The Role of Sleep in Causing and Treating Depression

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Words of wisdom from Homer

- "Even where sleep is concerned, too much is a bad thing" [Homer, *Odyssey*, 9th century BCE]

I've given a lot of thought to how I could best present this topic, and probably my best bet is to simply take you through my own thought processes as my thinking evolved.

When I was still a psychiatry resident, working in the outpatient clinic, I was looking after a young woman with a severe bipolar disorder. In the past, she had frequently stopped her medication, which consisted of two mood stabilizers as well as a hefty dose of rivotril. But at this point, she was doing well in her life, she was working, she was compliant with her medication, and she was happy to be well.

One day she called me, and I could immediately tell from her tone of voice and her pressured speech that she was very manic. As I had seen her in clinic just the day before, this was a complete surprise to both of us. Here is what had happened.

Her sister had become very ill, and my patient had spent the entire night, awake, at her bedside in the Intensive Care Unit. The next morning, my patient was floridly manic.

What had changed? She was still taking her medication, there had been no dosage changes. The answer seemed to be the sleep deprivation.

We hadn't covered this topic in medical school, so I hit the hospital library. Sure enough, there was quite a literature on the use of sleep deprivation to treat depression, and in common with other antidepressant treatments, sleep deprivation could also trigger mania.

Well, I thought, if sleep deprivation can cause mania, and mania and depression are on a spectrum, then it would make sense that too much sleep could cause depression.

Characteristics of Sleep

- 2 independent states: REM and NREM sleep
- REM sleep: 20-25%
  - First cycle: 60-90 min after sleep onset
  - Recurs every ~90 min
  - Successive stages generally get longer
- NREM sleep: 4 stages, based on EEG
  - Stage 1: 3-8%
  - Stage 2: 45-55%
  - Stage 3 & 4 (Slow wave sleep, delta sleep): 15-20%

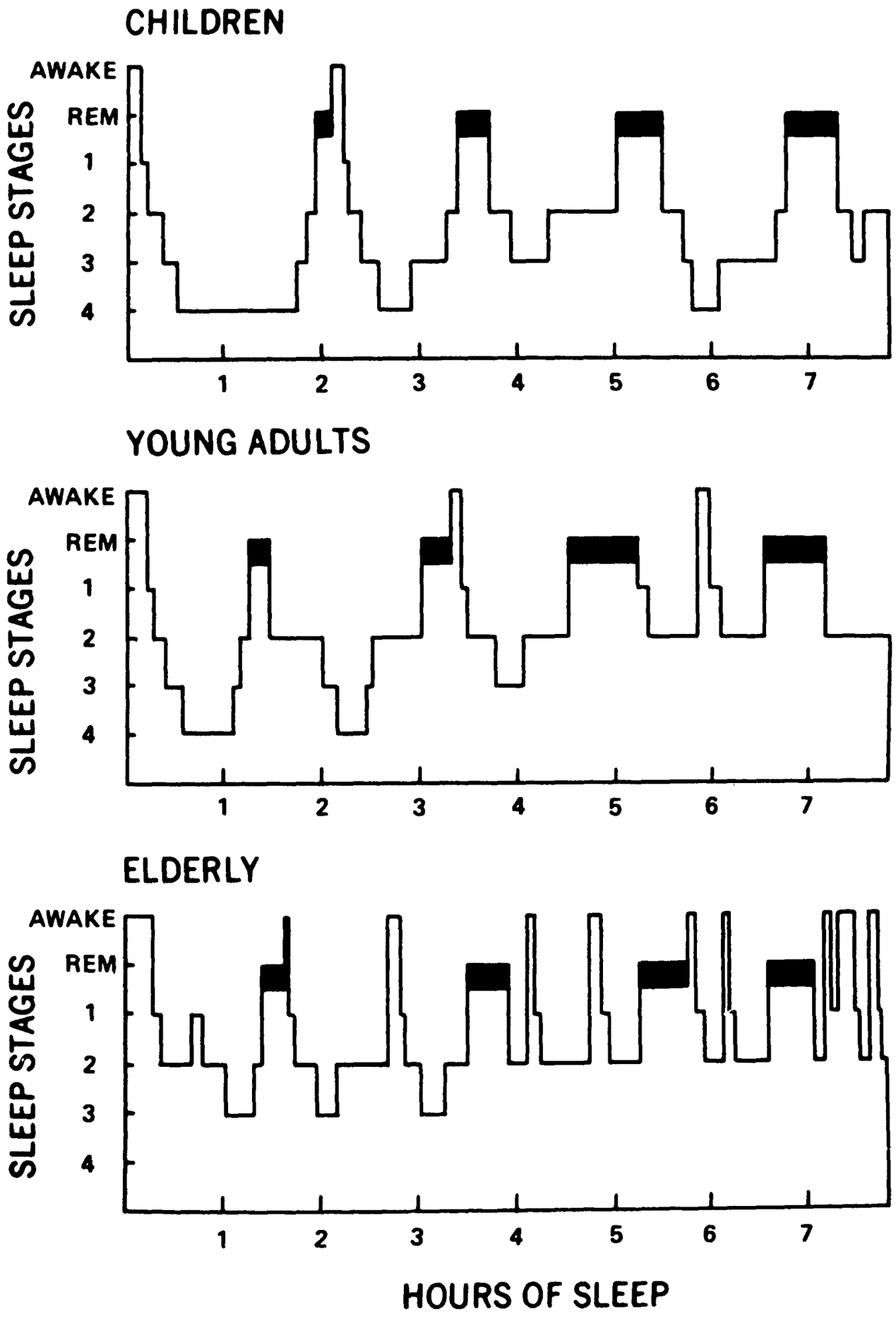
Too much sleep. What the heck does that mean? Let's look a bit deeper into sleep.
In spite of tons of research, we still don't know what sleep is for. However, there are some intriguing hints.
♥
Sleep consists of two major states: rapid eye movement sleep, REM sleep for short, also called paradoxical sleep.
And then there is non-rapid eye movement sleep, or NREM sleep.
♥
REM sleep is the stage during which we do most of our dreaming. All our muscles are usually completely paralysed, except for the muscles of respiration and our eye movement muscles. During this stage of sleep, our eyes move rapidly back and forth, as if we're looking at things. Our brain waves during this stage of sleep look just like they do when we're awake, however.

Many researchers believe that REM sleep is when newly learned information is converted to long-term memory.
♥
NonREM sleep is further broken down into 4 stages, based on various electro-encephalogram criteria. Stages 3 and 4 are usually referred to as slow wave sleep or delta sleep, and this is the portion of sleep that is thought to be the deep, restorative, and refreshing sleep.

However, nonREM sleep does not appear to be essential. Some people think that it exists simply to provide a frame for the essential REM sleep.

EEG Stages of Normal Sleep

- Note decrease in stage 3 and 4, and increase in awakenings, with aging
- REM sleep occurs every 90 minutes, and increases through the night



This slide shows three typical somnogram recordings. The thick black bars represent REM sleep. What I particularly want you to note is that each successive REM period gets longer through the night.

Sleep Deprivation as an Antidepressant

- Total sleep deprivation: antidepressant response in 60%

Beersma DG, van den Hoofdakker RH. Can non-REM sleep be depressogenic? J Affect Disord. 1992;24:101-108.

  - Can trigger mania in BAD patients, normals

Wright JB. Mania following sleep deprivation. Br J Psychiatry. 1993;163:679-680.

- Selective REM sleep deprivation: same antidepressant effect as total sleep deprivation

Vogel GW, Thurmond A, Gibbons P, Sloan K, Walker M. REM sleep reduction effects on depression syndromes. Arch Gen Psychiatry. 1975;32:765-777.

- Late partial sleep deprivation (5 hrs max between 8 pm and 2 am) was effective; early PSD (5 hrs max between 2 and 8 am) was not

Leibenluft E, Moul DE, Schwartz PJ, Madden PA, Wehr TA. A clinical trial of sleep deprivation in combination with antidepressant medication. Psychiatry Res. 1993;46:213-227.

There are quite a few studies out there showing that total sleep deprivation ♥ can reverse depression in about 60% of patients, the same day. Unfortunately, when these patients sleep again, the depression often returns. And you can't keep on doing total sleep deprivation indefinitely, so as a clinical treatment, it hasn't been useful, except perhaps to kickstart a response when other antidepressant treatments are used.

♥

Like other antidepressant treatments, total sleep deprivation can trigger mania in patients with bipolar affective disorder, as I saw with my patient. Interestingly, total sleep deprivation also can stimulate mania in people who have never been psychiatrically ill. Does this mean they have a bipolar disorder anyway?

♥

If you hook somebody up to an electroencephalogram and also monitor eye movements, you can arrange to wake them up every time they go into REM sleep. This selective REM sleep deprivation is also effective against depression.

♥

What I found most interesting, however, is that partial sleep deprivation can also be effective, and can be carried on for a period of time. The timing of the awake part seems to be very important, however.

REM sleep and depression

- Reserpine increases REM sleep, causes depression

Leibenluft E, Moul DE, Schwartz PJ, Madden PA, Wehr TA. A clinical trial of sleep deprivation in combination with antidepressant medication. Psychiatry Res. 1993;46:213-227.

- REM sleep is increased in depression, suicidal patients, PTSD, irritable bowel syndrome

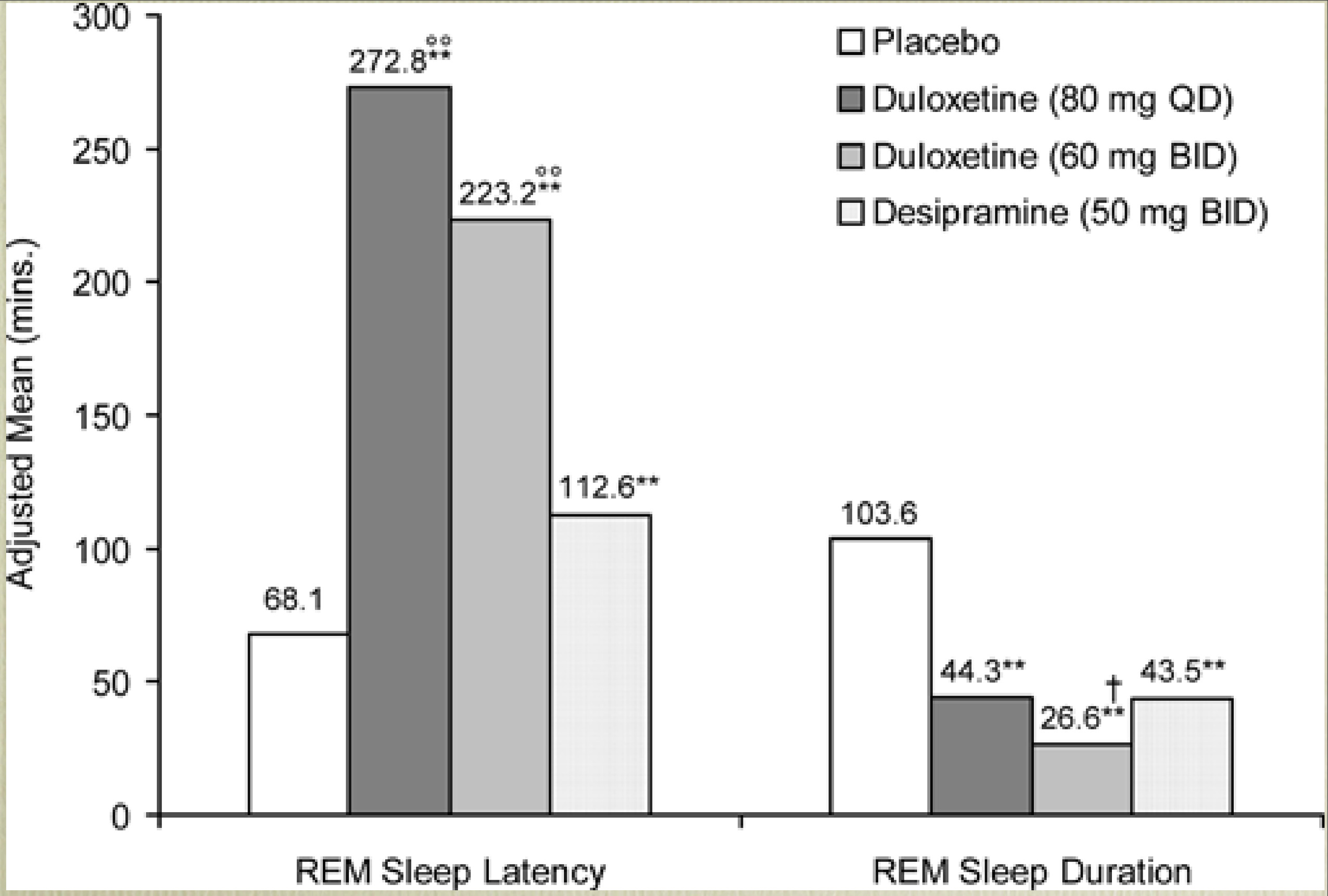
Thase ME, Reynolds CF, 3rd, Frank E, et al. Polysomnographic studies of unmedicated depressed men before and after cognitive behavioral therapy. Am J Psychiatry. 1994;151:1615-1622.
Agargun MY, Cartwright R. REM sleep, dream variables and suicidality in depressed patients. Psychiatry Res. 2003;119:33-39.
Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev. 2003;23:377-407.
Orr WC. Sleep and functional bowel disorders: can bad bowels cause bad dreams? [editorial; comment]. Am J Gastroenterol. 2000;95:1118-1121.

- Effective antidepressant treatments (including SSRIs, TCAs, MAOIs, ECT, psychostimulants, exercise, and total sleep deprivation) suppress REM sleep

eg, Nofzinger EA, Reynolds CF, 3rd, Thase ME, et al. REM sleep enhancement by bupropion in depressed men. Am J Psychiatry. 1995;152:274-276.

Research into the use of sleep deprivation to treat depression noted something important: the likelihood of relapse into depression could be predicted based on how much REM sleep was contained in the sleep after the sleep deprivation. This, along with the finding of an antidepressant effect based on selective REM sleep deprivation, brought home the point that REM sleep was intimately hooked up with depression.

Other bits of evidence connecting depression and REM sleep are shown on this slide.



Chalon S, Pereira A, Lainey E, et al. Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. Psychopharmacology (Berl). 2005;177:357-365.

Here is one example of the REM suppressing effects of antidepressants. Duloxetine, a recent antidepressant that goes by the name of Cymbalta, suppresses REM sleep very powerfully, and increases the time to the first REM period, compared to desipramine, which is no slouch in the REM suppression department either. This was a randomized, double-blind crossover study in 12 healthy young male adults. Each dosing period lasted 7 days.

"Depressiogenic Theory of Sleep"

- "Sleep may induce depression and sleep deprivation relieves it"
- "The depressiogenic effect of sleep may be specifically due to rapid eye movement (REM) sleep"

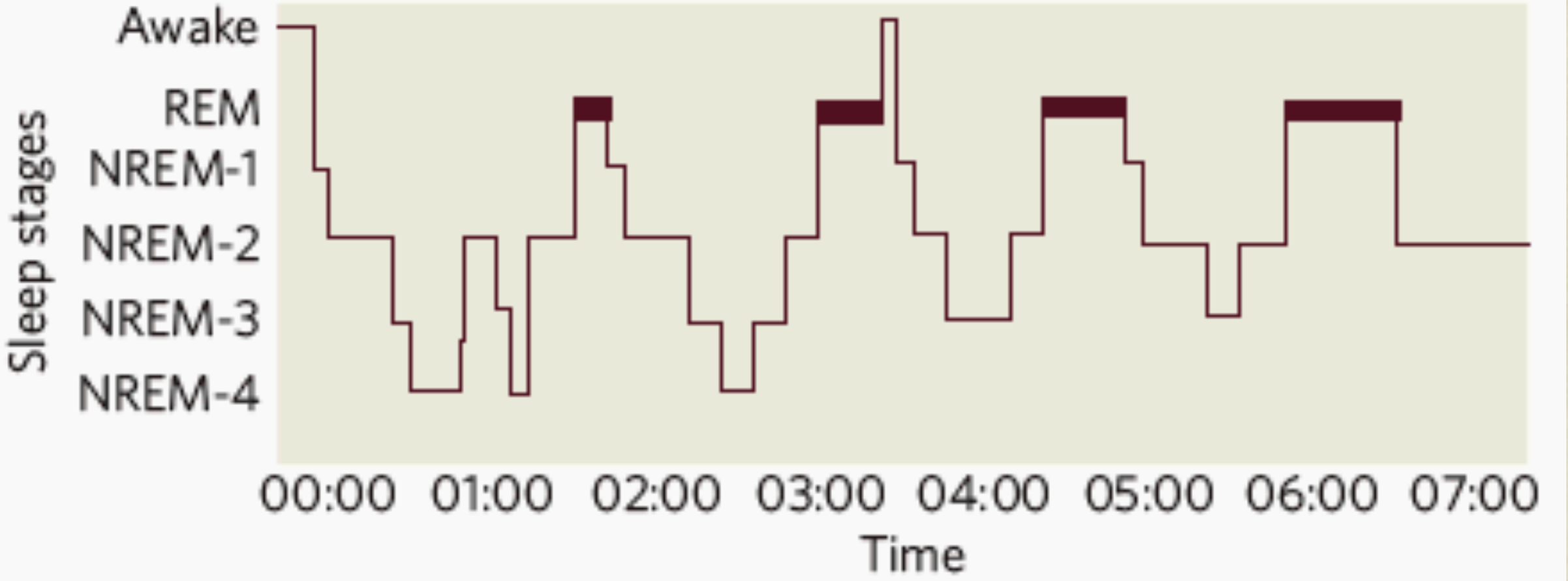
Wiegand M, Berger M, Zulley J, Lauer C, von Zerssen D. The influence of daytime naps on the therapeutic effect of sleep deprivation. Biol Psychiatry. 1987;22:389-392.

So if REM sleep is so intimately involved in depression and its treatment, is it perhaps too much REM sleep in particular that can cause depression?

Wiegand and coworkers expressed the same theory in an article in 1987.

Let's assume for the moment that their theory holds water. How would somebody go about getting too much REM sleep?

I already mentioned a medication, reserpine, which increases REM sleep and can cause depression. But the easiest way is to just sleep more. That will increase REM sleep.

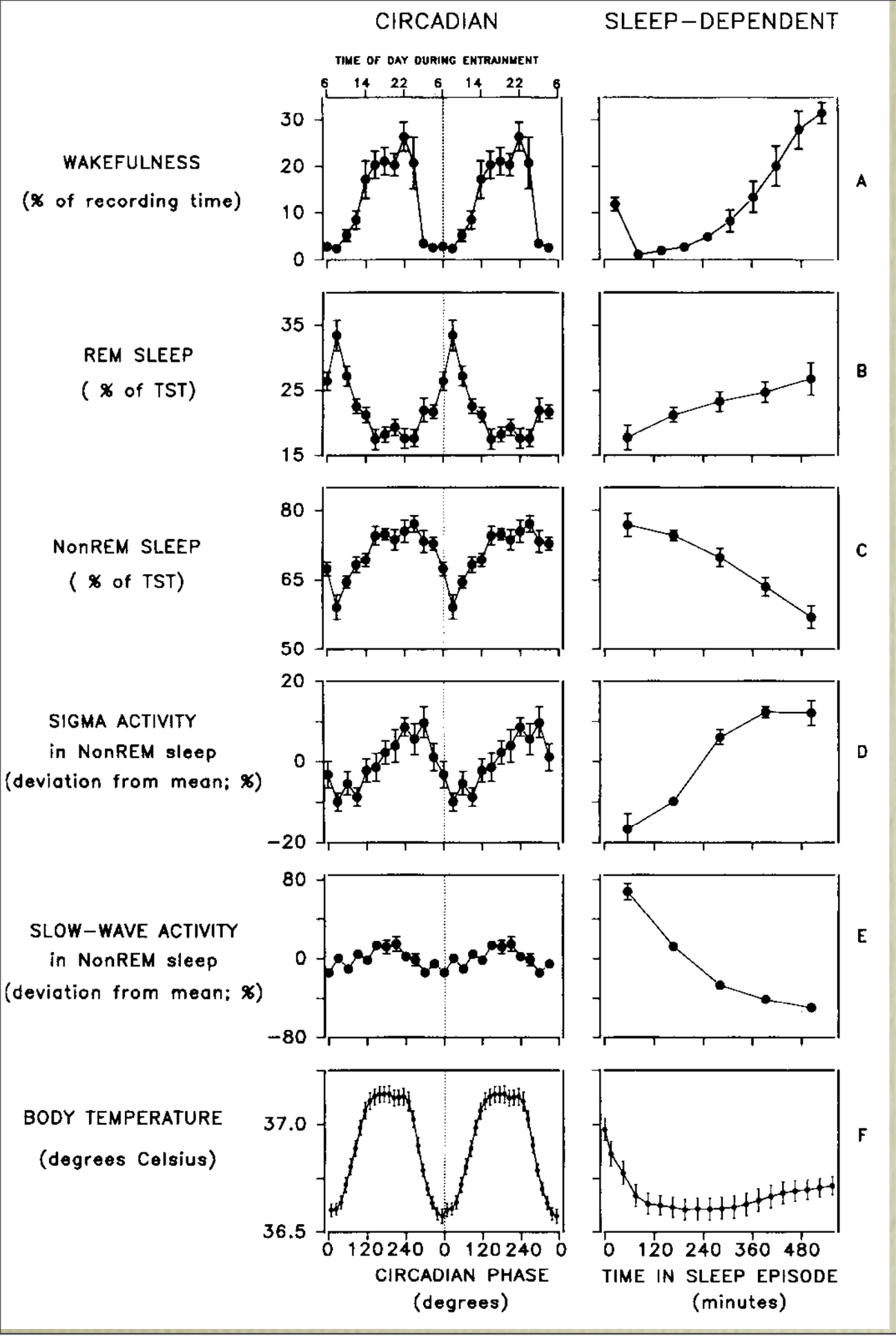


But it turns out that tacking on extra sleep in the morning has a much greater effect on the amount of REM sleep than going to bed earlier. This slide shows that each REM period through the night gets longer. This happens because REM sleep is powerfully controlled by our built-in circadian rhythm.

Circadian rhythms are complicated. They could take up an entire course in graduate physiology.

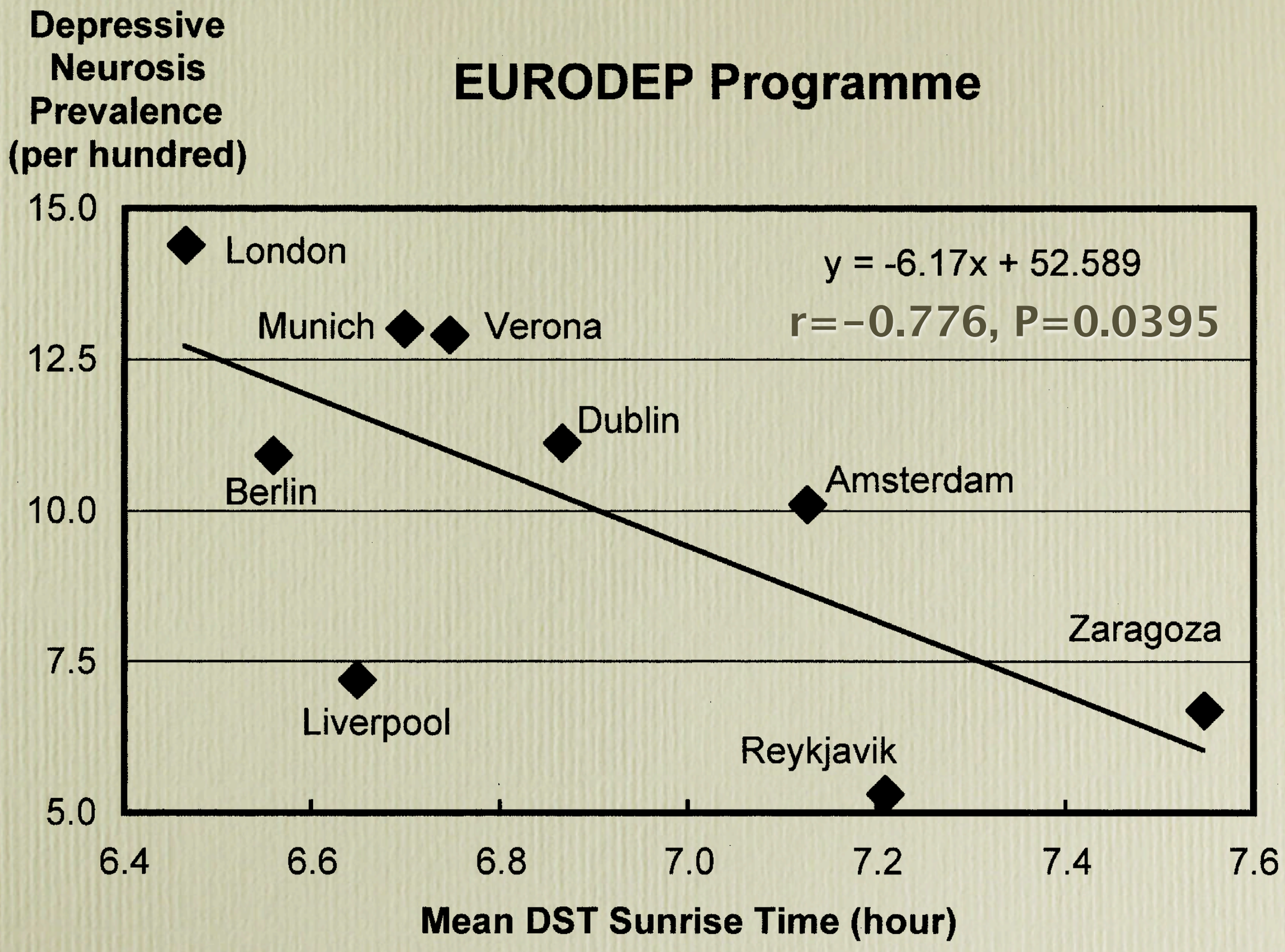
But very basically, circadian rhythms vary over the 24 hour period of the day, and affect all sorts of body processes, including body temperature, melatonin and cortisol secretion, how we feel, how well our brains work, and of course, how we sleep. And the most important factor that controls these rhythms is the transition from dark to light in our environment, which could be the dawn, or when we open the drapes in our bedroom, or just turning on the lights.

It turns out, though, that our sleep habits also control our circadian rhythms.



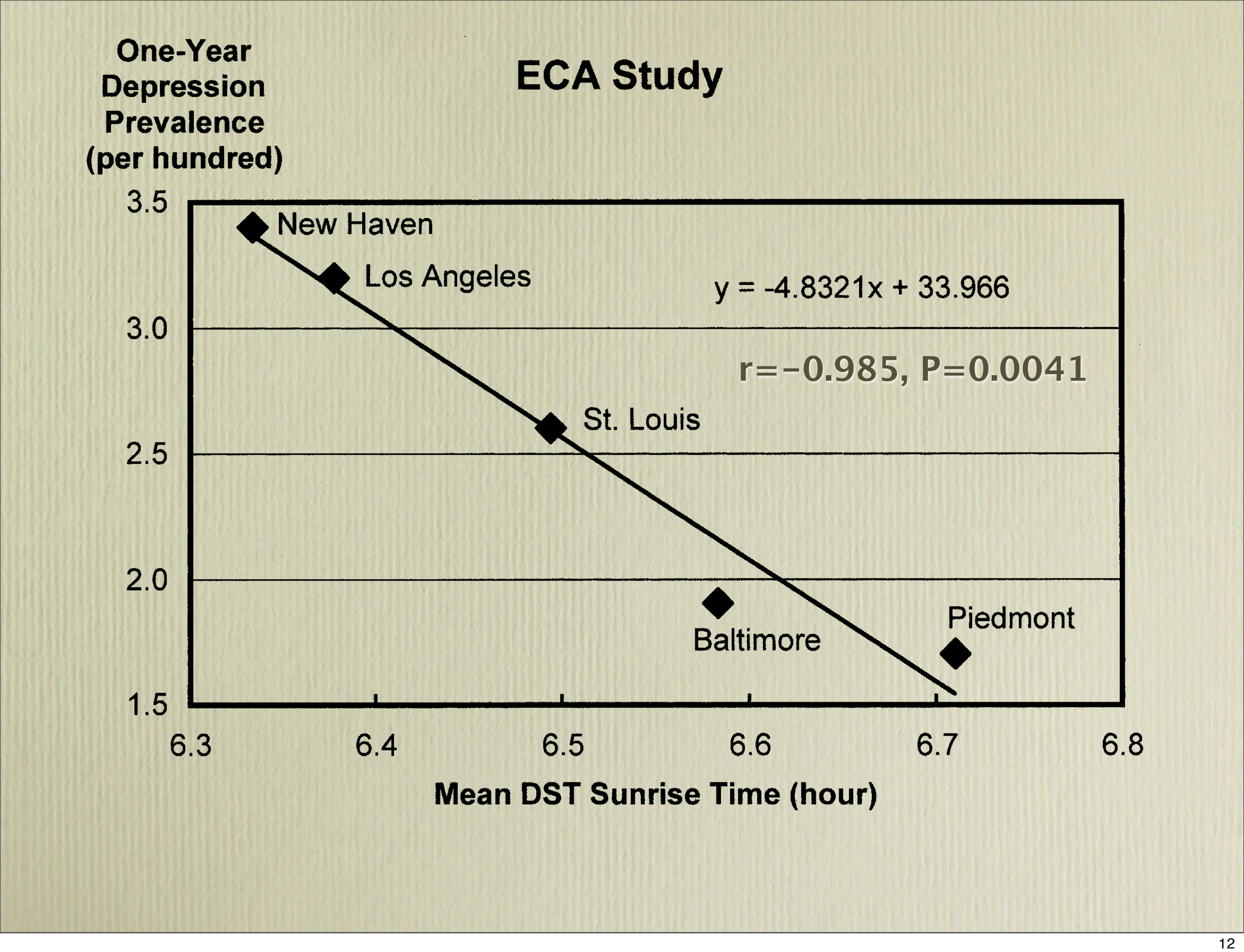
Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci. 1995;15:3526–3538.

This slide is an attempt to dissect out the independent effects on various aspects of sleep, due to either circadian rhythm, or to the effects of sleep itself. This was done by having volunteers sleep at all different hours of their endogenous rhythm, and then mathematically extracting the information. These graphs show, on the left, the influence of circadian rhythm, and on the right, that of sleep. Working up from the bottom, we have core body temperature, which is mostly affected by rhythm only; slow-wave sleep, very little affected by circadian rhythm; skip the next couple; second-last is REM sleep propensity, which again is mostly circadian, and at the top, wakefulness, which is mostly affected by sleep.
I looked long and hard for studies which related depression to sleep length or to rising times, without success. So I did my own...



Olders H. Average sunrise time predicts depression prevalence. J Psychosom Res. 2003;55:99–105.

I used the results of a study which looked at depression prevalence in nine European cities. Since city dwellers tend to get up by clock time rather than at dawn as many rural residents do, the getting up time will be relatively early or late, in comparison to the time of sunrise, and thus in comparison to their circadian rhythm when these are based on sunrise time. I predicted that early risers, in relation to sunrise time, would have less depression. Thus, cities with later sunrise times should have lower prevalences of depression. That's exactly the case in these nine cities. The Pearson correlation coefficient was -.776, with a probability of 0.0395



Even more impressive results were obtained for the depression prevalences reported for five urban areas in the US. Here, the Pearson correlation coefficient was -.895, with a probability of .0041.

What determines the average sunrise time for a city? It is based entirely on how far east or west a city is located within its time zone.

This suggests that one way to decrease depression would be to use daylight saving time year-round, or simply to adopt the time zone to your east. Individuals, of course, could just get up earlier.

Jet lag and affective disorder

- Eastbound travellers can develop mania
- Westbound travellers can develop depression

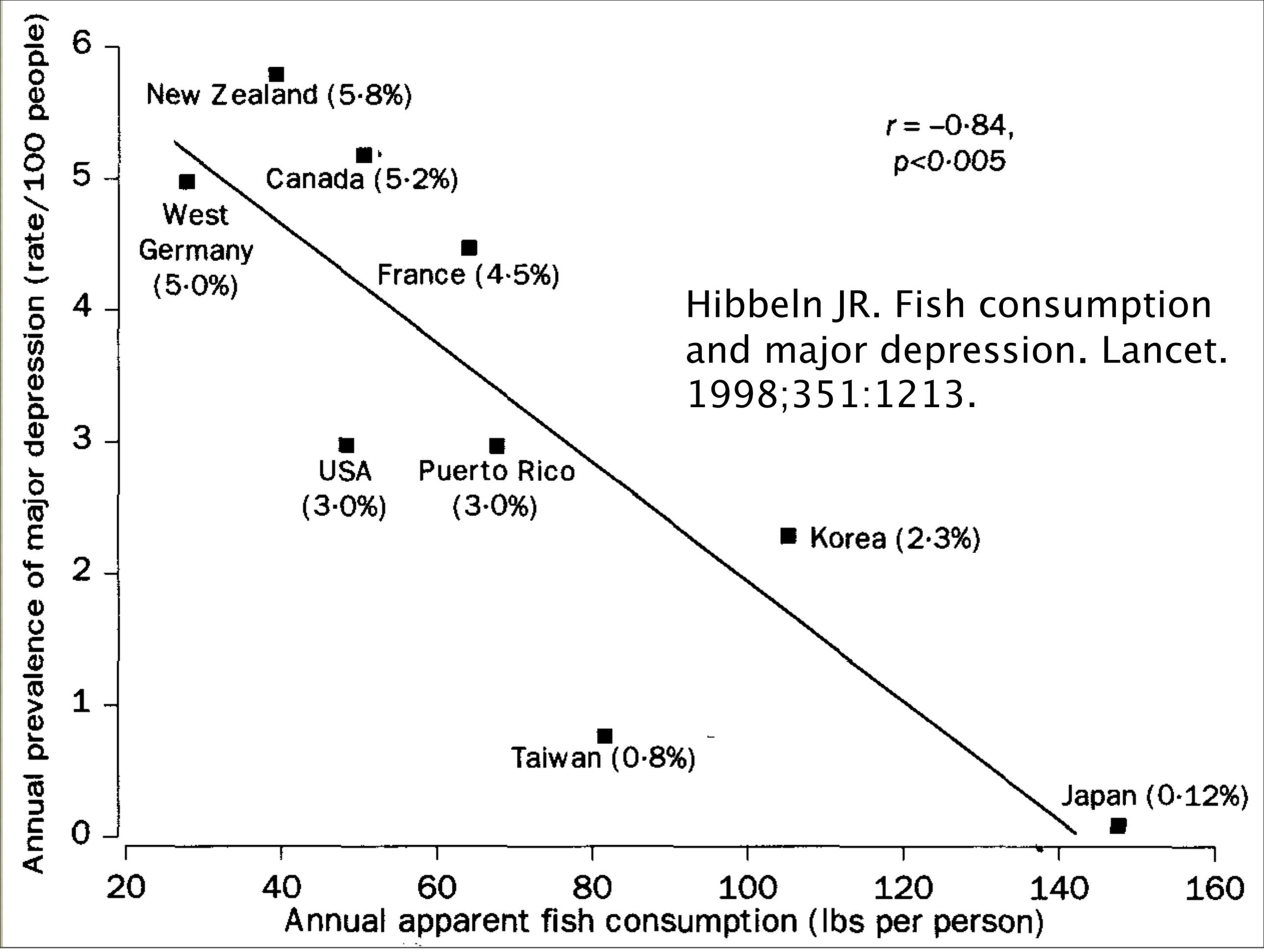
Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. Br J Psychiatry. 1982;140:231-235.

Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. Compr Psychiatry. 1995;36:224-228.

A sure-fire way to get your circadian rhythms out of synch with your sleep, is to fly across time zones, as many of you well know. It turns out that this is enough to make some people psychiatrically ill, so that they require hospitalisation.

Two separate studies have found that crossing several time zones in the eastbound direction, which means that you will be getting up much earlier than your usual time, when you get to your destination, is significantly more likely to trigger mania, while going west is more likely to result in depression.

I think the depression is caused by sleeping later than your usual if you attempt to follow the new local sleep schedule after you arrive at your destination.



Hibbeln JR. Fish consumption and major depression. Lancet. 1998;351:1213.

I wouldn't want to imply that the only thing that matters for depression is your sleep pattern. Many studies show that there is a strong genetic component, and another important factor appears to be the omega-3 fatty acid content of your diet. This graph compares depression prevalences with annual fish consumption, for a number of countries around the globe. Look where Canada sits.

What happens if you sleep too much or get up late?

- Students sleeping 10 or more hours: worn-out, tired, lethargic, irritable, fuzzy thinking, difficulty getting going

  Globus GG. A syndrome associated with sleeping late. Psychosom Med. 1969;31:528-535.

- Extended sleep impairs alertness

  Taub JM. Individual variations in awakening times, daytime alertness and somnograms as a function of ad libitum extended sleep. Int J Neurosci. 1983;21:237-250.

- Late rising correlates with lower GPA scores

  Trockel MT, Barnes MD, Egget DL. Health-related variables and academic performance among first-year college students: implications for sleep and other behaviors. J Am Coll Health. 2000;49:125-131.

- Longer sleep has higher mortality

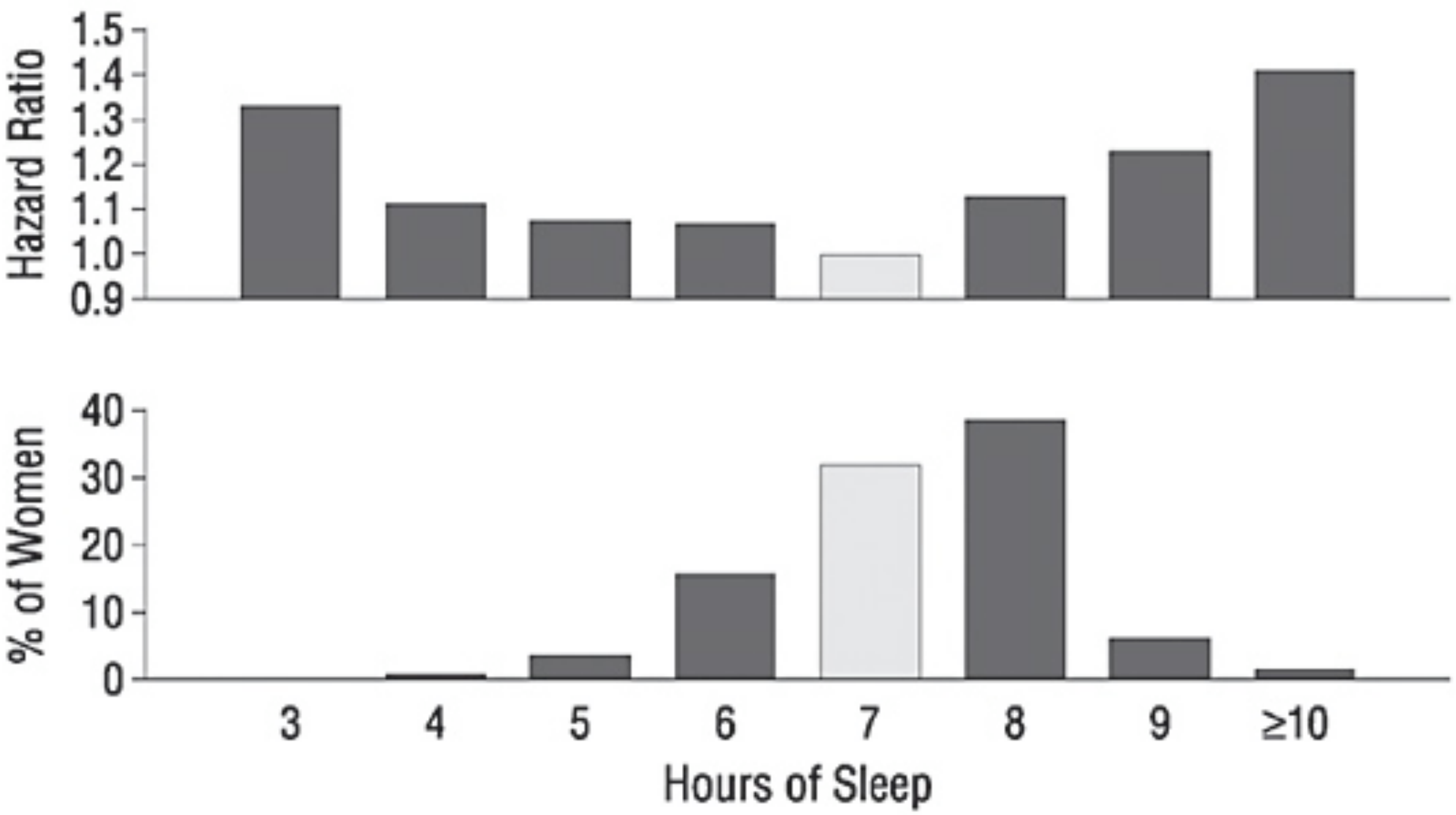
  Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry. 2002;59:131-136.

So, if only a small percentage of the population is likely to get depressed if they sleep too long or too late, what would happen to all those other people who are not genetically predisposed to become depressed?

This slide shows some of the research which touches on this question. I find it very surprising that this issue has been studied so little. Perhaps it's because so many people believe that the vast majority of North Americans are sleep deprived. We seem to have the idea that if too little sleep is bad, then more sleep has got to be good, right?

But think about this for a minute. Is there anything in life that we need, where we can have as much as we want with no ill effects? We need food, but too much food is unhealthy. We need sun, but too much sun causes skin cancer. We need oxygen, but too much oxygen causes blindness in premature infants. Even water; the big danger for marathon runners these days is drinking too much, a condition called water intoxication, which causes the brain to swell up and can even kill you!

You parents out there may want to pay particular attention to the third study, about college marks. These researchers looked at about 40 different psychosocial parameters; out of the forty, the only one which correlated significantly with GPA scores was the getting up time.



Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry. 2002;59:131-136.

This is a graph from the last article on the previous slide, about mortality. Here is what happens if you sleep either too long or too short, if you're a woman. The curve for men looks the same.

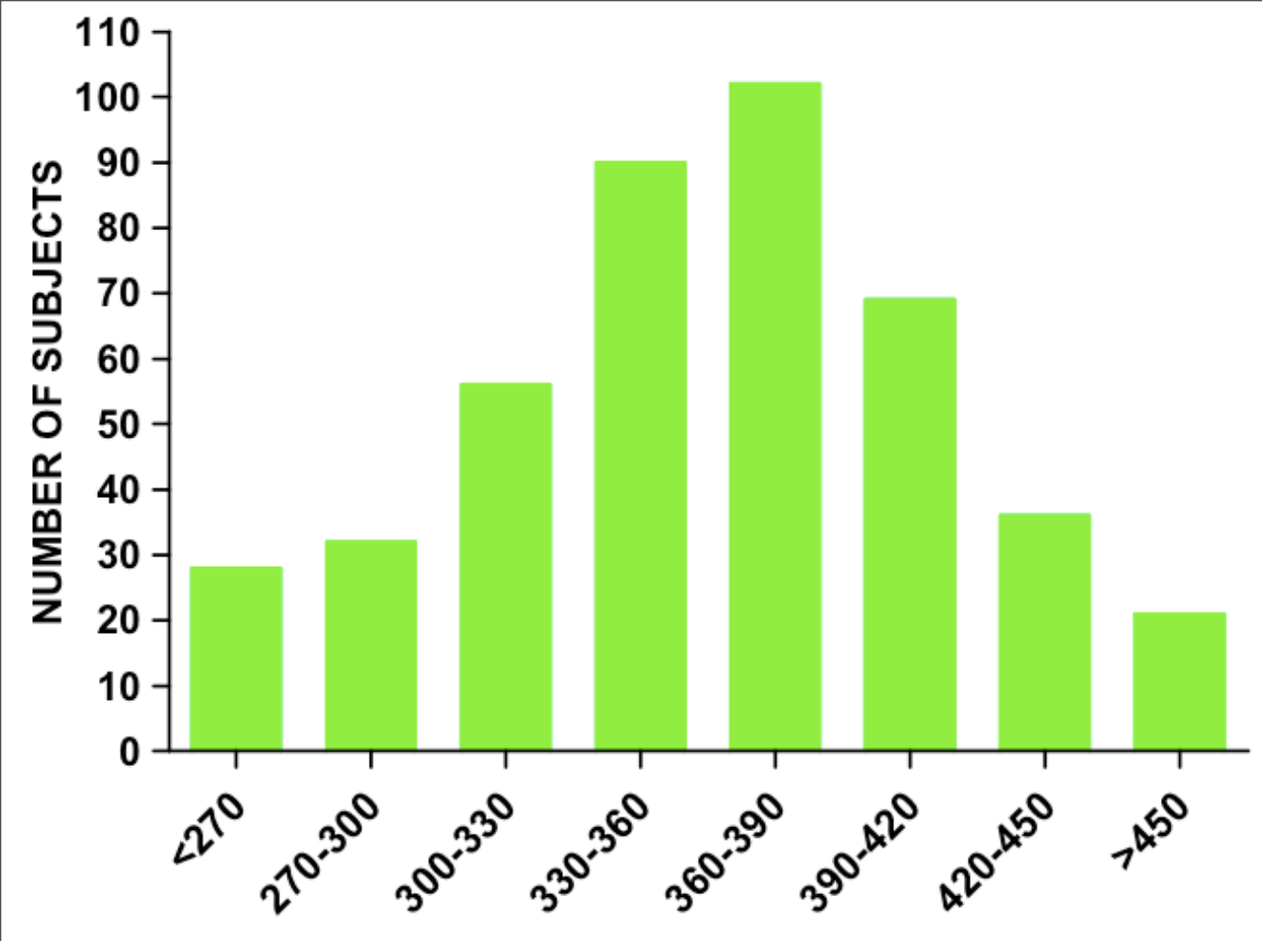
Clearly, it is better to sleep too little than to sleep too much.

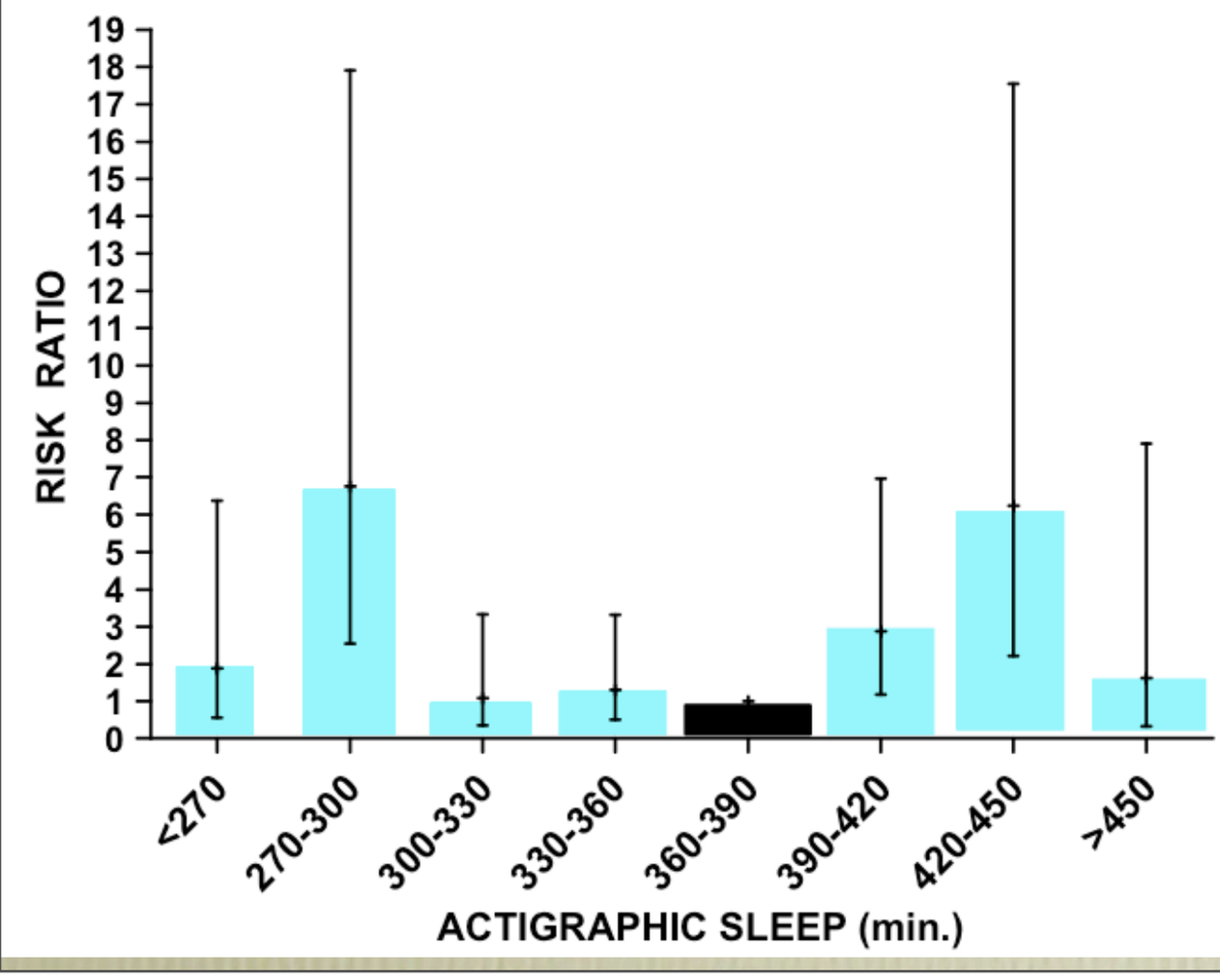
Long sleep associated with mortality has been looked at in a number of studies: compared with those sleeping 5 hours, women reporting 9 hours of sleep had a either a 15%, 30%, or 33% greater mortality risk, in 3 separate studies. And a number of possible causes have been implicated: obesity, diabetes, heart disease, and stroke are more common in those with prolonged sleep.

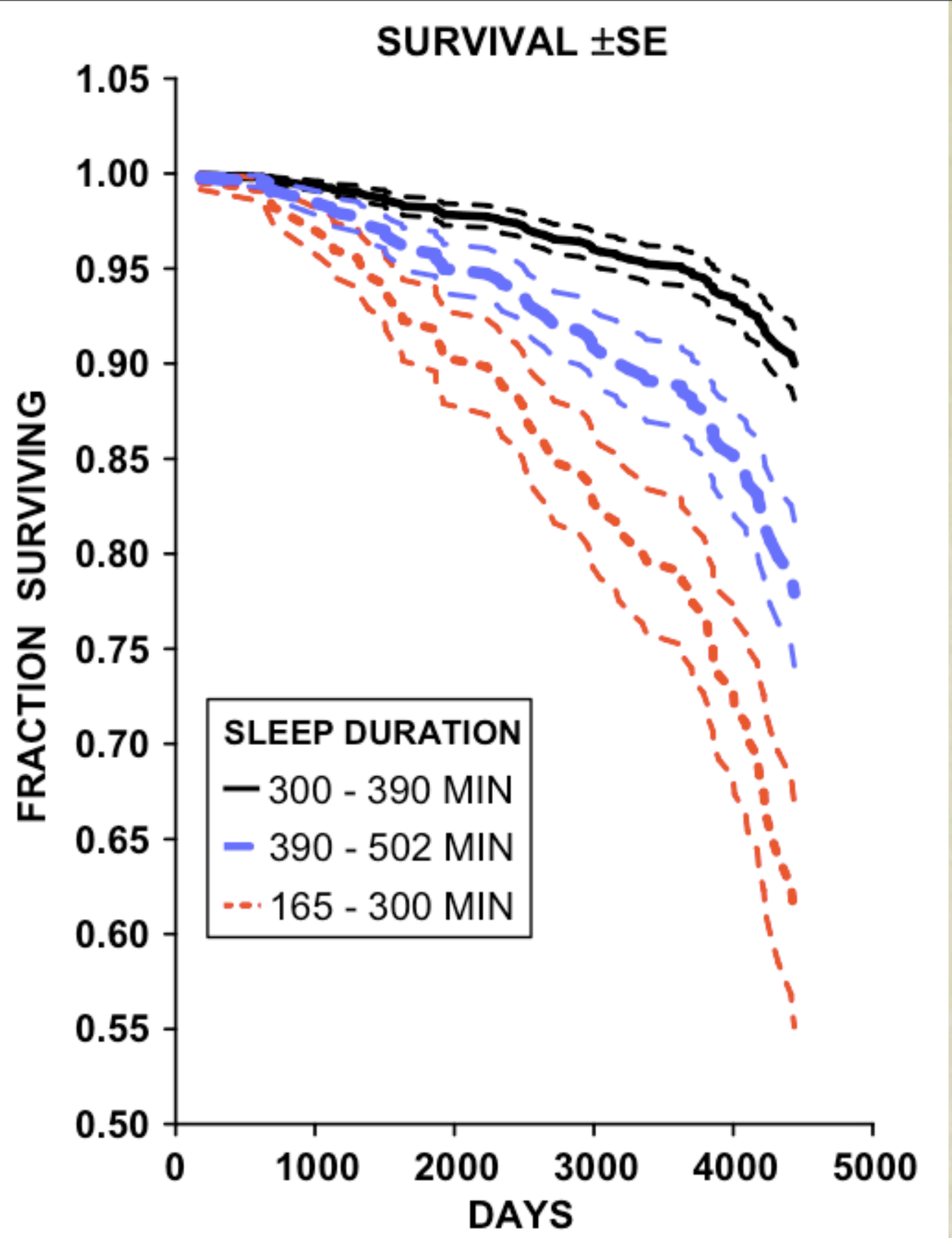
But all of these studies suffer from an important weakness: sleep duration was reported rather than being measured. In seniors where these diseases and mortality are of most concern, the association between self-reported vs objectively-recorded sleep duration is pretty loose.

To correct this deficiency, the same group that did the study shown in this slide looked at mortality in a group of women on whom they had collected actigraphic sleep recordings way back in 1995 through 1999. I am tempted to say that this study is "hot off the presses" but that would be inaccurate. In fact, it's so new that it's only available online so far.

An actigraph is a device that you wear on your wrist. It measures and stores movement data, using the same kind of accelerometers that your iPhone uses for playing games. A computer program analyses the movement data to predict whether you are awake or asleep.







Kripke DF et al. Mortality related to actigraphic long and short sleep. Sleep Med (2010), doi:10.1016/j.sleep.2010.04.016

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So this represents up to 14 years of followup. This slide shows the results. The green bars represent the number of subjects in each sleep duration group, for sleep durations ranging from less than 4 1/2 hours, 4 1/2 to 5 hours, 5 to 5 1/2 hours, and so on. ♥

The graph underneath shows the relative risk ratios for mortality for each group, using the group shown in black as the reference. ♥

The graph on the side shows the survival over time, for just 3 groups. The solid black line is the group whose actigraphically measured sleep was between 300 and 390 minutes, ie between 5 and 6 1/2 hours. This group had the lowest mortality. The dashed black lines on each side of the solid black line represent the standard error limits.

The blue lines, with intermediate survival, are for the group sleeping more than 6 1/2 hours, and the red lines for those sleeping less than 5 hours. This last group had the poorest survival over time.

Take home message: in this group of women between 50 and 81 years of age, sleeping between 5 and 6 1/2 hours had the best outcome. Not 8 hours, as everyone wants you to believe.

What happens if you sleep too much or get up late?

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Going back to this slide for a minute, I was impressed by the findings on lethargy, tiredness, fuzzy thinking, and decreased alertness, that were mentioned in some of those articles. At the time, I was working as a psychiatry consultant in the Oncology Clinic at the Jewish, and it seemed to me that those symptoms were very much like the fatigue, lack of energy, and lack of motivation that my cancer patients complained of. Could it be that these cancer patients were sleeping too long or getting up too late?

I did a questionnaire study to find out.

	Low Fatigue N = 74	High Fatigue N = 49	P value
Chronic fatigue score	1.7	10.5	<0.0001
Age (years)	58.3	51.7	0.0039
BDI score	4.7	14.4	<0.0001
Insomnia score	3.8	7.9	<0.0001
Hypnotic meds (times / week)	0.8	2.3	0.0071
Arising time	7.3	7.8	0.0324
Time in bed after 6 am (hrs)	1.5	2.3	0.0102
Total time in bed (hrs)	8.6	9.2	0.0223
Attitude re missing work	1.2	2.3	0.0016

http://henry.olders.ca/psychiatry/

I did a poster presentation on the study.

Here is one table from that poster. You can access the whole poster via the web link at the bottom of the screen.

The two columns represent the entire sample divided up by level of fatigue.

Briefly, compared to the cancer patients with low fatigue, the group with high fatigue levels were significantly more likely to be younger, they were more depressed, they had more insomnia, they used sleeping pills more, they got up later, they spent more time in bed in the morning and they spent more time in bed altogether.

Table 3. Correlations for 52 respondents with fibromyalgia

	Chronic fatigue	Insomnia score	Sleep attitudes	Depression
Insomnia score	.128	1		
Sleep attitudes	.418 P = .0053	.004	1	
Depression	.415 P = .0030	.090	.199	1
Pain score	.549 P < .0001	.074	.312 P = .0441	-.039
Time in bed	.445 P = .0032	.245	.284 P = .0931 ns	.325 P = 0.0333
Rise time	.218	.090	.235	.257 P = .0881 ns
Time in bed after 6	.270 P = .0760 ns	.117	.314 P = .0548 ns	.268 P = .0756 ns
Time in bed + nap times	.623 P = .0044	.239	.511 P = .0303	.356

http://henry.olders.ca/psychiatry/

Shortly after my cancer fatigue study, I received an invitation to speak to a self-help group of fibromyalgia sufferers. I agreed to give a talk on fatigue, if they would agree to distribute a questionnaire to the fibromyalgia patients attending the meeting. We collected the completed questionnaires at the end of the meeting, and several months later I presented the results to the group.

Here is one table from that study. The numbers in red are statistically significant Pearson correlation coefficients. You can see, again, that fatigue and depression scores were positively correlated with time in bed, in this group of individuals who had been diagnosed with fibromyalgia.

The longer they stayed in bed, the more fatigued and depressed they felt.

You can access the poster for this study at the same website.

	Prevalence, %	Odds Ratio	95% Confidence Interval
Any history of depressive symptoms	49.6%	1.86	1.75 - 1.98
Current depressive symptoms (no history)	6.1%	2.87	2.59 - 3.18
Any antidepressant use	16.7%	3.08	2.89 - 3.28
Current antidepressant use (without a history)	15.4%	3.50	3.25 - 3.77
Benzodiazepine use	2.8%	2.95	2.62 - 3.33

Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep. 2006;29:881–889.

Here is a study that looked for associations between long sleep duration and various illnesses, in women who were taking part in the Nurses Health II Study, which was started in 1989. This table looks at depression in long compared to average sleepers. In their sample, they had over 55,000 women who slept 7 to 8 hours, and about 4500 who slept 9 or more hours.

The table gives the prevalence for the group sleeping 7 - 8 hours per day. Odds ratio refers to the likelihood in the long sleep group compared to the average sleep group. For example, long sleepers were 2.87 times more likely than average length sleepers of having depressive symptoms at the time of the study; and were about 3.5 times more likely to report current antidepressant use.

The early literature

"As the olde englysshe prouerbe sayth in this wyse,
who soo woll ryse erly
shall be holy helthy and zely."
—Wynkyn de Worde: A Treatyse of Fysshynge wyth an Angle, 1496, Westminster

"Diluculo surgere saluberrimum est."
—William Lily (c. 1468-1522): Latin Grammar, 1513

So, there is some evidence that sleeping too much and getting up late isn't good for you. It may cause fatigue, lack of energy, lack of motivation, and even clinical depression.

Here are some results from the very early literature.

Do you think that the people who coined these bits of folk wisdom long ago, were aware of this relationship between getting up late and fatigue?

The earliest reference dates back to 1496, but it is clear that this proverb was already considered old at that time. The word "zely" means happy or fortunate.

The latin proverb translates as: "To rise early is very healthy".

More early literature

"At grammar-scole I lerned a verse, that is this, Sanat, sanctificat, et ditat surgere mane. That is to say, Erly rysyng maketh a man hole in body, holer in soule, and rycher in goodes."

—Anthony Fitzherbert (1470-1538): the Book of Husbandry, 1523

"Earley to bed and earley to rise,

makes a man healthy, wealthy, and wise."

—John Clarke (1596-1658): proverb collection Paroemiolgoia Anglo-Latina, 1639

And here are a couple more proverbs. You will recognize the bottom one, usually attributed to Benjamin Franklin, but it actually appeared in print about a hundred years before "Poor Richard's Almanack".

I want you to note that three out of the four proverbs make reference only to early rising. They say nothing about going to bed early. I suspect that was added just to make the rhyme sound better.

- Getting up late appears to cause fatigue and other depressive symptoms in some people
- May cause frank depression in predisposed individuals
- REM sleep seems to be involved
- Why?

So here I was, pretty convinced that getting up late could cause fatigue and other depressive symptoms in many people, and even cause the illness of depression in some individuals, and it seemed to do this by increasing REM sleep which somehow brought about the depressive symptoms.

But why, I asked? and how?

Of course, no one knows what causes depression, nor do we know why antidepressant treatments work. That hasn't stopped doctors from prescribing those treatments. In my case, when I encountered patients with depression or fatigue, I would get a sleep history, and if it appeared that a patient was sleeping too much or getting up later than usual, my treatment approach would be to encourage getting up earlier and not sleeping during the day. Psychostimulants such as ritalin, given early in the morning, were often helpful and produced results within days, instead of weeks as with the usual antidepressants. Even morning coffee has been shown to elevate mood.

There was one retired man, widowed about a year, who came to the emergency with his daughter. After his wife died, he developed insomnia, for which his family doctor prescribed a sleeping pill. After a few days, though, he started to feel more depressed than even his mourning could explain. Eventually, his doctor started an antidepressant, which didn't help. Neither did another antidepressant. The man got worse over a period of months, and when he started to think about killing himself, his doctor told him to go to the ER to be admitted.

I admitted him to one of the geriatric psychiatry beds that I was responsible for, and obtained a sleep history. When working, he had been accustomed to getting up at 6 in the morning. He continued to get up fairly early, around 7 or 7:30 after he retired. But after his wife died, he started spending more time in bed, not getting up until 9 or 10. He was trying to use sleep as a way to escape his painful feelings. Trying to sleep more than necessary soon led to insomnia. The sleeping pill helped, but seemed to trigger depression.

I explained to the patient that I thought the late rising was responsible for his depression, and suggested that he go back to his sleep pattern when he was working and doing well. He readily agreed to give it a try.

He had been admitted on a thursday afternoon. The following morning, the nursing staff on the psychiatry unit woke him at 6, and he got up as we had agreed. I saw him later that day, and he told me he no longer felt depressed, and asked if he could go home.

I could see that in fact he was feeling much better, but I was not about to discharge from the hospital a man who had been suicidal just the day before!

What I did go along with, after meeting again with his daughter, was for a weekend pass at her house. If she had any concerns about her father, she was prepared to bring him right back to the hospital, or to call Urgence Santé to take him if necessary.

On Monday, he came back to the hospital with his daughter. His depression had not come back. I discharged him home, and then followed him for the next several years, seeing him every 6 months to confirm that he continued to do well.

- many depressed patients insisted that they were waking very early, even at 2 or 3 am

- many others complained that they couldn't sleep, so how could they be sleeping too much?

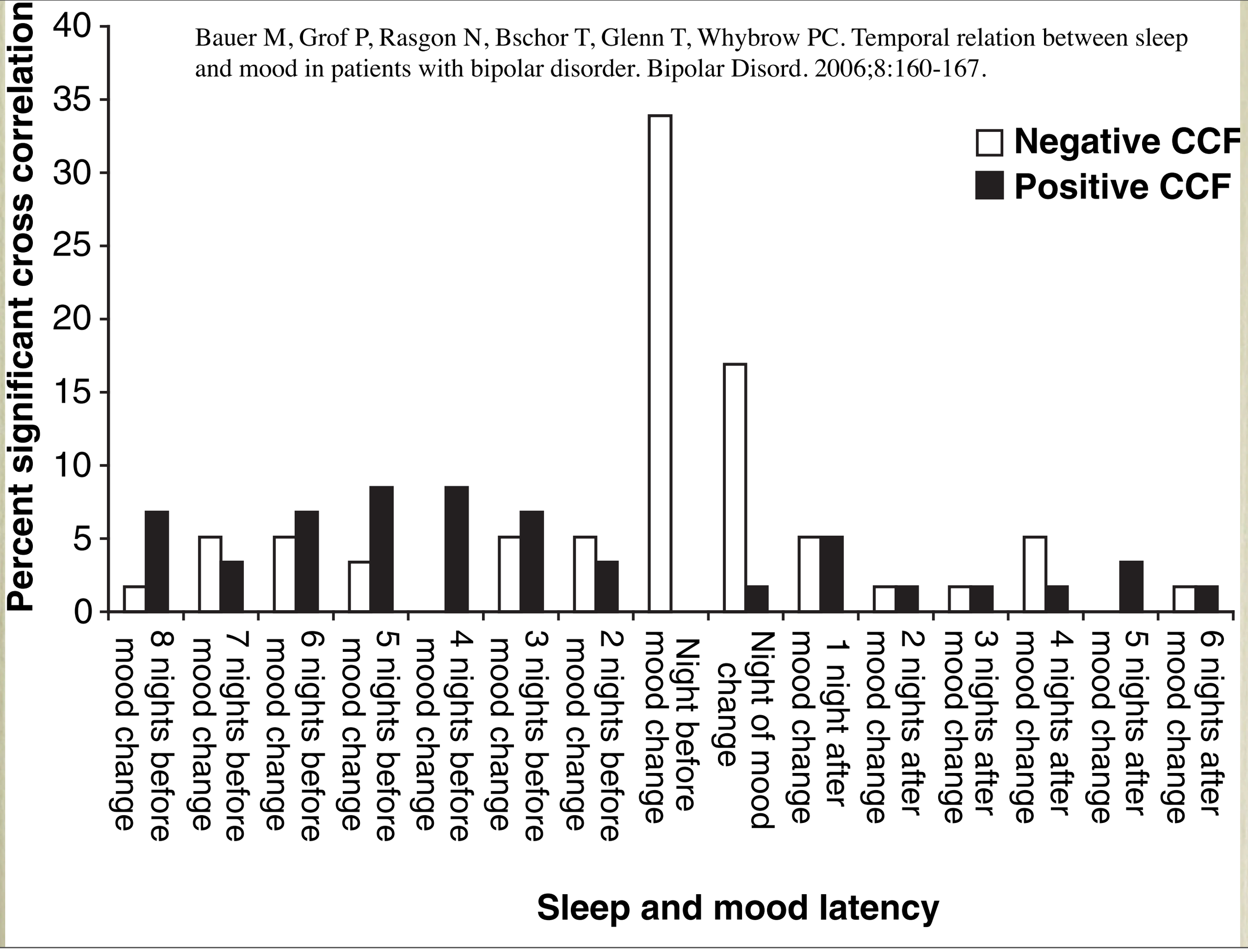
Although his case was a convincing demonstration of how getting up late might cause depression, there were many other cases where patients insisted that they were waking very early, or they had insomnia and couldn't sleep, so how could I possibly suggest that they were sleeping too much?

For those waking too early, it was helpful to ask what they did after waking. Some would say they got up and had tea, or made breakfast, or watched TV, or just sat.
And then what did you do?
Had a cigarette.
And after that?
Went back to bed.
So what time did you get out of bed, for the day?
Oh, about 9 or 10.

On the other hand, the insomniac patients were often misjudging how long they actually slept. It appears that most cases of what is called psychophysiologic insomnia, may actually be caused by trying to sleep more than you need. I won't go into detail because of time, but if you are interested, Scientific American posted an article I wrote on this topic, on their website. There's a link to that article on the web page I referred you to earlier.

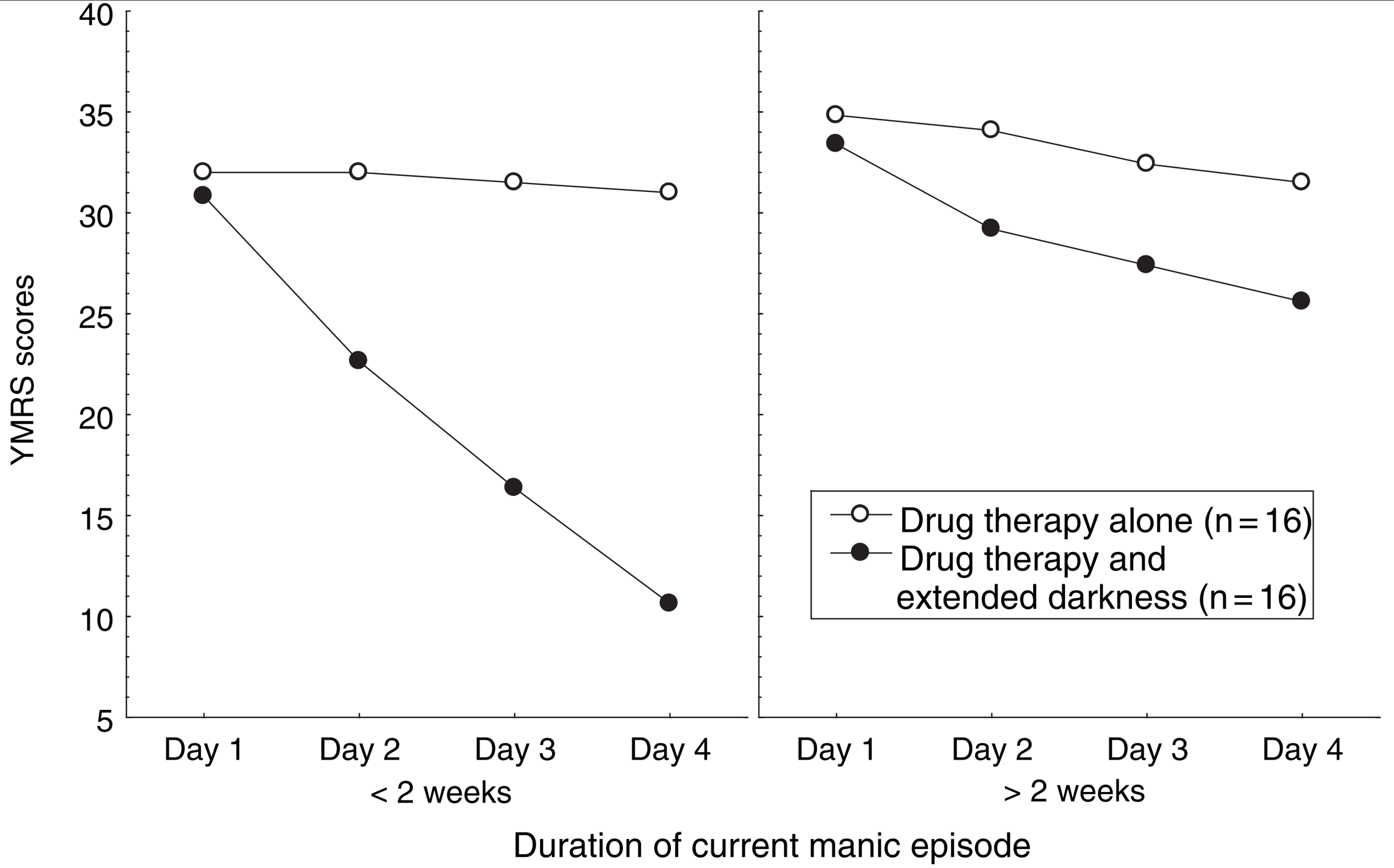
There are lots of studies showing that the best treatment for this kind of insomnia is restricting the amount of time spent in bed. So with these people, I could help their insomnia along with their depression, with a primarily behavioural approach.

Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow PC. Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disord. 2006;8:160-167.



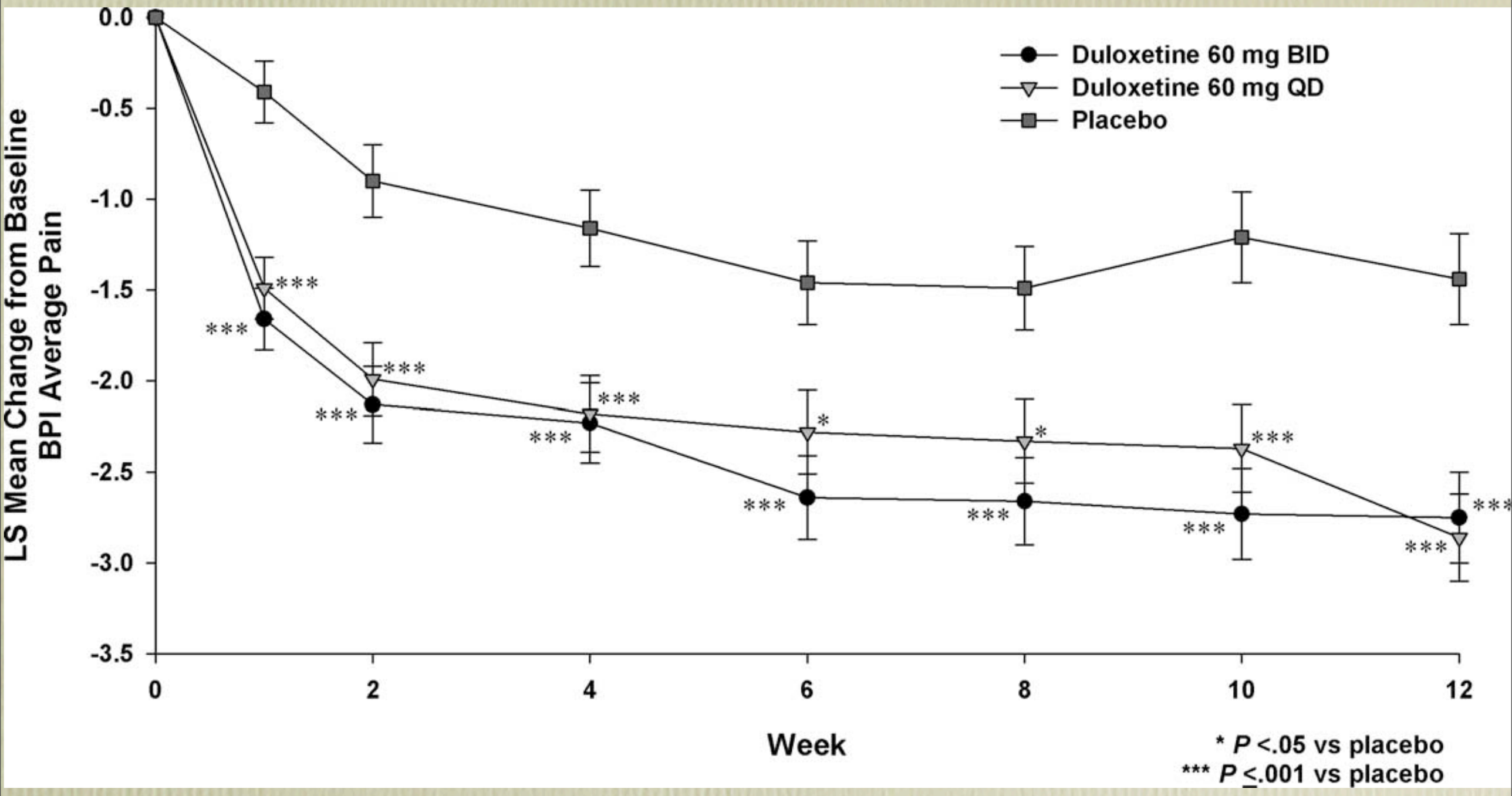
I'm always on the lookout for research findings that deal with sleep and affective disorder, or fatigue. There is a group in the States, who have been using what they call Social Rhythms therapy in patients with bipolar disorder. The idea is to try to get patients to have regular habits not only for sleep, but also things like meals and social activities. Unfortunately, they haven't been able to demonstrate in a convincing way that their approach is better than other treatments at helping patients remain stable.

Here is an article, however, which demonstrates convincingly the connection between sleep and mood. This study looked at the daily sleep, bedrest, and mood of 59 bipolar outpatients receiving their usual treatment. They collected on average 169 days' worth of data for each patient. They then performed what is called a cross-correlation to determine what the latency is between changes in sleep and bedrest, and changes in mood. This graph shows the results, for sleep plus bedrest cross-correlated with mood. The strongest correlations occurred the night before or the night of a mood change. About 35% of patients had a significant negative correlation between mood change and change in sleep plus bedrest the night before the mood change; in other words, if they stayed in bed longer, they were likely to have a deterioration in mood the following day; less time in bed predicted an improvement in mood the following day.



Barbini B, Benedetti F, Colombo C, et al. Dark therapy for mania: a pilot study. Bipolar Disord. 2005;7:98–101.

And here is another recent study. 16 bipolar inpatients having a manic episode received either their usual drug therapy, or drug therapy plus a regimen of enforced dark for 14 hours nightly for 3 consecutive days, from 6 pm to 8 am. If done within the first two weeks of the manic episode, dark therapy significantly reduced manic symptoms.



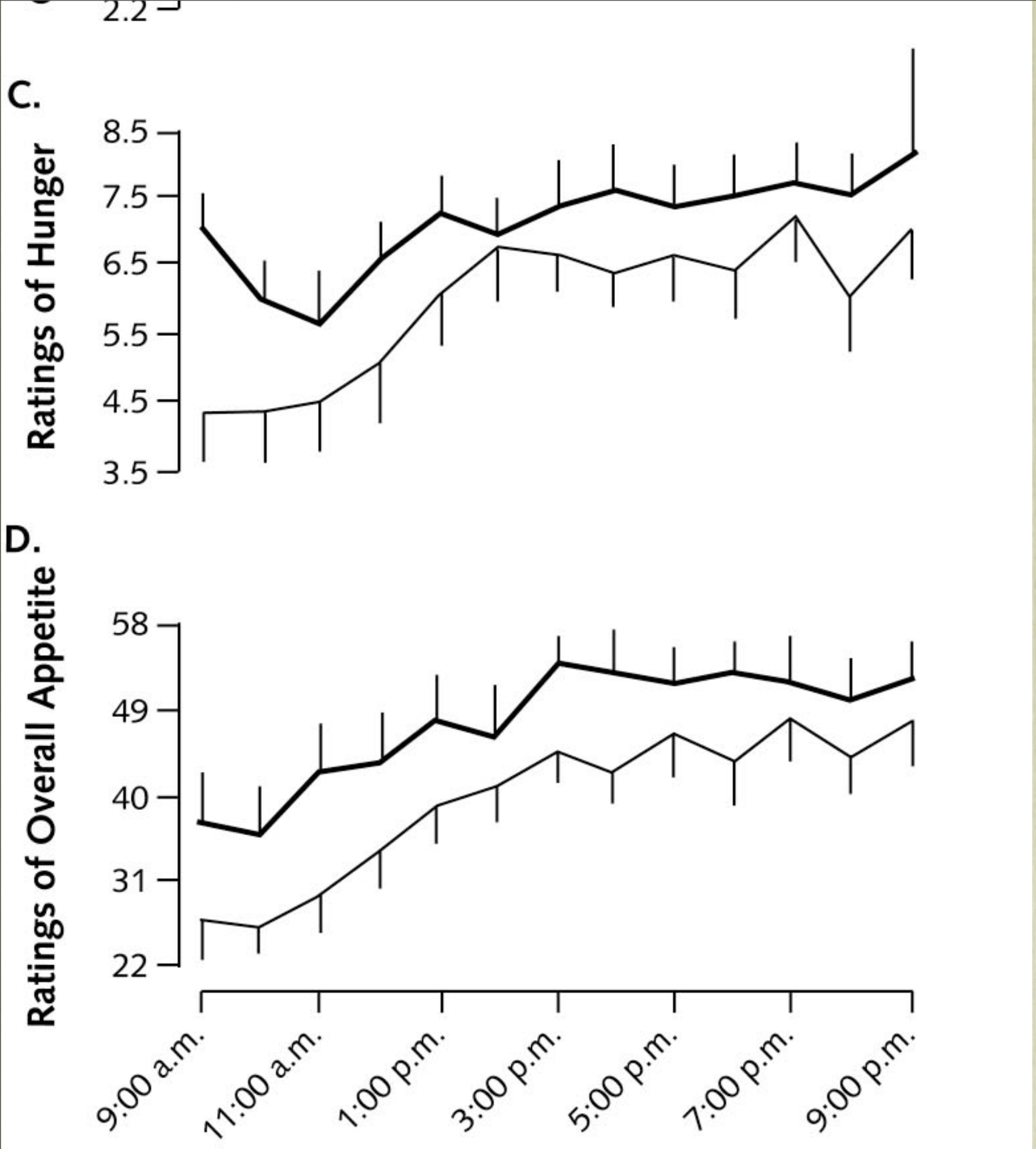
Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005;119:5-15.

To recap at this point: bipolar affective disorder seems to have a strong connection to sleep patterns. But there are other symptoms, such as fatigue and even pain, which also seem to have strong connection to sleep and in particular to REM sleep. Here is a study in which that new antidepressant, duloxetine, that I mentioned earlier, which suppresses REM sleep so strongly, was evaluated for its effect on pain.

It's a 12-week, randomized, double-blinded placebo-controlled trial of duloxetine at two different dosages, in 354 women outpatients with fibromyalgia. BPI stands for Brief Pain Inventory. You can see that both dosages of the medication brought about significant reductions in pain, compared to placebo.

OK, so now we have two symptoms, fatigue and pain, which seem to be tied to sleep. Are there others? What about appetite?

It's been known for a long time that short sleepers are more likely to be obese. That suggests that long sleepers may have decreased appetite.



Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141:846–850.

12 healthy young men were subjected in a crossover design to 2 nights with only 4 hours of sleep (1 am to 5 am) or 2 nights with 10 hours of sleep (10 pm to 8 am). With the longer sleep, both hunger as well as appetite for a range of different food groups were significantly less. The upper thicker line in each graph represents the restricted sleep condition, and the lower line the extended sleep.

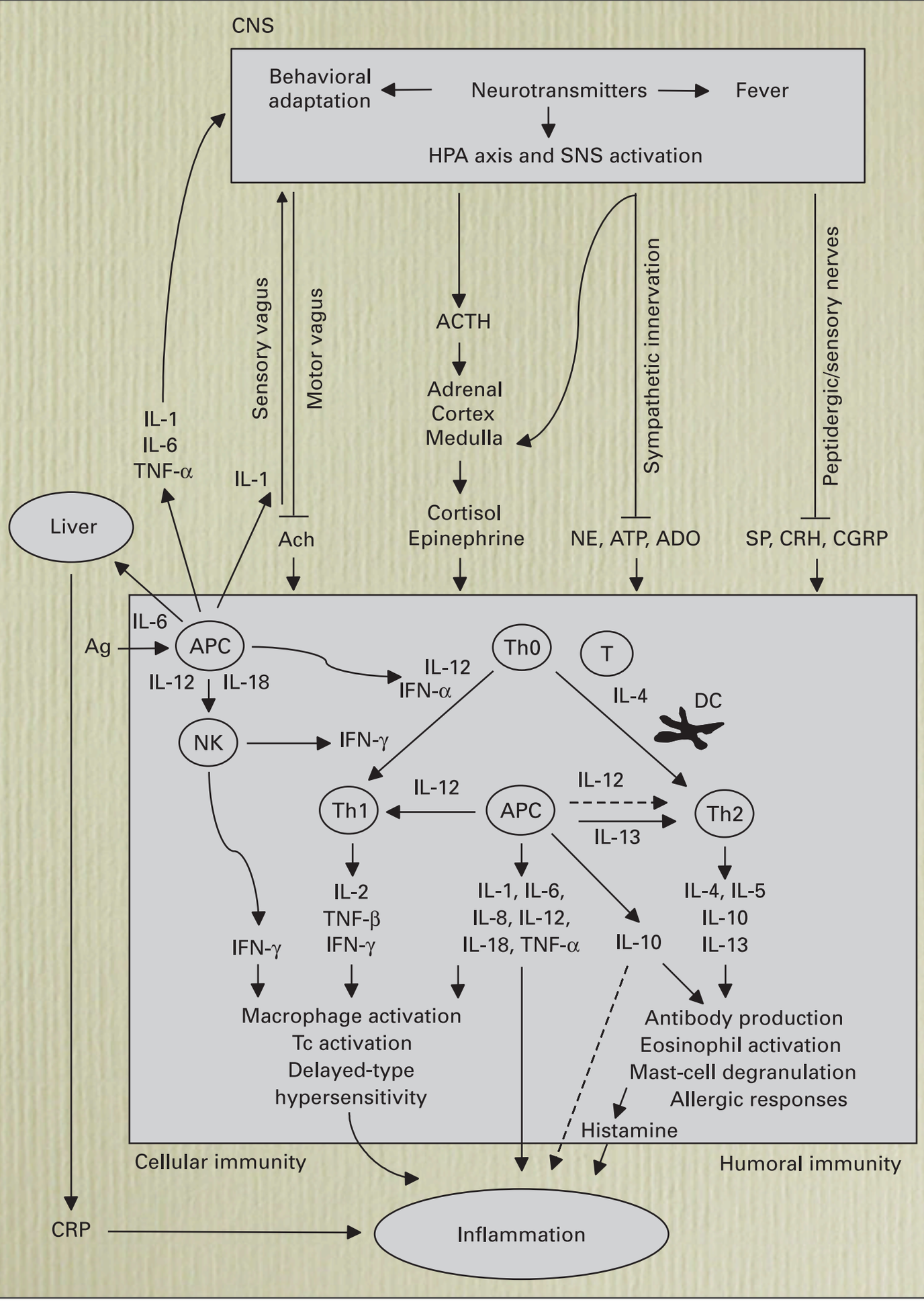
Sickness Syndrome

- Decreases in:
  - general activity
  - exploratory behaviour
  - social interaction
  - sexual interaction
  - food and water intake
  - preference for sweets (anhedonia)
- Altered sleep
- Impaired learning
- Hyperalgesia

I now want to talk about something completely different. It's been known for a long time that there is an intimate connection between the body's immune system, sleep, and certain symptoms such as fatigue and lassitude. For example, if you inject substances that are known to produce an immune response, not only will you get fever, but also sleepiness, lack of energy and interest, and so on. This group of symptoms is known as the "sickness syndrome" and it has usually been viewed as a way for the organism to conserve energy when there is an infection.

That's always seemed to me a pretty weak explanation.

In any case, the phenomenon appears to be mediated by cytokines.



Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation. 2005;12:255–269.

This is what the authors of this article laughingly called a “simplified” scheme of cytokine actions. I’m most intrigued by this mark, here; is this some sort of Rorschach inkblot? I couldn’t find any reference to it in the article.

Bottom line: the whole system is incredibly complex.

What we know is that some of these cytokines which are part of the inflammatory response, promote sleep. This includes interleukin-1, or IL-1, IL-2, IL-6, IL-15, tumour necrosis factor alpha, or TNF-alpha, and interferon-alpha, at least in some species of animals.

Furthermore, the treatment of hepatitis C, malignant melanoma and other conditions with interferon-alpha frequently has depression and cognitive impairment as side effects.

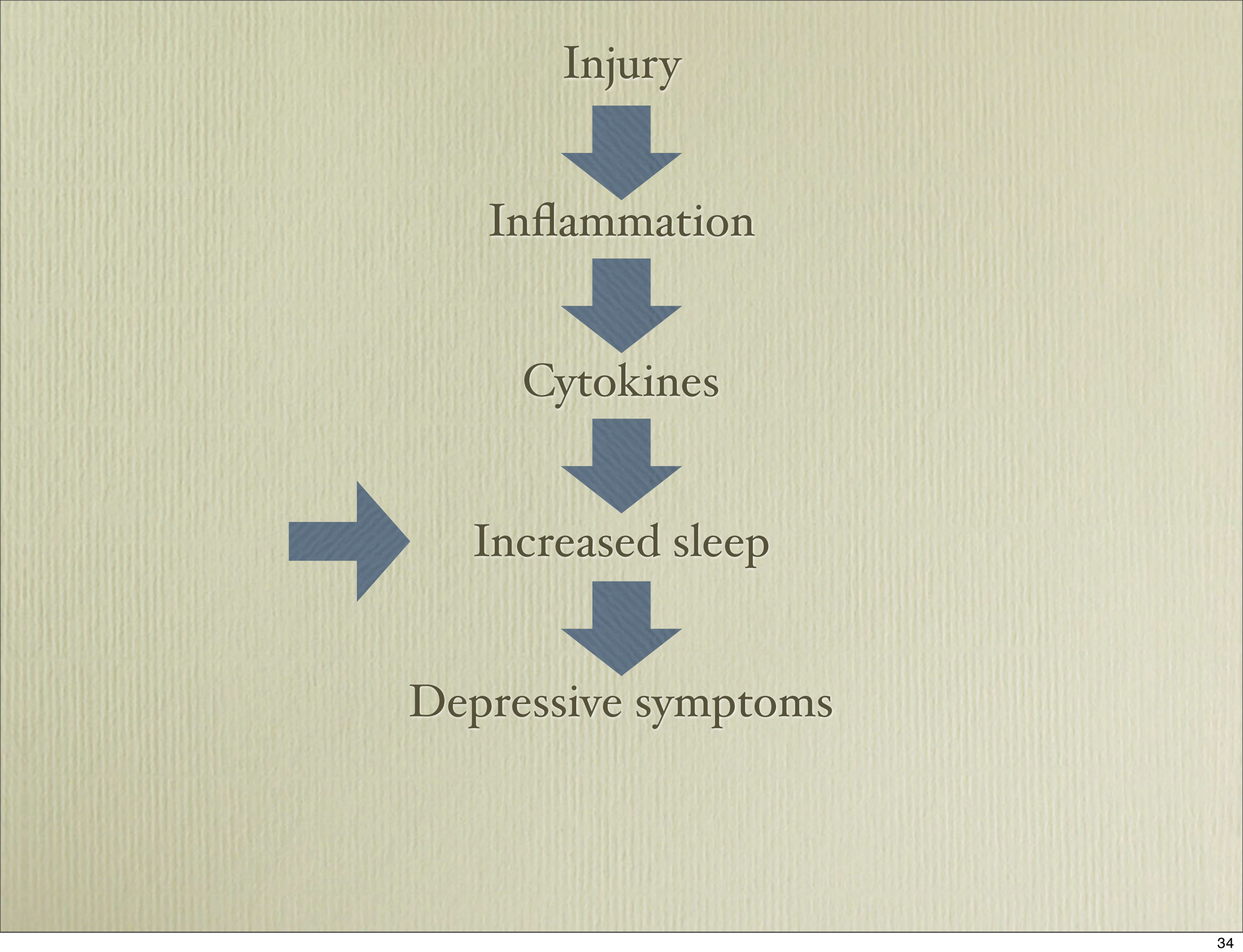
Severe Injury

I had to ask, what would the possible point be of having these depressive symptoms built in as a response to inflammation? I just couldn't imagine how an animal would be more likely to survive an infection if it became cognitively impaired and fatigued. Why would evolution build in these symptoms?

It eventually hit me that there is one important condition which occurs often in nature, where an animal with depressive symptoms would be more likely to survive than an animal without those symptoms. That condition is ♥ severe injury, like surviving a fall in a powerpoint slide.

Consider a wild animal, for example a wolverine, that has gotten injured in a fight with another animal. Suppose it has a gash, down to the bone, from a shoulder all the way to the hip. What should this wolverine do to heal? Have the veterinarian sew up the wound, obviously!

In the wild, the injured wolverine needs to remain as still as possible while the wound knits together. Even though complete healing might take weeks or months, the first few days are the most important: excessive movement during this period will cause the wound to reopen, delaying or even preventing healing and certainly increasing the risk of life-threatening infection. The animal is least likely to move if it spends most of its time sleeping; having no appetite means no forays to seek food; no sex drive means no expeditions to find sexual partners; fatigue and lack of energy and interest reduce the desire to do anything active. Thus, all of these symptoms, which we recognize as the symptoms of a retarded depression, may be essential to this animal's survival. Even pain, not only musculoskeletal pain from the injury but also the type of pain all over that patients with fibromyalgia experience, can be helpful as it will minimize the likelihood of movement during the period when movement may reopen a wound which has just begun to heal.



So here's my hypothesis: when an animal is ♥ injured, the ♥ inflammatory reaction causes ♥ cytokines to be produced. Some of these inflammatory cytokines induce ♥ sleep. The extra sleep, above and beyond the animal's usual needs, bring about ♥ symptoms such as fatigue, lack of interest, lack of appetite, no sex drive, anhedonia, apathy, lack of energy, and perhaps pain all over.

But it's possible to sleep too much ♥, even without injury and inflammation. Too much sleep, particularly too much REM sleep, will still produce these depressive symptoms, even though they are no longer helpful for survival if there has not been an injury.

- Opportunity (retirees, people with illnesses, people who have lost their jobs, friends, or spouses)
- Full refrigerators and pantries (no need to spend all day looking for food)
- Decreased working hours; flex-time; part-time work
- Media pressure (everyone needs 8 hours sleep)
- Medications that increase sleep
- Obstructive sleep apnea
- Escape from psychological pain
- Vicious circle (effect of too much sleep)

But why would anyone sleep too much?

♥ People who have stopped working or going to school, whether retired or fired, or because of illness, have more opportunity to sleep.

♥ With easy-to-prepare meals and modern kitchens, it's no longer necessary to get up at 5 to fire up the stove and go out to the henhouse for eggs.

♥ Compared to 60 years ago, when the average work week was 48 hours, even full time people work less. Then there are those on flextime, or working from home, or putting in part-time hours...

♥ People no longer trust their own bodies to tell them what's healthy. When you hear, over and over, on TV, the radio, and read in the newspaper that everybody needs at least 8 hours of sleep a night, it's not easy to resist. But most adults that spend 8 hours in bed are guaranteed to be tossing and turning for one or two hours each night.

♥ Many people take sleeping pills, which are designed to increase the amount of sleep. But anti-anxiety pills, many antihistamines, cold medications, alcohol, antidepressants, and antipsychotic medications are often powerful sedatives as well.

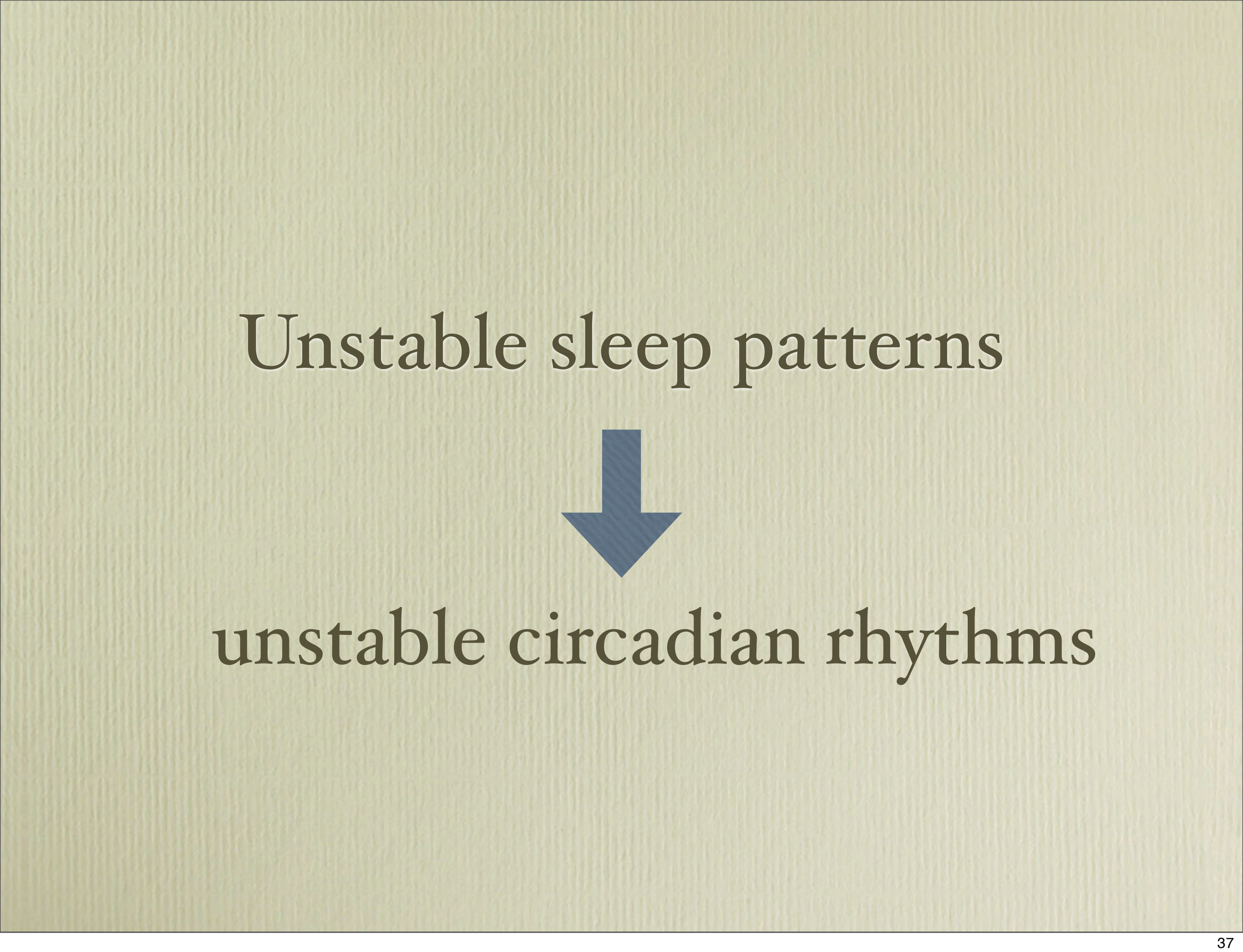
♥ With the increase in obesity in the general population, obstructive sleep apnea as a cause of daytime sleepiness is also on the rise.

♥ People who have had an important loss, whether of a loved one, a job, a financial setback, their home due to fire or flood, and especially their health, may attempt to escape their psychological pain through sleep. This may be the mechanism by which stress appears to trigger depression.

♥ If you are feeling fatigue caused by excessive REM sleep, you may interpret this lack of energy as a result of insufficient sleep. This is especially likely if you also have insomnia. You may try to fix it by sleeping even more.

- Nursing home practices and routines

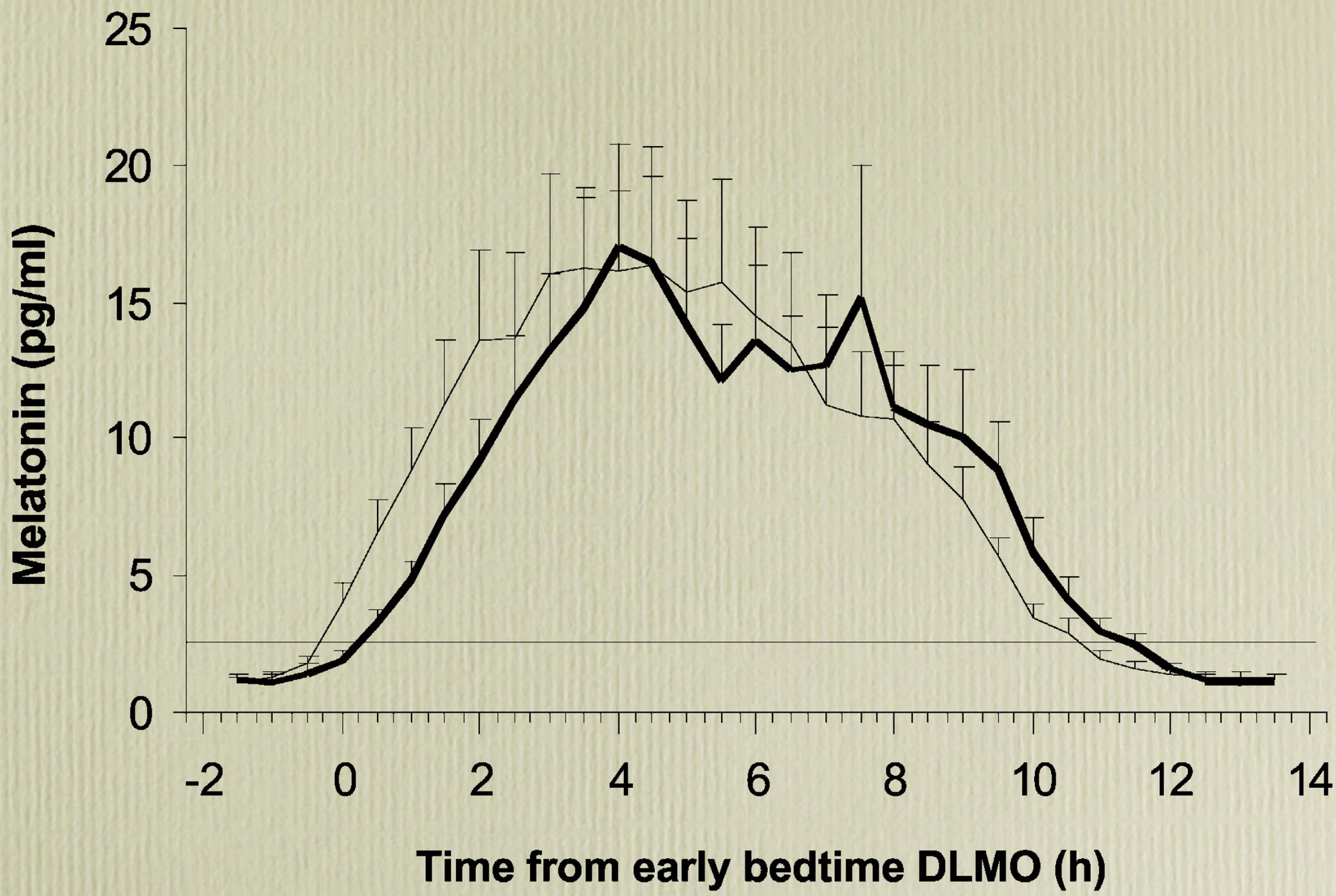
Most elderly people will do very well with about 6 hours of sleep or even less. But nursing home residents will get put to bed at 8 pm or even earlier, with the expectation that they should sleep until at least 6 or 7 am. This is impossible without either extended periods of wakefulness or sedating medication.



Even individuals, for example many of our residents, who are autonomous for going to bed, often go to bed at 9 pm, because that's when they get their bedtime medication, and there may be little else to do. This early to bed eventually results in what is called advanced sleep phase syndrome.

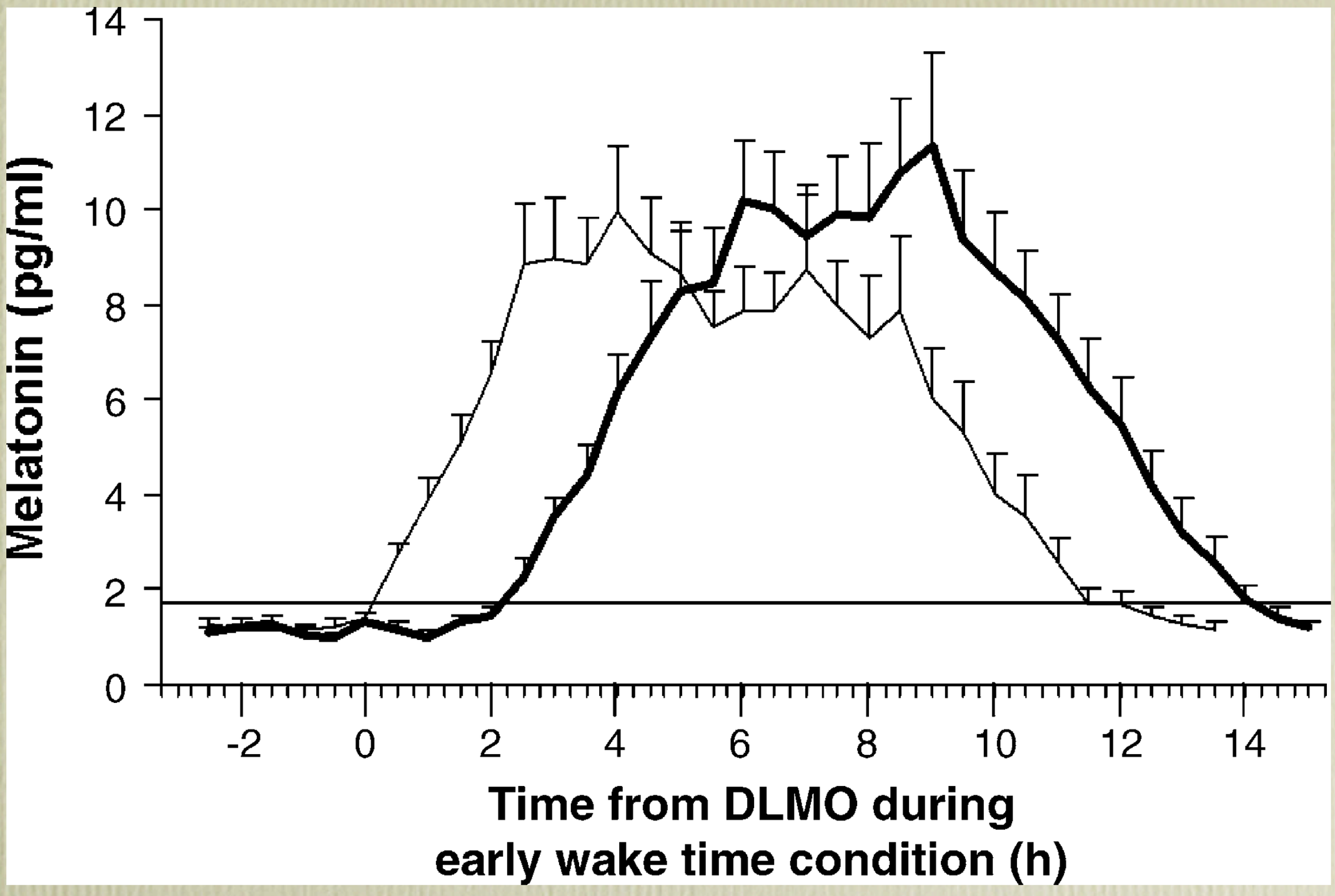
If a person who needs 6 hours sleep goes to bed at 9 pm, they are likely to wake at 3 am. Neither the individual nor the staff are happy with this, so the person may be prescribed a sleeping pill. Or, if the early rising triggers some manic symptoms such as irritability, aggressiveness, or paranoia, an antipsychotic medication may be given. Or even if no medication is given, the resident may go back to bed at some point, and not get up until 7 or 8 am or even later. Then there is the afternoon nap, almost mandatory on some floors.

All of these practices conspire to prevent a quality natural sleep which begins and ends at the same time from one night to the next. ♥ This instability of sleep patterns prevents a stable circadian rhythm from developing. This problem is compounded by the fact that circadian phase delays happen faster than phase advances. Here are some studies that demonstrate this.



Burgess HJ, Eastman CI. Early versus late bedtimes phase shift the human dim light melatonin rhythm despite a fixed morning lights on time. Neurosci Lett. 2004;356:115-118.

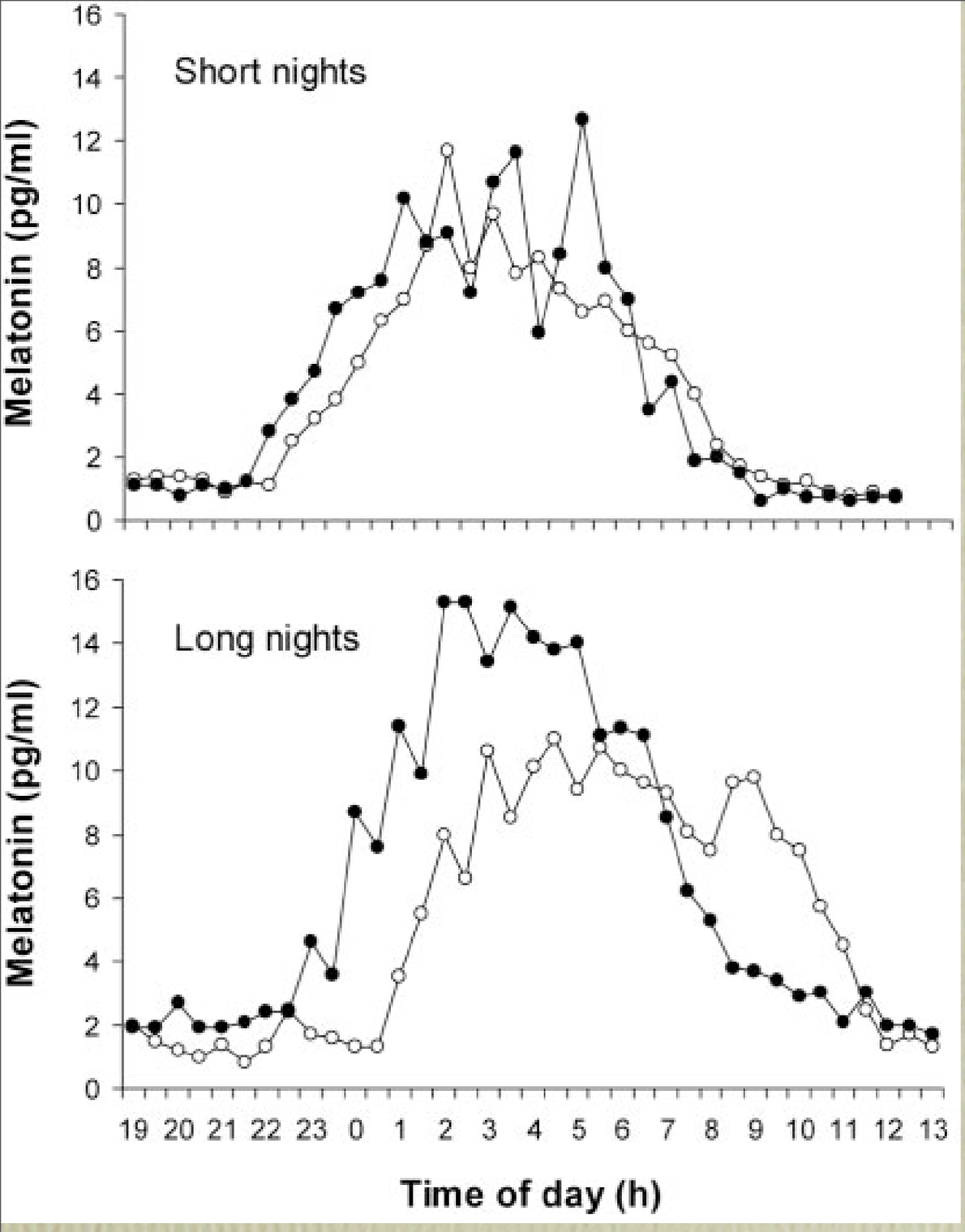
In this study, subjects went to bed at either 10 pm for 7 to 19 days, or 3 hours later, at 1 am, also for 7-19 days, in a crossover design. Rising time was held constant, at 7 am. Late bedtimes, shown by the dark line, delayed the circadian rhythm by about 0.6 hours.

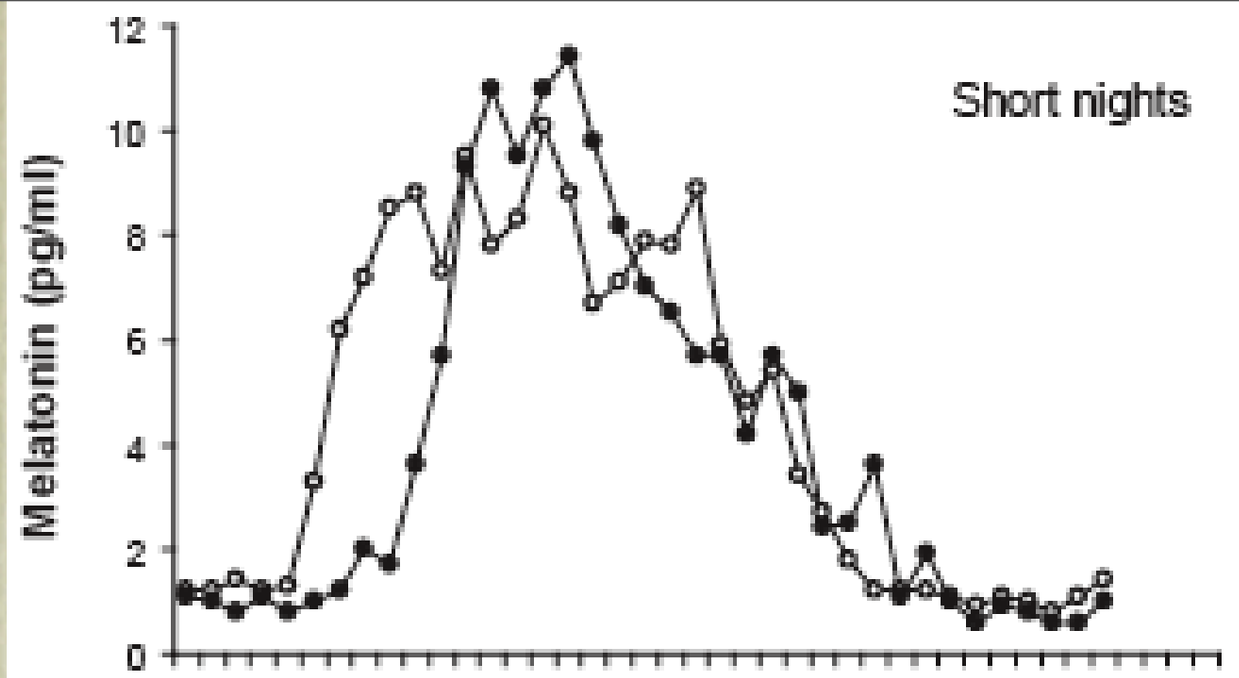


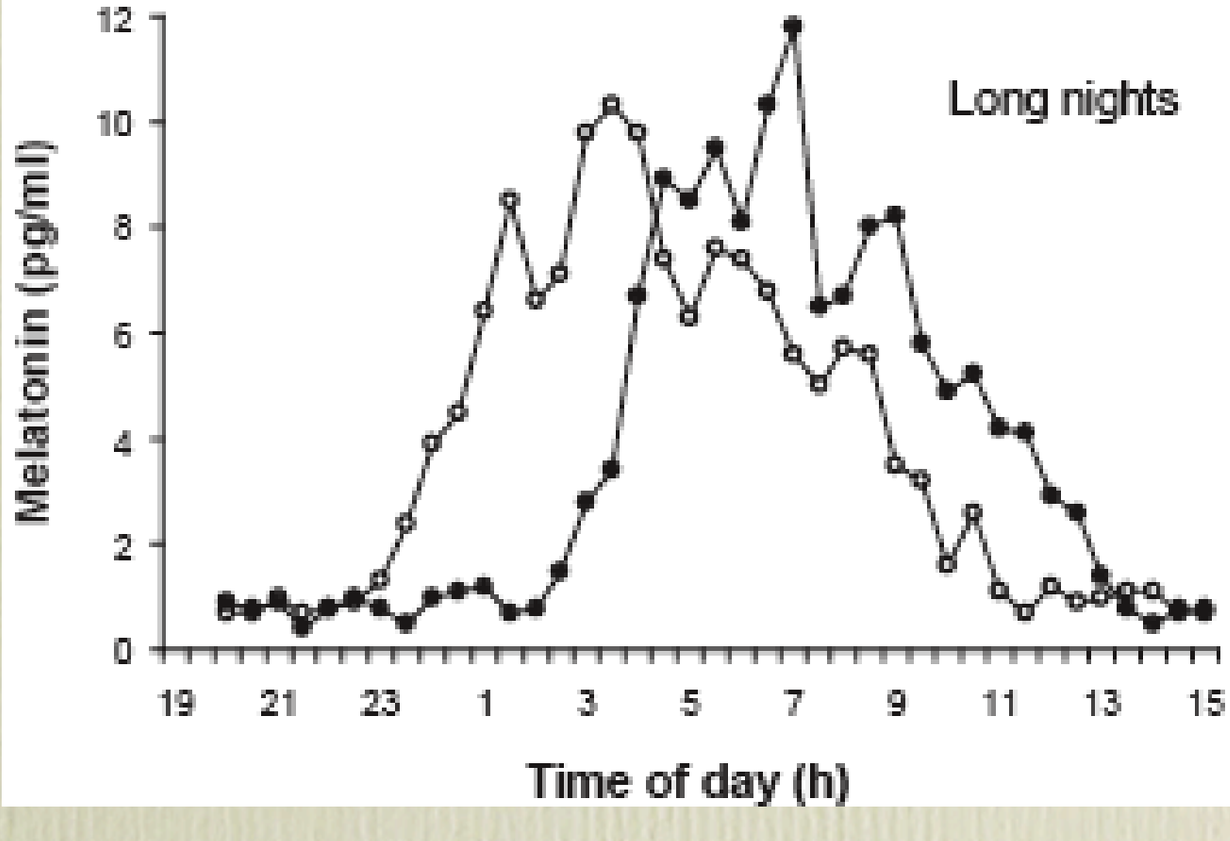
Burgess HJ, Eastman CI. A late wake time phase delays the human dim light melatonin rhythm. Neurosci Lett. 2006;395:191–195.

This study, by the same group, looked at rising time instead of bedtime. Getting up 3 hours later than usual for 2 weeks, while keeping bedtimes fixed, causes a circadian rhythm phase delay of 2.5 hours. The light line is the early wake time, and the dark line is the delayed wake time.

Clearly, rising time is more important than bedtime in adjusting circadian rhythm.







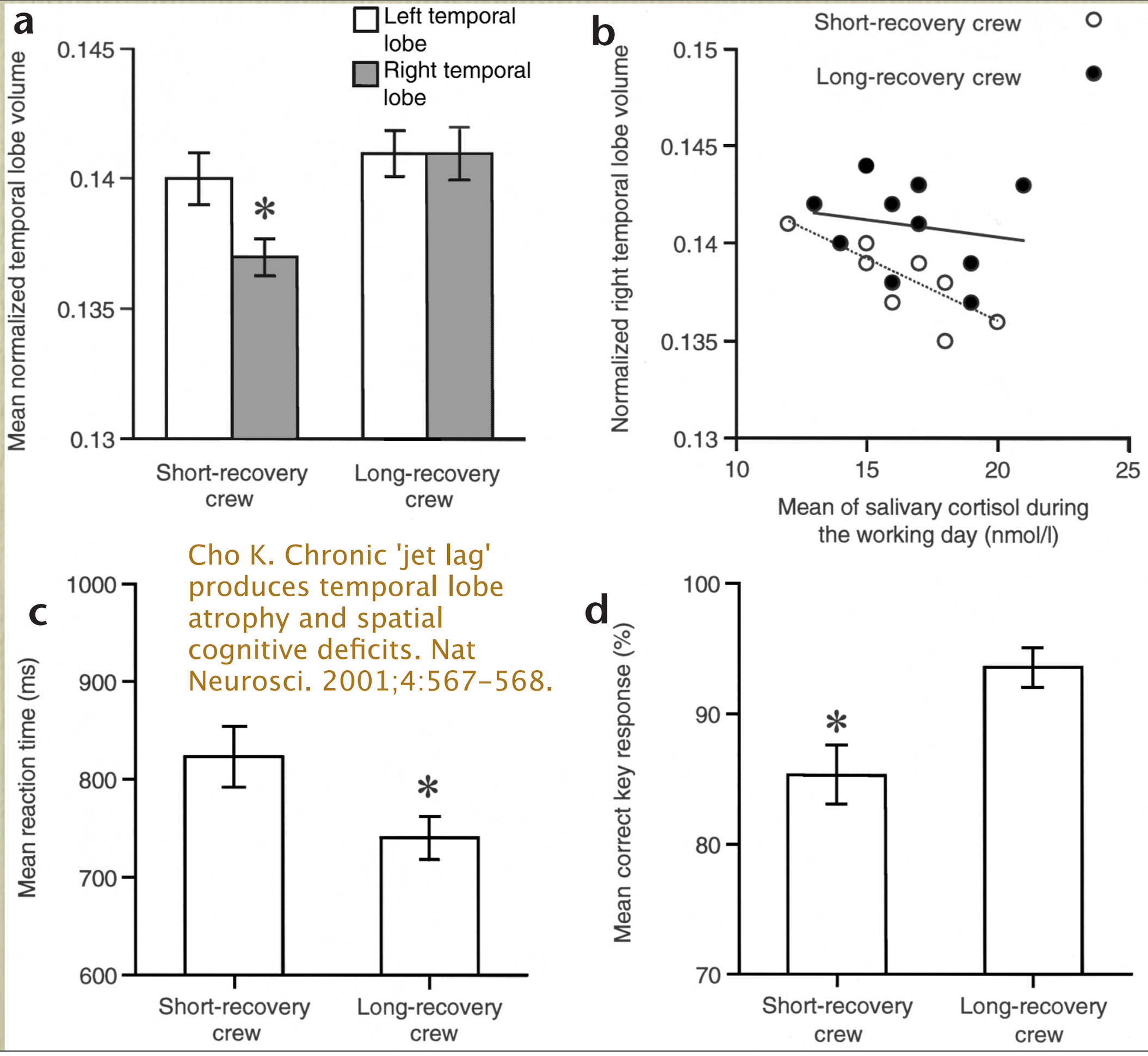
Burgess HJ, Eastman CI. Short nights attenuate light-induced circadian phase advances in humans. J Clin Endocrinol Metab. 2005

Burgess HJ, Eastman CI. Short nights reduce light-induced circadian phase delays in humans. Sleep. 2006;29:25-30.

This is a pair of studies, by the same group, showing that short nights of 6 hours sleep reduce the effect of bright light on either advancing or delaying our circadian rhythms, compared to long 9 hour nights. On the left are curves showing the effect of bright light early in the morning, advancing by 1 hour each day for a total of 3 days. On the right, the effect of bright light in the evening, delaying by one hour each day for 2 days. Not only do long nights result in a more powerful effect, but phase delays are more pronounced than phase advances.

What this means, in practical terms, our residents who go to bed early and get up late, are more likely to have their circadian rhythms banged around all over the place by people turning lights on and off during the night.

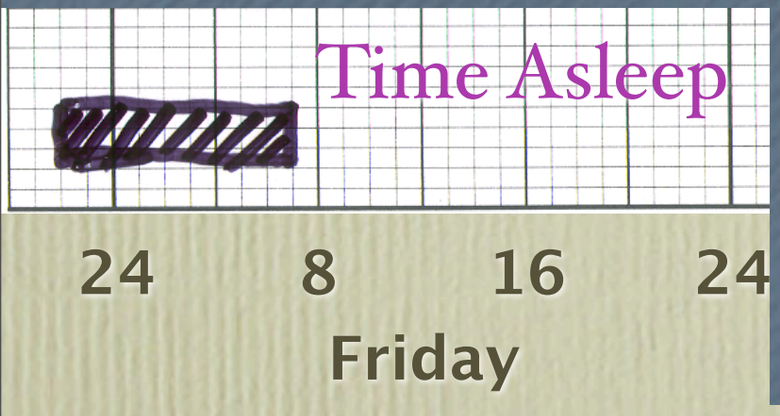
Waking up earlier or later than usual is much the same as jet lag. And jet lag is definitely not good for the health.



Cho K. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. Nat Neurosci. 2001;4:567-568.

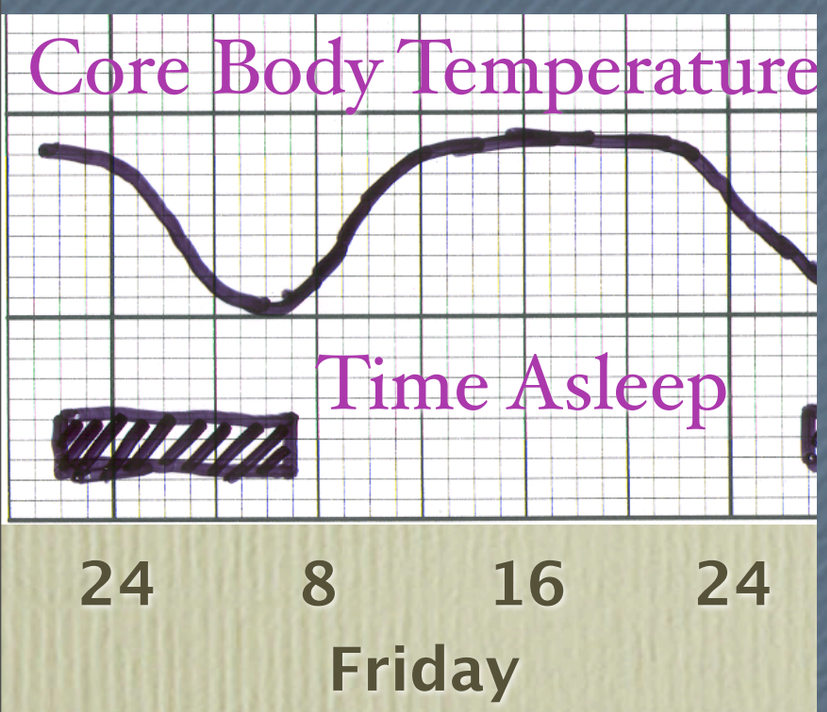
In this slide, we can see the deleterious effects of chronic jet lag on 20 young female flight attendants, who had worked for 5 years for commercial airlines, either with a work schedule involving short intervals of 5 days or less between outward flights involving crossing at least 7 time zones, versus a long-recovery group with 14 or more days between flights crossing 7 or more time zones. The short-recovery group had significantly smaller right temporal lobe volume, more salivary cortisol, longer reaction times, and fewer correct responses on a visual spatial cognitive task. It is thought that these effects are due to the higher cortisol levels induced by chronic stress. Jet lag causes brains to shrink!

We can simulate this effect with our patients by putting them to bed early, so that they wake up at a variety of different times from one day to the next.

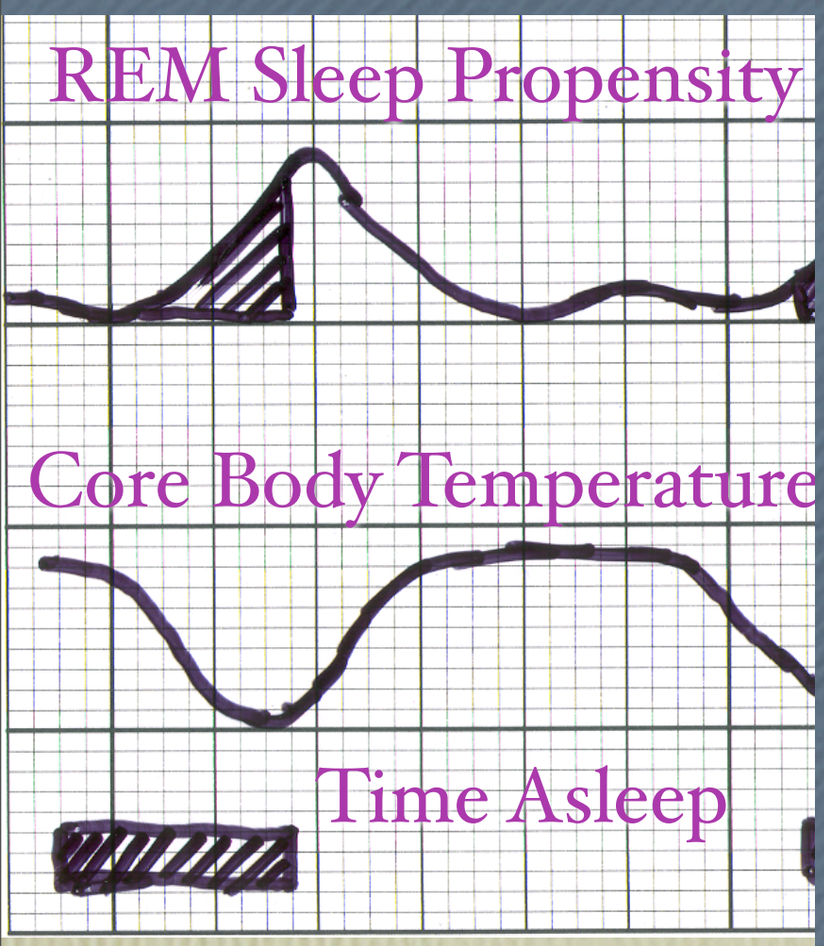


In case you think I'm kidding about the jet lag, I'll demonstrate with a simple example that many of you are familiar with.

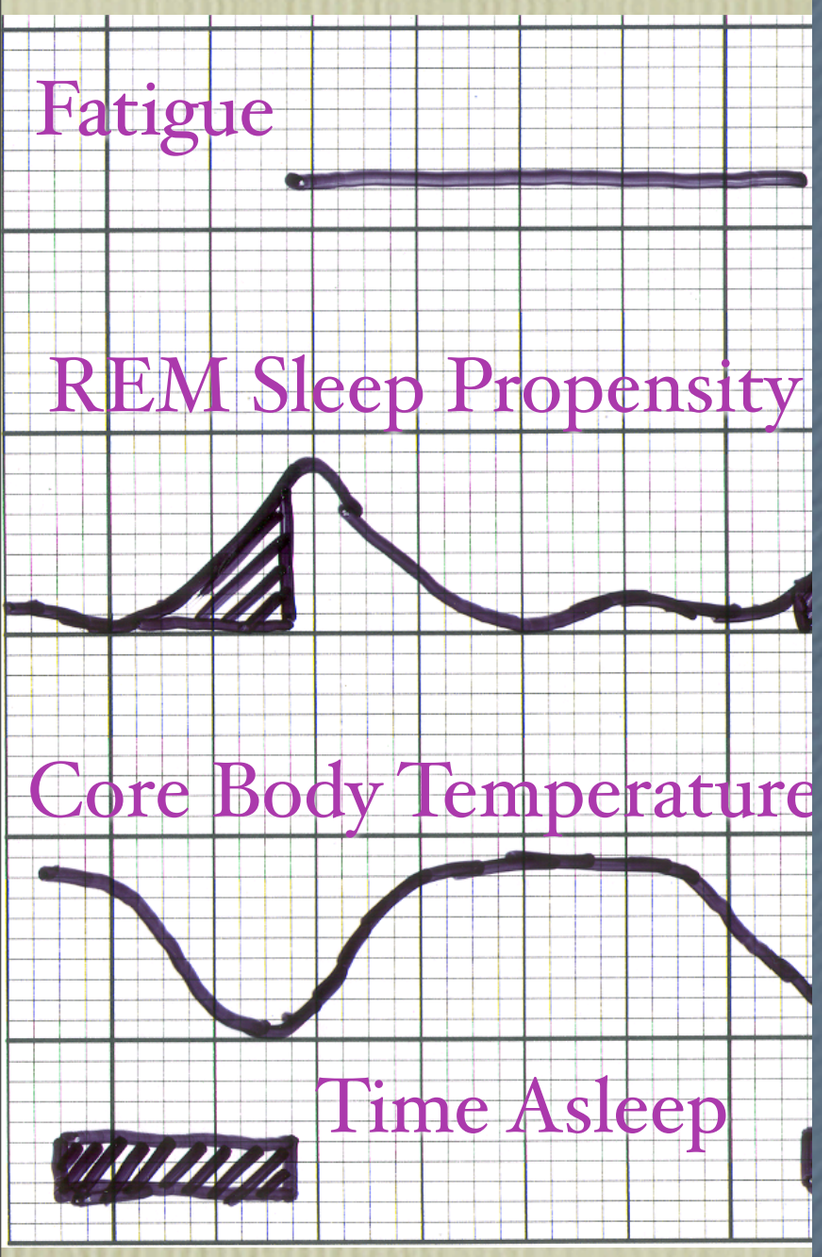
John is a typical adolescent. This graph showing time asleep starts on Thursday evening. John has gone to bed at his usual weeknight time of around 10 pm, and got up at his usual schoolday time of 7 am.



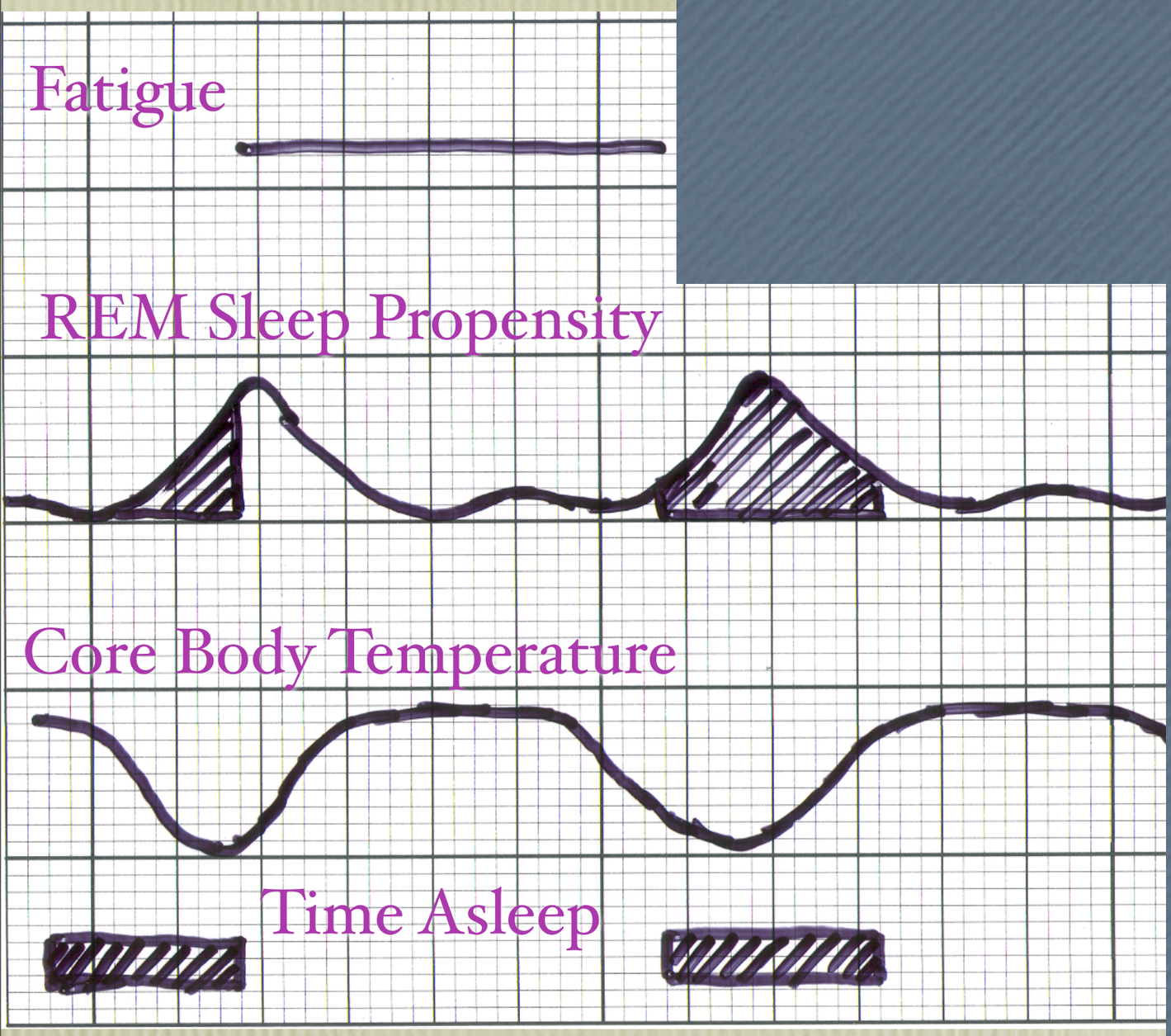
This chart adds John's core body temperature, which is a good indicator of his endogenous circadian rhythm. Core body temperature usually has its minimum about an hour before rising time, which is at 6 am in John's case, assuming that his circadian rhythms are stable and locked onto his rising time.



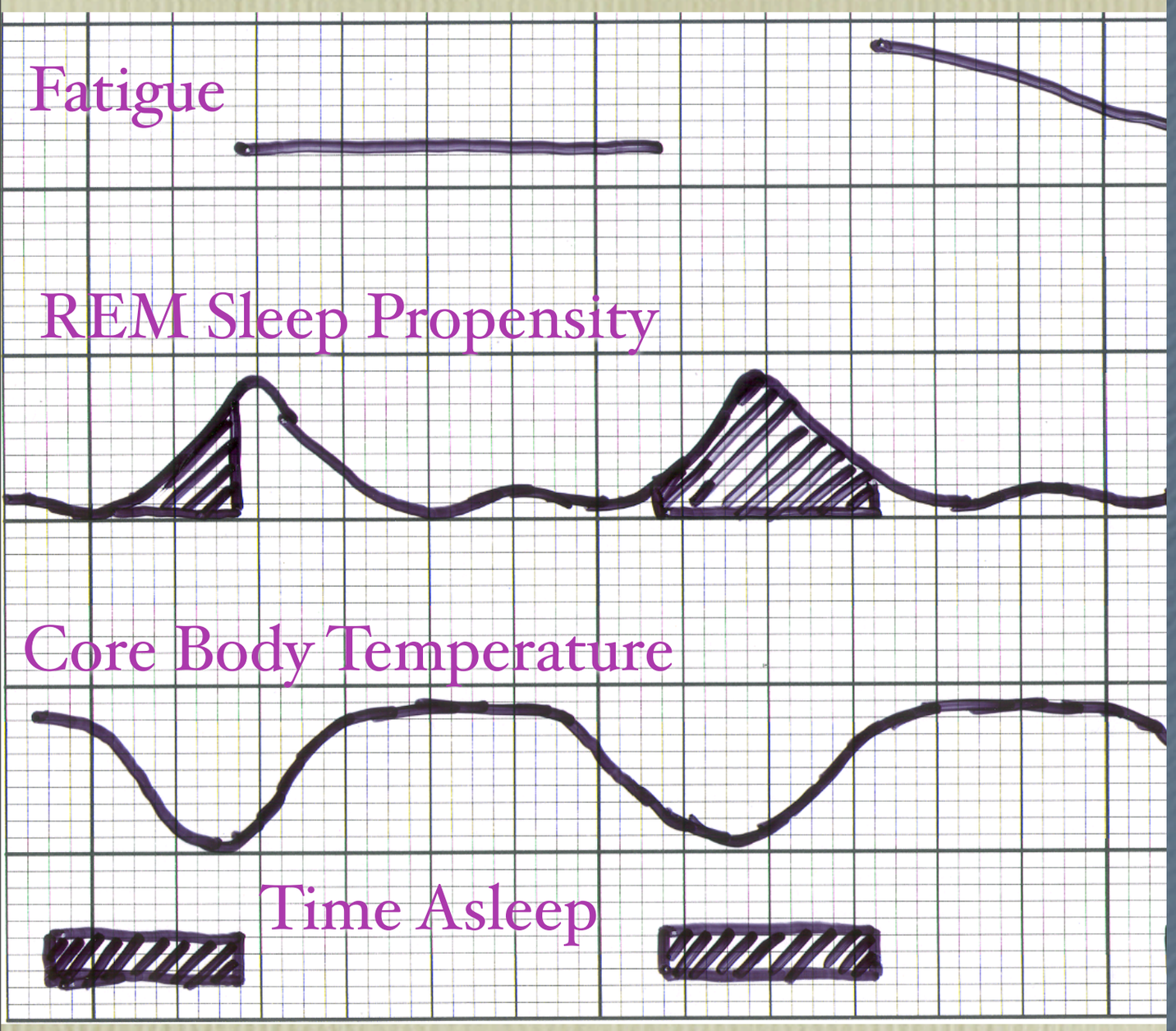
We saw earlier that REM sleep propensity, shown here, is determined mostly by the circadian rhythm, and tends to peak about an hour after rising time if the circadian rhythms are stable. The filled-in area under the curve starts and stops at the beginning and end of John's sleep, and thus represents the amount of REM sleep obtained.



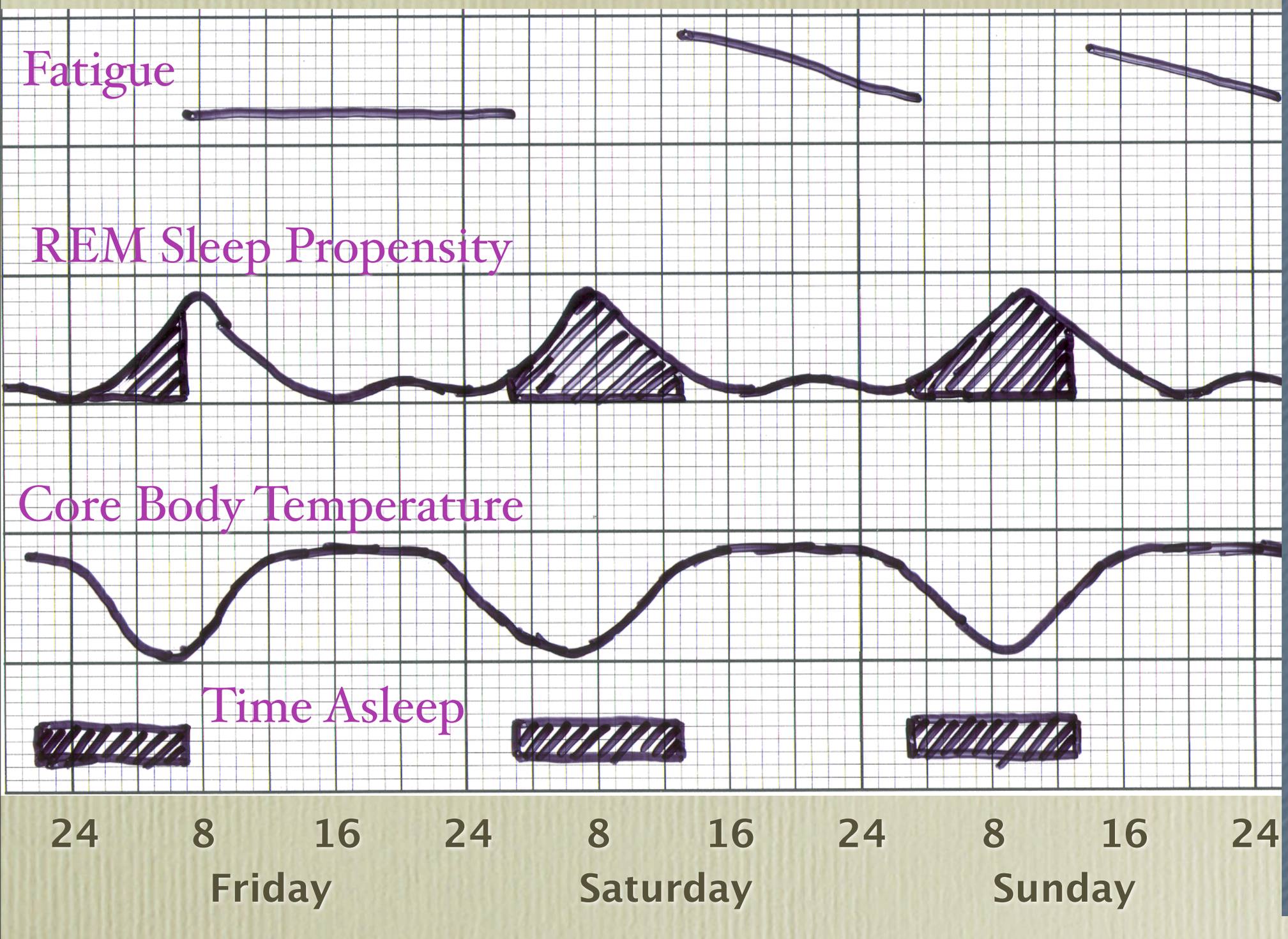
The top line represents John's fatigue level. On friday, being the end of the week, his fatigue level is pretty low, meaning he has plenty of energy, so he goes out with his friends to a party on Friday night.



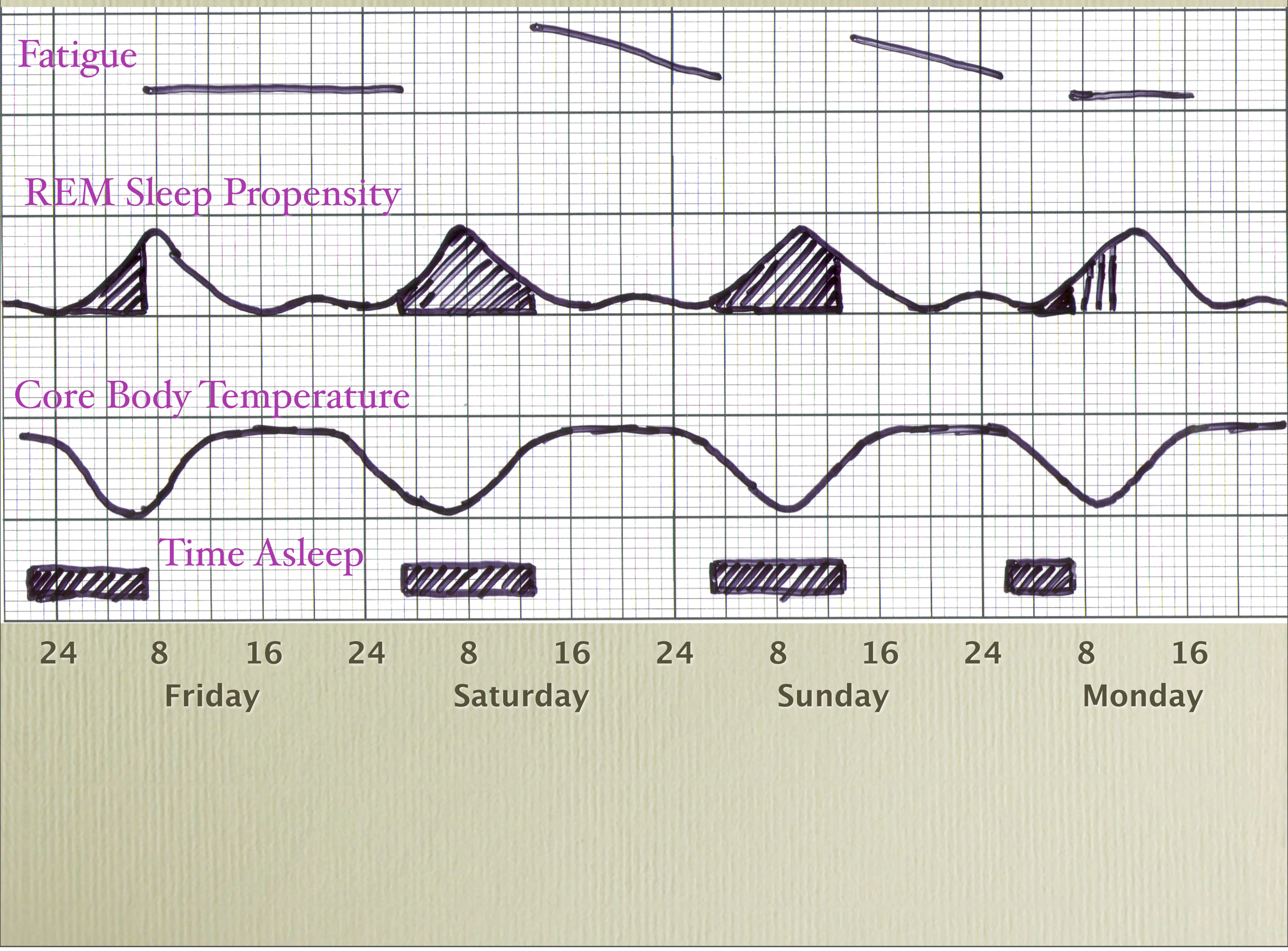
Being a typical teenager, with lots of energy and corresponding poor judgment, John gets home about 2 am. Too wound up to sleep right away, it's 3 am before he nods off. Not to worry, though, the next day is saturday, so John sleeps in until one in the afternoon.
This is 6 hours after his usual rising time, so it will start to phase delay the core body temperature, let's say by two hours. Of course, during this saturday morning sleep, he will still be on his usual circadian rhythm with a REM sleep peak at around 8 am. You can see that he therefore gets lots of REM sleep



What does this do to his fatigue level? You will recall that the depressiogenic theory of sleep calls for higher levels of fatigue and other depressive symptoms as a result of excessive REM sleep.
All of you who have teenagers, will recognize the effect on John's behaviour on Saturday afternoon after sleeping in. Little energy or motivation to do anything beyond watch tv or play video games. Chores? Forget it! In other words, a high level of fatigue.



But his fatigue gradually grows less, the further away he gets from his extended sleep. Finally, at around 11 or 12 on saturday night, John again feels energetic and is ready to go partying again. The cycle repeats itself, although probably with somewhat less REM sleep than the night before. This is because the REM peak is now two hours later, at around 10 am. If he again gets up at 1 in the afternoon, his circadian rhythm, as measured by core body temperature, will likely be phase delayed another 2 hours.
With a bit less REM sleep from Sunday morning, John may have a bit less fatigue on sunday afternoon, which improves the further away he gets from his oversleeping.



Sunday night, John's parents insist that he get to bed early, as it's school the next day. Try as he might, though, John can't fall asleep until about 2 in the morning. He's just not sleepy, having been awake only since 1 that afternoon.
John thus gets about 5 hours of sleep before it's time to get up again at 7 am for school.

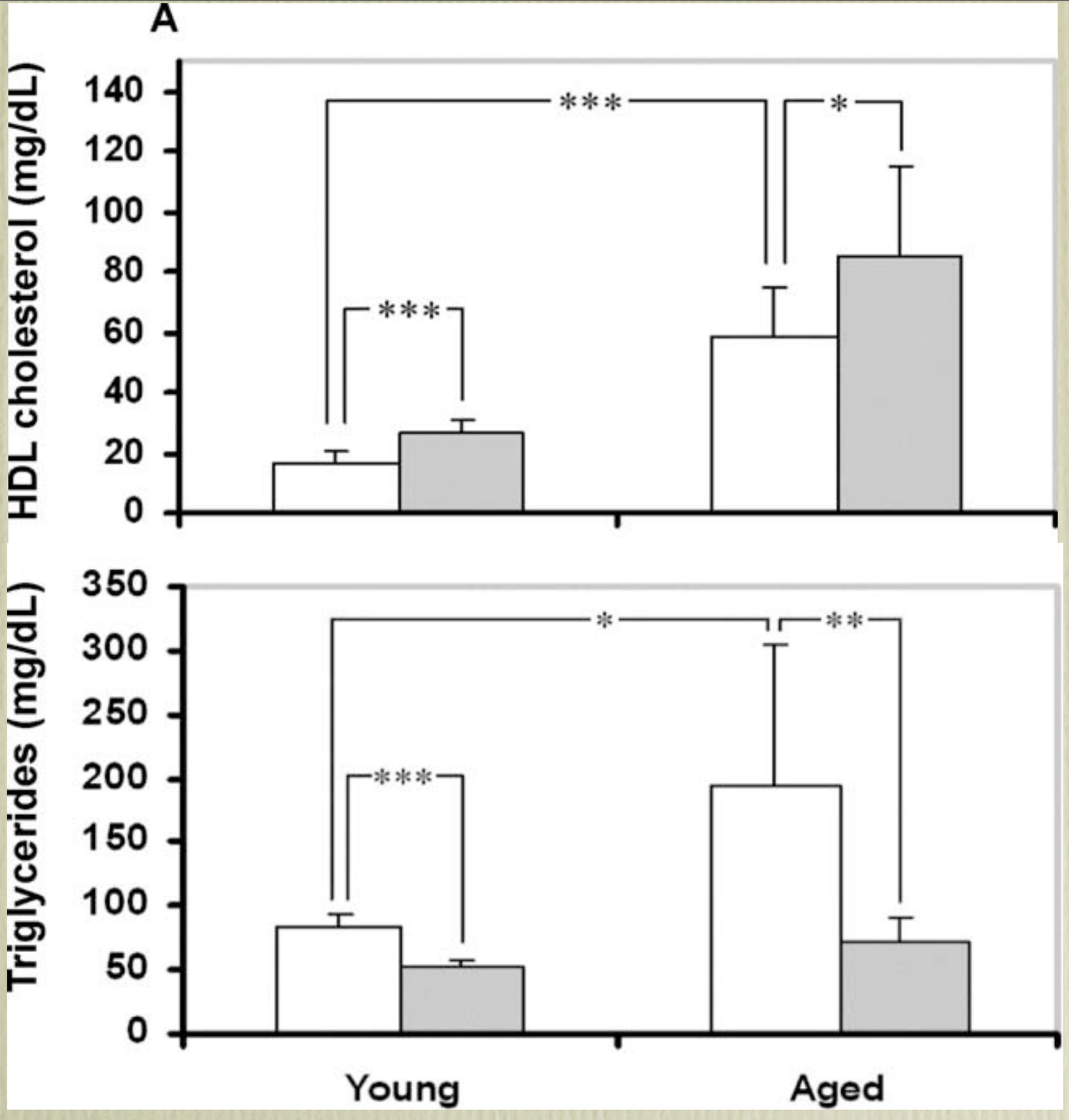
Because his circadian rhythm is about 4 hours delayed from where it was on friday, REM sleep will peak at around noon instead of 8 am. This means that John will actually get very little REM sleep during his 5 hours of sleep. Instead of depressive symptoms, he is much more likely to manifest manic symptoms such as irritability and poor judgment. He may also be unable to stay awake on the bus to school or during his classes. His morning naps are likely to have a lot of REM sleep, however. I've attempted to show the nap REM sleep with the vertical lines, here.

I've shown his fatigue level as low, but it's entirely possible that John feels extremely miserable. This may be because even at 8 am on monday, his body and brain think it's 4 am, which is, like, the middle of the night!

During the subsequent week, with regular rising at 7 am, John's circadian rhythm will gradually phase advance. But as we've seen, phase advance goes much slower than phase delay. If we assume a phase advance of one hour per day, it will take all week until John's circadian rhythm is back in synch with his sleep pattern. Just in time for another weekend so that the whole cycle can start all over again!

What if John had been born in Europe 50 years ago, and had school on saturday morning? What if his parents made him go to church on sunday morning? Without the wild swings of circadian rhythm, would John's mood be more stable, with fewer depressive symptoms?

What about John's great-grandfather, who probably worked 6 days a week when he was young, and also had to get up early for church on sunday?
Do the flexible work and school schedules we have today, and the almost universal tendency to sleep late on weekends, have anything to do with the rising rates of depression over the past decades, especially among the younger generations?

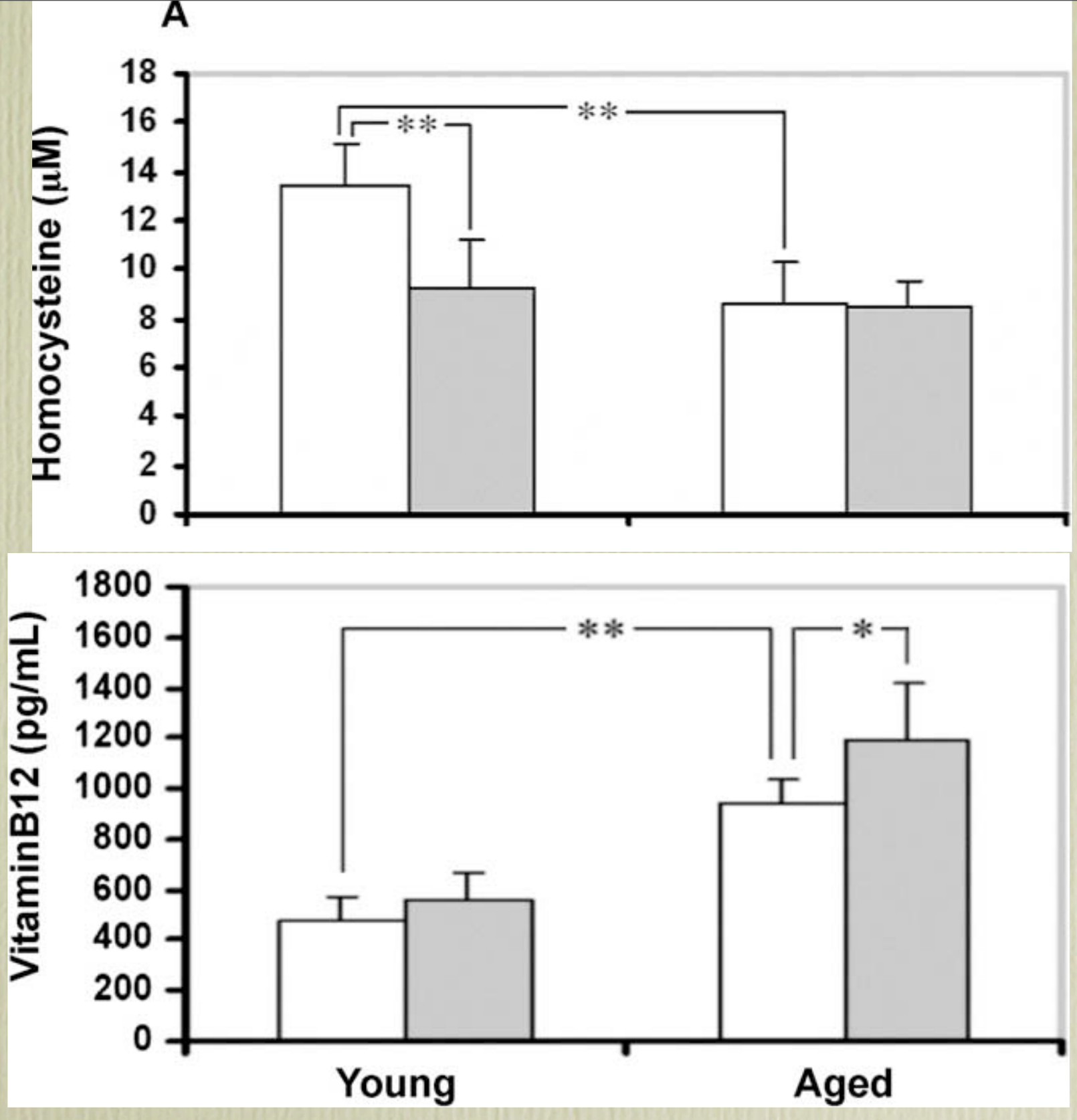


Andersen ML, Martins PJ, D'Almeida V, Santos RF, Bignotto M, Tufik S. Effects of paradoxical sleep deprivation on blood parameters associated with cardiovascular risk in aged rats. Exp Gerontol. 2004;39:817-824.

Have I convinced you that sleeping less can be good for you? Does anyone have any lingering doubts about the health effects of reducing your sleep?

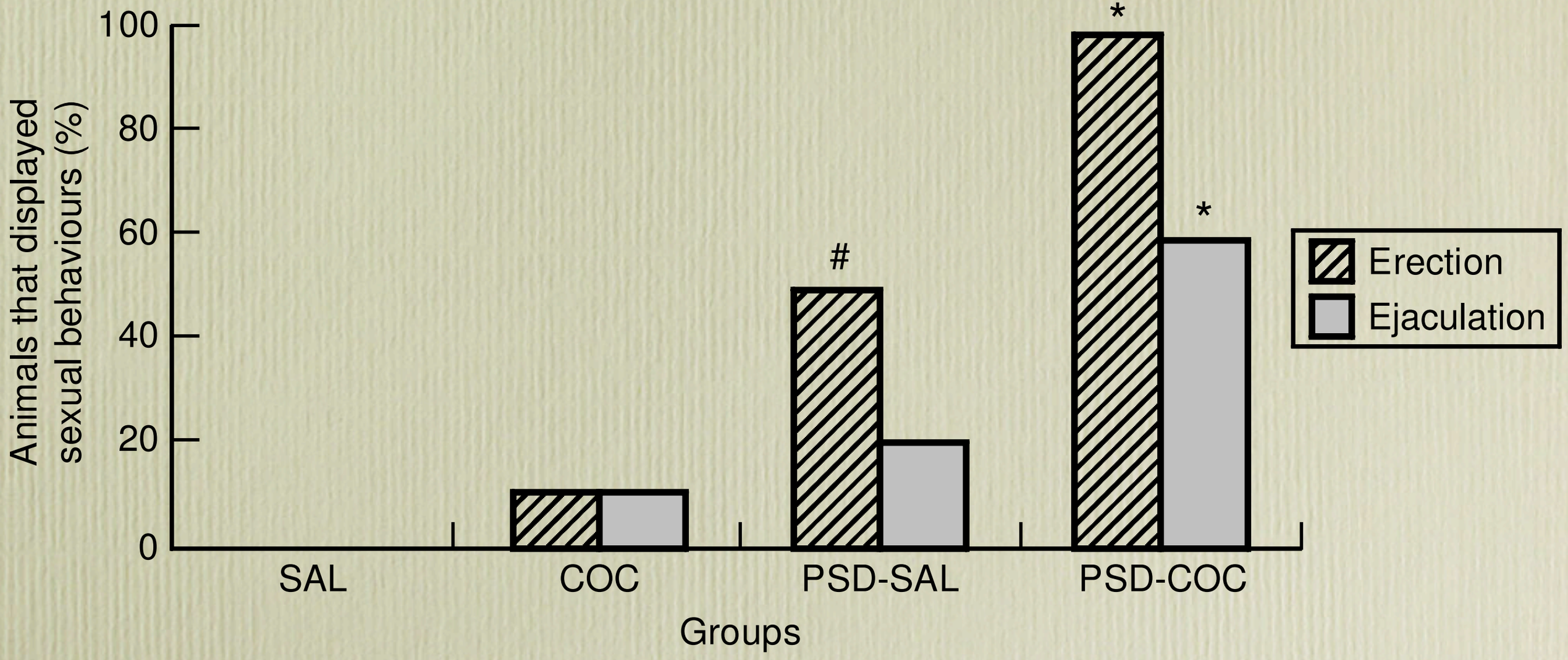
Here's a study of the effects of REM sleep deprivation on cardiovascular risk markers in young and in aged rats. The white bars are the control group, and the gray bars are the rats who were REM sleep deprived for 96 hours. You can see that the good cholesterol went up, and triglycerides decreased. Both heart-healthy!

LDL cholesterol went up, but VLDL cholesterol went down, which makes this more difficult to interpret.



Andersen ML, Martins PJ, D'Almeida V, Santos RF, Bignotto M, Tufik S. Effects of paradoxical sleep deprivation on blood parameters associated with cardiovascular risk in aged rats. Exp Gerontol. 2004;39:817-824.

Homocysteine and B12 status are also considered important in cardiovascular risk and in dementia. REM sleep deprivation improves both homocysteine and B12.



Andersen ML, Tufik S. Distinct effects of paradoxical sleep deprivation and cocaine administration on sexual behavior in male rats. Addict Biol. 2002;7:251–253.

The same researchers also looked at the effects of REM sleep deprivation on sexual behaviour in 40 male rats divided into four groups. The first group received saline, the second group cocaine, the third group, saline and REM sleep deprivation for 96 hours, and the fourth group, both cocaine and REM sleep deprivation. The graph shows the percentage of animals in each group that manifested erections or ejaculations.

The manufacturers of Viagra should be losing sleep over this finding, if you ask me!

In Debate

Does Almost Everybody Suffer From a Bipolar Disorder?

Scott B Patten, MD, FRCPC, PhD[1]

(Can J Psychiatry 2006:51:6–8)

The concept of a broad and inclusive bipolar spectrum disorders appear to be gaining momentum in the psychiatric literature, although cautionary comments have previously been made (for example, by Baldessarini; 1). The possibility that a large proportion of people diagnosed with depression actually have BD is an important clinical consideration and a natural corollary of this trend. I will not focus specifically on the unipolar-bipolar distinction, however, since the general trend toward broadening the diagnostic boundaries of BD raises similar issues for many other conditions (such as impulse control disorders and Axis II pathology). Rather, I will direct my comments toward the broad, ongoing debate about the bipolar spectrum concept. My intention is not to argue that existing diagnostic conventions are perfect or that a

criteria for hypomanic or mixed episodes. For some, the emphasis has been more deeply conceptual, typically targeting what is seen as an artificial distinction in the DSM-IV between unipolar and bipolar disorders. In this latter instance, the spectrum concept can be understood not simply as the broadening of a diagnostic category but as a more basic reappraisal, perhaps one that favours dimensional measurement.

The DSM-IV includes a kind of bipolar spectrum: BD I and BD II, as well as cyclothymic disorder. These are classified together with other mood disorders. Mixed states are treated much like manic states in the 6 DSM-IV coding categories for BD I. Further, the categories are fluid: a manic episode can move an afflicted individual from one category (such as major depressive disorder, recurrent) to another (such as BD I, most recent episode manic). However, the movement occurs as a result of signs and symptoms identified according to explicit

It is worthwhile to ask, so what if too much sleep causes depression, and too little causes mania. After all, the vast majority of individuals do not get either depressed or manic. Or do they?

These days, researchers talk about bipolar spectrum disorder, which covers a whole range of severity. And at the mild end, it shades imperceptibly into normal mood swings. Dr. Scott Patten wrote about this in 2006 in the Canadian Journal of Psychiatry, asking “Does almost everybody suffer from a bipolar disorder?”. So don’t be too sure that it doesn’t apply to you!

The last word

- "One hour's sleep before midnight is worth two hours after."
  —John Rays (1627-1705): A Compleat Collection of English Proverbs, 1670
- "Plough deep while sluggards sleep."
  —Benjamin franklin (1706-1790): Maxim prefixed to Poor Richard's Almanac, 1757
- "The early bird catches the worm."
- "My formula for success?
  Rise early, work late, strike oil."
  —J. Paul Getty

I'll let these people have the last word:

♥

♥

♥

My favourite is this last one, ♥ by billionaire oilman J. Paul Getty.

Homer, take two

"There is a time for many words,
and there is also a time for sleep”