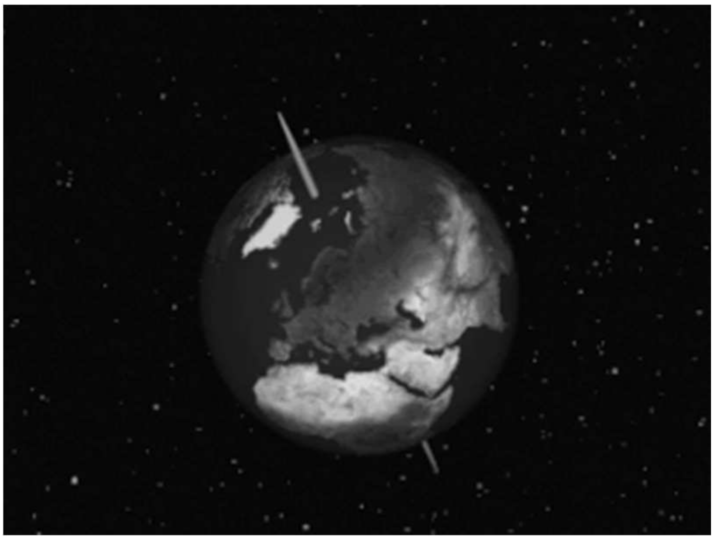
UNIVERSITÀ
DEGLI STUDI
DI FERRARA
- EX LABORE FRUCTUS -

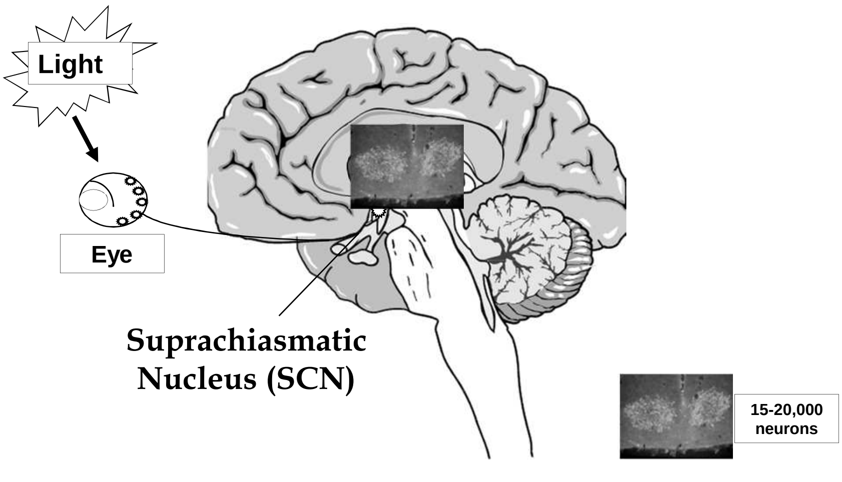
Biological rhythms in health and disease

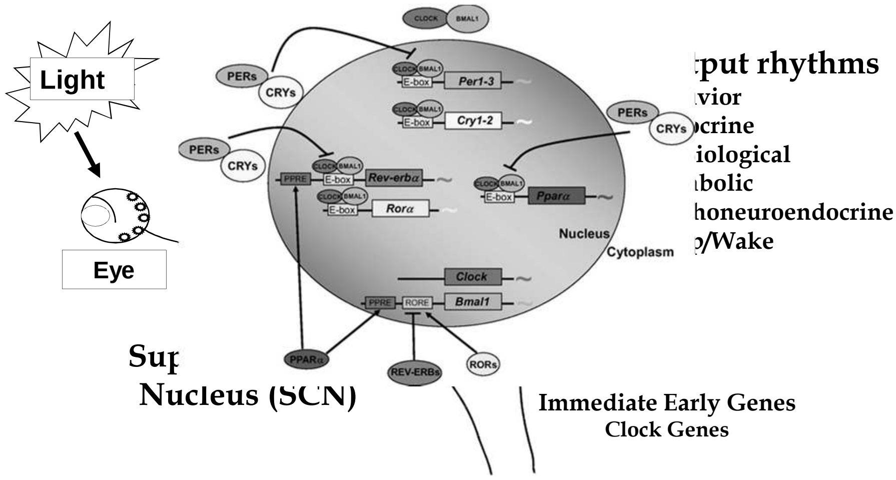
Roberto Manfredini

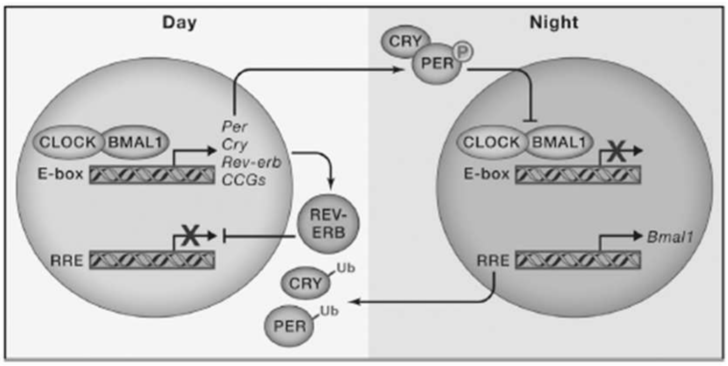
- **Circadian rhythms**
- **Circadian organization and control of bodily's functions**
- **Desynchronization of circadian rhythms**
- **Chronotype: morningness or eveningness?**
- **Chronotype and implications for general, metabolic and cardiovascular health**
- **Chronobiology and onset of CV diseases**

Circadian: from '*circa diem*' ≈24-hour the time of a complete earth rotation

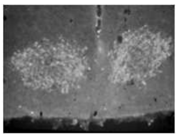


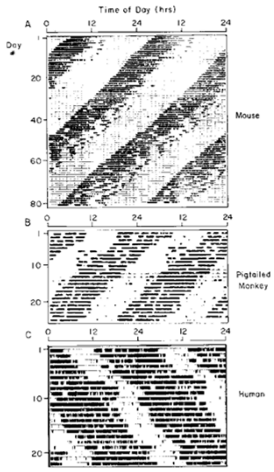


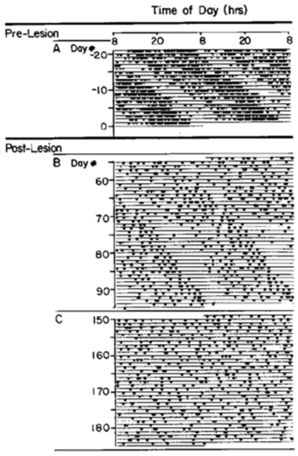


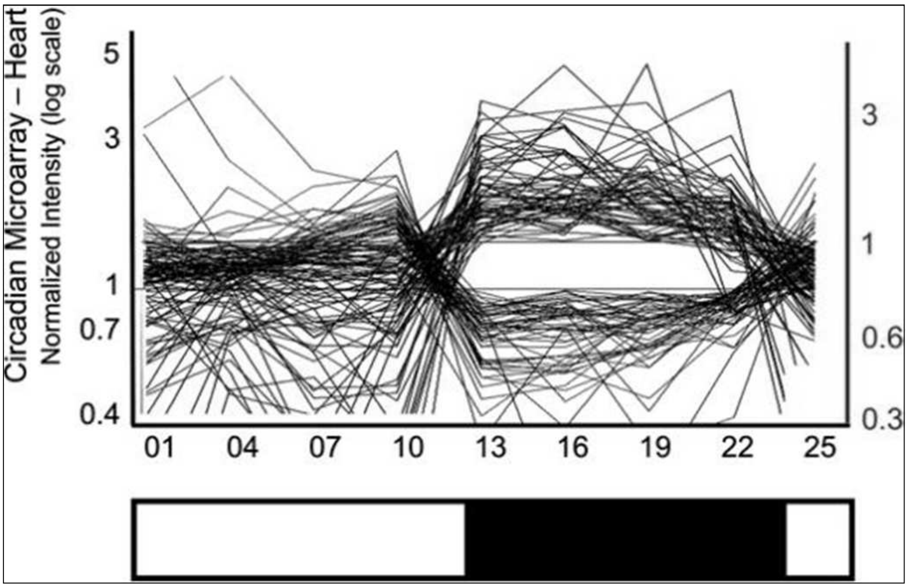


Asher & Sassone-Corsi, *Cell* 2015

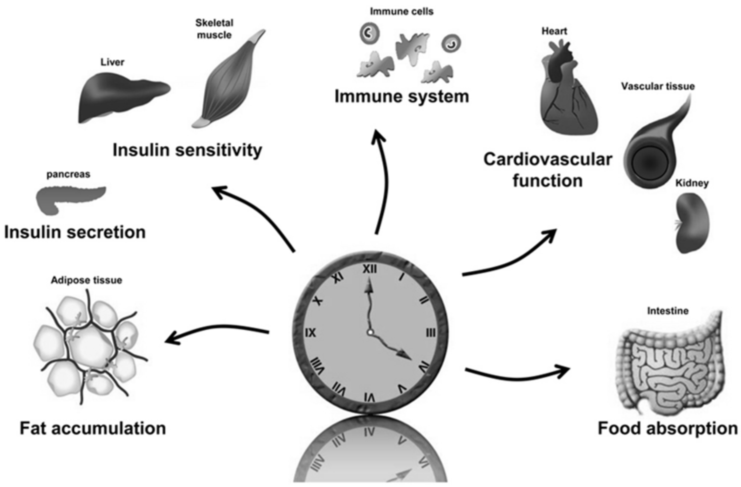


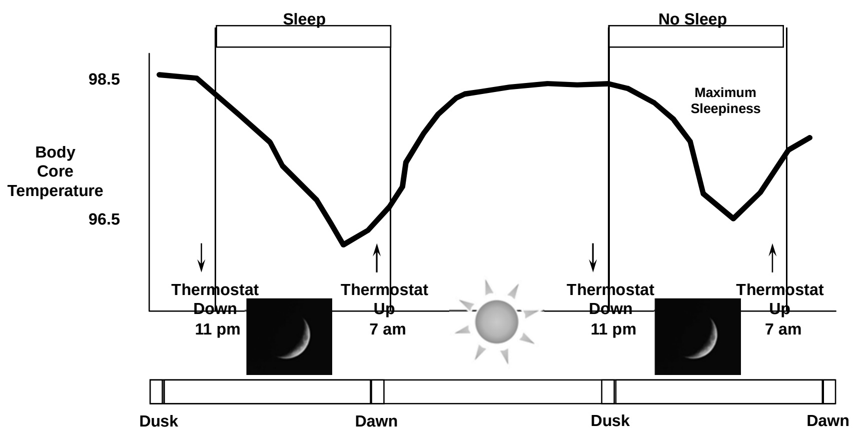

Time of Day (hrs)
A
Day
Mouse
B
Pigtailed Monkey
C
Human

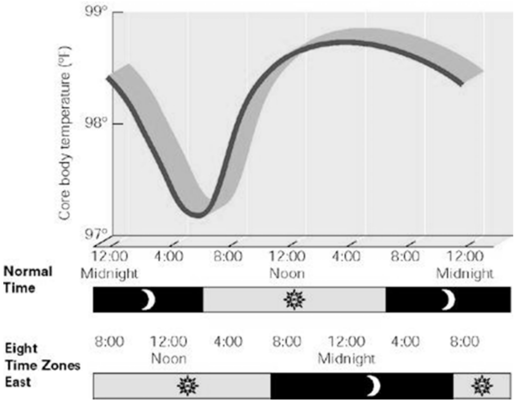

Time of Day (hrs)
Pre-Lesion
A Day #
Post-Lesion
B Day #
C

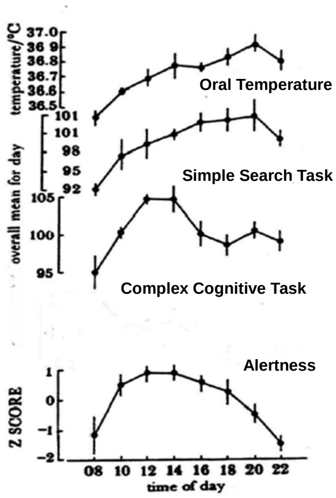

Circadian Microarray – Heart
Normalized Intensity (log scale)
5
3
1
0.7
0.4
3
1
0.6
0.3
01
04
07
10
13
16
19
22
25

The central biological clock (*masterclock*) regulates all body functions









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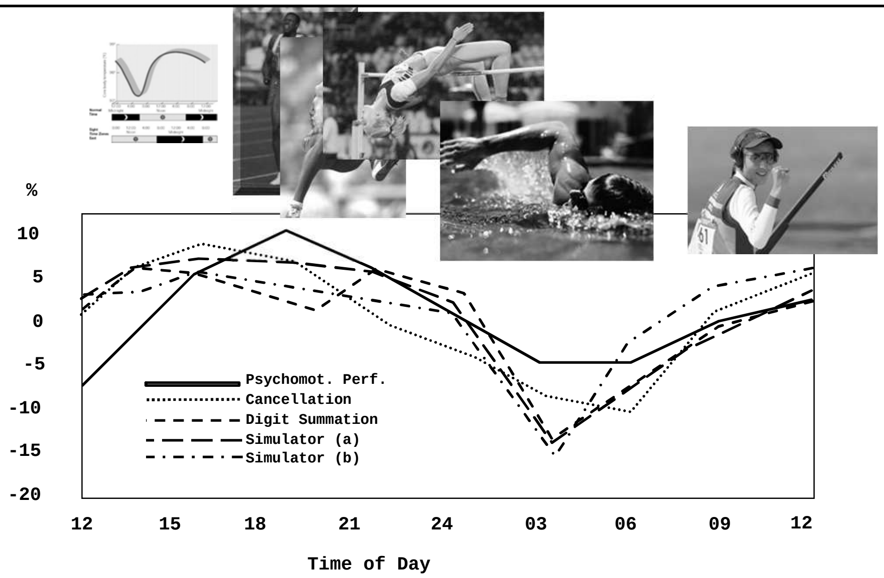
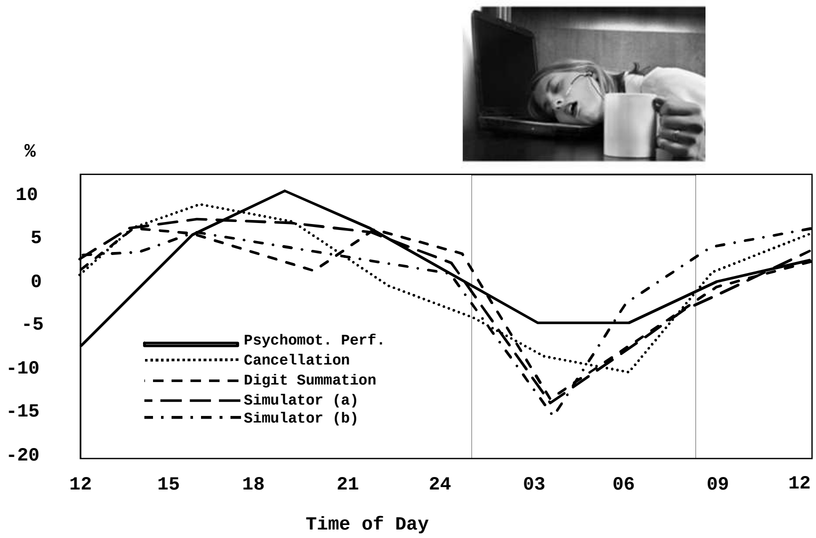

%
10
5
0
-5
-10
-15
-20
Psychomot. Perf.
Cancellation
Digit Summation
Simulator (a)
Simulator (b)
12 15 18 21 24 03 06 09 12
Time of Day


%
10
5
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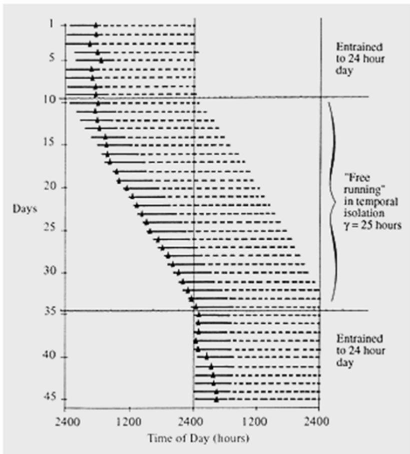
-20
Psychomot. Perf.
Cancellation
Digit Summation
Simulator (a)
Simulator (b)
12 15 18 21 24 03 06 09 12
Time of Day

‘free running’ rhythm



Sleep

- the innocent sleep..

The death of each day’s life, sore labor’s bath,

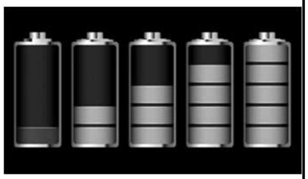
Balm of hurt minds, great nature’s second course,

Chief nourisher in life’s feast.

- - il sonno innocente... morte della vita d'ogni giorno, bagno ristoratore del faticoso affanno, balsamo alla dolente anima stanca, piatto forte alla mensa della grande natura, nutrimento principale nel banchetto della vita

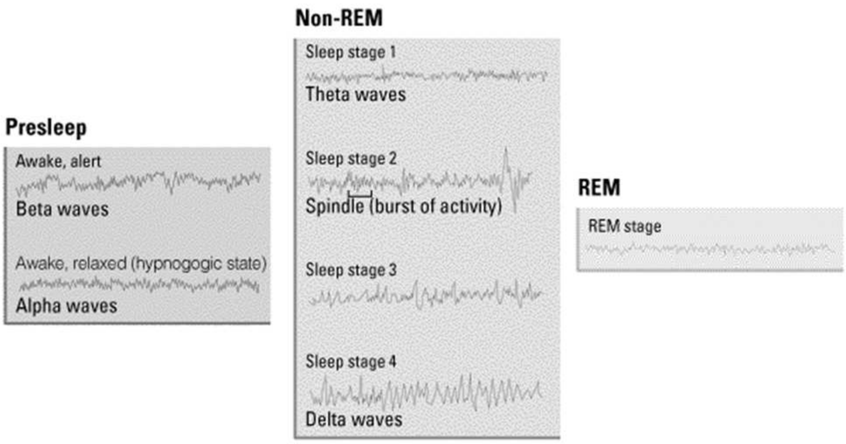
Shakespeare, *Macbeth* Act 2, Scene 2, Page 3

Sleep theories



- Restoration Theory
  - 'Recharging Battery' (cognitive, physical, emotional needs)
- Evolutionary Theory
  - Energy preservation, minimization of exposure to predators

Sleep stages



Stage 1 – Transition period

- Usually 10 minutes
- If awakened, the great majority of people say they weren't asleep
- "Micro-Sleeps"

Stage 2 – Deeper, reduced ocular movements

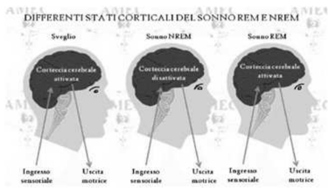
- Low restorative quality
- Near half of sleep time (adults) in stage 2
- About 20 min. are needed to pass to next stage

Stage 3 – Slow Wave Sleep (SWS)

- Most vital for recuperation, immune function
- SWS increases after intellectually challenging tasks
- Most SWS occurs during the first half of the sleep period

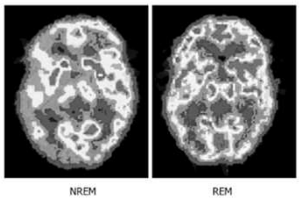
Rapid Eyes Movements (REM) sleep

- ‘*brain on, body off*’
- Rapid eye movements
- Wakeful EEG pattern
- Increased cerebral blood flow
- Absent spinal reflexes

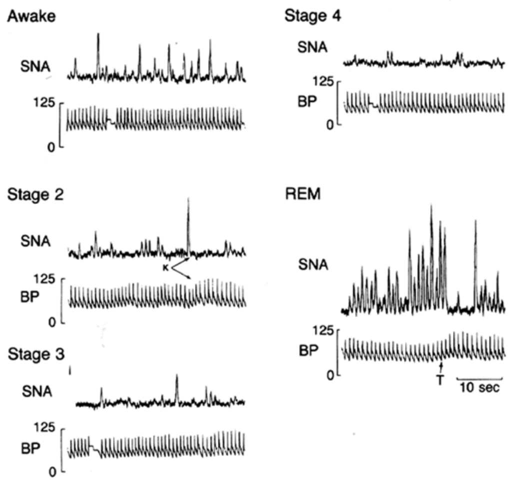


REM sleep

- First episode occurs after 90-120 min of NREM sleep
- Cycles of approx. 90 min., progressively more frequent arriving closer to wake-up

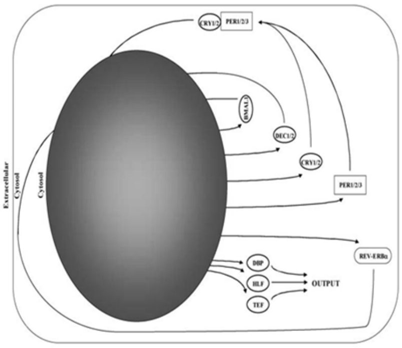


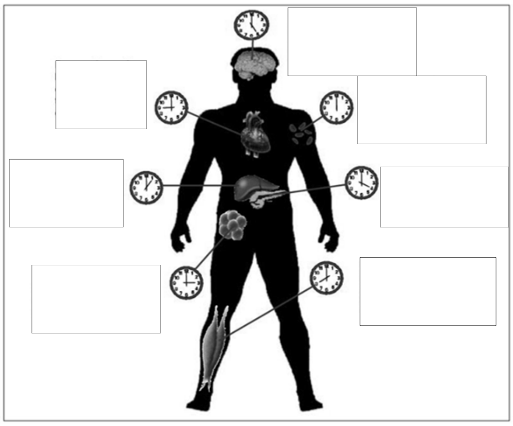
Autonomous nervous system and sleep



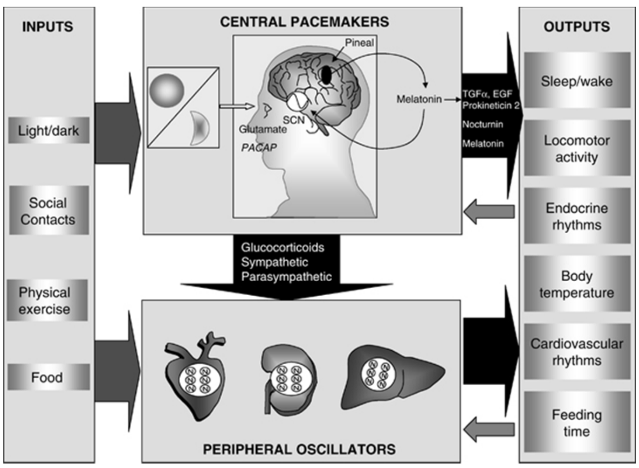
SNA
sympathetic-nerve activity

Peripheral biological clocks exist in multiple organs and cooperate with the *masterclock*



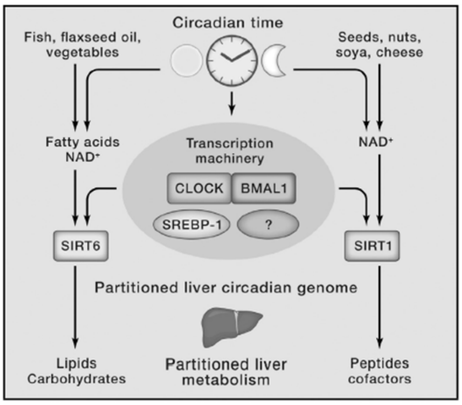


Other 'synchronizers' play a role as well



Time for Food: The Intimate Interplay between Nutrition, Metabolism, and the Circadian Clock

Gad Asher[1,*] and Paolo Sassone-Corsi[2,*]



Asher & Sassone-Corsi, *Cell* 2015

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Continuous light; frequent snacking; low physical exercise

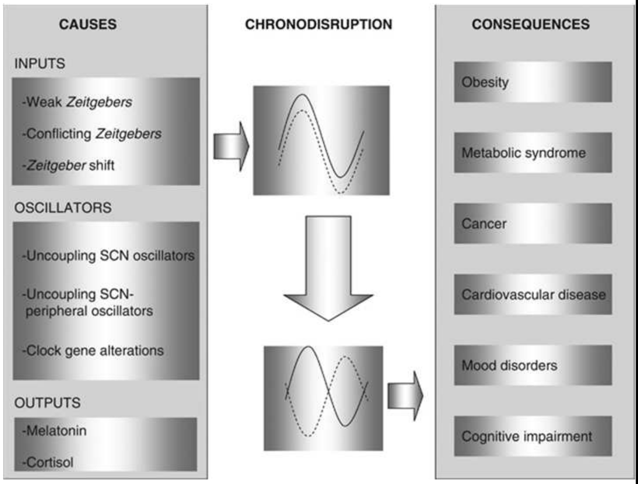
Light at night; nocturnal eating; nocturnal physical activity

Daylight-saving time; crossing time zone; shiftwork

Aging

Experimental models (knock-out)

Nocturnal melatonin suppression; loss of cortisol rhythmicity



Jet lag: symptoms

Headaches, irritability and loss of concentration

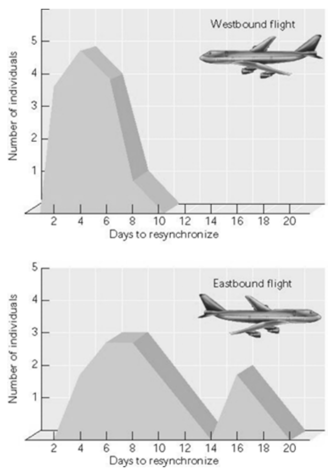
Loss of motivation and commitment

Knowing that you should be hungry……..
and yet loss of appetite, and feeling bloated after a meal

Indigestion and bowel irregularities

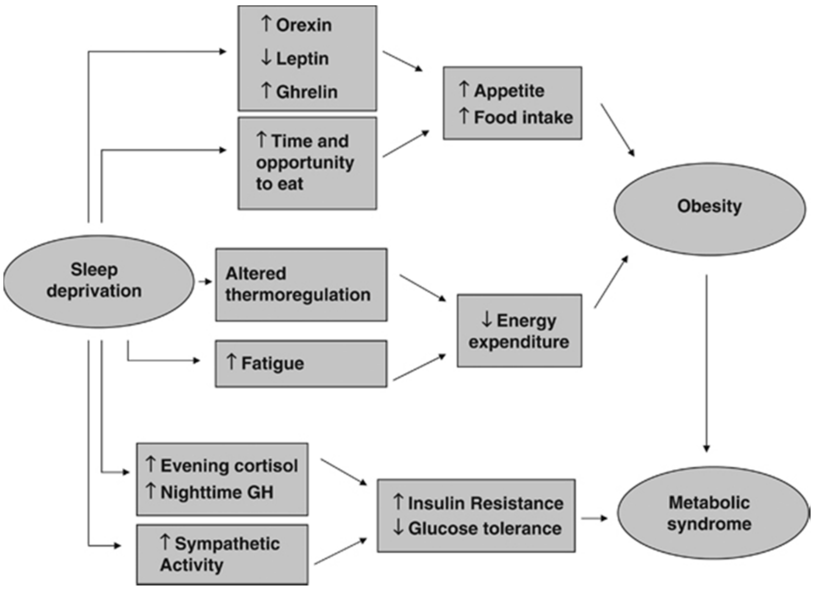
Fatigue in the new daytime…………
and yet inability to sleep at night

Jet lag: symptoms



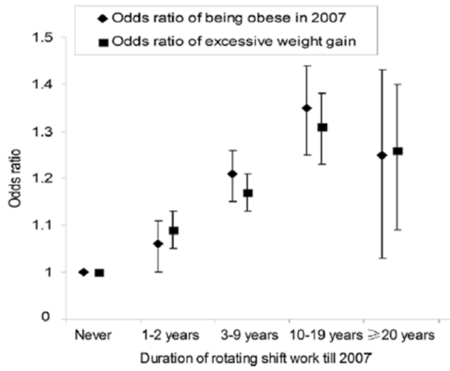
Unlike travel fatigue, they are:
- -slow to alleviate
- -worse when more time zones are crossed
- -worse at some times of day than others
- -worse when flying west to east (*West is best and East is least*) recovery: ~92 min/day (westwards, phase delay) and ~ 57 min/day (eastwards, phase advance), respectively

Desynchronization of circadian rhythms SLOW



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

An Pan[1], Eva S. Schernhammer[2,3], Qi Sun[1,3], Frank B. Hu[1,2,3]*



Pan et al, *PLoS Med* 2011

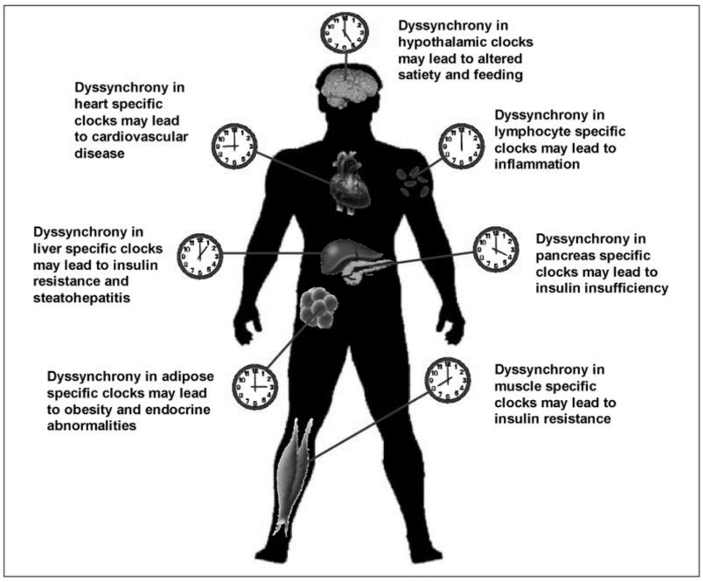
Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women

Céline Vetter, PhD; Elizabeth E. Devore, ScD; Lani R. Wegrzyn, ScD; Jennifer Massa, ScD; Frank E. Speizer, MD; Ichiro Kawachi, MD, ScD; Bernard Rosner, PhD; Meir J. Stampfer, MD, DrPH; Eva S. Schernhammer, MD, DrPH

Conclusions

Among women who worked as registered nurses, longer duration of rotating night shift work was associated with a statistically significant but small absolute increase in CHD risk. Further research is needed to explore whether the association is related to specific work hours and individual characteristics.

JAMA April 26, 2016 Volume 315, Number 16



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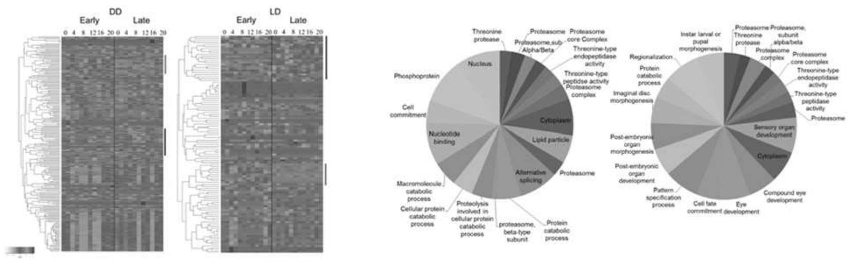
Individual circadian preference (chronotype)

Rather 80 different genes play a role in driving different chronotypes



In general, our results suggest that chronotype diversity is largely mediated by genes, which are downstream of the circadian clock. None of the *Drosophila* core clock genes seems to show substantial expression difference between the E and the L chronotypes. Yet, it is possible that variation in clock genes drives different chronotypes post-transcriptionally.

Pegoraro et al, *Front Neurol* 2015

Morningness-Eveningness Questionnaire (MEQ)

Final score	Result
70 – 86	Definite morning type
59 – 69	Moderate morning type
42 – 58	Intermediate
50 – 58	***Intermediate, with propensity to morning type***
42 – 49	***Intermediate, with propensity to evening type***
31 – 41	Moderate evening type
16 – 30	Definite evening type

Horne & Hostberg, *Int J Chrobiol* 1976

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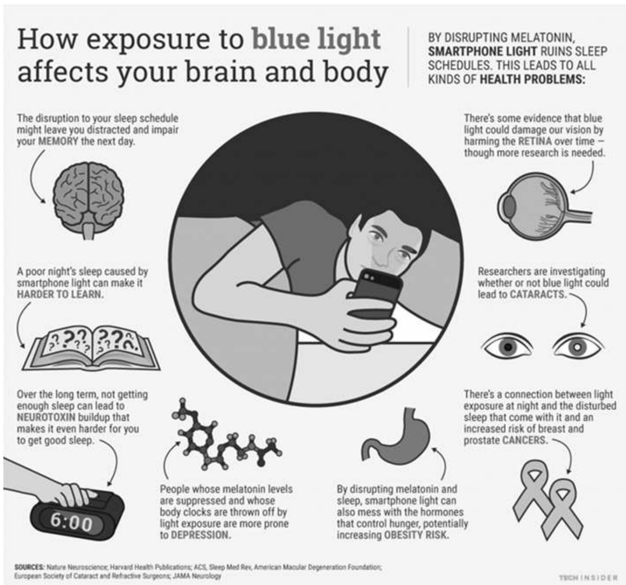


CHRONOBIOLOGY INTERNATIONAL
2016, VOL. 33, NO. 7, 863–882
http://dx.doi.org/10.1080/07420528.2016.1176927

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Chronotype, gender and general health

Fabio Fabbian[a,b], Beatrice Zucchi[a], Alfredo De Giorgi[a,b], Ruana Tiseo[b], Benedetta Boari[b], Raffaella Salmi[b], Rosaria Cappadona[a], Gloria Gianesini[b], Erika Bassi[b], Fulvia Signani[c], Valeria Raparelli[d], Stefania Basili[d], and Roberto Manfredini[a,b]

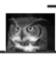
[a]School of Medicine, University of Ferrara, Ferrara, Italy; [b]Azienda Ospedaliera-Universitaria, Ferrara, Italy; [c]Azienda Unità Sanitaria Locale of Ferrara & University of Ferrara, Ferrara, Italy; [d]Sapienza-University of Rome, Roma, Italy

Fabbian et al, *Chronobiol Int* 2016

Tendency Toward Eveningness Is Associated With Unhealthy Dietary Habits

Noora Kanerva,[1] Erkki Kronholm,[1] Timo Partonen,[2] Marja-Leena Ovaskainen,[3] Niina E. Kaartinen,[1] Hanna Konttinen,[4] Ulla Broms,[2,5] and Satu Männistö[1]

TABLE 1. Mean (± SEM) or % of lifestyle, health, and sleep-related factors, and anthropometric measures by ME score quintiles




	ME score quintiles*					
	1 (n = 826, 18%)	2 (n = 946, 21%)	3 (n = 665, 15%)	4 (n = 1061, 24%)	5 (n = 995, 22%)	p trend[†,‡]
ME score, range	5–14	15–17	18–19	20–22	23–27	
Male sex, %	38	42	45	49	51	<.001
Age,[†] yrs	47 (.5)	50 (.4)	52 (.5)	54 (.4)	56 (.4)	<.001
Highly educated Subjects, %	46	42	35	33	27	<.001
→ Physically inactive	27	21	15	14	13	<.001
→ Current smokers, %	21	16	12	15	16	.003
Working evenings or night shift, %	3	1	<1	<1	1	<.001
BMI,[†] kg/m^2	27.0 (.2)	26.7 (.2)	26.5 (.2)	26.7 (.1)	27.2 (.2)	.35
Sleep <7 h/d,[†] %	13	8	9	9	12	.38
Sleep >8 h/d,[†] %	17	16	14	14	13	.008
Insomnia,[†¶] %	67	61	58	54	46	<.001
Experienced insufficient sleep,[†§] %	25	15	11	8	6	<.001
→ Good self-rated Health,[†] %	49	60	62	65	69	<.001
→ Good self-rated physical fitness,[†] %	37	45	48	54	59	<.001

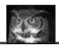
*Lowest ME score quintile represents strong tendency toward eveningness and highest quintile strong tendency toward morningness.

Kanerva et al, *Chronobiol Int* 2012

Tendency Toward Eveningness Is Associated With Unhealthy Dietary Habits

Noora Kanerva,[1] Erkki Kronholm,[1] Timo Partonen,[2] Marja-Leena Ovaskainen,[3] Niina E. Kaartinen,[1] Hanna Konttinen,[4] Ulla Broms,[2,5] and Satu Männistö[1]

TABLE 2. Food consumption by ME score quintiles

	ME score quintiles*†						
	1 (n = 826, 18%)	2 (n = 946, 21%)	3 (n = 665, 15%)	4 (n = 1061, 24%)	5 (n = 995, 22%)	*p* trend†¶	*p*†§
Whole grain, g/d	225 (5)	231 (3)	238 (3)	245 (3)	251 (4)	.012	<.001
Wheat, g/d	77 (1)	77 (1)	76 (1)	76 (1)	76 (1)	.08	.08
Rye, g/d	61 (1)	63 (1)	66 (1)	68 (1)	71 (1)	<.001	<.001
Potatoes, g/d	136 (3)	138 (2)	142 (1)	145 (2)	147 (3)	.021	<.001
Fried potatoes, g/d	9.9 (.4)	9.5 (.3)	9.0 (.2)	8.6 (.2)	8.2 (.3)	.008	.08
→ Vegetables/roots, g/d	266 (5)	271 (4)	277 (3)	282 (3)	287 (5)	.006	.002
→ Fruits, g/d	265 (6)	268 (4)	271 (3)	274 (4)	277 (6)	.17	.025
Butter g/d	7.6 (.2)	7.7 (.2)	7.8 (.1)	7.9 (.2)	8.0 (.2)	.74	.41
Margarine, g/d	13.3 (.3)	13.3 (.2)	13.2 (.2)	13.2 (.2)	13.1 (.3)	.34	.45
Oil, g/d	10.7 (.2)	10.5 (.1)	10.3 (.1)	10.2 (.1)	10.0 (.2)	.12	.65
Red meat/meat products, g/d	136 (2)	137 (2)	138 (1)	139 (2)	141 (2)	.35	.08
→ Fish, g/d	43 (1)	44 (1)	45 (1)	46 (1)	47 (1)	.10	<.001
Milk, g/d	359 (8)	361 (6)	363 (5)	366 (5)	368 (8)	.82	.27
Fruit juices, g/d	128 (4)	124 (3)	120 (2)	117 (3)	113 (4)	.17	.47
Softdrinks, g/d	98 (6)	79 (5)	69 (6)	87 (5)	73 (5)	.50	.015
Beer, g/d	113 (7)	105 (4)	98 (3)	90 (4)	82 (6)	.06	.51
→ Wine, g/d	26 (1)	23 (1)	20 (1)	17 (1)	14 (1)	<.001	<.001
→ Spirits, g/d	3.6 (.3)	3.0 (.2)	3.2 (.2)	3.0 (.2)	2.9 (.3)	.037	.99
Sweets, g/d	10.2 (.5)	10.2 (.3)	10.1 (.3)	10.1 (.3)	10.0 (.5)	.96	.001
→ Chocolate, g/d	10.2 (.4)	9.7 (.3)	9.1(.2)	8.6 (.3)	8.1 (.4)	.02	<.001

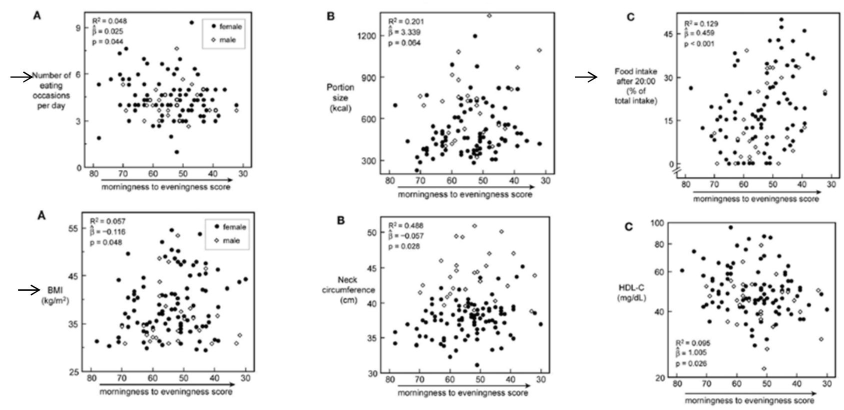
*Lowest ME score quintile represents strong tendency toward eveningness and highest quintile represents strong tendency

Kanerva et al, *Chronobiol Int* 2012

OPEN ACCESS Freely available online PLOS ONE

Evening Chronotype Is Associated with Changes in Eating Behavior, More Sleep Apnea, and Increased Stress Hormones in Short Sleeping Obese Individuals

Eliane A. Lucassen[1], Xiongce Zhao[2], Kristina I. Rother[3], Megan S. Mattingly[4], Amber B. Courville[1], Lilian de Jonge[4], Gyorgy Csako[5], Giovanni Cizza[4*], for the Sleep Extension Study Group



Lucassen et al, *PLoS One* 2013

Smoking, Screen-Based Sedentary Behavior, and Diet Associated with Habitual Sleep Duration and Chronotype: Data from the UK Biobank

Freda Patterson, PhD[1] · Susan Kohl Malone, PhD, RN[2] · Alicia Lozano, MS[2,3] · Michael A. Grandner, PhD, MTR[4] · Alexandra L. Hanlon, PhD[2]

Table 3 Regression models of physical activity, screen-based sedentary behavior, and diet variables on sleep duration and chronotype ($N = 439{,}933$)

Dependent variable	Physical activity (minutes/week)			Screen-based sedentary behavior (hours/day)		Diet variables		Tobacco use
	Walking	Moderate	Vigorous	Computer use	Television viewing	Fruit Servings/day	Vegetables Servings/day	
Comparison[a]	β (SE) 95 % CI	β (SE) 95 % CI	β (SE) 95 % CI	β (SE) 95 % CI	β (SE) 95 % CI	β (SE) 95 % CI	β (SE) 95 % CI	OR (SE) 95 % CI
Short sleep duration	0.060 (0.004) 0.052–0.068	0.049 (0.004) 0.041–0.057	0.093 (0.005) 0.083–0.102	0.049 (0.004) 0.042–0.056	0.201 (0.006) 0.190–0.213	0.017 (0.004) 0.010–0.024	0.008 (0.004) 0.001–0.015	1.450 (0.018) 1.415–1.486
Long sleep duration	−0.016 (0.006) −0.028 to −0.004	0.062 (0.007) 0.048–0.075	0.039 (0.008) 0.023–0.056	−0.067 (0.006) −0.078 to −0.056	0.614 (0.010) 0.595–0.633	−0.042 (0.006) −0.053 to −0.031	0.020 (0.006) 0.008–0.031	1.359 (0.027) 1.306–1.413
Early chronotype	0.090 (0.004) 0.083–0.098	0.100 (0.004) 0.092–0.108	0.130 (0.005) 0.121–0.139	−0.020 (0.004) −0.027 to −0.013	−0.006 (0.006) −0.018–0.005 (NS)	0.144 (0.004) 0.137–0.150	0.106 (0.004) 0.099–0.113	0.833 (0.012) 0.811–0.856
Late chronotype	−0.099 (0.006) −0.111 to −0.088	−0.080 (0.006) −0.092 to −0.067	−0.040 (0.008) −0.054 to −0.025	0.242 (0.005) 0.232–0.253	0.059 (0.009) 0.041–0.076	−0.103 (0.005) −0.113 to −0.092	−0.023 (0.005) −0.034 to −0.013	2.126 (0.034) 2.061–2.193

Patterson et al, *Ann Behav Med* 2016

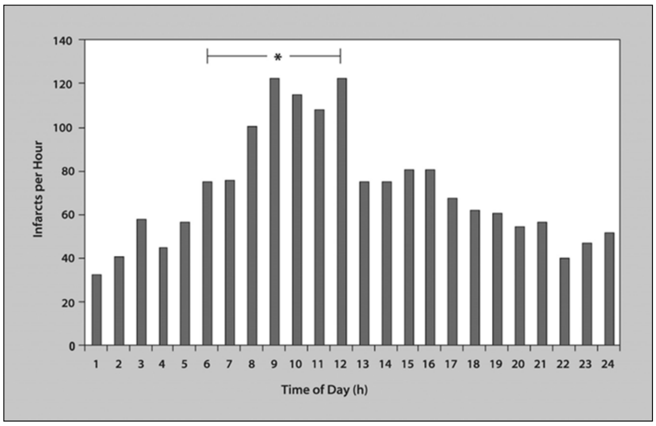
nature REVIEWS ENDOCRINOLOGY

Sleep: Late to bed, late to rise, could be cardiometabolically unwise

Phillips R, 2016 Jan; 12(1):1

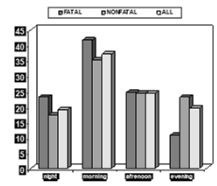
- Circadian rhythms
- Circadian organization and control of bodily's functions
- Desynchronization of circadian rhythms
- Chronotype: morningness or eveningness?
- Chronotype and implications for general, metabolic and cardiovascular health
- Chronobiology and onset of CV diseases

Myocardial infarction and time of day

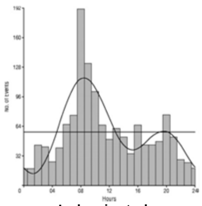


Muller et al, *N Engl J Med* 1985

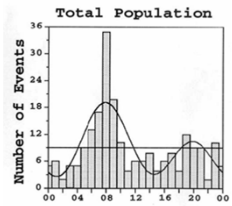
Circadian variation of acute CV diseases



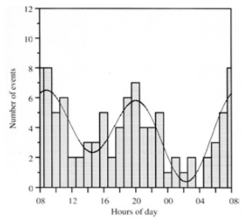
Acute myocardial infarction
Manfredini et al, *Am J Emerg Med* 2004



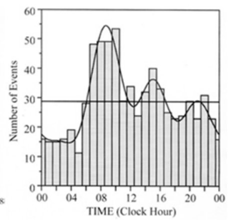
Ischemic stroke
Casetta & Manfredini, *Arch Neurol* 2002



Haemorrhagic stroke
Casetta & Manfredini, *JAMA* 2002

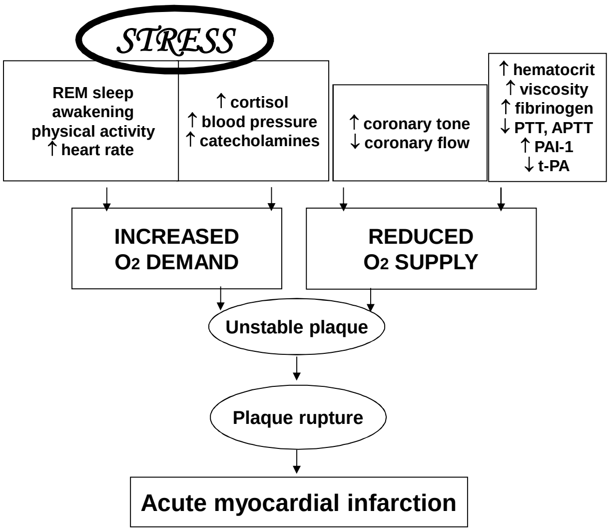


Abdominal aortic aneurysm rupture
Manfredini et al, *Lancet* 1999



Thoracic aortic aneurysm dissection
Mehta & Manfredini, *Circulation* 2002

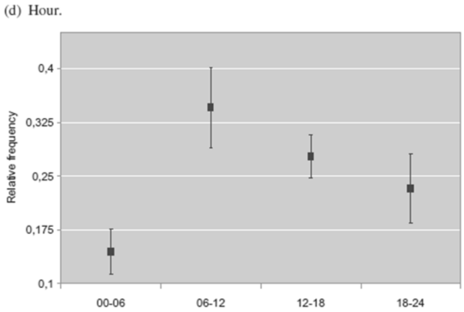
Myocardial infarction and time of day (concurring factors)



Manfredini et al, *Encyclopedia of Stress, Elsevier,* 2007

Chronobiology of acute aortic rupture or dissection: A systematic review and a meta-analysis of the literature

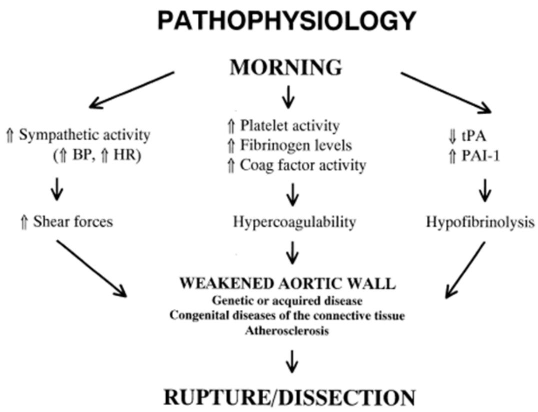
Josè Vitale[1], Roberto Manfredini[2], Massimo Gallerani[3], Nicola Mumoli[4], Kim A. Eagle[5], Walter Ageno[1], and Francesco Dentali[1]



Eight studies (n=1816 patients). Significant increased incidence between 6 a.m. and noon in comparison to the other hours (p<0.001). In the morning hours there is an absolute increased risk of 58% respect to remaining hours and of 139% respect to the night hours.

Vitale et al, *Chronobiol Int* 2015

Concurring pathophysiological factors



Manfredini et al, *J Vasc Surg* 2004

Available online at www.sciencedirect.com

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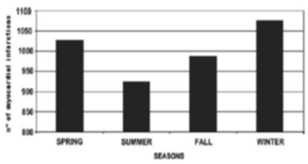
Progress in Cardiovascular Diseases

Chronobiology in Aortic Diseases – "Is This Really a Random Phenomenon?"

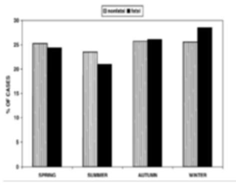
Roberto Manfredini[a, b,*], Fabio Fabbian[a], Fabio Manfredini[b], Raffaella Salmi[c], Massimo Gallerani[d], Eduardo Bossone[e]

Manfredini et al, *Progr Cardiovasc Diis 2013*

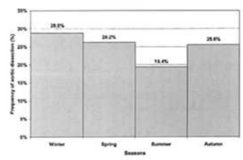
Seasonal variation of acute CV diseases



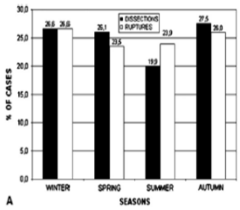
Acute myocardial infarction
Manfredini et al, *Chronobiol Int* 2005

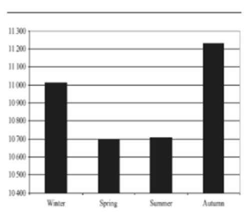


Acute myocardial infarction
Manfredini et al, *Am J Emerg Med* 2009



Acute aortic diseases
Mehta & Manfredini, *Circulation* 2002



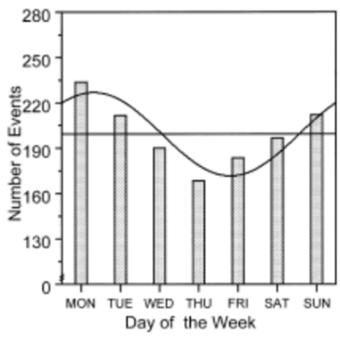


Acute aortic diseases
Manfredini et al, *J Thorac Cardiovasc Surg* 2008

Transient ischemic attack
Manfredini et al, *Clin Appl Thromb Hemost* 2010

Monday Preference in Onset of Ischemic Stroke

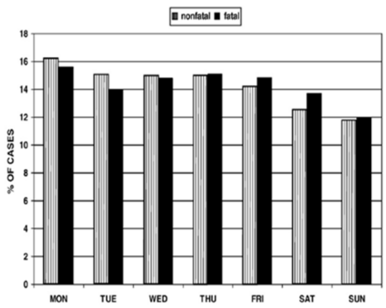
Roberto Manfredini, MD, Ilaria Casetta, MD,
Ezio Paolino, MD, Olga la Cecilia, MD,
Benedetta Boari, MD, Elisa Fallica, MD,
Enrico Granieri, MD



Manfredini et al, Am J Med 2001

Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction☆

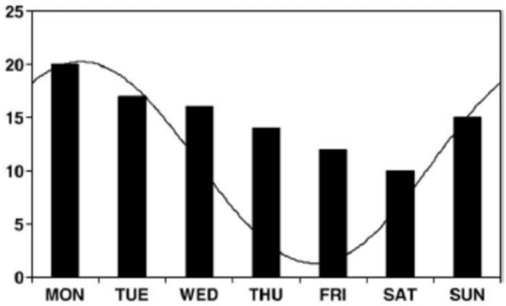
Roberto Manfredini MD[a,b,*], Fabio Manfredini MD[c], Benedetta Boari MD[d],
Elisabetta Bergami MD[d], Elisa Mari MD[d], Susanna Gamberini MD[b],
Raffaella Salmi MD[d], Massimo Gallerani MD[d]



Manfredini et al, Am J Emerg Med 2009

Monday preference in onset of takotsubo cardiomyopathy☆

Roberto Manfredini MD[*,a], Rodolfo Citro MD[b], Mario Previtali MD[c], Olga Vriz MD[d], Quirino Ciampi MD[e], Marco Pascotto MD[f], Ercole Tagliamonte MD[g], Gennaro Provenza MD[b], Fabio Manfredini MD[h], Eduardo Bossone MD, PhD[i]
for the Takotsubo Italian Network investigators

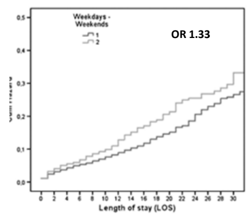


Manfredini et al, Am J Emerg Med 2010

Weekend and acute CV diseases

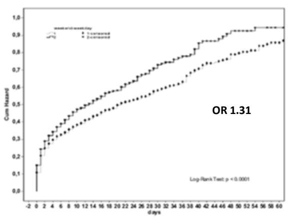
Weekend versus weekday hospital admissions for acute heart failure

Massimo Gallerani[a,*], Benedetta Boari[a], Fabio Manfredini[b], Elisa Mari[a], Cinzia Maraldi[a], Roberto Manfredini[c]



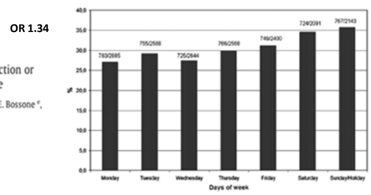
Higher mortality in patients hospitalized for acute aortic rupture or dissection during weekends

Massimo Gallerani, MD,[a] Davide Imberti, MD,[b] Eduardo Bossone, MD,[c] Kim A. Eagle, MD,[d] and Roberto Manfredini, MD,[a] *Ferrara and Milan, Italy, and Ann Arbor, Mich*



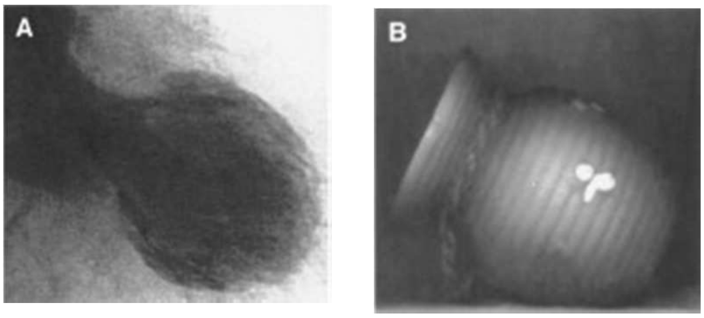
Outcomes of weekend versus weekday admission for acute aortic dissection or rupture: A retrospective study on the Italian National Hospital Database

M. Gallerani[a,*], S. Volpato[b], B. Boari[a], M. Pala[c], A. De Giorgi[c], F. Fabbian[c], V. Gasbarro[d], E. Bossone[e], K.A. Eagle[f], F. Carle[g], R. Manfredini[h]



Gallerani et al, *Int J Cardiol* 2011; *J Vasc Surg* 2012; *Int J Cardiol* 2013

Tako-Tsubo cardiomyopathy

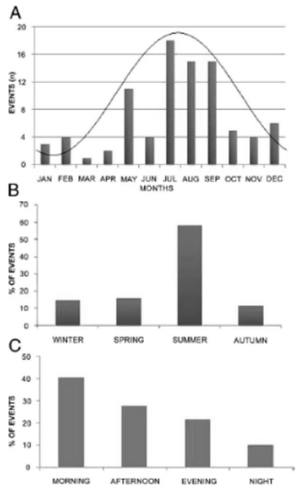


Chronobiological Patterns of
Onset of Tako-Tsubo Cardiomyopathy

A Multicenter Italian Study

*Rodolfo Citro, MD

Mario Previtali, MD
Daniella Bovelli, MD
Olga Vriz, MD
Costantino Astarita, MD
Marco Mariano Patella, MD
Gennaro Provenza, MD
Corinna Armentano, MD
Quirino Ciampi, MD
Giovanni Gregorio, MD
Massimo Piepoli, MD
Eduardo Bossone, MD, PhD
Roberto Manfredini, MD



Citro et al, *J Am Coll Cardiol* 2009

Monday preference in onset of takotsubo cardiomyopathy☆

Roberto Manfredini MD[*,a], Rodolfo Citro MD[b], Mario Previtali MD[c], Olga Vriz MD[d], Quirino Ciampi MD[e], Marco Pascotto MD[f], Ercole Tagliamonte MD[g], Gennaro Provenza MD[b], Fabio Manfredini MD[h], Eduardo Bossone MD, PhD[i]
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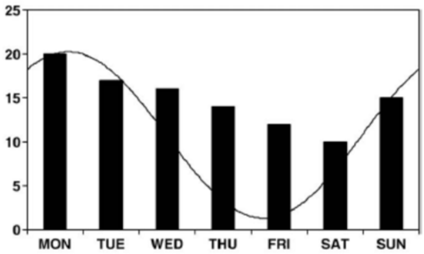

Manfredini et al, *Am J Emerg Med* 2010

Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction☆

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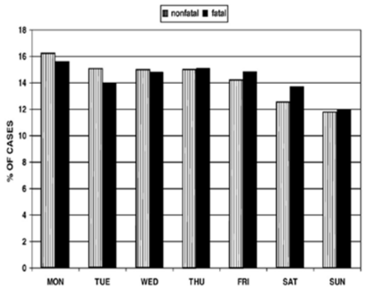
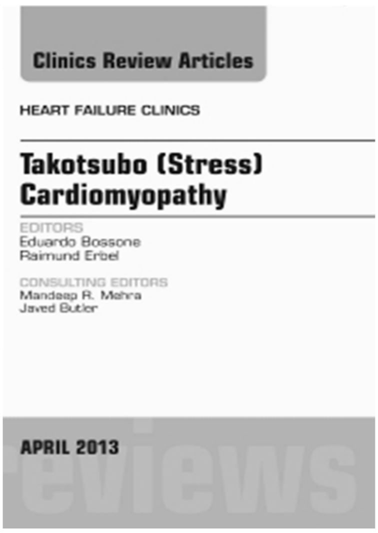
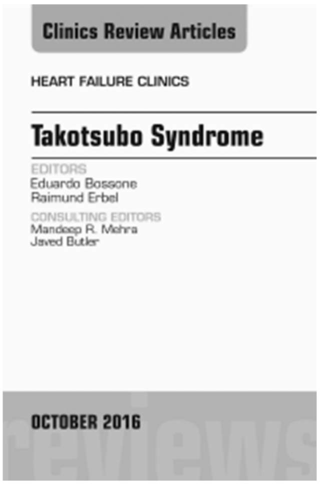


Manfredini et al, *Am J Emerg Med* 2009

Breaking Heart
Chronobiologic Insights into Takotsubo Cardiomyopathy

Roberto Manfredini, MD[a,*], Raffaella Salmi, MD[b], Fabio Fabbian, MD[c], Fabio Manfredini, MD[d], Massimo Gallerani, MD[e], Eduardo Bossone, MD[f,g]





Chronobiology of Takotsubo Syndrome and Myocardial Infarction
Analogies and Differences

Roberto Manfredini, MD[a,*], Fabio Manfredini, MD[b],
Fabio Fabbian, MD[a], Raffaella Salmi, MD[c],
Massimo Gallerani, MD[d],
Eduardo Bossone, MD, PhD, FCCP, FESC, FACC[e],
Abhishek J. Deshmukh, MBBS[f]

European Journal of Internal Medicine 24 (2013) 698–706

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Review article

Circadian rhythms and medical diseases: Does it matter when drugs are taken?

Alfredo De Giorgi [a], Alessandra Mallozzi Menegatti [a], Fabio Fabbian [a],
Francesco Portaluppi [b], Roberto Manfredini [a,*]

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[b] Hypertension Unit, Clinica Medica, Azienda Ospedaliera-Universitaria, Ferrara, Italy

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Sleep Medicine Reviews xxx (2016) 1–3

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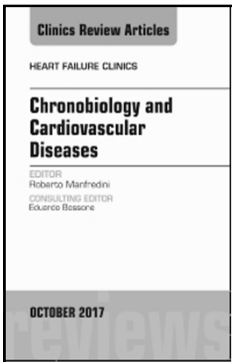
GUEST EDITORIAL

A pill at bedtime, and your heart is fine? Bedtime hypertension chronotherapy: An opportune and advantageous inexpensive treatment strategy

Roberto Manfredini*, Fabio Fabbian

Clinica Medica Unit, Department of Medical Sciences, University of Ferrara School of Medicine, Ferrara, Italy



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