National Toxicology Program
U.S. Department of Health and Human Services

Shift work at Night, Artificial Light at Night, and Circadian Disruption Workshop

Appendix C

Human studies: Non-cancer health outcomes

March 10-11, 2016

Office of the Report on Carcinogens (ORoC)
Office of Health Assessment and Translation (OHAT)
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

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Abstract

Background

Over 250 human epidemiologic studies of non-cancer endpoints and shiftwork published since 1965 were identified from published systematic reviews (when is appendix material referenced?). Overall, more than 250 studies of how shift work affects the cardiovascular system, diabetes, endocrine system, metabolic syndrome and obesity, reproductive system, and mental health. Most studies focused on mental health (78), metabolic syndrome and obesity (67), reproductive (51), and cardiovascular (50) endpoints. Fewer studies focused on outcomes related to the endocrine system (22) and diabetes (15). Endpoints were investigated using population registries, prospective cohorts, and in nested and population-based case control studies. These studies were conducted in more than 30 countries around the world and focused mainly on populations of medical professionals (nurses, doctors, residents-in-training) and factory or manufacturing workers, but some studies were also conducted on populations of truck drivers, firefighters, and off-shore oil rig workers, among others. Most studies examine the effects of rotating or nighttime shift work.

Exposure assessment

The most common exposure metrics for shift work in studies examining non-cancer health effects include ever working in shifts or amount of time (e.g., weeks, months, years) working night or rotating shifts, assessed usually through self-reported questionnaires or interview or employment records. The definition of “shift work” or “night work” varies across these studies, but some heterogeneity emerges. Most define night work by frequency of night shifts or the duration of night work. Detailed classifications of shiftwork (e.g., regular/irregular shift schedules, permanent/rotating night shifts, time schedules of each shift, intensity, direction and speed of rotation) have been employed in a few studies, such as consecutive night shifts, forward or backward rotations, permanent versus rotating shiftwork, classifications based on time schedules, and exposure window (age at first shift work, or timing before or after full-term pregnancy). Most studies also evaluated potentially relevant confounders for non-cancer health outcomes (e.g., age, BMI, education, gender, smoking and alcohol consumption).

Biomarkers

Few studies of shiftwork and non-cancer health effects incorporated biomarker measurements of circadian disruption. The primary measurements studied were melatonin and cortisol level relation to circadian disruption in shift workers.

Intervention studies

Several studies have examined the impact of behavioral and pharmacological interventions on various non-cancer endpoints. At least 14 studies describe changes to daily schedule of medical professionals by adding planned naps at various intervals between night shifts. More than 25 studies examine impacts of doses of melatonin, caffeine, and various other pharmacologic interventions on optimization of sleep and increased focus at work after night shifts.

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Table 1. Cardiovascular effects

		Shift work, Night
Cardiovascular	**Meta-analyses (No. studies)**	Vyas et al. (2012) (34); Frost et al. (2009) (14); Togo et al. (2008) (11); Ha et al. (2011) (8); Hwang and Hong (2012) (4)
	Study populations	nurses; nursing staff; municipal, fertilizer plant, pulp and paper, oil refinery, nuclear plant, heavy equipment plant, steel industry, viscous rayon factory, chemical plant, diaper and feminine hygienic materials plant, integrated circuit manufacturing industry, waste incinerator plant, forestry, and hospital workers; industrial organization workers; citizens in two counties in Sweden; workers from established cohorts (Japanese Collaborative Cohort Study, Danish Working Environment Cohort Survey, Finnish Longitudinal Census Data File, Helsinki Heart Study, Study of Health in Pomerani, Swedish Living Conditions Survey, Northern Sweden MONICA study and the Västerbotten Intervention Programme, Finnish Twin Cohort, Nord-Trøndelag Health Survey; workers from Swedish census data; workers born in catchment areas of 2 Swedish hospitals; patients admitted to hospitals (32 in Germany, 2 in Netherland, 5 in Japan, 22 in Japan, 2 in Denmark); emergency physicians, ambulance personnel; firefighters; long-distance truck drivers; healthcare providers
	Study designs	15 prospective cohort; 12 retrospective cohort; 11 case control; 1 longitudinal; 1 clinical trial
	Location	Austria; Denmark; Finland; Germany; Iceland; Italy; Japan; Netherlands; Norway; Qatar; Sweden; Taiwan; United Kingdom; United States
	Exposure metrics	total number of years worked rotating night shifts; ≥3 nights/month in addition to days and evenings in that month; ≥30 days shift work total, 3-shift continuous, forward rotating, 3-shift non-continuous, 7-day double-day shifts, and 5-day double-day shifts; 2- or 3-shift, irregular work, night work; 24-h shift; 2-shift; 3-shift discontinuous, 3-shift continuous (traditional), 3-shift continuous (rapidly rotating), permanent nighs, alternate day and night, double days; 3-shift rotating; 3-shift, night, evening, roster, and "other forms"; 3-shift, one week, forward rotating; 8-hour rotating shift cycle, starting with 2 morning shifts followed by 2 afternoon shifts and 2 night shifts; daywork, part-time, 2-shift, 3-shift, irregular, and night; during most recent 5 years, shift worker=hours beyond daytime and night worker=includes the time between 22:00 and 06:00; ever/never shift and night work or weekend work, regular work hours, shift work, variable hours, not employed; night (2140 to 0840h or from 2200 to 0600h); 2nd and 3rd shifts were considered evening and night shifts, respectively; occupational groups with ≥20% of individuals work evenings, night, or other shift; occupations with ≥50% in census reporting continuously day and night work; other than daytime; permanent day duty, two shifts, three shifts, fluctuating according to special schedule or rotation, permanent evening duty, permanent night duty, permanent morning duty, other; pre-night (1500-2300h), mid-night (2300-0700h), post-night shift (0700-1500h); rotating shift work; shift worked most of mainly day time, mainly night (fixed-night shift), or alternative night and daytime (rotating shift); swiftly rotating continuous 4-shift system with shorter morning and afternoon shifts (7h) , longer night shift (10h), and every 4 weeks one or two especially long day shifts (14h) over the weekends; total number of years worked rotating night shifts (≥3 nights/month in addition to days or evenings that month); night (23:35 to 05:35h, Mon-Sat); 3-shift rotating, fourth and fifth shifts introduced; 10 years of shift work (3-shift weekly or rapid rotating ,alternate days and nights, double days, others) since 1946, any interruption<6 months
	Confounders and effect modifiers	age; calendar year; sex; county; diabetes; hypertension; family history; smoking; BMI; employment status; living without a partner; noise; education; hospital; duration of employment; duration of exposure; marital status; exhaustion; menopause; alcohol consumption; leisure time activity; physical activity at work; job site location; professional status; income; socioeconomic status; job exposure variables; binge drinking; alcohol; life satisfaction; diurnal type; sleep length; use of hypnotics or tranquillisers; physical workload; working pace; questionnaire cycle; fruit and vegetable intake; hormone replacement; aspirin use; coronary disease; blood pressure; cholesterol; husband's education; snoring; sleep duration; atrial fibrillation; food frequency score; depression; poor sleep; residence; job strain; perceived stress; past medical history; year of starting work; hypercholesterolaemia; past oral contraceptive use; gemfibrozil use; weight; height; coldness; conflicts at work; high cognitive demands; ergonomic exposure; job insecurity; monotonous tasks; low decision authority; heat; walking or standing for long hours at work; low social support; carbon disulfide exposure

Table 2. Diabetes

		Shift work, Night
Diabetes	**Meta-analyses (No. studies)**	Gan et al. (2014) (12); Ulhôa et al. (2015) (6); Knutsson and Kempe (2014) (5); Bannai and Tamakoshi (2014) (1)
	Study populations	nurses; factory laborers; sash and zipper factory workers; large electrical company workers; large manufacturing company workers; two pulp and paper manufacturing plant workers; steel company workers; 9 different companies and public administrations workers; workers from Tongji-Dongfeng Cohort; blue-collar workers attending annual health check-ups; ; middle-aged persons from a population-based cohort
	Study designs	4 cross-sectional; 7 prospective cohort; 1 retrospective cohort
	Location	Belgium; China; Japan; Sweden; United States
	Exposure metrics	3-shift rotating; 2- or 3-shift (including night shift) with weekly clockwise rotation; night work at least once a week; 2-shift rotating (day/evening), 3-shift continuous (counterclockwise), 3-shift non-continuous; 4-team, 3-shift with clockwise rotation; 2- or 3-shift rotating; rotating night shift (≥3 nights/month in addition to days and evenings that month); day shift (8:00 to 16:45h) for 5-weekday and night shift (21:15 to 6:00h) for 5-weekday; do shift work; unusual or irregular working hours
	Confounders and effect modifiers	age; gender; race; menopausal status and hormone use; oral contraceptive use; family history of diabetes; current aspirin use; quintiles of total calorie; diabetes dietary score; BMI; health-related behaviour (smoking; alcohol consumption; physical activity level); total serum cholesterol; γ-GTP; uric acid; duration of employment; education; job strain; social support; use of technology; psychological distress; civil status; cohabitation status; waist circumference; diastolic blood pressure and HDL cholesterol; job; marital status; tea consumption; life stress

Table 3. Endocrine effects

		Shift work, Night
Endocrine	**Meta-analyses (No. studies)**	Ulhôa et al. (2015) (17); Niu et al. (2011) (5); Staufenbiel et al. (2012) (1); Wosu et al. (2012) (1)
	Study populations	nurses; electronic manufacturing and textile factory workers; unspecified workers and workers for same company; ambulance drivers
	Study designs	1 time series with a control group; 1 interrupted time series w/o control group; 1 comparative with concurrent control; 1 pseudo-randomized controlled trial; 1 case series; 1 case control
	Location	Germany; Japan; Netherlands; Sweden
	Exposure metrics	night; morning, evening, and night, fast-forward rotating; morning M 4 am-12 am, evening E 12 am-8 pm, night N 8 pm-4 am according to a system M, S, N 3/2, (3 work, 2 rest) and 7/5 (3M/2S/2N/5R, 2/3/2/5, 2/2/3/5); 24-h shifts on alternate days; simulating night shift; rotating shift (12-h day shift and 12-h night), 2 weeks working followed by 4 weeks off; rotating; irregular; night and day; 24-h shifts on alternate days; rotating, clockwise x counterclockwise; rotating, fast-forward vs. slow-backward
	Confounders and effect modifiers	NA

Table 4. Metabolic effects

		Shift work, Night
Metabolic Health	**Meta-analyses (No. studies)**	Bannai and Tamakoshi (2014) (1); van Drongelen et al. (2011) (12); Amani and Gill (2013) (15); Canuto et al. (2013) (10); Wang et al. (2014) (13); Adams et al. (2013) (2); Vermeulen et al. (2016) (39)
	Study populations	manufacturing company workers; steel workers; nurses; hospital night workers; nurses aids; security personnel; health services workers; incinerator plant workers; random male sample from Central Population Register; healthy non-obese men; electronics assembly factory workers; garbage collectors; chemical production plan workers; railroad workers; Vasterbotten intervention program workers; personal computer/printer manufacturing workers; offshore oil and gas personnel workers; residential nursing home and hospital workers; large company workers; electronic manufacturing workers; doctors, nurses, and auxiliaries; police officers; retired motor company employees; adult twins; sash and zipper factory workers; street cleaning/domestic waste collection workers; roaster, smelter, converter, anode casting, and fire and electronic refining workers; birth cohort; midwives
	Study designs	18 cross-sectional, 1 case-control; 4 cohort; 3 longitudinal cohort/nested case-control; 6 prospective cohort; 1 randomized crossover; 2 retrospective
	Location	Japan, Belgium; Brazil; Buenos Aires, Argentina; Denmark; Finland; France; Iran; Italy; Malaysia; Sweden; Taiwan; United Kingdom; United States
	Exposure metrics	night work (19:00-7:00, 20:00-4:00, 21:00-5:00); 3-shift; 2-shift; various shift work (2- or 3-shift system, continuous and non-continuous, counter clockwise rotation); permanent night work; evening shift; alternating shifts (4 team/3 shift system, continuous, clockwise rotation); permanent day work between 7:30-17:30; rotation shifts (continuous and non-continuous shift work starting at 05:00, 13:00, or 21:00); simulated night shift; alternating day and night work schedule; ever shift work; >=1 night/week shift work; currently or always shift work; regular work or irregular work; rotation shifts from 18:00-6:00 10 nights/month; >4 nights/month shift work from 21:00-7:00; >=7 and <=8, >8 and <=9, >9 and <=10, and >10 hours/day; Late shift (permanent night work or evening shift); at least 3 nights per month
	Confounders and effect modifiers	age; BMI; baseline BMI; alcohol; smoking; exercise; leisure physical activity; births during study; sports activities; years on shift; sex; co habitation; work hours/week; temperature of work environment; work physical activity; decision authority at work; psychological demands of work; opportunities to communicate with colleagues; work conflicts; job security; socio-professional level; professional seniority; fasting insulin levels; education; marital status; family history; physical job demands; waist circumference; diastolic blood pressure; high-density lipoprotein cholesterol; diet behaviors; work schedule; police rank; sleep duration; vegetable intake; snack food habits; insomnia symptoms and sleep difficulty

Table 5. Mental health effects

		Shift work, Night
Metabolic Health	Meta-analyses (No. studies)	Mansukhani et al. (2012) (13); Mansukhani et al. (2012) (14); Fossum et al. (2013) (15); de Cordova et al. (2012) (15); vandenBerg et al. (2010) (1); Girotto et al. (2013) (1); Staufenbiel et al. (2013) (1); Frank and Ovens (18)
	Study populations	nurses; underground miners; young individuals; elder care shift-worker nurses; firefighters; hospital night staff; physician residents; basic surgical trainee specialists; male aircraft maintenance engineers; various occupational shift workers; female undergraduate students; minimally-invasive surgical trainers; young hospital residents; interns and house staff in university-based residency programs; medical interns; emergency medicine residents; pediatric residents; oil and gas industry personnel; offshore workers; oil rig workers; oil industry personnel; onshore and offshore petroleum personnel; offshore drilling rig personnel; healthcare workers; nurses' partners; nursing assistants; truck drivers
	Study designs	5 case-series; 1 cohort; 3 comparative; 9 cross-sectional; 3 interrupted time series; 6 longitudinal; 1 prospective; 1 prospective study; 1 randomized crossover study
	Location	Australia; United Kingdom; Norway; Brazil; United States; Croatia
	Exposure metrics	permanent night shift; forward-rotating 10-hour night shift schedule; backward rotating 8-hour night shift schedule; simulated night shifts; shifts with rotation; day shift; evening shift; multiple shifts; single shifts; permanent night duty; morning shift; forward rotating 12-hour shift; ever/never shift; one night on call; night duty; extended work shifts; number of night shifts worked; 2-3 weeks of 12-hour shifts; fixed nights; swing shifts (12-hour shifts; 7 days, 7 nights; then 7 nights, seven days); varying shifts; night shifts (12 hours for 2 weeks); fixed shifts (14 days, 14 nights); nights with rotation; night-time travel
	Confounders and effect modifiers	individual differences; job type; work perceptions; working condition measures

Table 6. Reproductive effects

		Shift work, Night
Reproductive	**Meta-analyses (No. studies)**	van Melick et al. (2014) (11); Bonde et al. (2013) (13); Stocker et al. (2014) (15); Bonzini et al. (2007) (17); Bonzini et al. (2011) (19); Quansah and Jaakkola (2010) (10); Mozurkewich et al. (2010) (6)
	Study populations	nurses; midwives; active duty military women; Danish National Birth Cohort; members of a private health insurer; all women employed by a hospital (mixed occupations); nested cohort from the Nurse's Health Study II; pregnant nurses from a central register of health workers suffering a miscarriage; catchment area, Mansoura University Hospital; county population, women attending one hospital with a miscarriage; general population; female members of Swedish midwives association; pre-menopausal factory workers; population-based random sample; pregnancy-based antenatal attendees; all women delivering a live-born child in 4 hospitals in different towns; all pregnant women attending for antenatal care at 2 hospitals in different towns; textile workers
	Study designs	10 case-control; 2 cohort; 21 cross-sectional; 12 prospective cohort study; 9 retrospective cohort*
	Location	China; United States; Canada; Denmark; Germany; Italy; Poland; Spain; Finland; France; Sweden; Ireland; Egypt; Netherlands; Norway; Taiwan; Thailand; United Kingdom
	Exposure metrics	night; day; shift (no vs. yes); regular/irregular schedule; nights only; night work (no, occasionally, often); rotating including nights; day/evening rotation; always evening; days/evenings with no nights; rotating 2-shift; rotating 3-shift; permanent night shift; telephone duty; rotating night shifts + at least 3 nights per month; 12-hour shifts; fixed afternoon shift; fixed night shift; changing shifts
	Confounders and effect modifiers	"most relevant confounders"; age; gestation at interview; pregnancy history; smoking; alcohol; caffeine; marital status; parity; hours worked; BMI; medication; previous miscarriage; caffeine; race; tap water consumption; marital status; medical insurance status; education; nausea; calendar year; infection; age at menarche; physical activity; employment duration; pre-employment menstrual irregularity; partner's occupation; partner's shift work; gravidity; coital frequency; obstetric disease; medical disease; hormonal injection use; occupation

*Note that some studies were categorized differently by different SWs, and are counted twice.