# Light at Night and Health: The Nurses' Health Study Cohorts

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# OVERVIEW

1. Physiology of circadian rhythms

2. Impact of light at night (LAN) on cancer risk

3. Impact of LAN on cardiovascular disease risk

4. Current policies and preventive implications

# Light Entrains the Biologic Clock



R. Richards
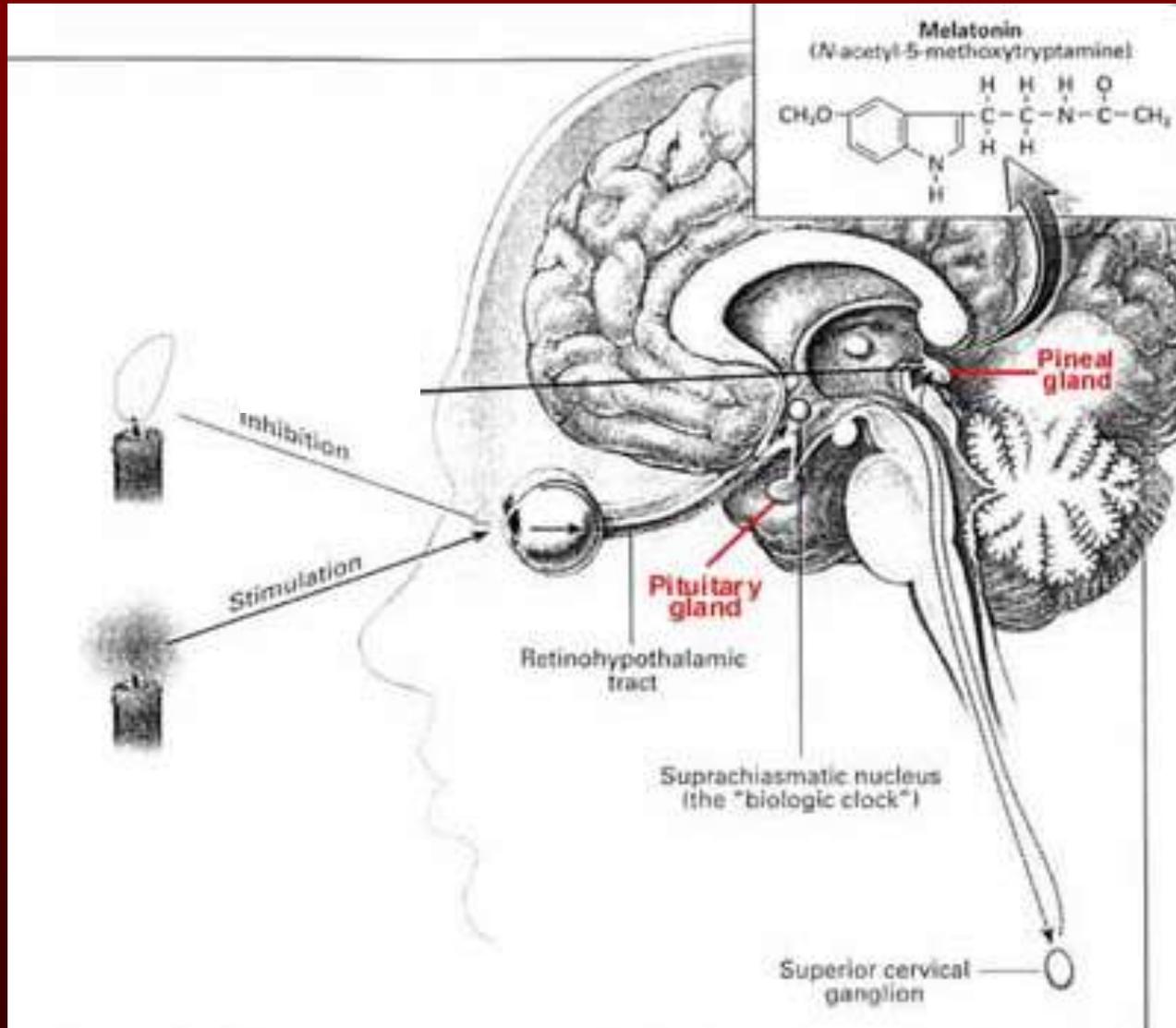
# Melatonin Peaks at Night
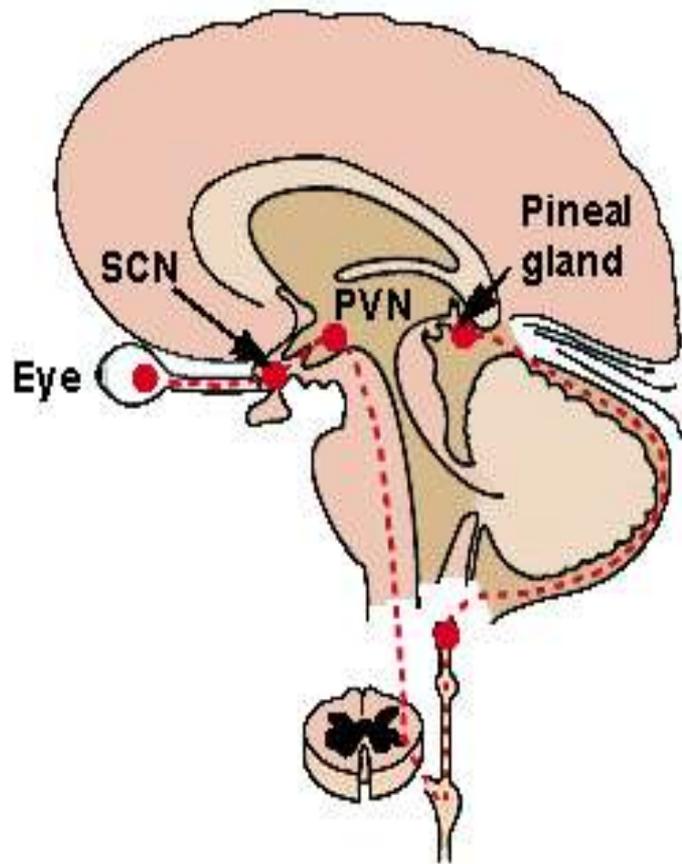


Human melatonin rhythm
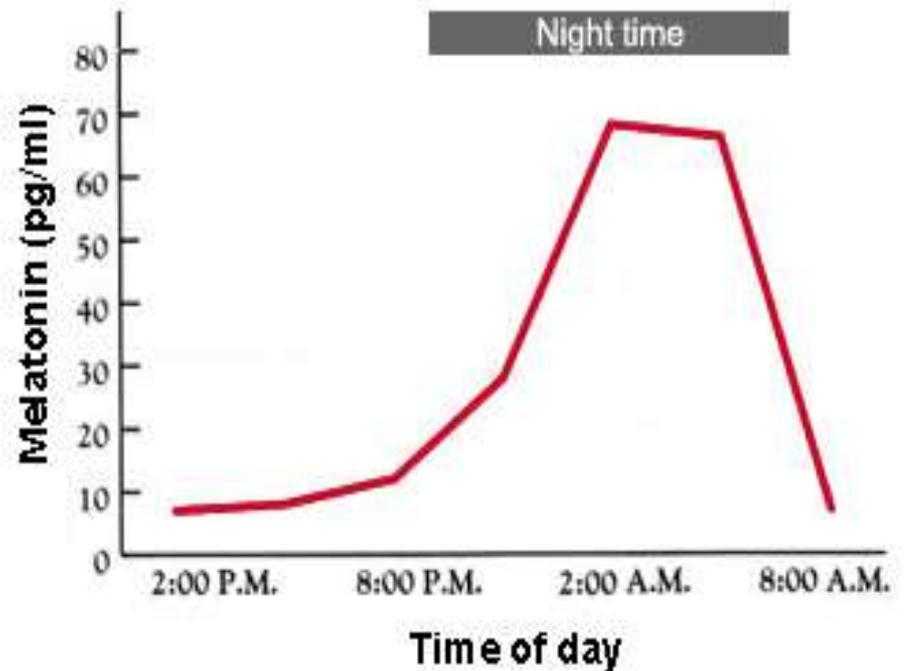
# Shiftwork and Melatonin

- Burch et al. (2005): Non-rotating shifts
- Night shift workers (10pm-6am) had lower <u>sleep : work</u> ratio of melatonin production than did other shifts

- Hansen et al. (2006): Denmark
- Significantly lower melatonin in night shift workers, compared to day shifts ($p < 0.01$)

# Shift Work and Melatonin

| | Total-sleep melatonin | Post-work melatonin | Sleep:work ratio |
|---|---|---|---|
| 1st shift 6am-2pm | 8.7 | 3.8 | 4.2 |
| 2nd shift 2pm-10pm | 5.3 | 3.1 | 4.5 |
| 3rd shift 10pm-6am | 4.8 | 5.2 | 2.3 |

Burch et al. (JOEM 2005)

# Short Term Effect of Night Work in the NHS Cohort
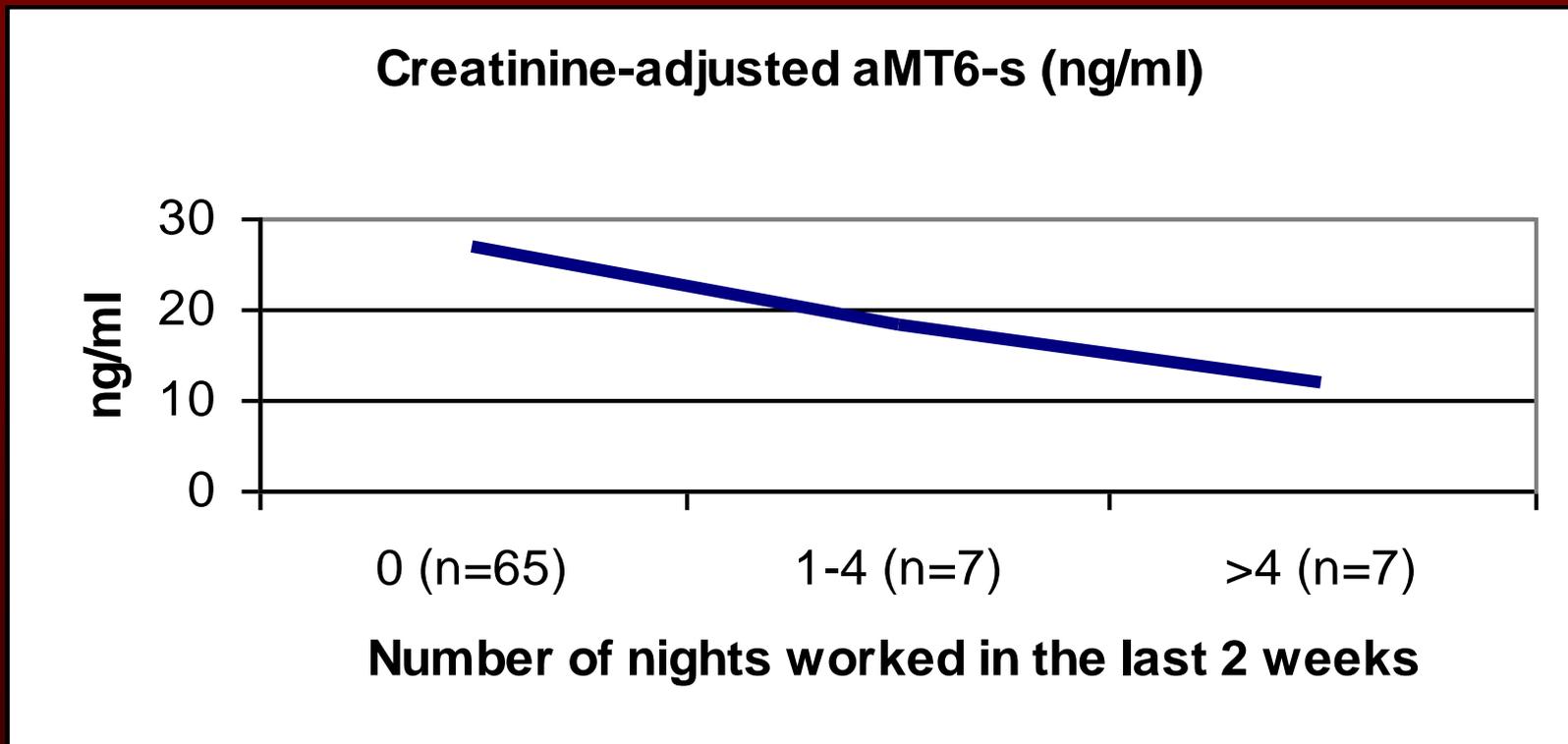
**Creatinine-adjusted aMT6-s (ng/ml)**

ng/ml

| Number of nights worked in the last 2 weeks |
| --- |
| 0 (n=65) | 1-4 (n=7) | >4 (n=7) |

Schernhammer et al, 2003

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# Cancer-inhibiting Properties of Melatonin

Most prominent mechanisms:



- Antioxidant activity
- Immunomodulatory

- Estrogen axis
  - Down-regulation of hypothalamic-pituitary reproductive axis
  - On the tumor cell level as a selective estrogen receptor (SERM) and enzyme (SEEM) modulator via altered estrogen receptor function
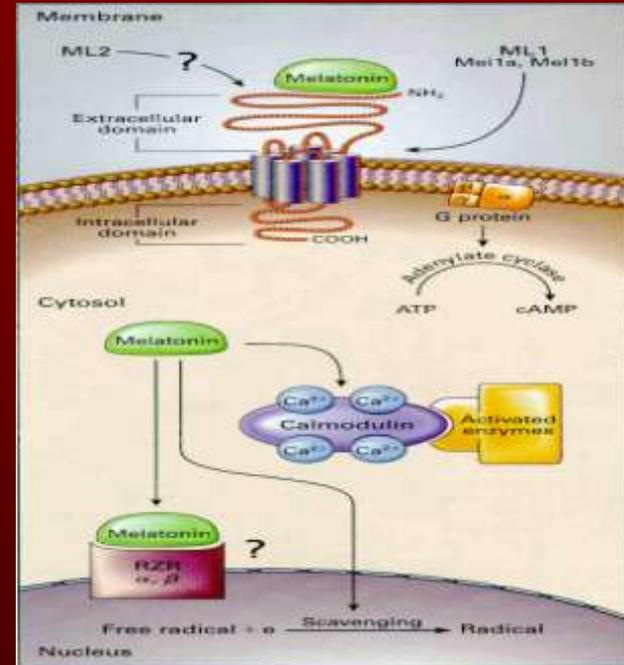
# Night Worker Population: Nurses' Health Study Cohorts

## NHS

- Started in 1976
- 121,700 registered nurses aged 30-55
- Biennial follow-up questionnaires
- Blood specimen sampled in ~1989

## NHS2

- Started in 1989
- 116,678 registered nurses aged 25-42
- Urine specimen sampled from 26,613 participants (1996-1999)

# Assessment of Night Work Status in NHS Cohorts

- Definition of rotating night shift:
  - "At least 3 nights/month, in addition to days and evenings in that month"

- NHS: 1988 (one-timed assessment)
  - "Total number of years worked on rotating night shifts (life-time)?"

- NHS2:
  - Since baseline (1989), updated information on numbers of years worked on rotating night shifts

# Shift Work Distribution in NHS



| | Never | 1-2 years | 3-5 years | 6-9 years | 10-14 years | 15-19 years | 20-29 years | 30+ years |
|---|---|---|---|---|---|---|---|---|
| % | 40.5% | 24.0% | 16.8% | 6.8% | 4.6% | 2.8% | 2.8% | 1.8% |
| N | 32408 | 19248 | 13423 | 5482 | 3684 | 2253 | 2210 | 1400 |
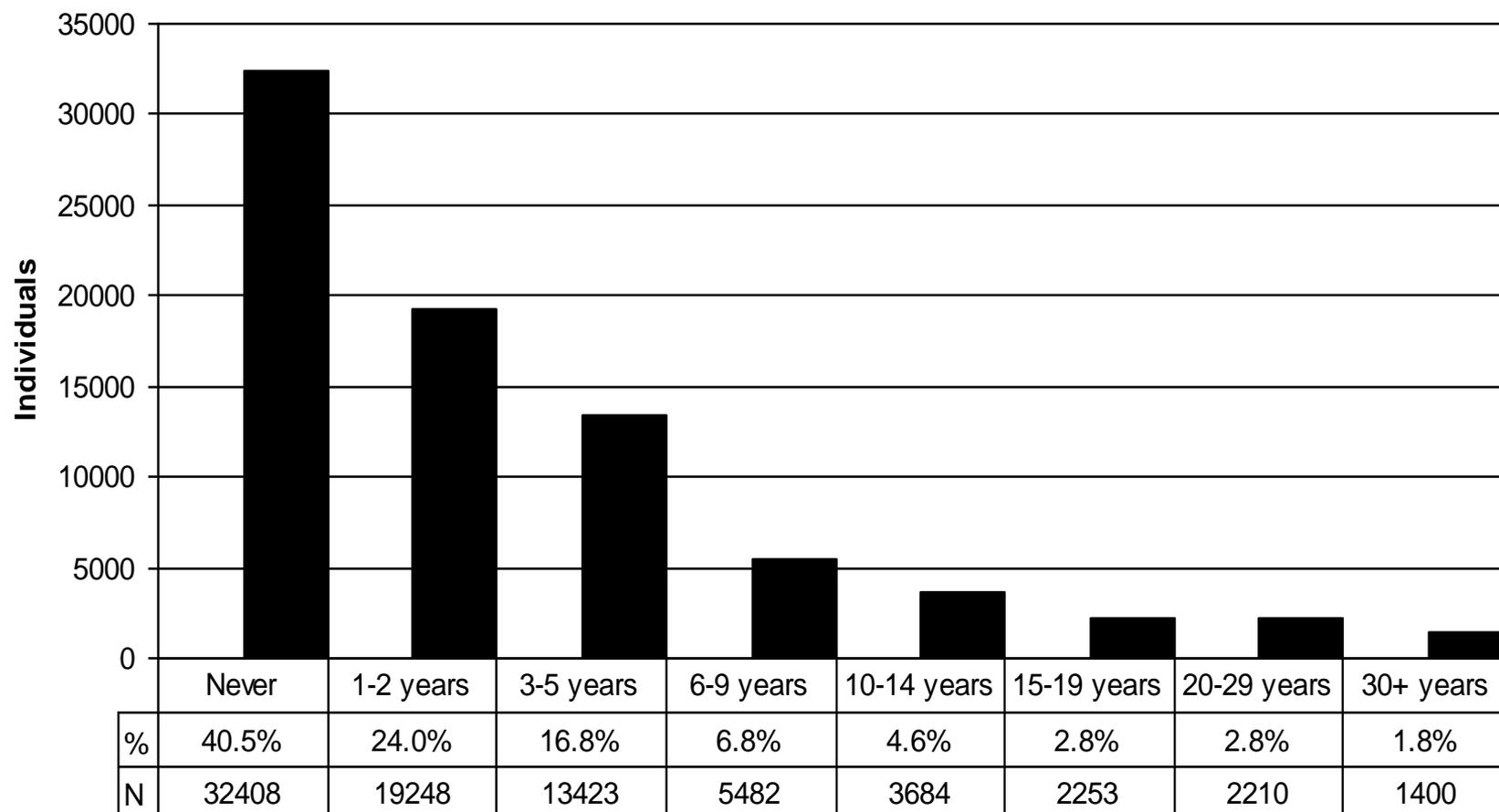
**Shift work**

# Summary Night Work and Cancer Risk in the NHS Cohorts

| Endpoint | Extended periods of rotating night work Relative Risk |
|---|---|
| Breast cancer (NHS) | 36% risk increase |
| Breast cancer (NHS2) | 79% risk increase |
| Colorectal cancer (NHS) | 35% risk increase |
| Endometrial cancer (NHS) | 43% risk increase |

# Melatonin and Breast Cancer Risk

| Cohort | Top vs. bottom quantile melatonin |
|---|---|
| Guernsey III, UK | No association |
| NHS2, USA | 41% risk reduction |
| ORDET post, Italy | 44% risk reduction |
| NHS, USA | 38% risk reduction |
| ORDET pre, Italy | No association (but possibly driven by subclinical disease) |

# ORDET cohort, premenopausal women

| | Relative Risk comparing highest to lowest melatonin levels (95% CI) | P for trend |
|---|---|---|
| Overall | 1.43 (0.83-2.45) | 0.03 |
| Excluding smokers | 1.00 (0.52-1.94) | 0.29 |
| Cancer within 1st year after urine | 14.8 (1.39-157) | 0.03 |
| Excluding cancers within first year after urine | 0.90 (0.45-1.82) | 0.40 |
| Excluding within 2 years | 0.68 (0.32-1.44) | 0.63 |
| Excluding within 8 years | 0.17 (0.04-0.71) | 0.01 |

# Summary

- Evidence accumulating for lower breast cancer risk among women with higher melatonin levels

- Provides biologic rational for the consistent observational evidence linking shift work with breast cancer

- These concepts likely apply to other cancers as well

- Role of sleep less clear

# Future Directions

- Night work / melatonin and other cancers? (men too)

- Role of morningness-eveningness

- Role of vitamin D

- Gene-environment interactions?

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# Cardiovascular Effects of Melatonin

- Pro-inflammatory and endothelial markers (e.g., cytokines, NK cells) follow robust circadian rhythm

- Insulin resistance: circadian genes of great relevance (obesity in knock-out mice etc)

- Melatonin and hypertension: well documented effect on endothelial dysfunction, reduction of blood pressure

# Distribution of CVD Risk Factors by Duration of Shift Work

| | Duration of Rotating Night Shift, y | | | | | |
|---|---|---|---|---|---|---|
| | 1-2 | 3-5 | 6-9 | 10-14 | 15 or More | |
| No. of subjects | 32 153 | 19 128 | 13 207 | 5353 | 3613 | 5655 |
| Smoking, % | 17.3 | 16.5 | 18.5 | 20.9 | 24.2 | 24.5 |
| Hypertension, % | 25.7 | 24.9 | 26.9 | 29.1 | 28.7 | 31.3 |
| Diabetes mellitus, % | 3.5 | 3.2 | 3.5 | 4.4 | 5.0 | 5.6 |
| Hypercholesterolemia, % | 23.2 | 22.9 | 23.8 | 23.7 | 23.8 | 23.8 |
| Past oral contraceptive use, % | 49.8 | 50.3 | 49.6 | 49.6 | 48.0 | 46.8 |
| Current use postmenopausal hormones, % | 23.5 | 24.4 | 23.2 | 22.8 | 22.7 | 20.5 |
| Parental MI before age 60, % | 13.2 | 13.6 | 13.8 | 15.3 | 14.1 | 15.4 |
| Alcohol intake, g/d | 6.7 | 7.0 | 6.8 | 6.2 | 6.1 | 5.4 |
| Physical activity, MET-h/wk | 13.7 | 15.0 | 15.3 | 15.4 | 15.1 | 15.5 |
| Body mass index, kg/m$^2$ | 24.7 | 24.7 | 25.0 | 25.5 | 25.8 | 26.3 |
| Married in 1980, % | 92.3 | 92.8 | 91.6 | 89.6 | 90.2 | 89.7 |

Kawachi et al., 1998

# Melatonin and Hypertension



Urinary melatonin and risk of hypertension
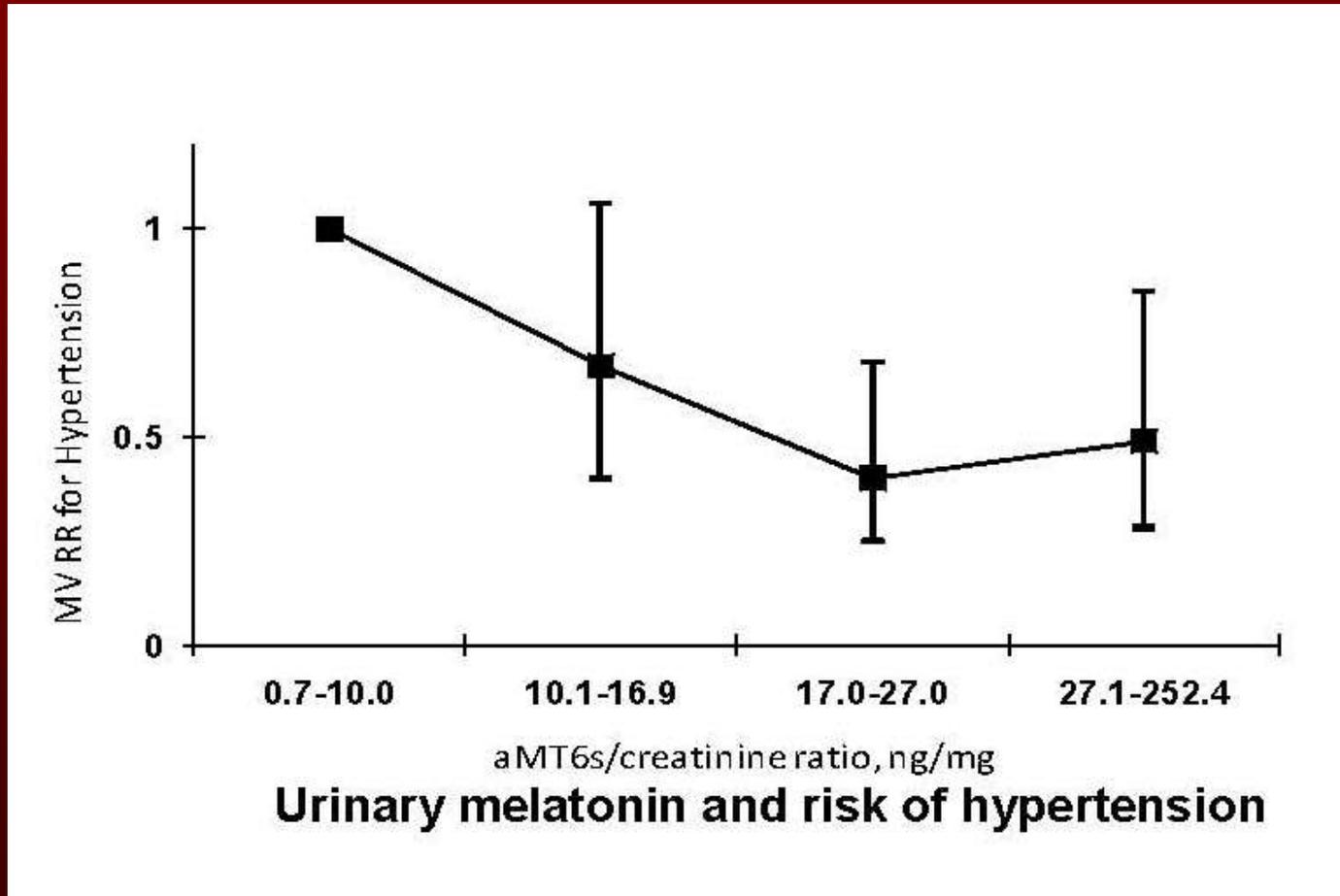
Forman et al., 2010

# Risk of Coronary Heart Disease by Shift Work

| End Point | Shift Work Status | |
| --- | --- | --- |
| | Never | Ever |
| Person-years | 123 299 | 179 665 |
| Fatal CHD | | |
| Cases | 15 | 29 |
| Age-adjusted relative risk | 1.00 | 1.23 (0.66-2.31) |
| Multivariate relative risk[1] | 1.00 | 1.19 (0.63-2.23) |
| Nonfatal myocardial infarction | | |
| Cases | 78 | 170 |
| Age-adjusted relative risk | 1.00 | 1.41 (1.08-1.84) |
| Multivariate relative risk[1] | 1.00 | 1.34 (1.02-1.75) |
| Total CHD | | |
| Cases | 93 | 199 |
| Age-adjusted relative risk | 1.00 | 1.38 (1.08-1.76) |
| Multivariate relative risk[1] | 1.00 | 1.31 (1.02-1.68) |

Kawachi et al., 1998

# Night Shift Work and Risk of Ischemic Stroke

- 1,660 ischemic strokes among 80,108 women from NHS

- Rotating night shift work associated with 4% increased risk of ischemic stroke for every 5 years of shift work

- May be confined to women with a history of 15 or more years of rotating shift work

Brown et al., 2009

# Summary

- Evidence is still scarce for associations between cardiovascular disease risk and melatonin levels

- Similarly, few studies that evaluated association between shift work and cardiovascular disease risk

- Taken as a whole, they are suggestive for a detrimental effect of shift work on cardiovascular disease risk and diabetes

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# Shiftwork Statistics

- Up to 17 percent of all full-time wage and salary workers work alternative shifts in the U.S. (15 Million Americans)

- African-Americans outnumber whites in professions involving night work (14% whites vs. 21% blacks)

- Fewer women than men work alternate shifts (12% vs. 17%)

- All age groups:



Shift work by age (US, 2004)
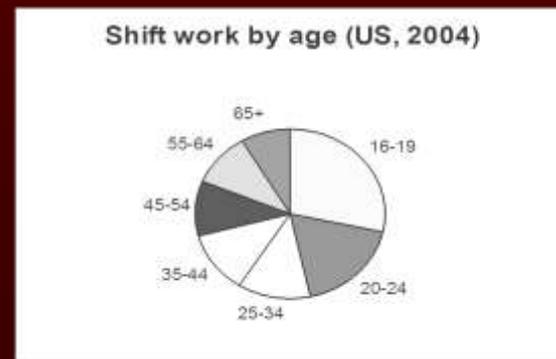
# Preventive Implications

- Melatonin supplementation:

- Optimal dose?
- Timing of administration?
- Long-term side effects?

# Preventive Implications

- Change light sources:

- Shift to 'red light', as opposed to 'blue light' (i.e. fluorescent and halogen lamps)

# Preventive Implications

- Tools to reduce light-induced retina-mediated melatonin suppression:

- i.e., wear orange goggles during night work

Observed light exposure and urine aMT6 with fitted circadian mixed model lines

**Top-left panel:** Observed light exposure and urine aMT6 with fitted circadian mixed model lines
Shift=day/off

**Top-right panel:** Observed light exposure and urine aMT6
With fitted circadian mixed model lines
Shift = day/off

**Bottom-left panel:** Observed light exposure and urine aMT6 with fitted circadian mixed model lines
Shift=night/24h

**Bottom-right panel:** Observed light exposure and urine aMT6
With fitted circadian mixed model lines
Shift=night/24h

Legend: Predicted aMT6; Predicted lux

**Shift-work and urine aMT6 level**
Among 138 nurses

Adjusted for age, BMI, number of nightshifts in the past 30 days, hormone use, and morning/evening type

**Shift-work and urine aMT6 level**
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**Shift-work and urine aMT6 level**
Adjusted for light exposure (bLux)

Adjusted for age, BMI, number of nightshifts in the past 30 days, hormone use, and morning/evening type

**Shift-work and urine aMT6 level**
Adjusted for light exposure (bLux)

Adjusted for age, BMI, number of nightshifts in the past 30 days, hormone use and morning/evening type

**Morning/evening type and urine aMT6 level**
Among current dayshift workers (past 30 days) with no nightshifts during the study period
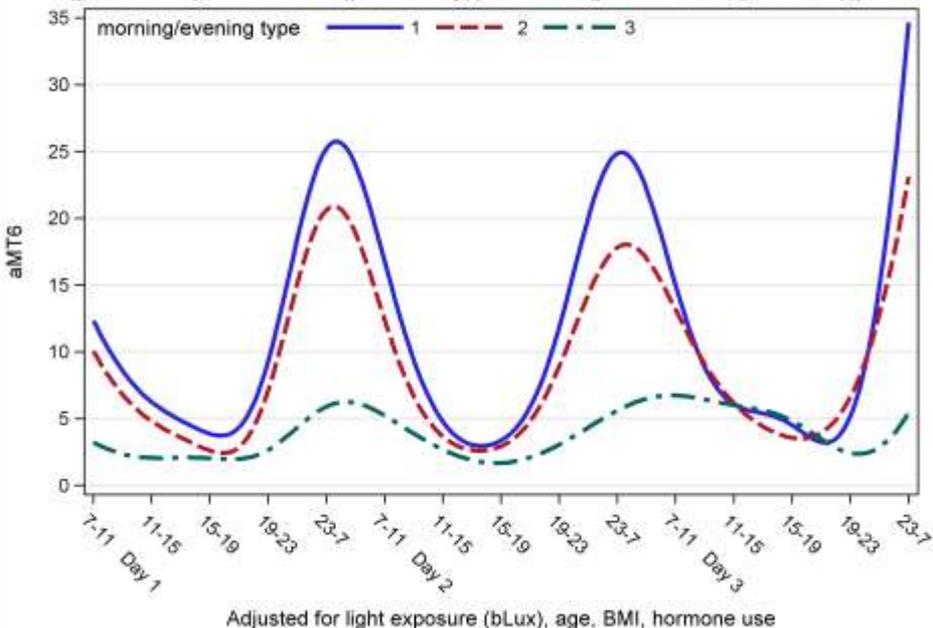
morning/evening type — 1 — 2 — 3

aMT6

7-11 Day 1 / 11-15 / 15-19 / 19-23 / 23-7 / 7-11 Day 2 / 11-15 / 15-19 / 19-23 / 23-7 / 7-11 Day 3 / 11-15 / 15-19 / 19-23 / 23-7

Adjusted for light exposure (bLux), age, BMI, hormone use

**Morning/evening type and urine aMT6 level**
Among current dayshift workers (past 30days) with no nightshift during the study period
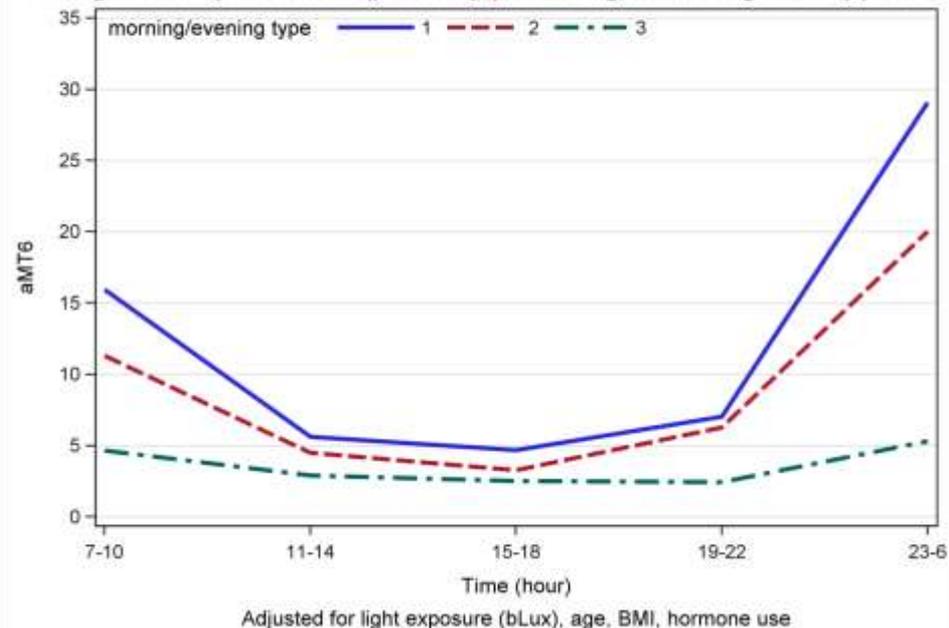
morning/evening type — 1 — 2 — 3

aMT6

Time (hour)
7-10 / 11-14 / 15-18 / 19-22 / 23-6

Adjusted for light exposure (bLux), age, BMI, hormone use

**Morning/evening type and urine aMT6 level**
Among nurses never worked on rotating nightshifts

morning/eveining type — 1 — 2 — 3

aMT6

7-11 Day 1 / 11-15 / 15-19 / 19-23 / 23-7 / 7-11 Day 2 / 11-15 / 15-19 / 19-23 / 23-7 / 7-11 Day 3 / 11-15 / 15-19 / 19-23 / 23-7

Adjusted for light exposure (bLux). age, BMI, hormone use, and morning/eveining type

**Morning/evening type and urine aMT6 level**
Among nurses never worked on rotating nightshifts

morning/evening type — 1 — 2 — 3

aMT6

Time (hour)
7-10 / 11-14 / 15-18 / 19-22 / 23-6

Adjusted for light exposure (bLux), age, BMI, hormone use
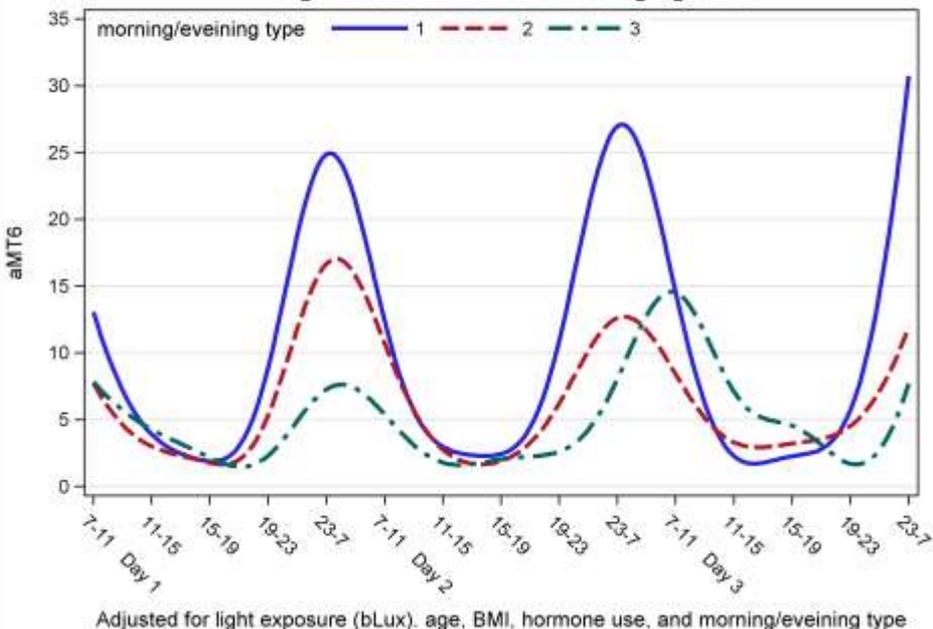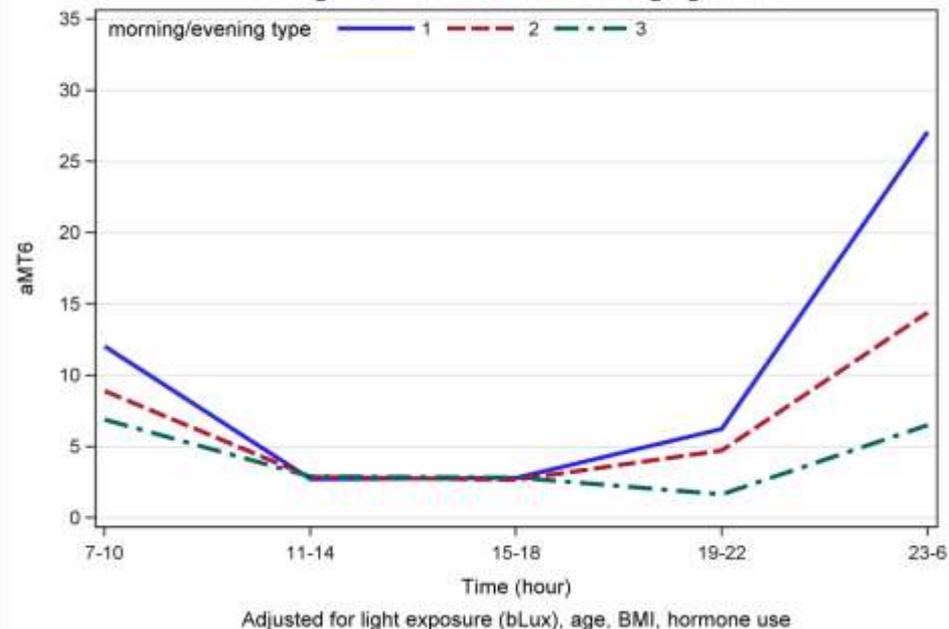
# Preventive Implications

- Define optimal night work schedule:

  - How many years?
  - Permanent versus rotating?
  - Frequency of rotation?
  - Split nights?
  - Critical time of exposure?

# 2009 NHS2 Questionnaire

Page 5 NURSES' HEALTH STUDY II

**50.** Use the codes below to indicate the occupation you held the longest during each time period. Write the 2-digit code in the boxes for each age range.

01: ER 02: OR 03: ICU
04: Other inpatient nurse
05: Nursing education or admin
06: Outpatient or community
07: Other hospital nursing
08: Nursing outside hospital
09: Non-nursing employment
10: Fulltime homemaker
11: Retired 12: Other

| | Age 20-25 | Age 26-35 | Age 36-45 | Age 46+ | Your CURRENT Job |
|---|---|---|---|---|---|
| | Neatly print each 2-digit code | | | | (If same job as age 46+ MARK HERE and skip this column.) |
| During each age range, did you work: | Full time / P/T | Full time / P/T | Full time / P/T | Full time / P/T | Full time / P/T |
| Number of years you worked in that occupation? | 1-2 / 3-4 / 5-6 | 1-2 / 3-5 / 6-7 / 8-10 | 1-2 / 3-5 / 6-7 / 8-10 | 1-2 / 3-5 / 6-7 / 8-10 | 1-2 / 3-5 / 6-7 / 8-10 |
| Average hours of sleep over a 24-hour period, during each age range? | <5 / 5 / 6 / 7 / 8 / 9 / 10+ | <5 / 5 / 6 / 7 / 8 / 9 / 10+ | <5 / 5 / 6 / 7 / 8 / 9 / 10+ | <5 / 5 / 6 / 7 / 8 / 9 / 10+ | <5 / 5 / 6 / 7 / 8 / 9 / 10+ |
| Your primary work schedule during each age range: (Consider your schedule "day/evening" if most work hours were between 7am-3pm, or 3pm-11pm, "night" if 11pm-7am; and "early morning" if 4am-9am) | Days/Eves Only / Nights Only / Early morns only / Rotating w/nights / Rotating no nights / Other/didn't work | Days/Eves Only / Nights Only / Early morns only / Rotating w/nights / Rotating no nights / Other/didn't work | Days/Eves Only / Nights Only / Early morns only / Rotating w/nights / Rotating no nights / Other/didn't work | Days/Eves Only / Nights Only / Early morns only / Rotating w/nights / Rotating no nights / Other/didn't work | Days/Eves Only / Nights Only / Early morns only / Rotating w/nights / Rotating no nights / Other/didn't work |
| On average, how many night shifts did you work per month? (Night shift is most of your work hours falling between 11pm and 7am.) | None / 1-2 / 3-4 / 5-6 / 7-8 / 9-10 / 11-15 / 16-20 / 21+ | None / 1-2 / 3-4 / 5-6 / 7-8 / 9-10 / 11-15 / 16-20 / 21+ | None / 1-2 / 3-4 / 5-6 / 7-8 / 9-10 / 11-15 / 16-20 / 21+ | None / 1-2 / 3-4 / 5-6 / 7-8 / 9-10 / 11-15 / 16-20 / 21+ | None / 1-2 / 3-4 / 5-6 / 7-8 / 9-10 / 11-15 / 16-20 / 21+ |
| For each time period, what is the total # of years that your schedule was "rotating with nights" (do not count permanent nights) | None / 1-2 yrs / 3-4 yrs / 5-6 yrs | None / 1-2 yrs / 3-4 yrs / 5-6 yrs / 7-8 yrs / 9-10 yrs | None / 1-2 yrs / 3-4 yrs / 5-6 yrs / 7-8 yrs / 9-10 yrs | None / 1-2 yrs / 3-4 yrs / 5-6 yrs / 7-8 yrs / 9-10 yrs / 11+ yrs | None / 1-2 yrs / 3-4 yrs / 5-6 yrs / 7-8 yrs / 9-10 yrs / 11+ yrs |

# Acknowledgement

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