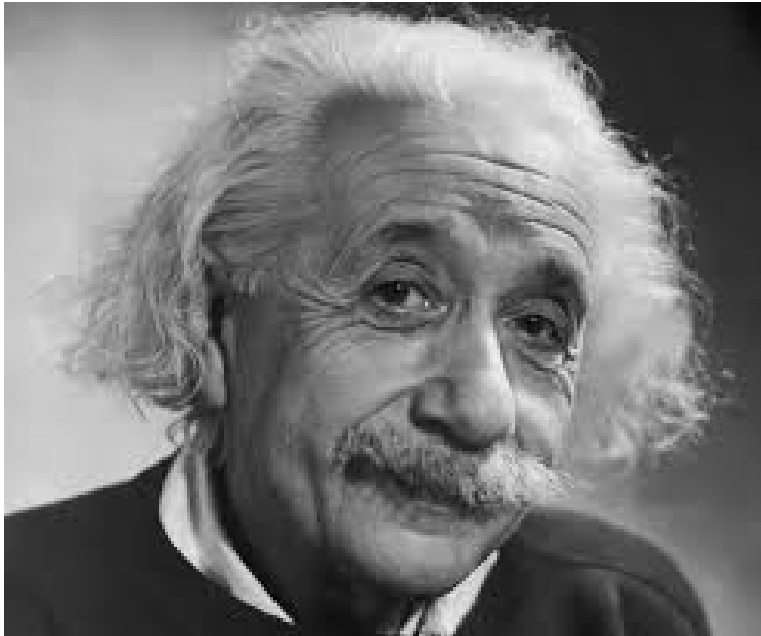# Sleep Duration

is NOT a risk factor for increased mortality in the elderly

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Albert Einstein
1879-1955
(Slept 12 hours a day)

Background- *The folk belief that we should sleep 8 h seems to be incorrect**

Several studies have identified an increased mortality associated with sleep duration in the elderly

- Wingard & Berkman (Alameda, CA) n=4713, age 30-69, f/u 7 yrs, 7% slept ≥9°
  - ↑age-adjusted mortality rate of 1.6- women and 1.7 men for sleep ≥9° vs 7-8°
  - With multivariate adjustment, RR decreased to 1.3
- Mesas (Spain) n= 3820, age 71.8±7.9- 38% slept ≥9°
  - 8° -RR 1.34 (1.02-1.76)
  - 9° – RR 1.48 (1.12-1.96)
  - 10°–RR 1.73 (1.3-2.29)   *6 hours- RR 1.23 (.90-1.69)
- Castro Costa (Brazil), n= 1742, age 68.9±7.1, f/u 7.5 yr, 15% slept ≥9°
  - HR 1.56 (1.12-2.18) ≥9° vs 7°
- Amagai (rural Japan) n=11,325, age 55±11, f/u 8.2 yr, 15% slept ≥9°
  - increased mortality sleep >9° in females only
- Hublin (Finland) n=21,268 twins, f/u 22 yr
  - Men HR 1.24 (1.09-1.41), Women HR 1.17 (1.03-1.34) ≥8° vs 7°
  - Frequent hypnotics- Men HR 1.31 (1.02-1.69), Women HR 1.39 (1.11-1.75)

Sleep Heart Health- 7.6-9.2% ≥ 9°
(Sleep Med Rev 2007; 11: 337-9)

Kripke, et. al.

Covariate-Adjusted* Mortality Hazard Ratios From the Cancer Prevention Study II (1982-1988)

	Women (n = 636 095)			Men (n = 480 841)		
	% of Women	Hazard Ratio	95% Confidence Interval	% of Men	Hazard Ratio	95% Confidence Interval
Hours of sleep						
3	0.1	1.33	1.08-1.64	0.1	1.19†	0.96-1.47
4	0.7	1.11	1.01-1.22	0.6	1.17	1.06-1.28
5	3.5	1.07	1.01-1.13	2.9	1.11	1.05-1.18
6	15.9	1.07	1.03-1.11	15.5	1.08	1.04-1.11
7	31.8	1.00	Reference	33.8	1.00	Reference
8	38.8	1.13	1.09-1.16	38.0	1.12	1.09-1.15
9	6.0	1.23	1.17-1.28	5.7	1.17	1.13-1.21
≥10	1.5	1.41	1.34-1.50	2.0	1.34	1.28-1.40

N= 1.1 million   1982-2002
Mainly friends and relatives of ACS volunteers in San Diego
Age 30-102 (mean 57±11 at entry)

*Any prescription sleeping pill use was also associated with significantly elevated hazard ratio

Depressed mood, alcohol consumption not assessed.

Hypertension

- Gottlieb (SHHS '06)- mean age 63±10
  - -8-9°- Adjusted OR 1.19 (1.04-1.37)- 22% of sample ≥ 8°
  - >9°- Adjusted OR 1.3 (1.04-1.62)- 7.6% of sample ≥ 9°

Diabetes/Impaired Glucose Intolerance

- Gottlieb (SHHS '05) >9°- Adj OR 1.87 (1.14-3.05) in those >70 years
- Ayas (Nurses Health Study- Adjusted RR 1.29 (1.05–1.59) sleep ≥ 9° (4.9%)
- Yaggi (Massachusetts Male Aging Study) n=1139
  - >8°- Adjusted RR 3.12 (1.53–6.37) 6.2% of sample
    - *Adjusting for waist circumference alone attenuates risk from 3.53 to 3.12*

Stroke

- Quereshi (NHANES 1)- ↑ risk with sleep > 8° c/w 6-8°.
- Ayas (Nurses Health Study) RR 1.38 (95% CI, 1.03-1.86) for sleep > 9 °
- Ikehara (JACC Study-Japan)
  - ↑Mortality from all cause, stroke, ischemic stroke, total CV disease, non-CV/non-Cancer with sleep ≥10°, some subgroups for ≥9°

Cancer Mortality

- Cai (China)
  - ↑All Cancer with sleep ≥10° (versus 7°)
    - Lung cancer - men HR 1.58 (1.06-2.35)
    - Colorectal cancer- men HR 2.17 (1.24-3.80), women 3.28 (1.70-6.32)

Variation in sleep duration grouping

- Alameda County   ≤6, 7 or 8, ≥9
- Cai (China)   4–5 , 6, 7, 8, 9, ≥ 10
- Mallon (Sweden)   <6, >8
- Heslop (Scotland)   <7, 7-8, >8
- Mesas (Spain)   ≤5, 6, 7, 8, 9, 10, ≥11
- Gayle (England)   ≤7, 8, 9, 10, 11, 12
- Gottlieb (SHHS)   <6, 6-<7, 7-<8, 8-<9, >9.
- Castro Costa (Brazil)   <6, 6-<7, 7-<8, 8-<9, >9
- Kojima (Japan)   >7, 7-8.9, 9-9.9, ≥10
- Amagai (Japan)   <6, 6-<7, 7-<8, 8-<9, >9
- Hublin (Finland)   <7, 7-8, >8
- Ferrie (Whitehall II)   ≤5, 6, 7, 8, ≥ 9

Causality

- If prolonged sleep duration is a genuine risk factor for mortality in so many studies, we should be able to identify what the specific cause of the mortality is by now.

  - Ideally there should be a <u>unifying factor among the causes of mortality</u> that we can identify.

  - Candidates- stroke, myocardial infarction, arrhythmia, diabetes, cancer, ?traumatic (accidents, suicide)

  - Not readily plausible that prolonged sleep duration could lead to all of these unrelated causes of mortality.

Gallicchio (2009)

Random effects meta analysis of 17 studies to 2008

- All cause mortality- pooled RR 1.23 (1.17-1.30)
  - Pooled all cause mortality remained significant even after Kripke (2002) was removed (>1 million in cohort)

- CV- related mortality- pooled RR 1.38 (1.13-1.69)
  - Females only – pooled RR 1.45 (0.93-2.28)- not significant
  - Males only – pooled RR 1.34 (0.79-2.28) - not significant

- Cancer-related mortality- pooled RR 1.23 (1.11-1.32)
  - Statistically significant for females, not males– pooled RR 1.21 (1.10-1.34)

- *Sleep duration assessed by self report in all studies*

- 16 of the adjusted RRs were in the direction of increase, however, only 8 were statistically significant for all cause mortality and long sleep.

Negative studies

All cause

- Kojima (Japan)- mean age 47, mean f/u 11.9 years
  - 9-9.9° vs 7-8.9°-- <u>All cause</u>-not significant men or women
- Heslop (Scotland) age<60 at baseline
  - >8°- <u>All cause</u>- HR 1.15 (0.88-1.50)
- Mallon (Dalarna, Sweden) n= 1870, age 56±6, f/u> 10 years
  - After multivariate adjustment, <u>increased RR of sleep>8 ° no longer seen</u> and only smoking, depression, diabetes and cardiac disease remained significant predictors of death.
- Kaplan (Alameda County Study)
  - 17-year follow-up to Wingard & Berkman – <u>no association duration and mortality</u>

- Westerlund (Swedish Nat'l March Cohort (n=41,192, age 52.8, mean f/u 13.2 yrs)
  - ≥8°- No significance with **CV Death**, **Stroke, CHF** , borderline-**MI**
- Amagai (Japan) > 9°- **CV Events**- not significant after adjustments for age, BP, BMI, smoking, alcohol
- Grandner (NHANES) no sig↑ risk for obesity, lipids, self-reported hypertension/ diabetes

Cai, et. al. (Shanghai 2015)

n=113,138   Mean f/u ≈ 6-7 years

↑HR for total mortality in men and women for sleep 8°< 9°< (≥10°)

- also significant for death from cardiovascular, stroke, diabetes, cancer and "other"

Unlike other studies, there was only borderline significance for women sleeping 4-5°

<u>Important confounders</u>

Sleep duration increased with:

- waist circumference, BMI, WHR   - less exercise

- less education   - high comorbidity scores

- more likely to drink alcohol   - low income

Cai, et. al.

Excluding those with known disease

Longer sleep durations were "still associated with total mortality, CVD and stroke mortality" after excluding individuals with known major comorbidities.

- But in In these very large cohorts, how precise are the characterization of underlying diagnoses?
  - ECGs, stress tests, glucose tolerance tests, colonoscopy, mammogram, cognitive testing
  - Cohort data published with 6-7 mean follow-up so the subjects may well have had a cancer and coronary artery disease at entry in many cases.
- Could the sicker, less educated people be less aware of the extent of their health problems while in the cohort?

Basic questions

- Is there something intrinsic to prolonged sleep duration itself (i.e., some cytokine, inflammatory, or pro-thrombotic marker) that is leading to increased mortality?

Or

- Is the long sleep associated with another factor which is actually causing the increased mortality?
  - Do we know what that factor(s) is and are we measuring it correctly in the research available?
  - Reverse causality- *this other factor is actually causing the long sleep*

Is self report of sleep accurate?

- Sleep Heart Health Study (2006)
  - One night of PSG
  - Total PSG sleep time 5.9°< self report of 7.1 °

- CARDIA study- Self reported sleep duration> actigraphy over 3 weeks
  n=669 aged 38-50
    - 6.65±1.19° weekdays > 6.06±1.2° actigraphy
      (7.26±1.31° weekends)

- Van den Berg – Rotterdam Study (n=969 community dwelling elderly)
  - In 34% of subjects, the estimated TST in diaries deviated > 1° from TST quantified by actigraphy.
  - Actigraphically measured poor sleep was often accompanied by longer subjective estimates of sleep.
  - Subjective poor sleepers tended to report shorter TST c/w actigraphy

Furthermore, how does a survey question about sleep duration in the past year (or past two years) correlate with actigraphy?

Am J Epidemiol 2006:164:5-16
J Sleep Res 2008; 17:295-302

How is sleep duration asked about?

-Variation in questioning

Characterization of sleep often based on 1-2 questions bundled within a large survey

- On the average, how many hours do you sleep each night?"
  Kripke 2002

- How many hours of sleep in a 24 hour period?   Heslop/Patel

- How many hours did you sleep each day including sleeping during the day and night but not including time if you woke up between two periods of sleep?
  Cai

- Time in bed- During weekdays (weekend) in the last month, at what time did you on average, lie down to go to sleep, and leave the bed?

  Castro-Costa

Given noted % differences in long sleep, either the populations differ or we are potentially asking about different things.

Need to account for naps in elderly

Age 50–59 years
Mean duration = 7hr. 16min.

Age 70 + years
Mean duration = 7hr. 40min.

Hours
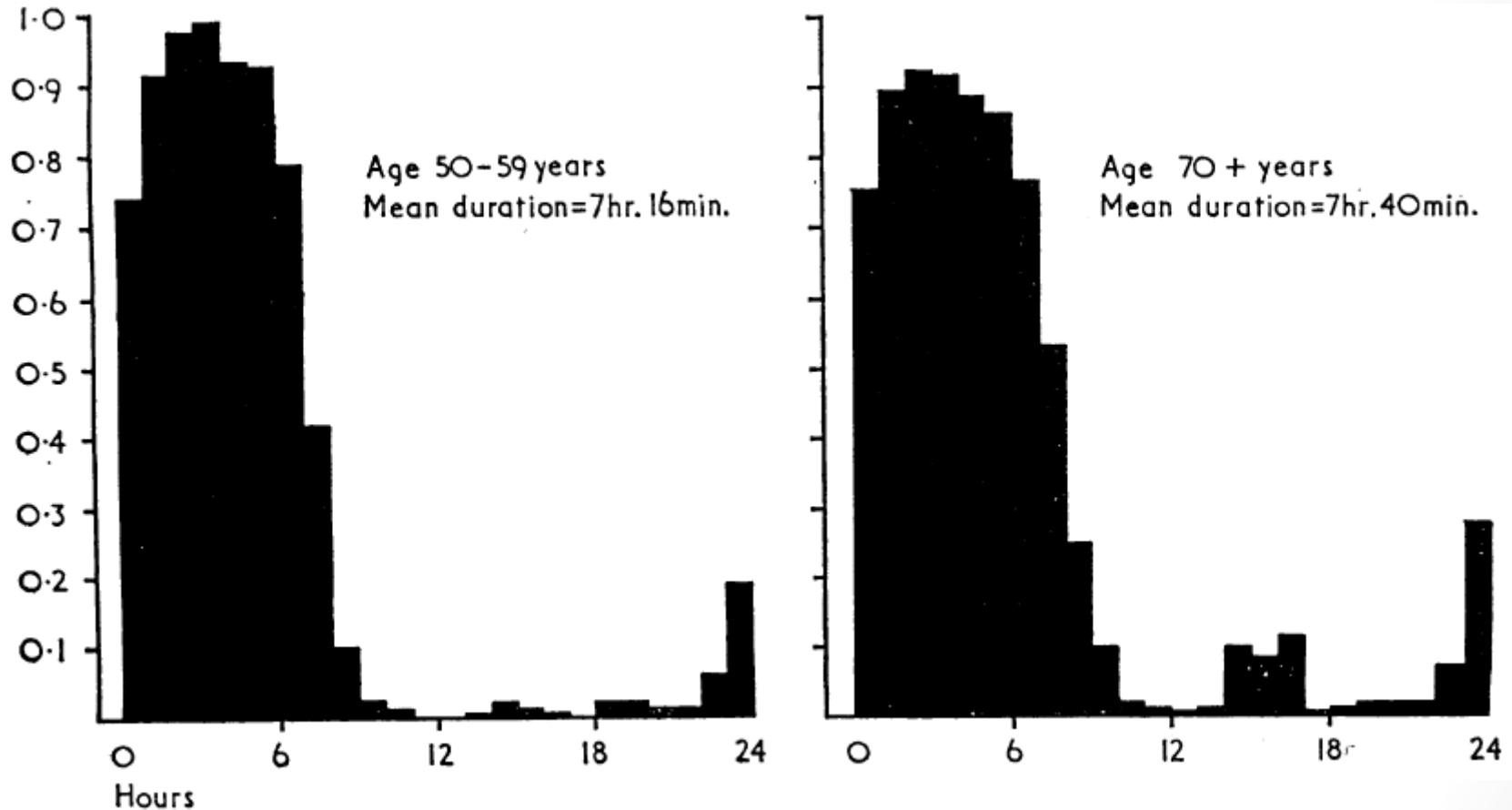
*The older subjects were able to achieve a higher average duration
of sleep per day than the middle-aged by taking compensatory midday naps.*

8 weeks record of sleep timing accurate to within
nearest 30 minutes

A moving target:
Sleep may change over time in these cohorts

- Hublin (Finnish Twin) found that in 1/3 of cohort, sleep either changed in duration or quality over a 6-year period
  - A decrease in sleep was associated with ↑mortality risk
  - An increase in sleep from average to long - ↑mortality risk
    - Seems unlikely that the change in sleep caused the mortality

- Ferrie (Whitehall II) found ↑mortality rate in those that shortened or lengthened their sleep (4-8 year period)
  - An increase in sleep from 7 or 8 hours at baseline was associated with a fully adjusted HR for total mortality 1.75 (1.24-2.47) and non-CV mortality 2.06 (1.38-3.08)

Changes length in sleep are common and may be reflective of a problem and not the cause of it

Which studies ask about snoring?

Symptoms may not correlate with OSA, especially in the elderly
(more potential contributors to sleepiness, more interindividual variation, less apt to have a bed partner to hear the snoring)

- Castro Cosa (Brazil) - Snoring and daytime sleepiness (OSA proxy)
  - No reported effect

- Mallon (Sweden)
  - No association between snoring & mortality

- Hublin (Finnish Twin Study)
  - Asked about quality, duration and snoring
  - No reported effect of snoring on mortality

- Ancoli-Israel (1991)
  - Snoring? Only 65% people could answer this question; the rest did not know if they snored.
  - "Snoring did not contribute to the discriminate prediction of RDI"

Which studies have sleep study data?

- Ancoli-Israel 1991/1996- Portable sleep testing
  - Total sleep time on HST, no reported survey of sleep duration

- Sleep Heart Health Study
  - full PSG in home 1993-95 in 3368 subjects (2006)
  - Mean sleep efficiency highest in 7-<8° sleepers (83.1%) and lowest in those sleeping ≥9° (78.1%)

- Kripke- Actigraphy in 444 elderly females
  - Next slide

SURVIVAL ±SE

SLEEP DURATION
300 - 390 MIN
390 - 502 MIN
165 - 300 MIN
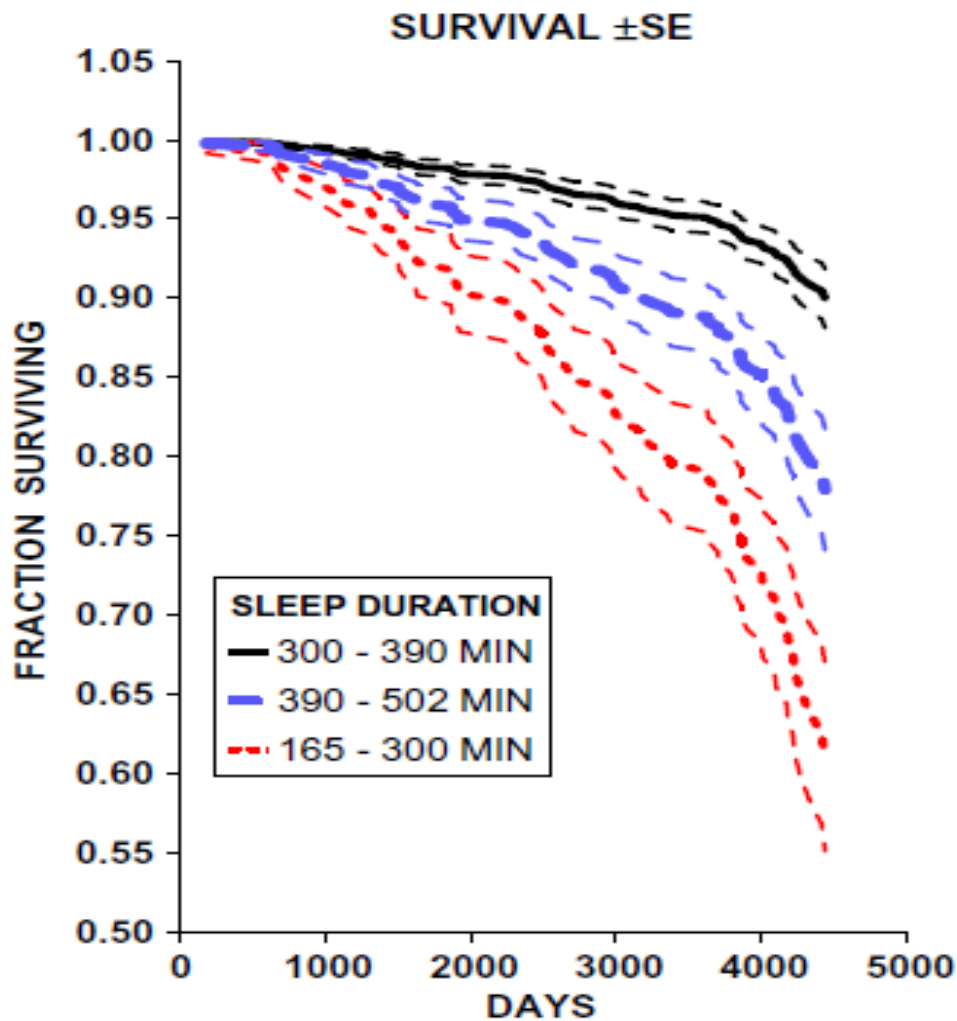
N=444 women
One-week actigraphy
Age- 67.6 years
1999-2010

78% survival (73–85%, 95% C.I.) for those with actigraphic sleep >390 min (≥6.5°)
90% survival (85–94%, 95% C.I.) for those with sleep 300–390 min (5°-6.5°)

Why is it important to measure sleep disordered breathing?

1. Self report of sleep duration may be complicated by the inherent decreased efficiency, ↑WASO/Stage 1%/napping of OSA

2. Sleep disordered breathing is common in the elderly
   - 24% with AI ≥5 and 62% had a RDI ≥10 in a community based sample.
     (Ancoli-Israel 1991)

   Prevalence increased "across decades"
   - 2.9% - 60 yr olds, 33.3% - 70 yr olds, and 39.5% - 80 yr olds with AHI >5

3. Subjects with OSA may have longer sleep duration

4. Sleep apnea is associated with arrhythmias, stroke, high blood pressure, glucose intolerance and mortality

Sleep 1991; 14(6):486-95
Sleep 2006; 29(8): 1009-14

Sleep 2011; 34 (2): 147-52
PLoS One 5(8): e12065 (August 11, 2010))
Lancet2005; 365:1046-53

Zaragoza Sleep Cohort Study

Mean f/u 10.3 years
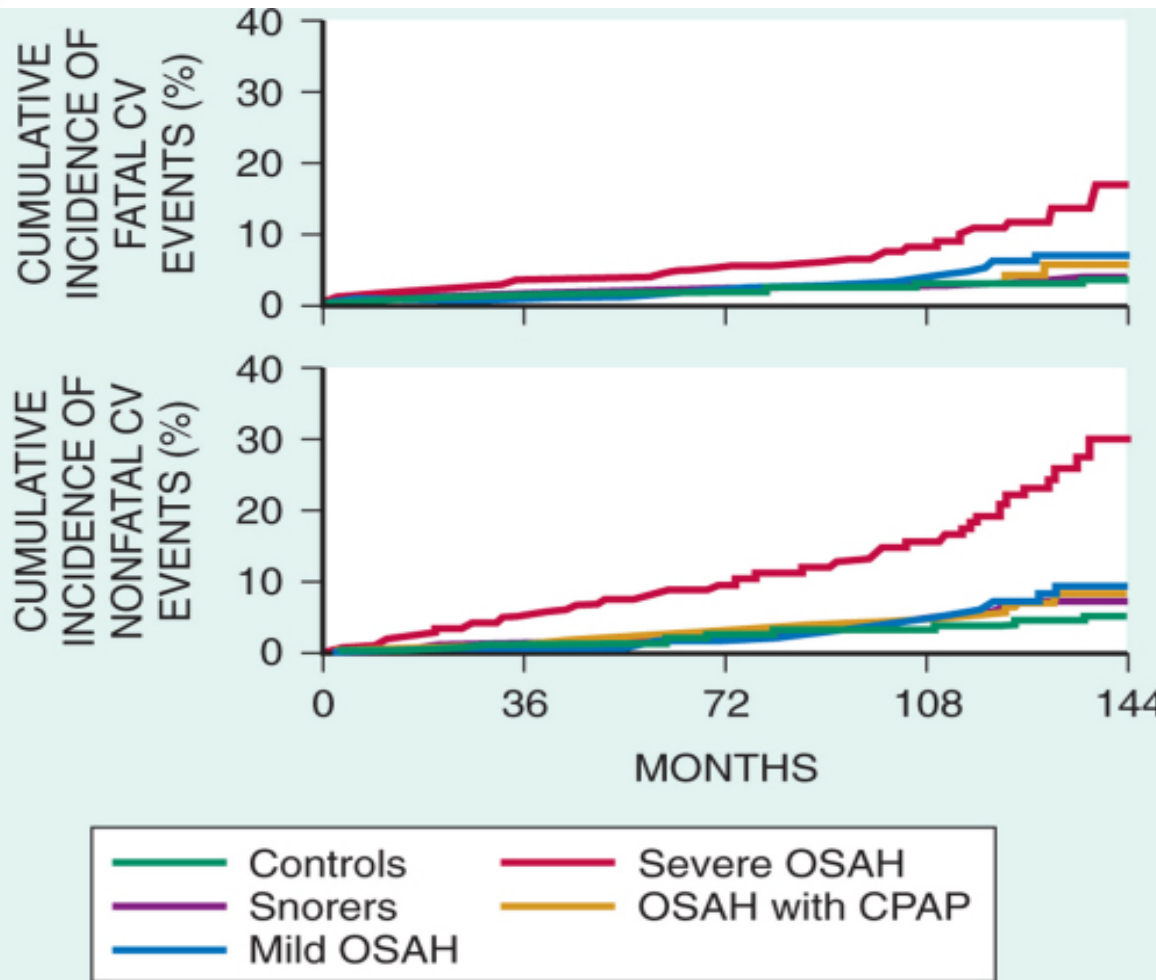
Untreated severe OSA ↑ risk of fatal MI or stroke (OR 2.87) compared with controls

Mild= AHI<30   Severe = AHI>30

Lancet 365:1046-53, 2005

How can we associate prolonged sleep duration with known consequences of sleep disordered breathing (myocardial infarction, stroke) when there is limited data on whether or not these cohorts had sleep apnea or not?

Causal Pathway?

In order to accept that long sleep is a risk factor for mortality,

we need to understand what factors may explain this finding.

Confounders

Mediators

Causal Associations
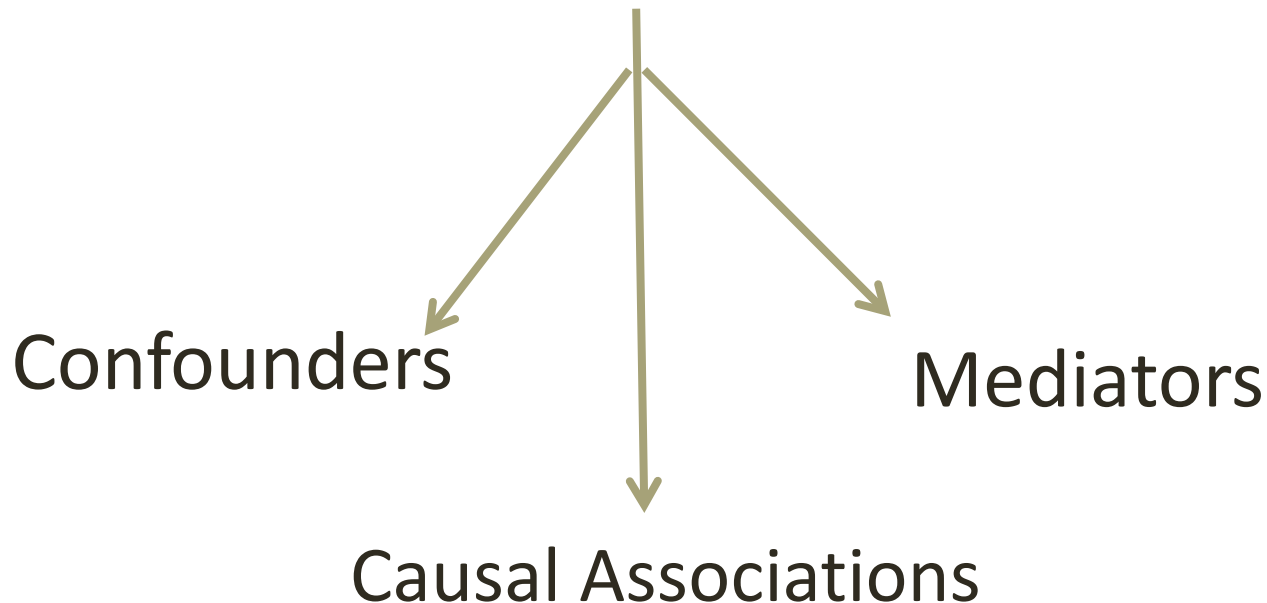
Sampling of confounders measured with longer sleep

- Yaggi (Massachusetts Male Aging Study)
  - Men reporting 7 h of sleep were <u>younger</u>, <u>more educated</u>, in <u>better health</u>, and had higher <u>testosterone</u> levels

- Heslop (Scotland)
  - Those who slept ≥8° -<u>more alcohol</u>, <u>less frequently married</u>

- Mesas (Spain)
  - Those who slept ≥8° were <u>older</u>, <u>less educated</u>, <u>less physical activity</u>, <u>more alcohol and coffee</u>, <u>more suboptimal health</u>, <u>depression and cognitive dysfunction</u>

- Faubel (Spain)
  - <u>Cognitive impairment</u> in those >60 years increased progressively across sleep duration categories from 7 to > 11 hours.

Potential sleep/biologic factors clinically associated with prolonged sleep duration

- all more common in the elderly

- Underlying disease
  - Depression
  - Poor health
  - Cancer fatigue (Ferri)
  - Heart disease
  - Sleep apnea

- Sleep fragmentation
  - nocturia
  - pain
  - periodic limb movements/restless legs
  - hypoxemia
  - cough

- Am fatigue leading to sleep extension or morning nap
- Alcohol/Hypnotic agents
- Medication effects- *sicker people take more meds*

More potential sleep/biologic factors clinically associated with prolonged sleep duration

- ?Are there somnogenic cytokines from underlying inflammation which are related to the cause of mortality

- Genetics
  - Hereditary effect identified with sleep duration in Finnish twin cohort   (Sleep 1983; 6:179-85)

- ?Reduced physiologic reserve- those who need more sleep are less able to fight off illness   (Patel 2004)

Sedentary lifestyle

- More common in the elderly
  - Castro-Costa -85-88% reported no exercises in the last 90 days

- Associated with increased mortality

- Associated with longer sleep duration
  - Ayas (Nurses Health Study)- "physical activity was the primary confounder of long sleep times"

- Experimental data it is harmful
  - 7-10 days of sedentary living resulted in deterioration of glucose tolerance and reduction in resting metabolic rate in endurance trained athletes   J Applied Physiol 1998; 84(4): 1365-73
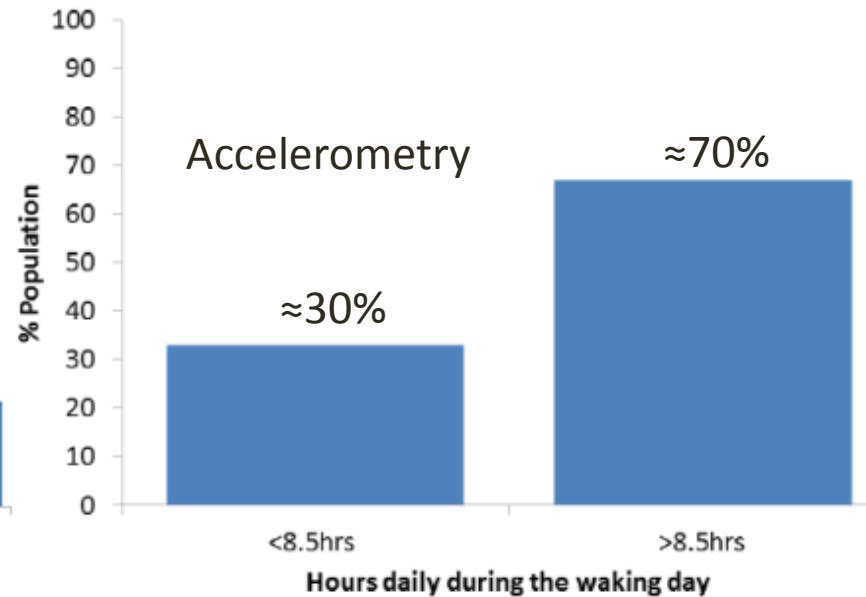
Sedentary lifestyle

Pooled Cumulative Prevalence of Sitting Time Reported by Older Adults

Self report

≈25%

Pool %

Hours of Sitting Daily
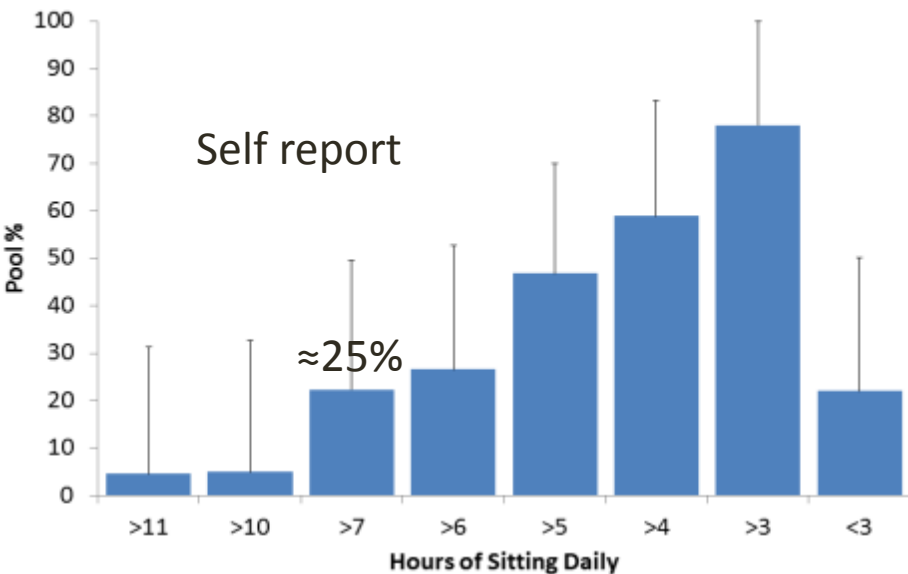
n = 372,550 older adults

Older Adults Sedentary Time by Accelerometry

Accelerometry

≈70%

≈30%

% Population

Hours daily during the waking day

n= 649 older adults

Int. J. Environ. Res. Public Health 2013;10: 6645-61
Int J Epidemiol 2012; 41: 1328–37

Socioeconomic disadvantage & long sleep

- Hale (2005)   Long sleep more common in:
  - High school education (OR 1.61, p<0.001) vs those with college education
  - Being single (OR 1.28, p<0.05) vs married

- Patel (Hispanic Community Health Study/Study of Latinos 2015)
  - unemployment, low household income, low level of education, and being born in the mainland US were independent predictors of long sleep
  - (Of note, this was also an important recent study that did not show significantly increased mortality with long sleep)

- Patel Nurses Health Study II)
  - Living alone -OR 1.31 (1.18-1.45)
  - Never married -OR 1.37 (1.22-1.54)
  - Lack of employment- OR 2.4 (2.3-2.6)

- Those with a job and/or married lead a more structured life and have to avoid extremes in sleep duration or timing.

- Socioeconomic status interrelated with depression

Depression

Long sleepers were "worriers" and were chronically somewhat depressed or anxious; they scored higher than the short sleepers on most tests of pathology   Arch Gen Psychiat 1972; 26:463-8

- Has been associated with increased sleep duration
  - Gottlieb 2006
  - Patel 2006 (NHS II)
    - Antidepressant use OR 3.1 (2.9-3.30

-Has been associated with increased sleep duration and mortality
- Mallon (Sweden)
  - After multivariate adjustment sleep>8°, depression (along with smoking, diabetes and cardiac disease) remained significant predictors of death   *J Int Med 2002; 251: 207±216*
  - In males, depression increased risk of total mortality - RR 2.3 (1.3-4.2)

Despite multiple studies, lack of causality in Long Sleep
- co-morbidities of short sleep may have an explanation

- Short Sleep has been associated with:
  - Decreased microvascular function (post ischemic capillary recruitment)
  - Inflammatory factors associated with mortality- ↑ CRP, IL-6, TNF-α
    - Adjustment attenuated ↑mortality of short sleep in Health ABC
  - Metabolic factors-
    - Higher evening cortisol and a predisposition to insulin resistance
    - Activation of the sympathetic nervous system
    - Experimentally- decreased leptin (Spiegel/Van Cauter) and increased BP (Lusardi 1996)
  - *Increased diabetes, hypertension and CV disease with short sleep actually plausible.*

Need experimental evidence that long sleep can induce potentially harmful factors

J Sleep Res 2015: 24:140-17
Sleep 1997; 20: 865– 70
Sleep 2015;38(2): 189-95

Why would long sleep be causing harm? - mediators of effect

- Perpetuating factor in insomnia
  - Spend more time in bed to make up for inefficient sleep
- Too much time in bed

  - Sleep fragmentation and low sleep efficiency

  -Facilitating sense of fatigue, depression
- Lack of physiologic challenge → muscle catabolism/sarcopenia with less use
- ? Effects on immune function
- Photoperiodic abnormalities
- ↑Fibrinogen (Women's Health Initiative)-associated with sleep ≥9°, all cause mortality, and coronary heart disease
  - Could suggest an underlying inflammatory condition
  - N.B. increased fibrinogen also seen in sleep apnea, fragmented sleep

J Public Health 2005; 27(2): 205-11
J Sleep res 2009;18: 145-7
Sleep Med Rev 2007; 11: 341-60
J Sleep Res 2013; 22: 305-14.

"Longer" Sleep is intrinsically natural

We each have a unique sleep need that would seem to approach an equilibrium in the right circumstances

- People slept longer in the past
  - Healthy adults> 60 years most commonly slept 8.0 -8.9° in an American Cancer Society 1959 survey   (Arch Gen Psychiatry 1979; 36:103-16)

- Increased leptin, decreased ghrelin and better food choices with sleep extension of 10 hours   *(Ann Intern Med* 2004; 141:846-850)

- Healthy men maintained in a constant routine of 10 hours light and 14 hours dark *naturally* slept >8 hours   (Am J Physiol 1993;265: R846-57)

- Seven days of extending sleep to 12° not associated with glucose intolerance   (Lancet 1999;354: 1435-9)

Need more specific investigation of these effects in the elderly
- But how much time is needed to see the ill effects of prolonged sleep and is such an experimental intervention even possible?

Conclusions

- Existing research seems to raise more questions than answers about the effects of long sleeping on mortality in the elderly
- No mechanism available, just causal inference
- Confounding explains the duration effect in some studies, not all
  - Do we know what these confounders are?
  - Are we correctly measuring the confounders involved?
- Sleep duration is based on subjective reports
  - Prone to errors in recall at the time points measured
  - Questionnaires not validated in the elderly, the sick, or at later time points
  - Lack of objective sleep duration data
    - Limited PSG data and that is available suggests an overestimate with self report
- Lack of objective characterization data at baseline
  - Diagnoses based on self-report and subject to prior healthcare engagement and availability

Is prolonged sleep duration a risk factor for increased mortality in the elderly?. . . No

- Many observational studies available in a variety of populations and with notable variation in characterization of the populations and the confounding variables.

- Too many suspicious confounders known to be associated with mortality are present to say that it is the prolonged sleep duration itself.

- Is it a sign that something may be wrong? POSSIBLY.
- Should we be advising the elderly to go out of their way and sleep 7 hours or less? NO

What is needed *ideally?*

- Sleep duration verified by actigraphy
  - Reassessments of any change in sleep duration and *quantify consistent exposure*
- Quantify sleep disordered breathing (HST)
- Waist circumference/WHR (or other measure of adiposity)
- Measure of sedentary lifestyle- self report or accelerometer
- Depression scale
- Self report of functional limitations
- Inflammatory markers
- Hypnotic assessment and medications with sedation
- Socioeconomic measures/access to care
- Living alone/living with others

Clinical trial?

- A prospective RCT in a healthy elderly population may clarify
  - Could a behavioral intervention such a long term manipulation in reducing sleep duration in the elderly be successfully done?
    - Adherence to the schedule/motivation bias
    - How long would such a study need to be to show any difference in co-morbidities?
- Youngstedt et.al. (Contemp Clin Trials 2013; 36 (1))
  - 4 sites over 5 years, n=200
  - "Examine health, mood, quality of life and performance effects of moderate restriction of time in bed"
  - 12 weeks of sleep restriction (reduce TIB by 1 °) or control in long sleepers and average sleepers

Once completed, then more focus can be placed on intervening on the potential real factors associated with harm in long sleep- sedentary lifestyle, depression, early detection of cancer and atherosclerosis and disease modification, and addressing the socioeconomic disparities that perpetuate it.