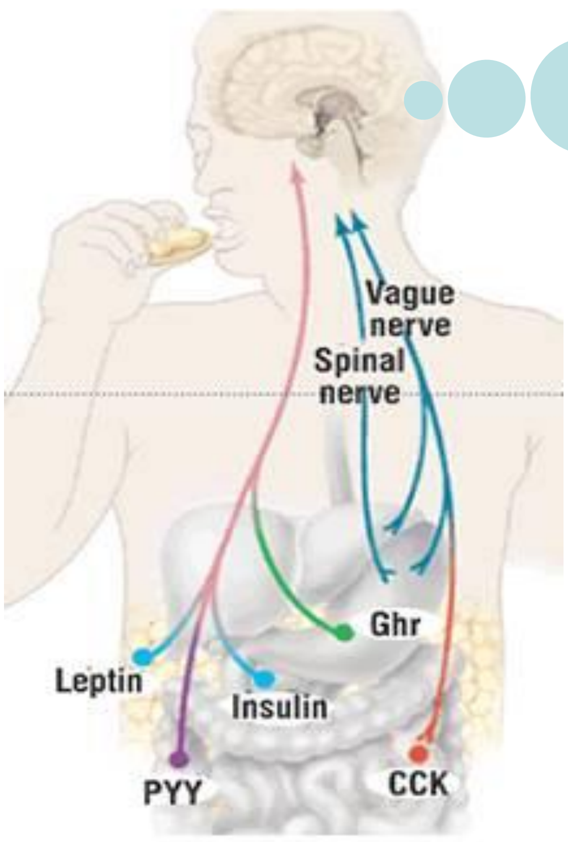
- Sleep deprivation laboratory data:
  - Sleep deprivation resulted in ↑inflammatory markers (IL-6)

Haack M, et al. Sleep 2007

- Chronic insomnia:
  - Shifting of secretion pattern of IL6 and TNF

Vgontzas AN et al. Metabolism 2002

5. Sleep curtailment & Appetite regulation



Restriction of sleep on metabolic and endocrine function

→ Ghrelin (gut-derived peptide) ↑

→ Leptin (induces satiety)↓

→ Change in appetite & hunger

Spiegel K et al. Ann Intern Med 2004
Taheri S et al. PLoS Med 2004

6. Depression: ?mediating the relationship of sleep & diabetes risk

- Depression as a highly co-morbid condition of diabetes
- Longitudinal studies: depression is associated with a 60% increased risk of incident diabetes, effect independent of BMI

Mezuk B et al. Diabetes Care 2008

Diabetes-related distress, depression & Glycemic control

- Diabetes distress, as measured by Chinese version of diabetes Distress Scale (CDDS), was found to have high correlation with:
  - Diabetes distress: correlation with depression 0.511 ($p<0.01$)
  - HbA1c: correlation with diabetes distress 0.185 ($p<0.05$)
- Higher distress (depression) → poorer DM control (HbA1c)

Diabetes-Related Distress and Physical and Psychological Health in Chinese Type 2 Diabetic Patients

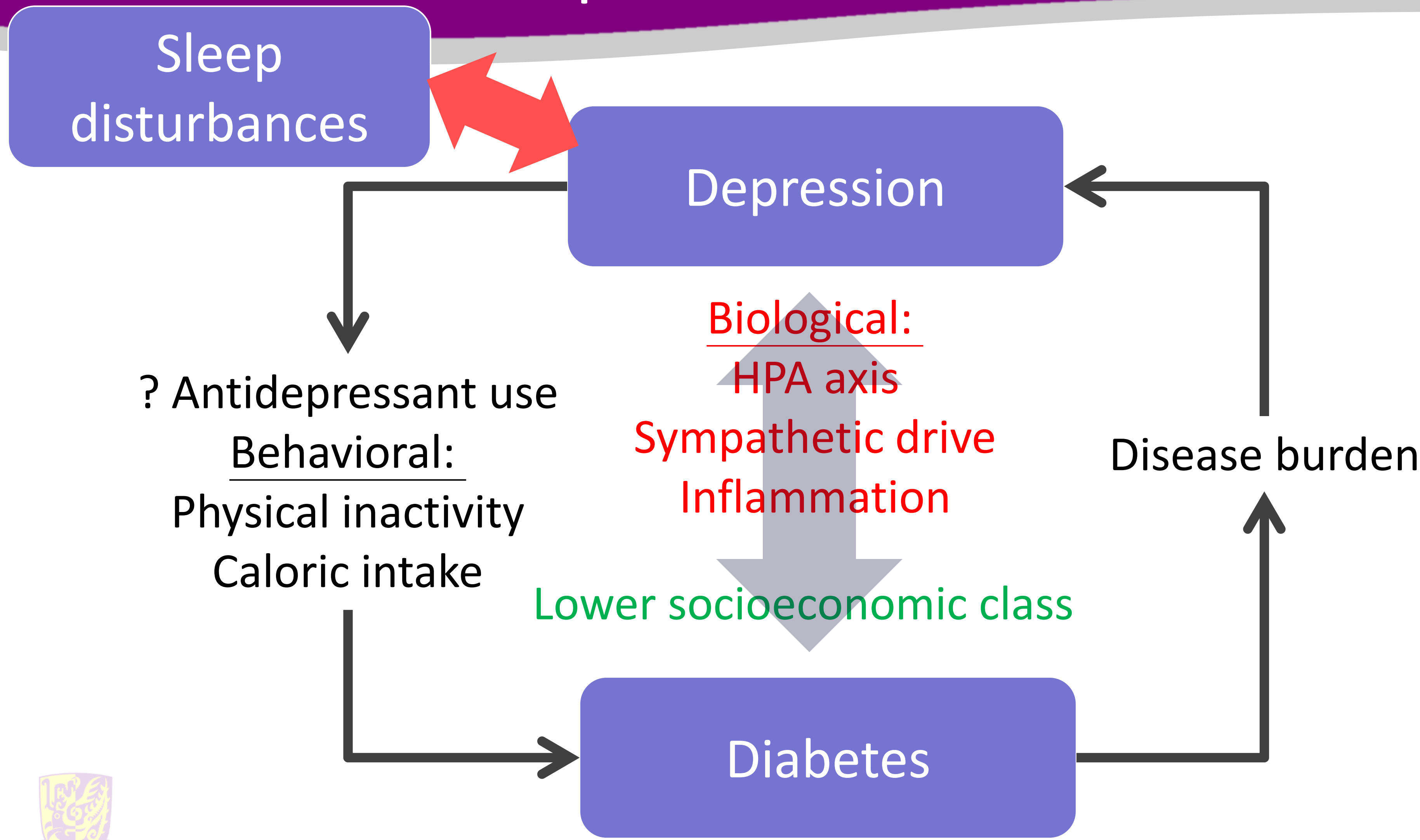
Rose Z.W. Ting, MRCP[1]
Hairong Nan, PhD[2]
Mandy W.M. Yu, MPH[3]
Alice P.S. Kong, FRCP[1]
Ronald C.W. Ma, FRCP[1]
Rebecca Y.M. Wong, MSc[1]
Kitman Loo, BSc[1]
Wing-Yee So, MD[1,2]
Chun-Chung Chow, FRCP[1]
Gary T.C. Ko, MD[1,2]
Yun-Kwok Wing, FRCPsych[3]
Juliana C.N. Chan, MD[1,2]

repeated the questionnaire 4–6 weeks later for test-retest reliability. The study was approved by the clinical research ethics committee.

Statistical analyses were performed using the Statistical Package for Social

Ting R… Wing YK et al. Diabetes Care 2011

6. Depression: mediating the relationship of sleep & diabetes risk



LONG SLEEP DURATION & DM RISK

Long sleep duration & DM risk

- Possible factors mediating the association:
  - Depression
  - Lower socio-economic class

Patel SR et al. Sleep 2006

- Inflammatory markers & long sleep duration:
  - Habitual long sleep duration was found to correlate with higher CRP & IL 6

Patel SR et al. Sleep 2009

Sleep disorders and DM

OSAS & DM

OSAS & insulin resistance

Ip MS, et al. Am J Respir Crit Care Med 2002

Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance

MARY S. M. IP, BING LAM, MATTHEW M. T. NG, WAH KIT LAM, KENNETH W. T. TSANG, and KAREN S. L. LAM

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong S.A.R., PR China

TABLE 3. STEPWISE MULTIPLE LINEAR REGRESSION MODELS FOR FASTING INSULIN

	BMI + Waist/Hip Ratio*			BMI + Waist*	
	Estimate ± SE	p Value		Estimate ± SE	p Value
R^2 = 22.6%			R^2 = 22.6%		
BMI, kg/m^2	0.060 ± 0.010	< 0.001	BMI, kg/m^2	0.060 ± 0.010	< 0.001
AHI, event/h	0.005 ± 0.002	0.020	AHI, event/h	0.005 ± 0.002	0.020
Age, yr	−0.009 ± 0.004	0.020	Age, yr	−0.009 ± 0.004	0.020
R^2 = 22.2%			R^2 = 22.2%		
BMI, kg/m^2	0.061 ± 0.009	< 0.001	BMI, kg/m^2	0.061 ± 0.009	< 0.001
Min Sa_{O_2}	−0.007 ± 0.003	0.041	Min Sa_{O_2}	−0.007 ± 0.003	0.041
Age, yr	−0.009 ± 0.004	0.019	Age, yr	−0.009 ± 0.004	0.019

270 non-DM patients referred for PSG

Findings:

1. OSA subjects were more insulin resistant (↑ level of fasting serum insulin)
2. AHI & minimum SaO2 as independent determinants of insulin resistance
3. Relationship between OSA & insulin resistance was also seen in non-obese subjects

OSAS & insulin resistance: replicated in pediatric population

- 94 obese children, mean age 12, 77.7% boy
- Underwent overnight PSG & metabolic studies
- OSA defined as AHI >1

	Non-OSA	OSA	OR (95%CI)	*P*-value
Weight (kg)	63.0 (49.6–75.3)	66.0 (54.2–82.5)	1.02 (0.99–1.04)	0.180
Height (cm)	150.0 (137.0–160.0)	149.0 (144.9–159.0)	1.00 (0.97–1.03)	0.937
Waist (cm)	84.5 (77.0–87.5)	87.0 (77.8–94.5)	1.05 (1.00–1.09)	0.053
BMI z-score	2.34 (2.04–2.68)	2.48 (2.16–2.73)	1.13 (0.59–2.20)	0.710
Age (years)	11.6 (9.0–13.4)	12.0 (10.5–13.9)	1.06 (0.91–1.24)	0.461
Oxygen saturation nadir (%)	89 (80.0–91.0)	79 (71–84)	0.00 (0.00–0.05)	0.002
Percentage of total sleep time with saturation <90%	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.00 (0.00–0.00)	0.022
INS (mIU/L)	13.8 (11.7–18.9)	18.7 (12.5–26.7)	1.10 (1.03–1.17)	0.004
HOMA	3.0 (2.6–4.4)	4.1 (3.0–6.4)	1.51 (1.15–2.00)	0.003
GLU (mmol/L)	5.1 (4.8–5.4)	5.2 (4.9–5.6)	2.16 (0.83–5.62)	0.116
TC (mmol/L)	4.6 (4.0–5.1)	4.6 (4.1–5.2)	1.34 (0.80–2.26)	0.274
TG (mmol/L)	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.17 (0.57–2.40)	0.665
HDL (mmol/L)	1.3 (1.1–1.5)	1.2 (1.1–1.4)	0.52 (0.13–2.02)	0.343
LDL (mmol/L)	2.6 (2.1–3.0)	2.8 (2.3–3.2)	1.68 (0.87–3.23)	0.123

TABLE 4—Logistic Regression Analysis, Factors Associated With OSA

	Coefficient	SE	Odds ratio (95% CI)	*P*-value
Insulin levels	0.074	0.033	1.077 (1.011–1.048)	0.022
Saturation nadir	−6.738	2.718	0.001 (0–0.244)	0.013

Li AM et al. Pediatric Pulmonology 2006

Childhood OSAS is associated with impaired glucose tolerance

Li AM & Wing et al. submitted 2011

- 88 children (age 9-16), cross sectional survey
- Cases: OAHI ≥1; control: OAHI<1

	Control (n= 60)	Case (n= 28)
Age (yr)	13.7 (10.4- 16.6)	12.3 (9.4- 15.3)
Male (%)	22 (36.7)	21 (75.0)**
BMI z-score	0.38 (-0.04- 0.80)	2.01 (0.98- 2.17)**
OAHI (/hr)	0.39 (0-0.69)	3.63 (2.11- 6.69) **
Fasting glucose (mmol/L)	4.70 (4.40- 4.98)	4.70 (4.60- 5.00)
Fasting insulin (mIU/L)	6.96 (4.84- 11.08)	10.26 (4.48- 13.40)
120min glucose (mmol/L)	**6.15 (5.43- 6.78)**	**6.60 (5.63- 7.68)***
AUC glucose (mmol/Lxmin)	**841 (725- 897)**	**879 (792- 1033)***
HOMA-IR	1.42 (0.89- 2.42)	2.26 (0.97- 2.76)
Whole body insulin sensitivity index	131 (68- 186)	75 (57- 139)
IGT (n, %)	2 (3.3)	6 (21.4)

Effect independent of BMI

Variable	B	SE	Odds ratio (95% CI)	p value
O_2 nadir	-0.236	0.104	0.790 (0.644—0.969)	.024
Age	0.266	0.134	1.304 (1.004—1.695)	.047

Logistic regression analysis of the effect of PSG parameters adjusted for BMI, z-score, age, gender, and puberty upon prevalence of IGT

Li AM & Wing et al. Submitted 2011

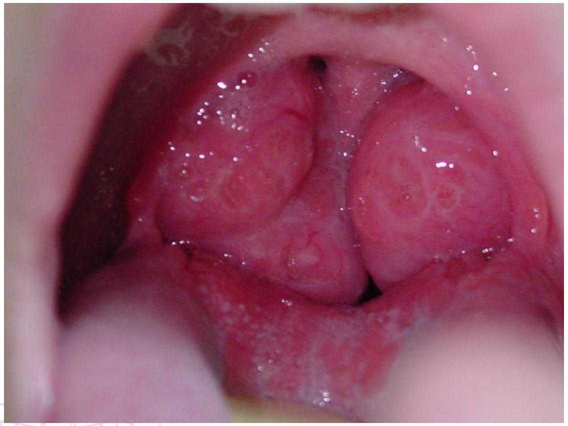
Childhood OSAS: also complicated by the obesity pandemics

Dayyat E et al: (Sleep Medicine Clinics 2007):

Spectrum of OSAS from predominant lymphadenopathy to obesity

Type I:
Marked lymphadenoid hypertrophy

Type II:
Obesity
? Similar to adult OSAS



Need for further research

- Increasing obesity epidemic → increasing OSAS?
- Need to look for ?Interactions of sleep duration/ sleep disturbances, obesity & OSAS on DM risk
- Childhood OSAS - ?IGT/DM

Current findings on associations of sleep disorders and DM

Sleep disorders	Associations with DM
OSAS	
Adult	+++
Children	+
Restless legs syndrome	+
Narcolepsy	+/-

Sleep Irregularity/Circadian rhythm & metabolism

Secular changes of sleep patterns

Irregularity of sleep –
short sleep duration in weekdays, & compensation by longer sleep duration in weekends and holidays

The Effect of Weekend and Holiday Sleep Compensation on Childhood Overweight and Obesity

AUTHORS: Yun Kwok Wing, FRCPsych, FHKAM(Psych),[a] Shirley Xin Li, MA,[a] Albert Martin Li, MRCP, FHKAM(Paed),[b] Jihui Zhang, MD,[a] and Alice Pik Shan Kong, FRCP, FHKAM[c]

Departments of [a]Psychiatry, [b]Pediatrics, and [c]Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China

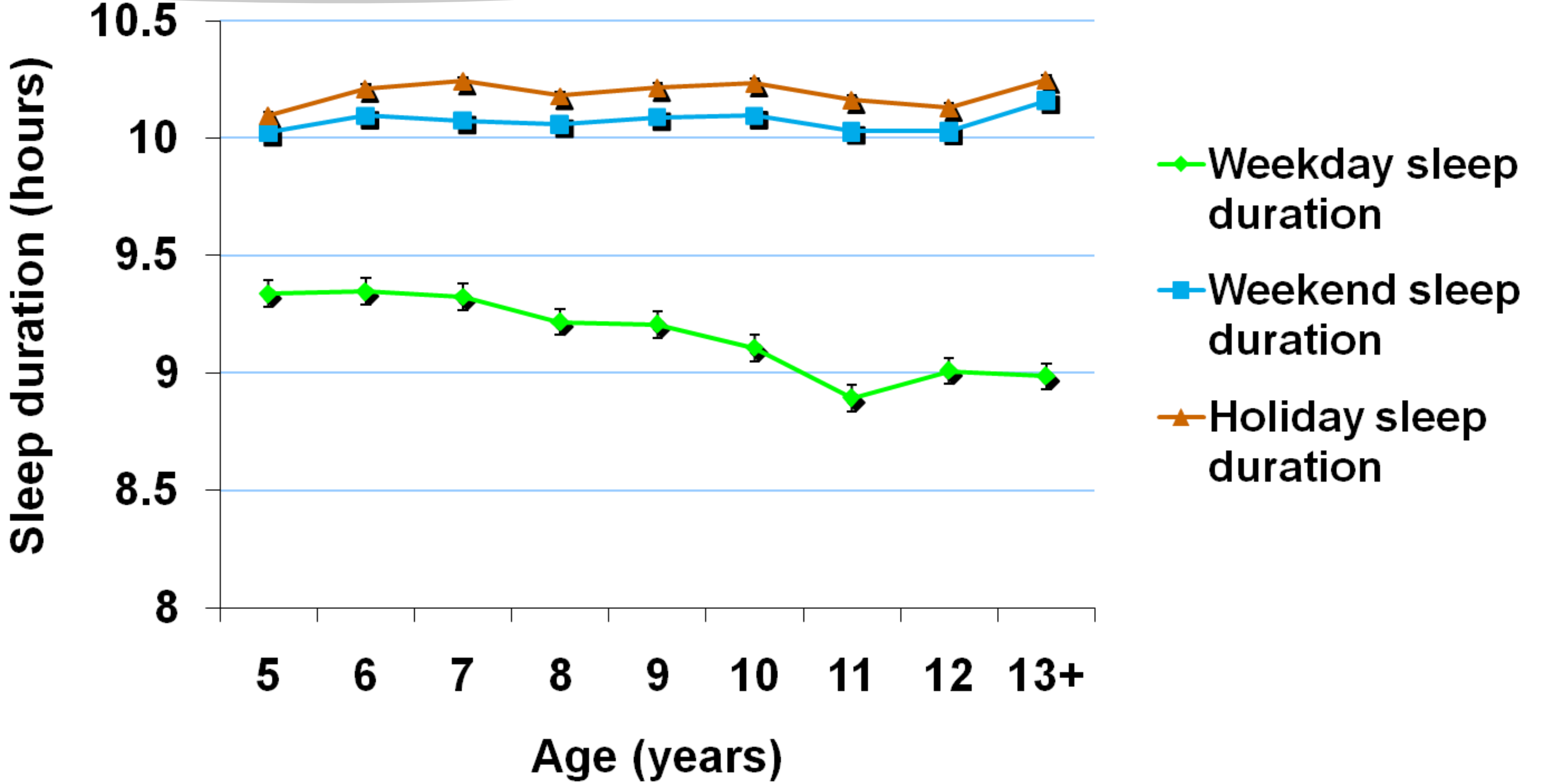
13 primary schools in HK
(Shatin & Tai Po)
Target population: 9172 children
(Age range: 5-15 yrs old)

Parental completion of sleep questionnaires

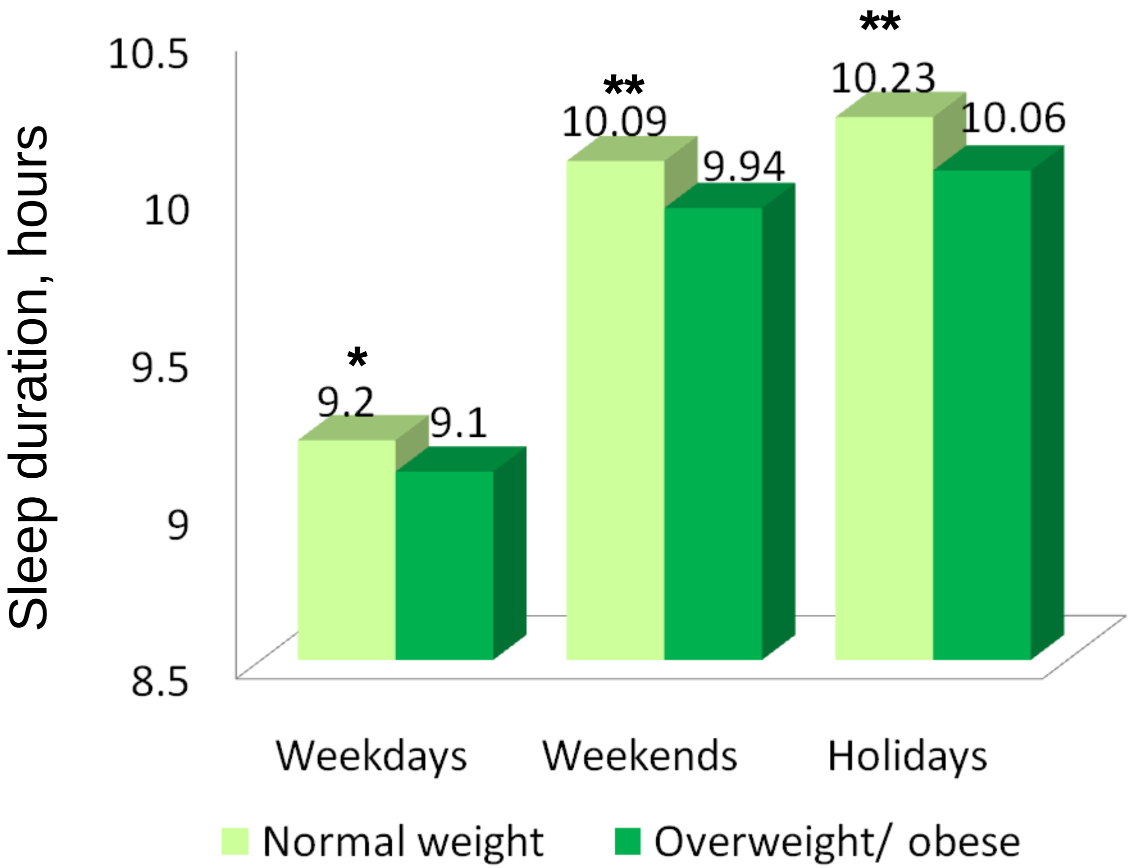
6447 Questionnaires completed
(**70.3% Response Rate**)

Wing YK et al. Pediatrics 2009

Result (1): Sleep durations vs. Age



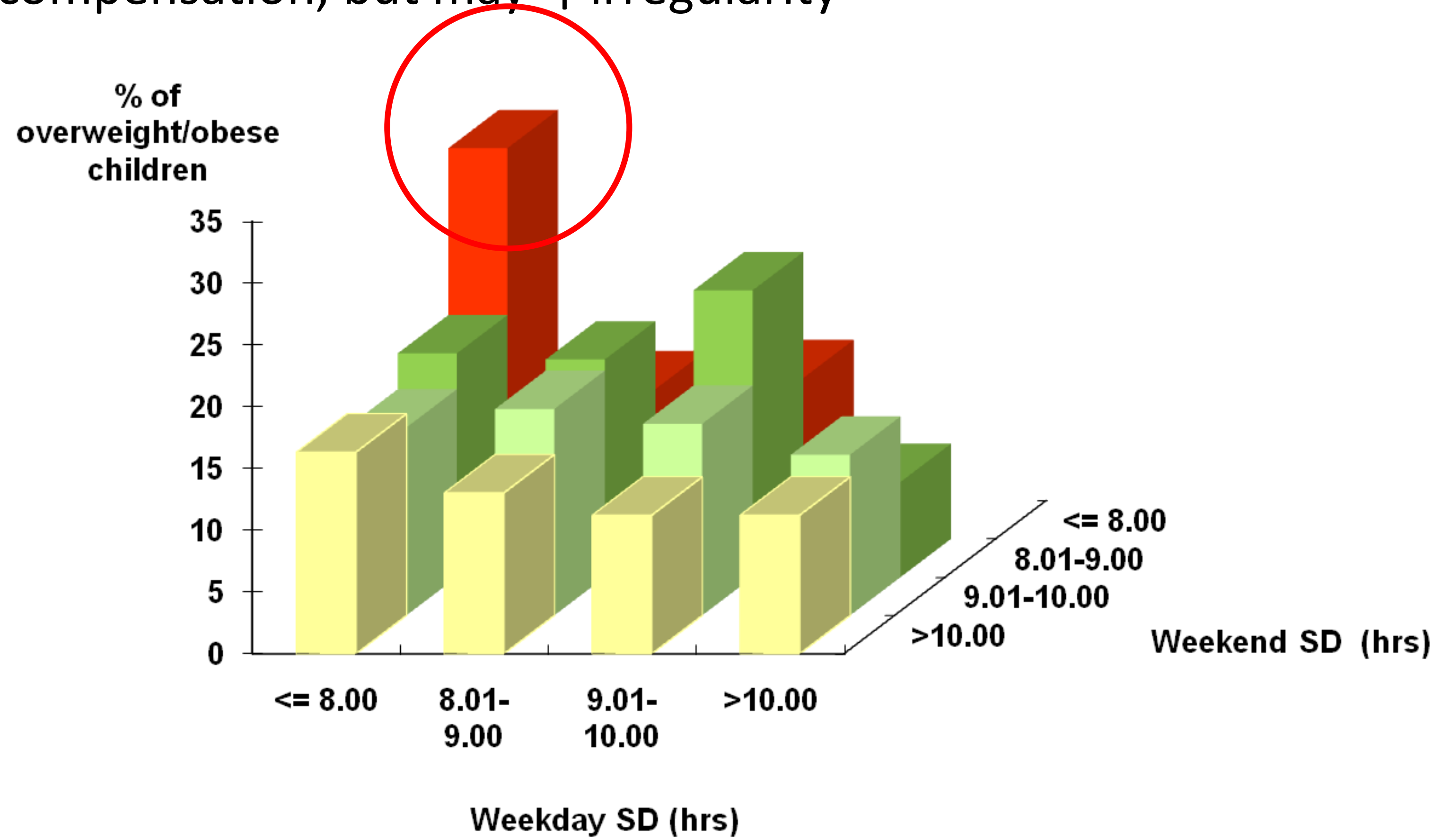
Result (2): Sleep duration & body weight



* p<0.01 **p<0.001

Sleep durations - Interaction effect

Percentages of overweight/obesity as a function of weekday and weekend sleep durations – weekend compensation, but may ↑irregularity



Effect of irregular sleep: not only obesity, but also alter insulin

- 308 children (age 4-10 years of age)
- Cross sectional study
- Findings:
  - Obese children has shorter sleep duration and had more variability at weekends
  - Presence of short sleep & high variance in sleep duration was associated with altered insulin, LDL and high sensitivity C-reactive protein plasma levels.

Spruyt K et al. Pediatrics 2011

Shift work & DM risk

Suwazono Y et al. Chronobiol Int 2009

- 14 years prospective FU of > 7000 male workers, annual check up
- Duration of shift work is positively associated with increase in HbA1c
- Dose response
- Effect independent of BMI

TABLE 4 Dose-response relationship between length of shiftwork period and relative increases in HbA1c level compared to levels at the entry year of the study

	HbA1c increase by ≥ 10%			HbA1c increase by ≥ 15%			HbA1c increase by ≥20%		
Length of shiftwork period	Person-years at risk	OR* (95% CI†)	*p*	Person-years at risk	OR* (95% CI†)	*p*	Person-years at risk	OR* (95% CI†)	*p*
0 yrs (control)	17,215	1.00		21,465	1.00		24,127	1.00	
1 to 3 yrs	9,381	1.41 (1.30, 1.52)	<0.001	11,608	1.27 (1.15, 1.40)	<0.001	13,029	1.16 (1.02, 1.33)	0.027
4 to 10 yrs	5,879	1.27 (1.16, 1.39)	<0.001	10,036	1.45 (1.31, 1.60)	<0.001	13,152	1.38 (1.22, 1.57)	<0.001
≥11 yrs	595	0.83 (0.62, 1.11)	0.218	1,479	1.74 (1.42, 2.12)	<0.001	2,258	2.41 (1.98, 2.93)	<0.001

Circadian misalignment & DM risk: Laboratory evidence

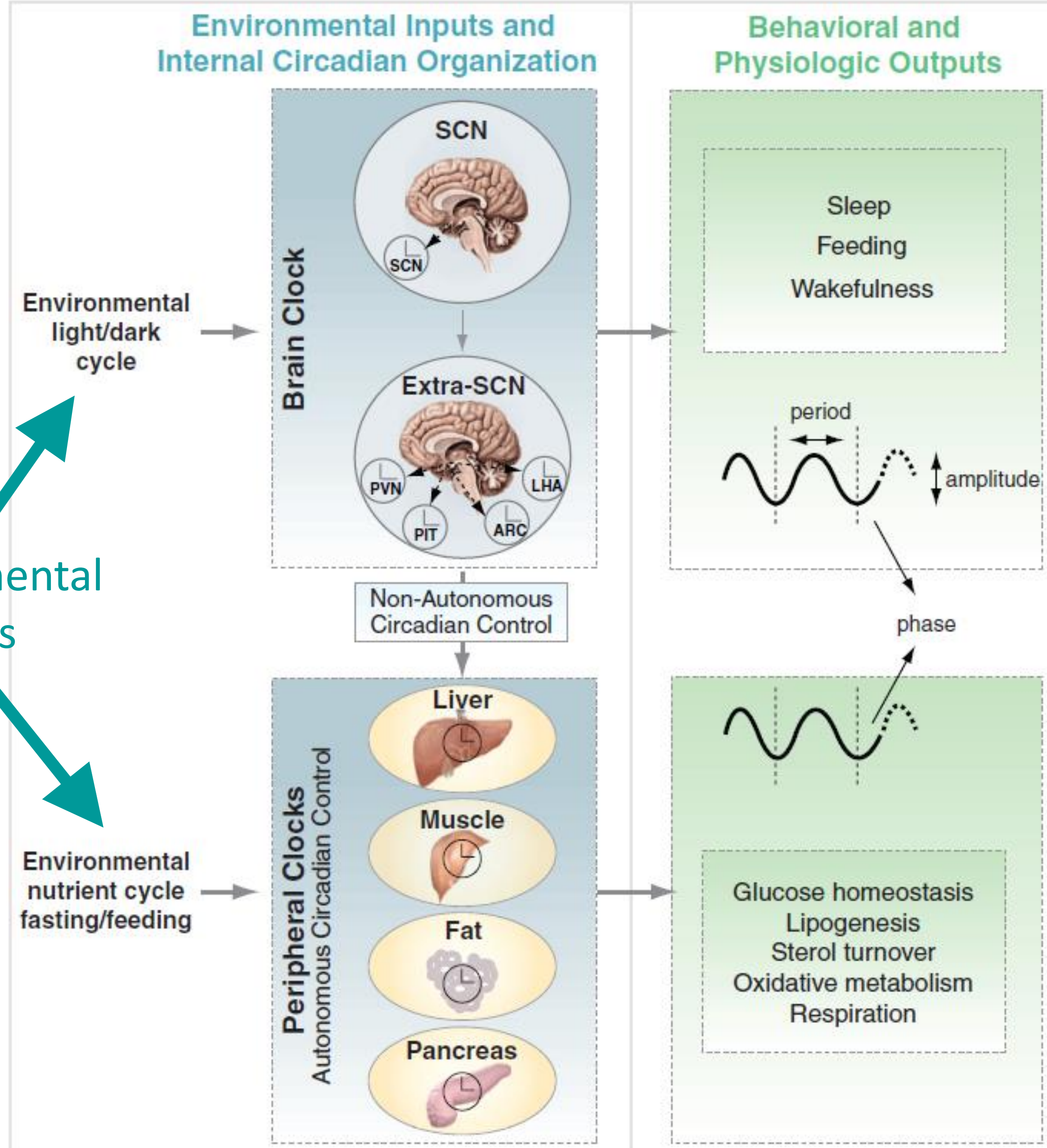
- Laboratory protocol by scheduling a recurring 28-h "day" for 8 days
- When the subjects ate and slept ~12h out of phase from their habitual times→ misalignment between behavioral cycles and endogenous circadian cycles:
  - Decreased leptin
  - Insulin resistance
  - Reversed daily cortisol rhythm

Scheer FAJL et al. PNAS 2009

Central Clock

Environmental clues

Peripheral Clocks regulating metabolism



Bass J et al. Science 2010

Clock Genes & DM risk

Open access, freely available online PLoS BIOLOGY

BMAL1 and CLOCK, Two Essential Components of the Circadian Clock, Are Involved in Glucose Homeostasis

R. Daniel Rudic[1], Peter McNamara[2], Anne-Maria Curtis[1], Raymond C. Boston[3], Satchidananda Panda[4], John B. Hogenesch[4], Garret A. FitzGerald[1*]

1 Center for Experimental Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America, 2 Phenomix Corporation, La Jolla, California, United States of America, 3 School of Veterinary Medicine, University of Pennsylvania, Kennett Square, Pennsylvania, United States of America, 4 The Genomics Institute of the Novartis Research Foundation, La Jolla, California, United States of America

nature

LETTERS

Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes

Biliana Marcheva[1,2], Kathryn Moynihan Ramsey[1,2], Ethan D. Buhr[2], Yumiko Kobayashi[1,2], Hong Su[3], Caroline H. Ko[2], Ganka Ivanova[1,2], Chiaki Omura[1,2], Shelley Mo[4], Martha H. Vitaterna[5], James P. Lopez[6], Louis H. Philipson[6], Christopher A. Bradfield[7], Seth D. Crosby[8], Lellean JeBailey[9], Xiaozhong Wang[3], Joseph S. Takahashi[10,11] & Joseph Bass[1,2,5]

Brain and m… a component of the molecular clock, regulates adipogenesis

Shigeki Shimba*, Norimasa Ishii, Yuki Ohta, Toshiharu Ohno, Yuichi Watabe, Mitsuaki Hayashi, Taira Wada, Toshinori Aoyagi, and Masakatsu Tezuka

Urbanization

24/7 society

Limited time, for unlimited tasks

Asian university students has shorter sleep duration

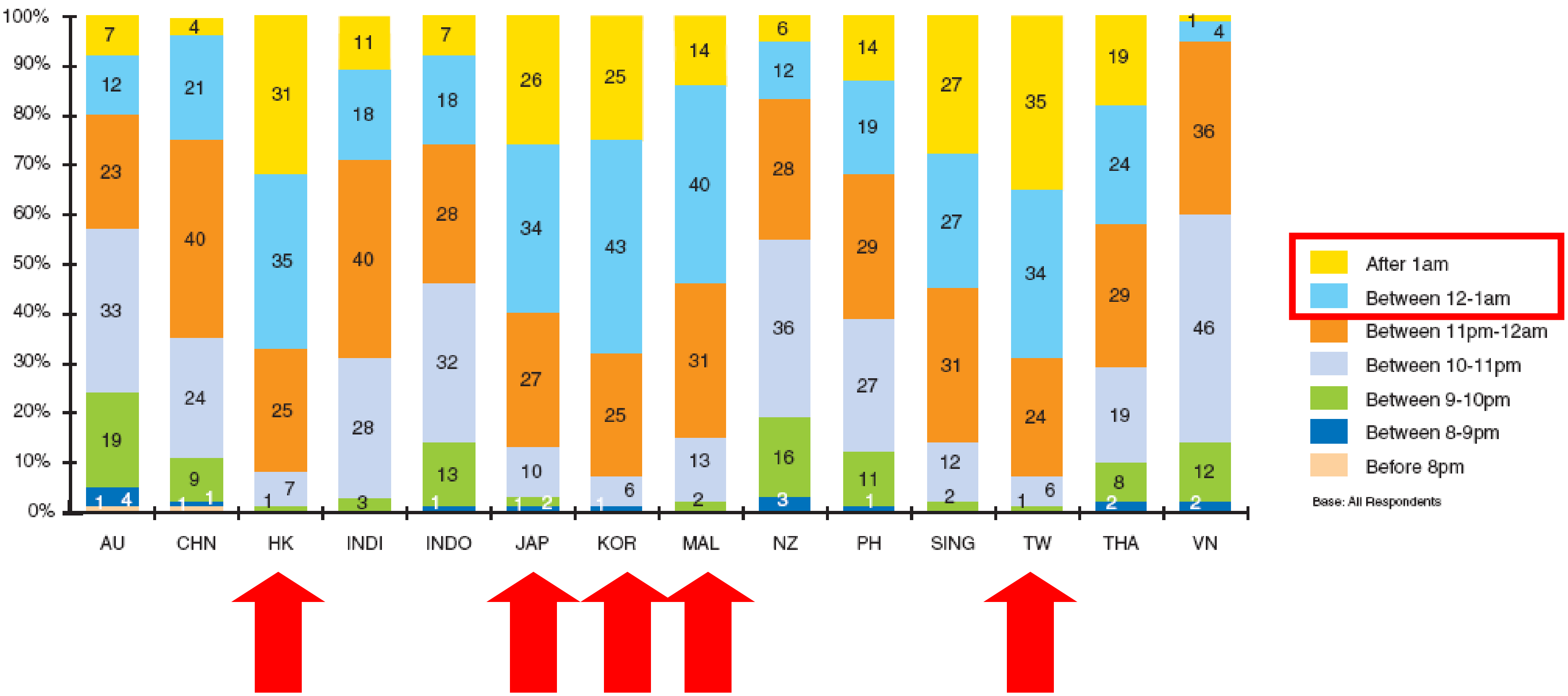
Steptoe A et al, 2006

Table 1. Mean Sleep Duration and Self-rated Health by Country and Sex

	Men			Women		
Country	Mean Sleep Duration, h (95% CI)	No.	Poor Self-rated Health, %	Mean Sleep Duration, h (95% CI)	No.	Poor Self-rated Health, %
Belgium	7.69 (7.54-7.84)	244	7.4	7.90 (7.76-8.04)	261	7.3
Bulgaria	7.81 (7.68-7.93)	336	10.4	8.00 (7.88-8.12)	377	14.1
Colombia	7.14 (7.02-7.26)	378	4.0	7.24 (7.11-7.37)	325	6.5
England	7.40 (7.29-7.52)	372	8.3	7.37 (7.24-7.49)	330	10.0
France	7.55 (7.42-7.68)	312	6.4	7.73 (7.60-7.86)	322	13.4
Germany	7.39 (7.26-7.52)	309	10.4	7.60 (7.48-7.71)	372	6.5
Greece	7.86 (7.74-7.98)	350	3.7	7.87 (7.75-7.99)	371	7.5
Hungary	7.55 (7.39-7.71)	216	8.8	7.55 (7.42-7.68)	323	12.4
Iceland	7.21 (7.07-7.34)	294	7.1	7.56 (7.43-7.68)	337	6.8
Ireland	7.21 (6.98-7.44)	97	11.3	7.67 (7.55-7.80)	329	8.2
Italy	7.58 (7.49-7.67)	641	8.0	7.71 (7.64-7.78)	1092	14.5
Japan	6.20 (6.03-6.38)	172	38.4	6.09 (5.92-6.26)	186	45.7
Korea	6.80 (6.64-6.96)	208	35.6	6.86 (6.75-6.97)	440	42.7
Netherlands	7.79 (7.65-7.92)	275	8.7	7.92 (7.81-8.04)	404	8.9
Poland	7.24 (7.11-7.37)	312	4.5	7.42 (7.30-7.53)	390	10.5
Portugal	7.72 (7.61-7.83)	431	10.7	7.84 (7.73-7.95)	431	16.0
Romania	8.04 (7.91-8.16)	337	12.8	7.72 (7.60-7.84)	365	27.9
Slovak Republic	7.76 (7.66-7.86)	511	8.6	7.59 (7.50-7.68)	663	9.8
South Africa	7.26 (7.12-7.40)	268	14.2	7.71 (7.57-7.84)	289	12.8
Spain	8.02 (7.87-8.18)	215	6.0	7.82 (7.68-7.97)	257	7.4
Taiwan	6.61 (6.43-6.79)	162	18.5	6.51 (6.33-6.68)	171	31.0
Thailand	6.95 (6.82-7.08)	306	25.2	7.08 (6.98-7.18)	520	23.3
United States	7.17 (7.07-7.28)	463	4.3	7.08 (7.01-7.15)	1069	4.7
Venezuela	7.32 (7.19-7.44)	323	2.8	7.31 (7.18-7.44)	309	3.9
Total	7.45 (7.29-7.60)	7532	10.1	7.49 (7.32-7.65)	9933	13.6

Abbreviation: CI, confidence interval.

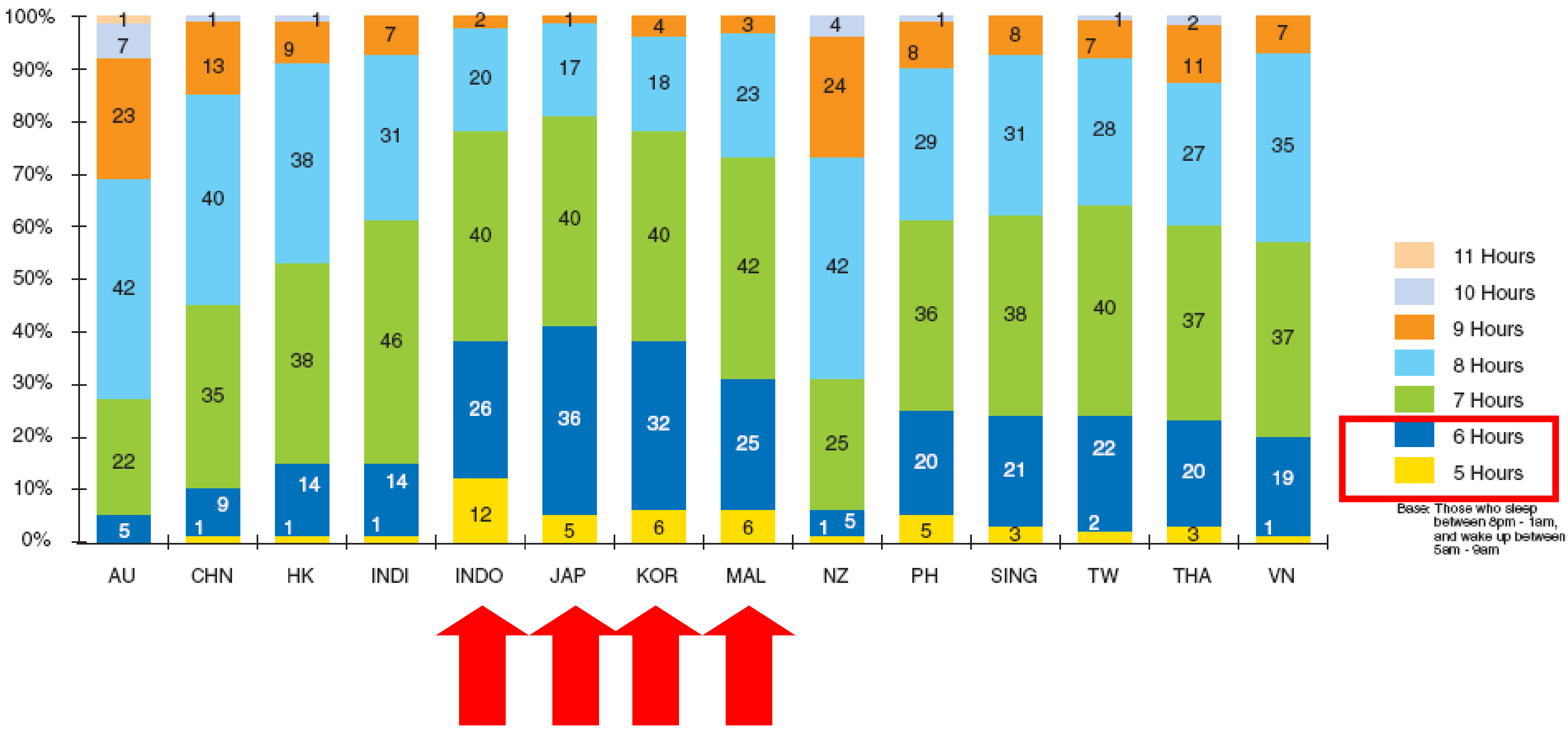
Late Bedtime in Asia Pacific



The Taiwanese are the region's night owls – 35% go to bed after 1am, followed by 31% of Hong Kongers and 27% of Singaporeans. The Australians are the earliest to bed – 24% of Aussies are in bed by 10pm!

ACNielsen 2004

Short sleep time in Asia Pacific



Kiwis and Aussies get the most sleep! 31% of Aussies and 28% of Kiwis get more than 9 hours sleep!
With all their early rising, 12% of Indonesians get an average of 5 hours, with 38% getting 6 hours or less.
Most aleep deprived are the Japanese, with 38% getting 6 hours or less.

DIABETES
2) PEDIATRIC POPULATION

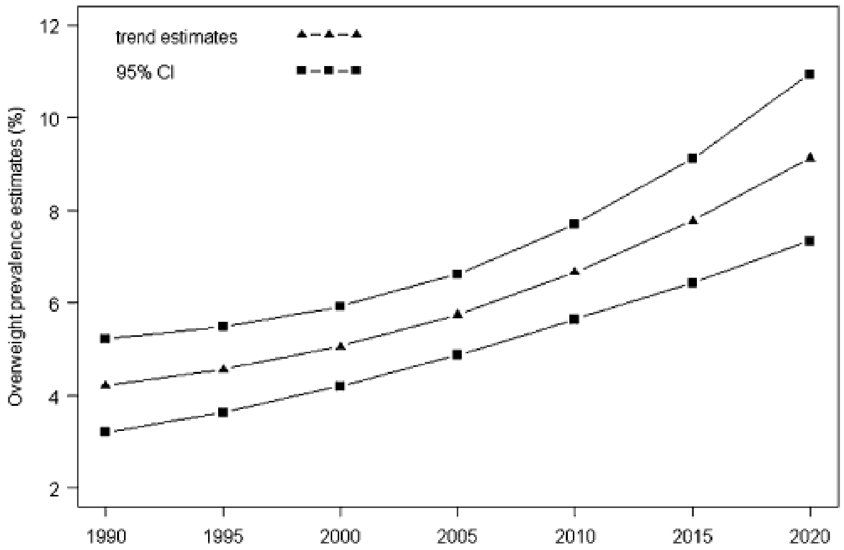
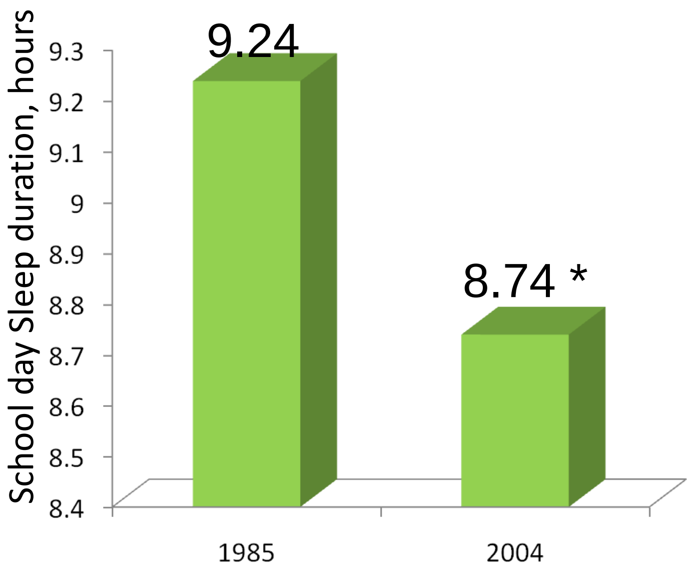


FIGURE 1. Global prevalence and trends of overweight and obesity among preschool children.

Mercedes de Onis et al.Am J Clin Nutr 2010

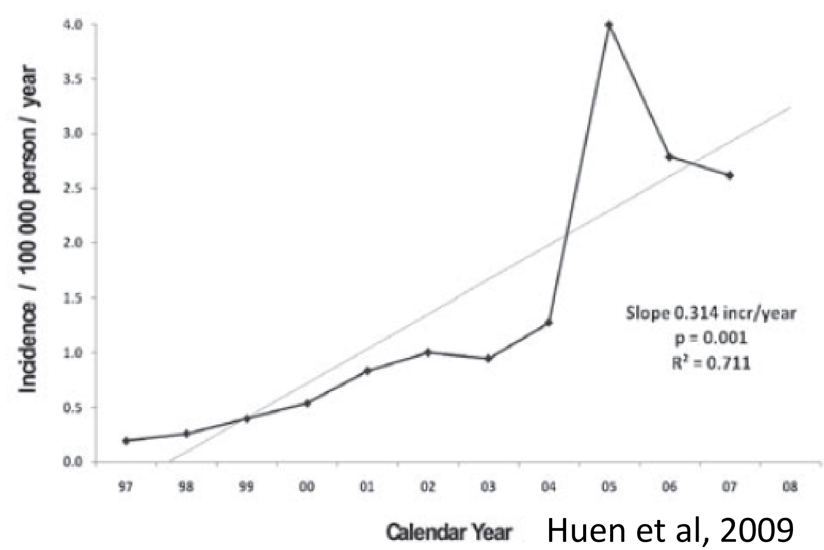
These epidemics also seen in children & adolescents:

1) Overweight & obesity
2) Higher proportion of T2DM
3) Shorter sleep duration

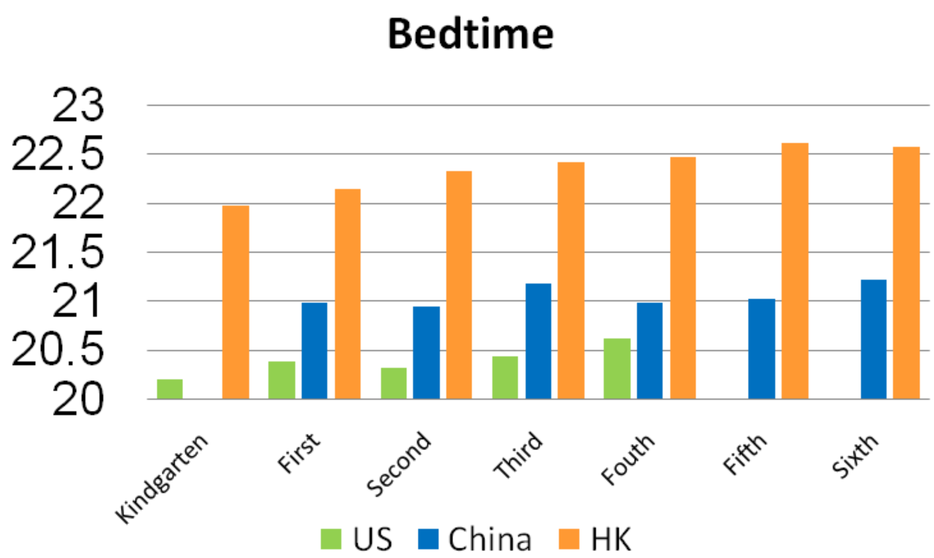


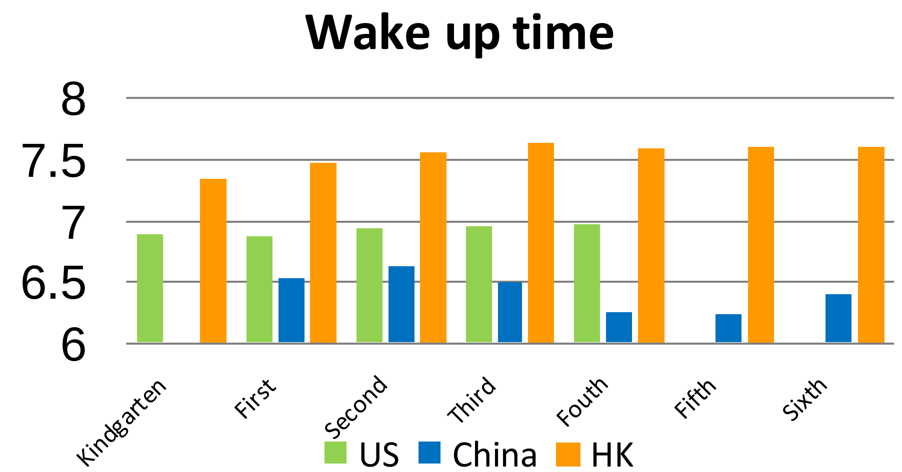
Dollman, et al. 2007

*p<0.0001, 10-15 years old

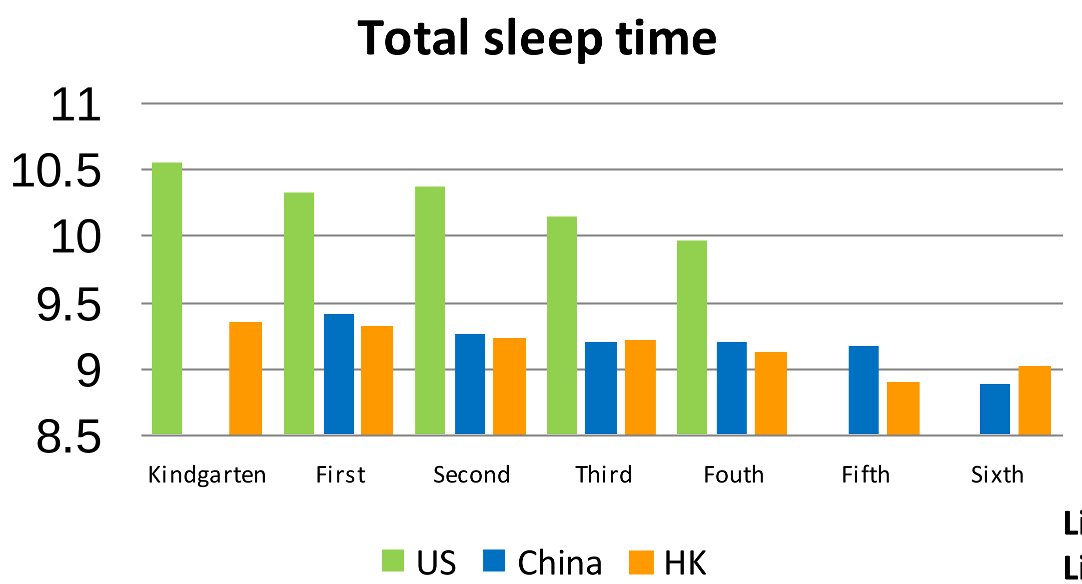


Huen et al, 2009



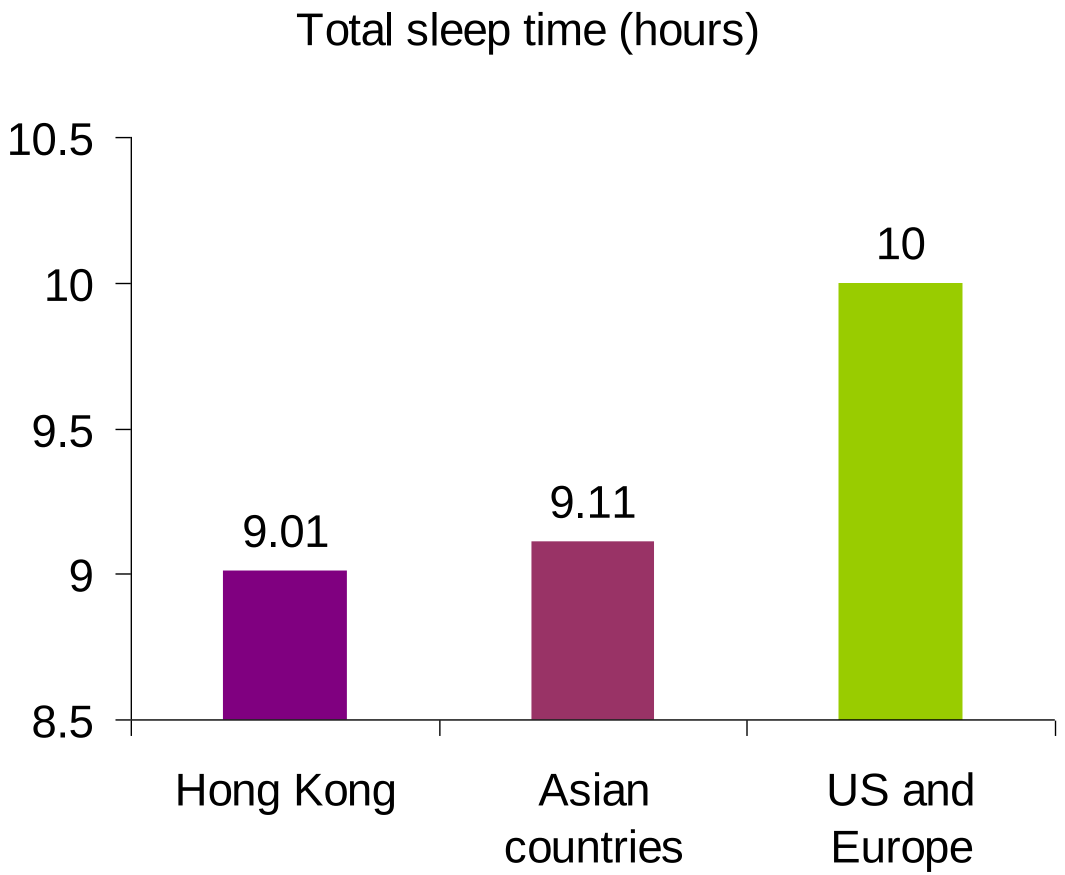


Children in China & HK sleep less and have later bedtime than US children



Liu X et al. Pediatrics 2005
Li & Wing et al. Pediatrics 2009

Shorter sleep duration: also found in toddlers in Asia



2007-2008: a world-wide large scale questionnaire survey had been conducted. Sleep data of ~30,000 children aged 0-3 years had been collected from 16 countries.

Short Sleep Duration in Infancy and Risk of Childhood Overweight

Elsie M. Taveras, MD, MPH; Sheryl L. Rifas-Shiman, MPH; Emily Oken, MD, MPH; Erica P. Gunderson, PhD; Matthew W. Gillman, MD, SM

Objective: To examine the extent to which infant sleep duration is associated with overweight at age 3 years.

Design: Longitudinal survey.

Setting: Multisite group practice in Massachusetts.

Participants: Nine hundred fifteen children in Project Viva, a prospective cohort.

Main Exposure: At children's ages 6 months, 1 year, and 2 years, mothers reported the number of hours their children slept in a 24-hour period, from which we calculated a weighted average of daily sleep.

Main Outcome Measures: We used multivariate regression analyses to predict the independent effects of sleep duration (<12 h/d vs ≥12 h/d) on body mass index (BMI) (calculated as the weight in kilograms divided by the height in meters squared) *z* score, the sum of subscapular and triceps skinfold thicknesses, and overweight (BMI for age and sex ≥95th percentile) at age 3 years.

Results: The children's mean (SD) duration of daily sleep was 12.3 (1.1) hours. At age 3 years, 83 children (9%) were overweight; the mean (SD) BMI *z* score and sum of subscapular and triceps skinfold thicknesses were 0.44 (1.03) and 16.66 (4.06) mm, respectively. After adjusting for maternal education, income, prepregnancy BMI, marital status, smoking history, and breastfeeding duration and child's race/ethnicity, birth weight, 6-month weight-for-length *z* score, daily television viewing, and daily participation in active play, we found that infant sleep of less than 12 h/d was associated with a higher BMI *z* score (β, 0.16; 95% confidence interval, 0.02-0.29), higher sum of subscapular and triceps skinfold thicknesses (β, 0.79 mm; 95% confidence interval, 0.18-1.40), and increased odds of overweight (odds ratio, 2.04; 95% confidence interval, 1.07-3.91).

Conclusion: Daily sleep duration of less than 12 hours during infancy appears to be a risk factor for overweight and adiposity in preschool-aged children.

Arch Pediatr Adolesc Med. 2008;162(4):305-311

Meta-Analysis of Short Sleep Duration and Obesity in Children and Adults

Francesco P. Cappuccio, MD, FRCP[1]; Frances M. Taggart, PhD[1]; Ngianga-Bakwin Kandala, PhD[1]; Andrew Currie, MB ChB[1]; Ed Peile, FRCP[2]; Saverio Strranges, MD, PhD[1]; Michelle A. Miller, PhD[1]

[1]Clinical Sciences Research Institute and [2]Institute of Education, University of Warwick Medical School, Coventry, UK

Sleep 2008

Children data

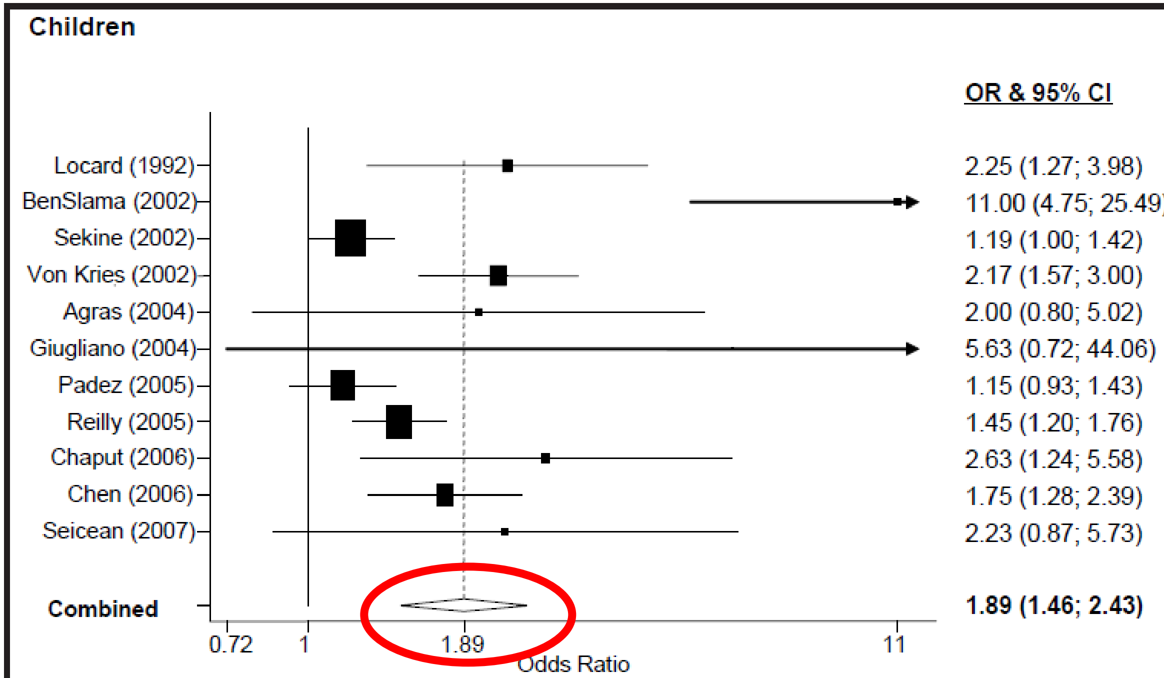


Figure 2—Forest plot of the associations between short duration of sleep and obesity in studies carried out in children. OR and 95 CI indicate odds ratio and 95% confidence intervals.

Sleep duration & insulin resistance: also extend to adolescents

Javaheri S et al. J Pediatrics 2011

N= 387, mean age 15.7±2.1

Findings:

- "u-shape" relationship between sleep duration & HOMA

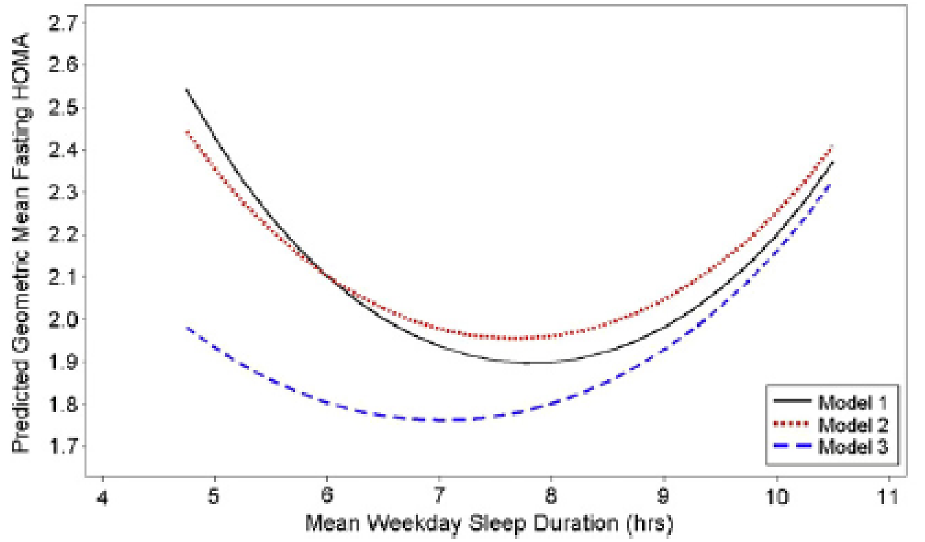


Figure. Predicted geometric mean HOMA levels as a function of mean weekday sleep duration from repeated measures analyses. Model 1 is adjusted for age; model 2 is adjusted for subject characteristics (age, sex, race, preterm status, moderate/vigorous daily activity); model 3 is adjusted for subject characteristics and obesity (waist circumference).

HOMA: Homeostasis model assessment, measure of insulin sensitivity in adult & children; increased with insulin resistance

What contributes to the short sleep duration/ irregular sleep pattern?

Sharing our study result on children sleep/wake pattern

- Community-based study:
- Participants: Over 4400 families (Father-mother-child trios)

ORIGINAL ARTICLES

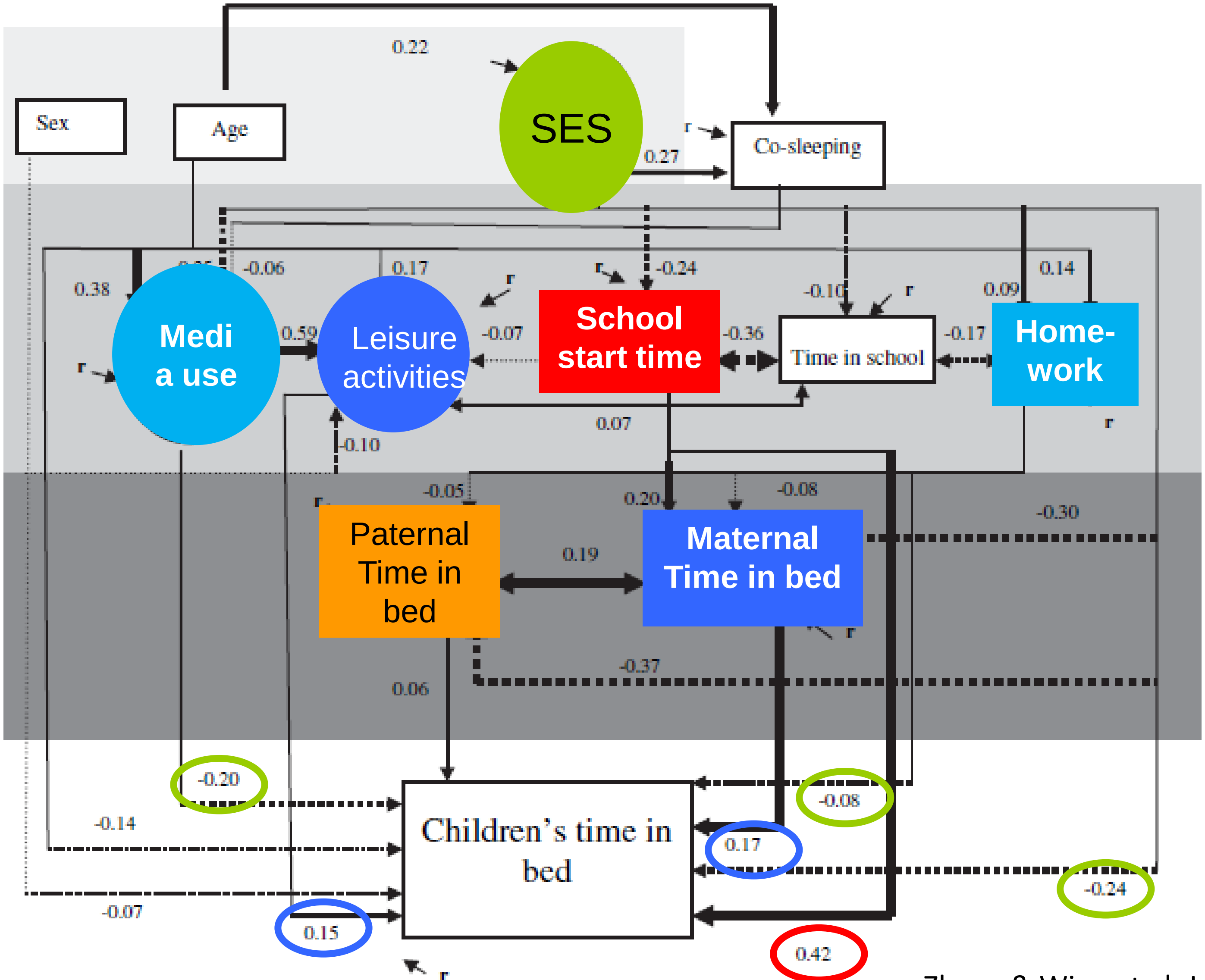
www.jpeds.com • THE JOURNAL OF PEDIATRICS

Roles of Parental Sleep/Wake Patterns, Socioeconomic Status, and Daytime Activities in the Sleep/Wake Patterns of Children

Jihui Zhang, MD, Albert Martin Li, MRCP, MD, FHKAM (Paed), Tai Fai Fok, FRCP, MD, and
Yun Kwok Wing, FRCPsych, MRCP, FHKAM (Psych)

Zhang & Wing et al. J Pediatr 2010

Structural equation modeling for children's time in bed & its correlates



Zhang & Wing et al. J Pediatr 2010

A new trend of learning: weekly schedule of a 10-year old boy/girl in HK

	Mon	Tue	Wed	Thurs	Fri	Sat	Sun
0645	Wake up						
0715	School bus						
0800- 1530	School time					Piano class 0930-1030 Violin class 1130-1230	Music theory 1000-1100
1530- 1615	School bus					English class 1500- 1700	
1615-1700	TV/ Rest						
1700-1900	Mandarin class	Swimming class	Math class	Swimming class	Calligraphy		
1900-2000	Dinner						
2000-2230	Homework						
2230-2330	Bathing, “private time” : surfing internet…						
2330/ 0000	Bedtime						

Sleep curtailment: a family & community issue

Roles of parents in children's sleep time:

- Genetics
- Environment:
  - Share socioeconomic status
  - Activities:
    - A modern trend for "intensive training" since early age with sacrifice of sleep for "higher achievement"

The Way Forward

“Better sleep, better health”

Emphasis the importance of sleep & recognize the adverse effect of sleep disorders, at multi-level:

- Children
- Parents
- School/ workplaces
- Health care professionals
- Public education


RECOMMENDATIONS JUNE 2011

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the nation • Improving health

For more information visit www.iom.edu/obesityyoungchildren

Early Childhood Obesity Prevention Policies

Goals, Recommendations, and Potential Actions

Early Childhood Obesity Prevention Policies offers the following policy recommendations and potential actions for implementation designed to prevent obesity in infancy and early childhood by promoting healthy environments for young children.

EARLY CHILDHOOD OBESITY PREVENTION POLICIES

For sleep curtailment…

- Adequate sleep for all age groups!
  - From children to elderly
  - Regular sleep-wake schedule
  - Good balance between rest & activities

IOM recommendation

Sleep

Goal: Promote age-appropriate sleep durations among children.

Recommendation 6-1: Child care regulatory agencies should require child care providers to adopt practices that promote age-appropriate sleep durations.

Potential actions include:

- creating environments that ensure restful sleep, such as no screen media in rooms where children sleep and low noise and light levels during napping;
- encouraging sleep-promoting behaviors and practices, such as calming nap routines;
- encouraging practices that promote child self-regulation of sleep, including putting infants to sleep drowsy but awake; and
- seeking consultation yearly from an expert on healthy sleep durations and practices.

Recommendation 6-2: Health and education professionals should be trained in how to counsel parents about their children's age-appropriate sleep durations.

Sleep education

- School Sleep education

Australia: Moseley & Gradisar Sleep 2009

Japan: Shiga model

Hong Kong …….2012

School-based specific intervention: successful pilot study in US

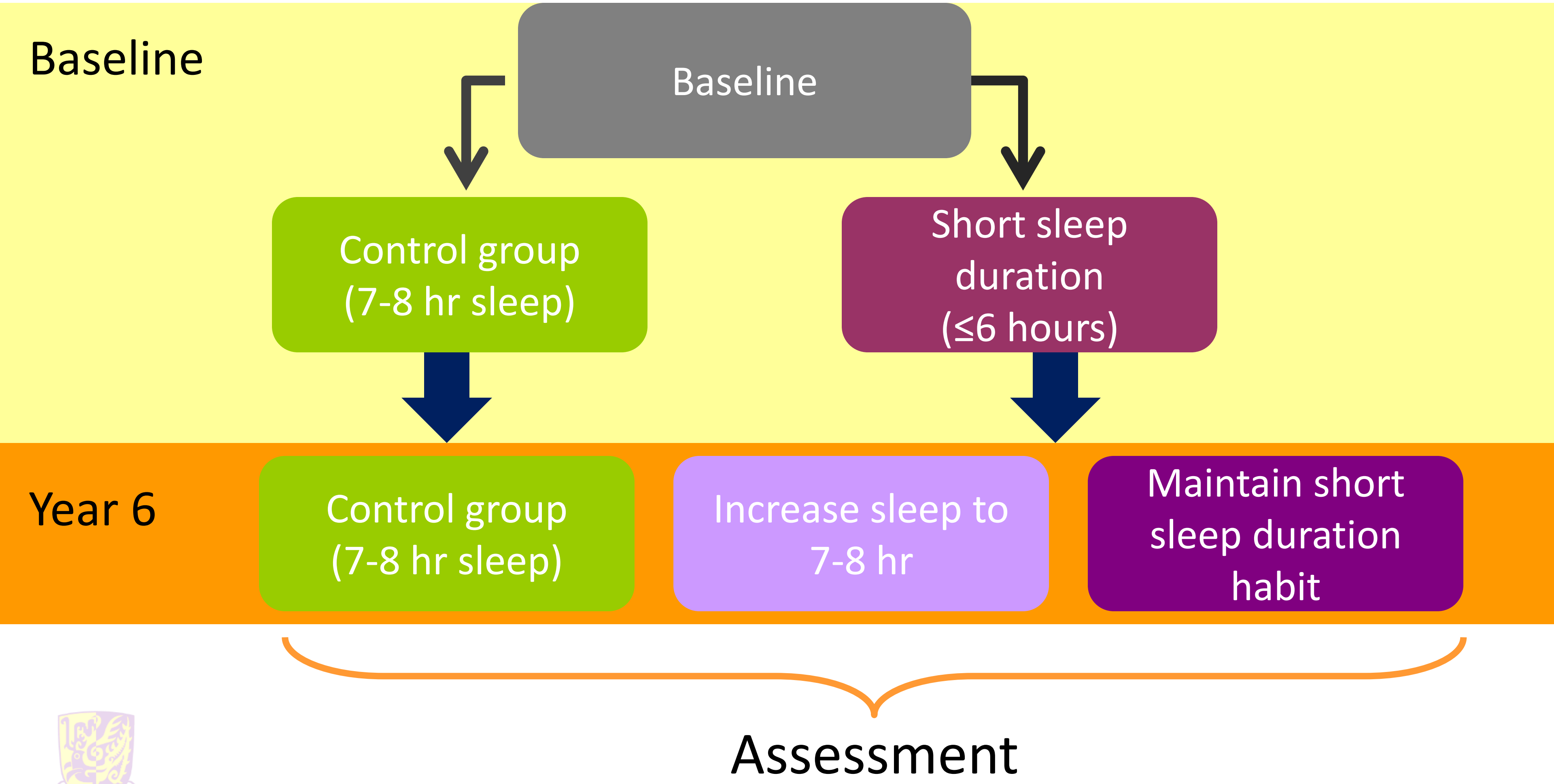
ARTICLE

Impact of Delaying School Start Time on Adolescent Sleep, Mood, and Behavior

Judith A. Owens, MD, MPH; Katherine Belon, BA; Patricia Moss, PhD

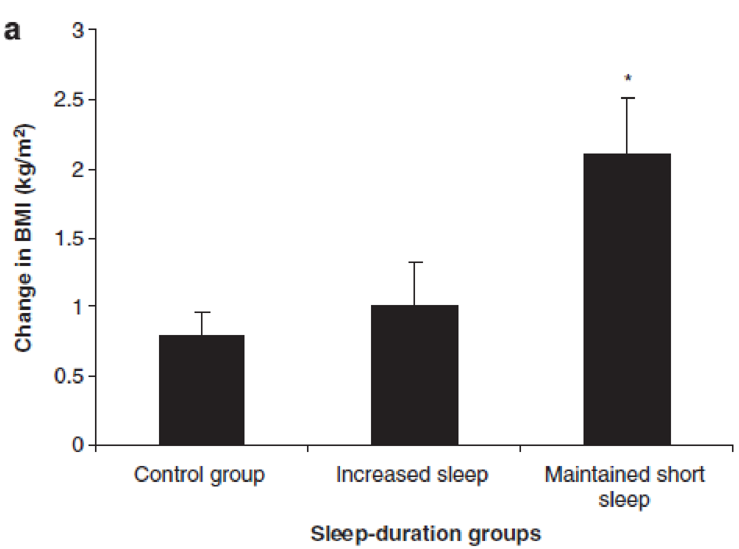
- US study
- A secondary school's schedule was delayed by 30 minutes across all junior grades (N= 201) (8:00 to 8:30)
- 3- months intervention
- Compared to baseline, significant improvement in adolescents' sleep duration
- Consequent enhancement of alertness, mental and physical health

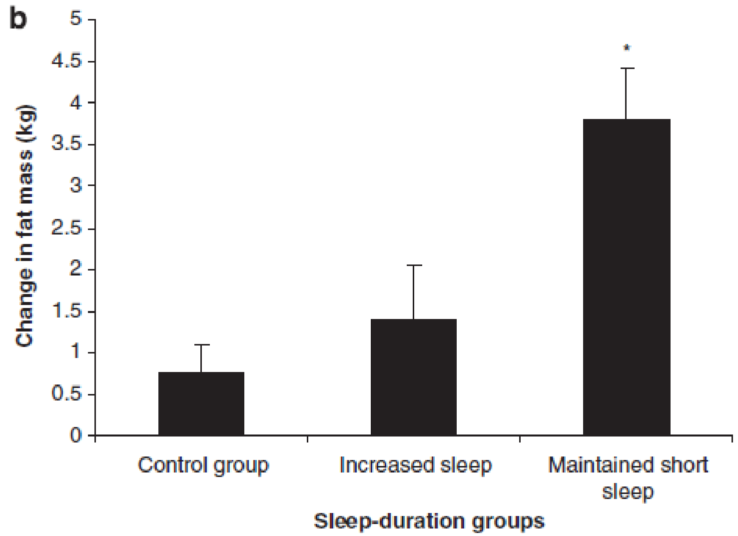
Does elongation of sleep duration help to lower adiposity gain?

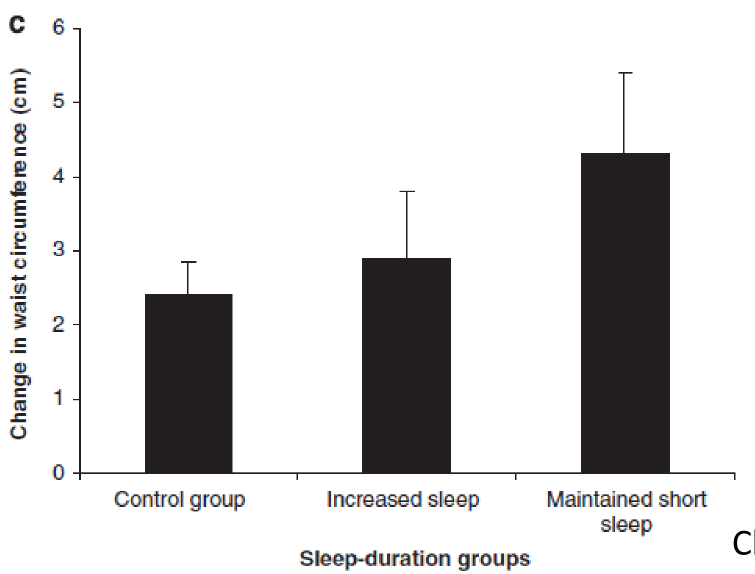


Chaput JP et al. Int J Obesity 2011

Result







Chaput JP et al. Int J Obesity 2011

For DM patients…

- For DM patients:
  - Aware of the high prevalence of various sleep disorders, & their detrimental effects on DM control
    - Active screening & early detection!
  - Identify potential confounding, e.g. depression
  - Integrating management of sleep problems into diabetes care – OSAS, sleep duration and disturbances

Public Health & Research directions

- Need integrated, concerted effort across countries – healthy sleep as top priority ..
- Research:
  - Need large scale, multiphase studies
  - Need intervention study
- Can we, sleep healthcare workers, contribute to decrease global obesity and diabetes epidemic?
- Young children as the top priority of sleep education!

Research teams & collaborators

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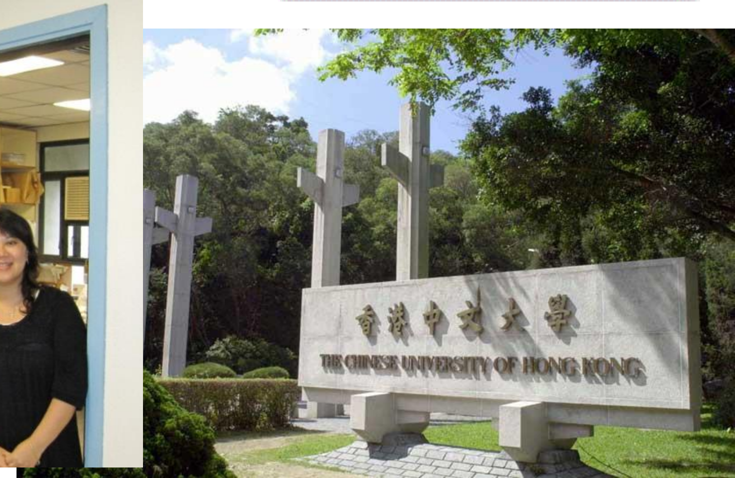

THANK YOU