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Novel Circadian Exposure Metrics for Shift Workers

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List of Terms and Abbreviations.

WHO	World Health Organization
NHS2	Nurses' Health Study 2
NHS	Nurses' Health Study
NHS3	Nurses' Health Study 3
T2DM	Type 2 diabetes mellitus
BMI	Body-mass Index
yrs	years
MEQ	Morningness-Eveningness Questionnaire
IQR	Interquartile range
SD	standard deviation
OR	Odds ratio
MV	Multi-variable
95% CI	95% confidence interval
p_{trend}	P-value for trend test
T	Tertile

Abstract.

Novel Exposure Metrics for Shift Workers

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Worker groups studied. Almost 15 million Americans regularly work alternate shifts (1). Observational studies have consistently associated rotating shift work with increases in cancer risk, prompting the WHO in December 2007 to classify night shift work a probable carcinogen – the main operating mechanism being assumed circadian disruption by means of melatonin suppression (2). The broad range of other adverse outcomes affected by working at night implied the necessity for improved tools to comprehensively capture the "exposure" of relevance, i.e. circadian disruption. Future research would benefit from a tool that aids in a more complete description of work schedules and their effects on human cancer risk.

Approach. Building on detailed information regarding work hours and sleep in two distinct, prospective cohorts, novel exposure metrics were created that aimed to juxtaposition internal (i.e. preferred sleep timing) with external (i.e. work schedule) clock. In addition to the work and sleep assessments, these two cohorts, Nurses' Health Study 2 (NHS2) and 3 (NHS3), also offer rich information participants' numerous health and lifestyle variables which have been regularly assessed by the biennial mailed questionnaire in NHS2 since 1989, and in NHS3 since its inception in 2010, enabling careful control for potential confounding factors, including use of medications, including antidepressants, anxiolytics, anti-hypertensive and cholesterol-lowering drugs, anti-inflammatory agents, plus health issues including depression, depressive symptoms, hypertension, high cholesterol, diabetes, cardiovascular disease, neurologic diseases, etc. Besides BMI, there is also detailed information on diet and chronotype in both cohorts.

Key Findings. Over the past decade, our own work, using data from the Nurses' Health Study cohorts has produced landmark findings and generated provocative novel hypotheses related to the health effects of night work and sleep deprivation: We showed that night shift work increases the risk of a number of different cancers (3-9); we also linked rotating night shift work, through its profound effects on metabolism and weight (i.e. obesity) with other major chronic diseases, including cardiovascular disease (10), metabolic syndrome (11), hypertension (12, 13), stroke (14), endometriosis (15), type 2 diabetes (T2DM) (16, 17). Building on this large body of prior work, in our current project, we were able to successfully demonstrate the utility of two novel and independent exposure metrics capturing circadian strain in night workers, thus providing an important tool in future research, which has been hampered by imprecise exposure assessments leading to bias towards the null in several published studies.

How the results relate to improvements for worker safety or health. This project's results will not have any direct impact on the NHS cohorts, but the findings may lead to changes in shift work practice that may benefit women who work rotating night shifts in the future. Ultimately, as outlined in detail in our proposal, the newly developed exposure metrics, once further validated, are geared towards enabling researchers to more fully delineate the adverse health effects of night shift work by also considering the biologically relevant substrate, i.e. circadian disruption in their exposure assessments.

SECTION 1

Significant or Key Findings.

Aim 1: We derived two new night work exposure measures in large prospective cohort studies of nurses: the NHS2 and NHS3 cohorts. Specifically, based on a participant's morning versus evening preference (chronotype), and the relative frequency of a given shift within a month, we computed the *mismatch score*. The *shift lag* in contrast used individual mid-sleep times on free days, an established proxy for chronotype, and mid-work times to derive the lag between mid-sleep and mid-work. While for the *mismatch score*, higher scores represent presumably more of a strain, the more the *shift lag* is centered around 12h the better, as work hours 12h opposed to the mid-sleep at least likely to curtail sleep times. We were able to assign detectable mismatch to one third of the population, supporting the utility of these new exposure measures

Aim 2: We set out to study how these newly created measures of circadian strain related to body mass index (BMI; a higher BMI among night workers is one known adverse effect of circadian disruption in that population), first in NHS3, and then replication in NHS2. Both analyses confirmed that a higher mismatch score was correlated with higher BMI. results suggest that we have developed a potentially useful set of exposure metrics that can help inform individual-level circadian strain in shift workers. Future work is needed to examine the metrics in relationship to other disease endpoints. In addition, intervention and simulation studies can use the score to predict and monitor circadian strain in the workplace setting.

Translation of Findings.

Our findings suggest that we have developed a potentially useful set of exposure metrics that can help inform individual-level circadian strain in shift workers. Future work is needed to examine the metrics in relationship to other disease endpoints. In addition, intervention and simulation studies can use the score to predict and monitor circadian strain in the workplace setting.

Research Outcomes/Impact.

We were funded to comprehensively describe and develop novel shift work metrics, to continue work towards improving exposure assessments in night shift workers, that more fully capture the one aspect that is central to adverse health outcomes in this population – circadian strain. All aims are completed and manuscripts are currently prepared and will be submitted over the next year.

Using two novel exposure metrics that incorporate both sleep and work hours to address the phenomenon of circadian strain in night workers (i.e. sleeping at hours that are at odds with the preferred sleep time that our internal clock or circadian system dictates), we were able to confirm a correlation between higher circadian strain and higher BMI. Hence, these newly developed tools merit further attention, and warrant application in future studies to confirm their utility also for other relevant disease endpoints. Ultimately, these novel exposure metrics could represent a substantial step forward in the aim to improve exposure assessment in night shift workers, to better delineate the multi-facetted negative health effects of night work.

SECTION 2

Scientific Report

Background.

The periodic alternation between activity and rest – or wake and sleep – is one of the most notable and evolutionary oldest human behaviors. Its rhythmicity is orchestrated by our circadian system (18), which in addition to sleep regulates a vast number of important bodily functions, including the timing of gene expression (19, 20), physiology (21, 22), metabolism (23, 24), and cognition (25). The synchronization between the internal, biological rhythm and the 24h sunlight/dark cycle (26-29) produces a specific phase relationship between the two, also referred to as chronotype (30-32). Late chronotypes typically have a 'slow' circadian clock (cycle length of >24h), which will embed later within the 24h day, so that they fall asleep and wake up later within the 24h day as early types ('faster clocks', <24h). As with sleep and wake behavior, other bodily rhythms (e.g. core body temperature, melatonin (33, 34), and gene expression (35-37)) occur with peaks and troughs later within the 24h day in late chronotypes compared to early ones.

This elaborate timing system is chronically challenged in shift workers, as the body tries to adapt to ever changing work-induced light/dark cycles (and concomitant activity patterns), eventually leading to a loss of synchrony between rhythms. The resulting circadian strain (also referred to as circadian-, or chrono-disruption (38, 39)) is thought to underlie the consistently observed associations between shift work and adverse health outcomes, including sleep, metabolic, and mood disorders, cardio-vascular outcomes and cancer (17, 40-55). Although based on small case numbers, a few recent studies report that the health risk imposed by shift work may vary by chronotype (56-60)**.** We, too, previously evaluated the combined effects of chronotype and shift work in the Nurses' Health Study 2 (NHS2). We found that chronotype is significantly associated with the risk of type 2 diabetes (T2D), but that this risk depends on work schedules: among women who work day schedules only, early chronotypes did not have a higher T2D risk, whereas late chronotypes experienced a significantly higher T2D risk. By contrast, among women exposed to night shift work, only late chronotypes experienced hardly any increases in T2D risk, whereas the risk for early chronotypes increased steadily with increasing number of years of night work. These results further underlined the need for more detailed occupational work schedule assessments, which also take into account a person's chronotype when delineating the aspects of work schedules critical for chronic disease risk. We aimed to close this gap by developing and applying circadian strain metrics that quantify the combined effect of chronotype and working times. The Nurses' Health Study 3 (NHS3) had recently and for the first time incorporated detailed work schedule and chronotype assessments (32, 61). This put us in the unique position to derive circadian exposure metrics quantifying individuals' work schedule-associated circadian strain. By making use of the detailed assessments in NHS3, this innovative and exploratory project aimed to significantly push forward the field by providing the basis for further delineating the acute and chronic effects of circadian disruption on health and wellbeing.

Specific Aims. The following specific aims were proposed in the original application:

Aim 1: Development of novel, personalized circadian exposure metrics using two most commonly used measures of chronotype:

a. Development of **mismatch score** between shift work type and chronotype, based on the categorical chronotype measure of diurnal preference.
b. Computation of '**shift lag**', i.e. the difference between mid-points of sleep (the second most common measure of chronotype) and work, to quantify circadian strain.
c. Comparison and correlation of both metrics across various work schedules to identify similarities, strengths, and potential weaknesses.

Secondary Aim*:* We will provide a summary and description of contemporary health care work schedules in NHS3. We will also classify schedules by circadian strain, potentially informing chronotype-specific prevention strategies.

Aim 2: Application of the novel circadian exposure metrics to examine associations between circadian strain and body mass index (BMI) in NHS3 and, for validation, in NHS2. BMI is a central chronic disease risk factor that has previously been linked to alterations of the circadian system.

a. Hypothesis: increased circadian strain is positively associated with BMI.
b. Assessment of the interaction effect between circadian strain and further work schedule characteristics (such as weekly and daily working hours, on call, part time vs. full time, rotational *vs*. permanent schedules) on BMI.

Procedures and Methodology.

Study Population

The Nurses' Health Study 3 has enrolled 38,295 women aged 19-46 since 2010. Male health care workers will be recruited from January 2015 onwards, significantly improving the generalizability of the study. Via a web-based infrastructure, this cohort answers questionnaires every 6 months, until the introduction of synchronized yearly assessments in 2016. Detailed occupational and chronotype assessments are included in the annual and bi-yearly questionnaires so that all registered and newly recruited participants will have the possibility to respond to these critical questions. Additionally, lifestyle factors, health status, medication use, and environmental exposures are queried systematically. Response rates in the cohort are relatively high, spanning from 72% to 89%, depending on questionnaire cycle since its start in 2010. For Aim 2, we will additionally make use data of the Nurses' Health Study 2, a prospective cohort study of 116,430 women (25-42 yrs at baseline in 1989). Bi-annual, self-administered questionnaires collect exposure and disease information. In 2009, the primary work schedule (*i.e.*, permanent daytime schedule, permanent night shifts, permanent early morning shifts, rotating schedules including or excluding night shifts), and a categorical assessment of diurnal preference, indicative of chronotype, have been assessed. In this cohort, response rates are in general as high as 90%.

Study Design and Study Procedures

All study materials were mailed to participants. The study was approved by the Harvard School of Public Health and the Brigham and Women's Hospital Human Subjects Committee, and written informed consent was obtained from subjects.

Exposure and Outcome Assessments

Chronotype. In the NHS2, chronotype was queried in 2009 based on a single question of diurnal preference, resulting in a categorization of 'definitely a morning type', 'more of a morning than an evening type', 'more of an evening than a morning type', 'definitely an evening type', 'neither'. This single question was derived from one of the earliest, and to date still prime measure of chronotype, the Morningness/Eveningness Questionnaire (MEQ (61)) and was validated using sleep logs (62). The same categorical assessment is introduced to the NHS3, along with the second most common newly emerging chronotype assessment, using sleep timing on free days. More specifically, this assessment uses the mid-point of sleep on free days (MSF) as a marker for circadian phase of entrainment or chronotype (30, 32, 36, 63). In shift workers this approach resulted in an extensive questionnaire that relies on the assessment of sleep/wake behavior during all shifts and free days, collecting a large amount of information (64). However, such lengthy assessment is not feasible in large-scale epidemiological research. Given that mid-sleep only shows moderate after-effects of the previous shift worked (i.e. maximum delta between means = 40min) (64), we can use a general free day sleep behavior for chronotype assessment, which has recently been implemented in NHS3. Additionally, sleep timing has proven useful as a proxy for chronotype, as it also correlates well with physiological phase markers, such as dim light melatonin onset (34, 36, 63). Though chronotype has been suggested to change with age, this applies especially to adolescence, where teenagers progressively change into later and later types (65, 66). Therefore, in the current study, we deem age-effects negligible given the adult age range in both NHS2 and NHS3. Finally, both chronotype measures, diurnal preference and sleep timing, correlate relatively well with one another (correlation coefficients between -0.5 (34) and -0.7 (67)).

Working Times. The web-based format of the NHS3 allows, for the first time within the existing Nurses' Health Studies, to systematically query exact start and end times (0.5h resolution) for each shift that is part of the participants' schedule. In addition to these directly collected variables, we will be able to derive shift duration (daily working hours), and compute a mid-work variable (mid-point between work start and end) that we can then relate to individual chronotype. Exact working times are unavailable in the largely paper-based NHS2; we will therefore rely on pre-specified working times that the 2009 questionnaire collected (e.g. night shifts between 23:00 and 7:00).

Additional work schedule characteristics. In addition to working times, the NHS3 questionnaires gathers a range of additional work schedule characteristics, such as intensity of the schedule (i.e. relative frequency of shifts), duration of exposure to the current schedule (i.e. in years and month). Participants also indicate whether they work full or part time, and if they work other jobs, which will provide valuable information on potential time for recovery. Last, we will be able to label schedule as permanent or rotating. For NHS2, a range of work schedule characteristics were assessed in 2009, both for the current position, but also retrospectively from age 20-25, 26-35, 36-46 and 46+. Specifically, we know whether women worked full or part time, the primary work schedule (*i.e.* 'days/evenings only', 'nights only', 'early mornings only', 'rotating with nights', or 'rotating without nights'), the intensity of night shift work (number of night shifts), and duration of exposure (in years).

Body Mass Index. Weight and height are queried in the NHS3 on every questionnaire; in the NHS2, bi-annual questionnaires have assessed body weight and height since 1989. We will use this information to extract body mass index (in kg/m2).

Ascertainment of other Covariates. Numerous health and lifestyle variables have been regularly assessed by the biennial mailed questionnaire in NHS2 since 1989, and in NHS3 since it inception in 2010, enabling careful control for potential confounding factors, including use of medications, including antidepressants, anxiolytics, anti-hypertensive and cholesterol-lowering drugs, anti-inflammatory agents, plus health issues including depression, depressive symptoms, hypertension, high cholesterol, diabetes, cardiovascular disease, neurologic diseases, etc. Besides BMI, we have data on diet (in NHS3, the first dietary assessment takes place in 2015), physical activity, etc. Validation studies have confirmed the information is well-reported. These data are updated repeatedly, thus we can take lifestyle/health changes into consideration.

Results.

Aim 1:

As part of this aim, we derived the exposure metrics *mismatch score* (Aim 1a; mismatch between diurnal type and the shift worked on) as well as *shift lag* (Aim 1b; the difference between the mid-point of work and sleep times) in NHS3. A reduced mismatch score was also derived in NHS2, where only night shifts frequency, but not morning and evening shift frequency, was available as queried in 2009. In NHS3, we derived the mismatch score based on i) a categorical measure of diurnal preference to assess chronotype (question 19 of the MEQ, Horne and Ostberg, 1976), and i) relative shift frequency within a month. After excluding all individuals who did not report chronotype, sleep timing, or work schedule information, the final analytical sample comprised 17,844 NHS3 participants. Of those, 19.6% were self-reported early types, 64.3% intermediate ones, and 16.2% late chronotypes. Nearly 80% reported that their current schedule included day shifts (median and inter-quartile range for start and end times: start: 7:30, IQR: 7:00;8:00; end: 17:00; IQR: 16:00, 19:00), 6.6% worked early morning shifts (start: 6:30; IQR: 5:30; 7:00; end: 16:00, IQR: 14:30; 18:30), 13.3% worked evening shifts (start: 15:00; IQR: 13:00; 15:00; end: 23:00, IQR: 19:30; 23:30), and 21% reported night shift work (start: 19:00; IQR: 19:00; 19:00; end: 7:30, IQR: 7:00; 7:30). This high-resolution information on work schedules is also useful to gain an understanding of the contemporary work schedule amongst nurses in the NHS3. Based on a participant's chronotype, and the relative frequency of a given shift within a month, we computed the *mismatch score* (mean, SD). The *shift lag* in contrast used individual mid-sleep times on free days, an established proxy for chronotype, and mid-work times to derive the lag between mid-sleep and mid-work. While for the *mismatch score*, higher scores represent presumably more of a strain, the more the *shift lag* is centered around 12h, the better, as work hours 12h opposed to the mid-sleep at least likely to curtail sleep times. We use the absolute difference between mid-sleep time (mean: 3:22, SD: 1:17) and shift-specific mid-work times, weighted by the relative shift frequency in a month's schedule. The mean mismatch score in NHS3 (N=17,844) is 5.2 (SD: 8.8), but only about 1/3 of the population has detectable mismatch according to this metric (N=5,993). Within those participants, the mean mismatch score is 15.4. Shift lag is a more fine-grained metric, and in the NHS3 participants, the average lag between mid-sleep and mid-work was 8.9h (SD: 3.2h).

With regards to the two, central chronotype measures - diurnal preference and sleep timing, we observed that they correlate well with each other (Spearman's rank correlation, r= 0.48, p<0.001).

Aim 2:

In the NHS3 online questionnaires, we also queried information on current body weight (continuous, in lb), and together with height information collected at the baseline from each participant, we computed body mass index.). Replication analyses were conducted in the NHS2 with a reduced mismatch score and BMI, both assessed in 2009. We assessed the cross-sectional association between the novel circadian exposure metrics and BMI/obesity status. As described above, the mismatch score was highly skewed, and 75% of NHS3 participants had a score of 0. Comparing those a mismatch score of 0 to those with a score >0 showed that NHS3 participants experiencing mismatch were 30% more likely to be obese. Amongst the 5,993 with any mismatch score, a higher mismatch score was associated with higher odds of obesity (T1: Ref; T2: OR=1.27, 95%CI = 1.09-1.49; T3: OR=1.38, 95%CI = 1.18-1.62, p_{trend} = 0.0005). Multivariable (MV) adjustment accounted for age (years), sex, marital status, number of children, sleep duration, snoring, chronic diseases, such as cancer or cardiometabolic disease, and depression. Shift lag was much more evenly distributed in the cohort, due to its higher resolution. Compared to those with the lowest shift lag (i.e. where work hours are closest to their sleep midpoint), those with less shift lag were less likely to be obese (MV Q2: OR=0.88, 95%CI=0.80,0.97; Q3: OR=0.73, 95%CI=0.66,0.81; OR=0.70, 95%CI=0.63,0.78; p_{trend}<0.0001).

In NHS2, few women were still currently work night shifts, namely 3.8%. We therefore created a binary classification (mismatch, yes/no). Having a current mismatch score >0 was associated with higher BMI, even after multivariable (MV) adjustment (mean difference in BMI: 0.58, 95%CI: 0.35, 0.82), and a 19% higher odds of being obese (MV OR=1.19, 95%CI: 1.08, 1.31). MV adjustment included age (in months), husband's education, marital status, number of children, household income (census-tract), menopausal status, sleep duration, snoring, physical activity (in quintiles), diet quality (in quintiles), and comorbidities such as cancer or cardiometabolic disease. Based on the number of years women worked in each schedule they indicated night shift exposure, we could extrapolate an estimation of a lifetime mismatch score. Women with a higher lifetime mismatch score (in quartiles) were more likely to have a higher BMI (Q1 vs. Q4: 1.08, 95%CI: 0.96, 1.21, p_{trend}<0.001) and to be obese (Q1 vs. Q4: 1.44, 95%CI: 1.36, 1.52, p_{trend}<0.001). Overall, results were similar when we examined BMI as an outcome.

Discussion and Conclusion.

Shift work is an indispensable part of modern life. In the United States, almost 15 percent of full-time wage and salary workers work alternative shifts (68). A growing body of literature provides evidence linking night-shift work with increased risk of several malignancies including breast cancer (4-6, 69-75), endometrial cancer (8), prostate cancer (76, 77), colorectal cancer (78), and lymphoma (79). Night-shift work is also believed to be associated with other health problems such as cardiovascular disease, diabetes, gastro-intestinal disorders, and sleep disorders (80-82). One hypothesis is that night shift work impacts the health of shift workers through disruption of circadian rhythm (83).

Several results of previously published literature have been hampered by severe exposure misclassification,
In 2011, a group of experts convened by the International Agency of Research on Cancer (IARC) called for improved shift work exposure assessment that take into account chronotype and rely on more detailed work schedule assessments (84). However, to date, exposure metrics have not changed fundamentally. We therefore aimed to close this gap and systematically develop and apply circadian metrics that quantify the combined effect of chronotype and working times.

For the first time, we have made use of the newly included detailed work schedule assessment in juxtaposition with the two most commonly used chronotype measures in the Nurses' Health Study 3 (NHS3), a large-scale cohort study, which began enrollment in 2010. By developing improved exposure metrics, directly reflecting circadian strain as one of the central biological mechanisms linking shift work and adverse health outcomes, we sought to develop easy, and widely-applicable metrics for personalized occupational risk assessment. This research, and the preliminary validation of our newly derived metrics, has the potential to significantly facilitate future studies examining the adverse health and safety outcomes associated with work schedules, directly taking into account chronotype. Ultimately, the newly developed metrics can be used to examine the relationship between occupational circadian strain and health and safety outcomes, and identify critical doses for prevention strategies, across industry settings and sectors. Our application addresses primarily the NIOSH sector program 'Exposure Assessment', but its implications will also be relevant to the programs 'Prevention through Design' as well as 'Total Worker Health'.

Publications.

Journal Article

Vetter C, Gaskins A, Lawson CC, Rich-Edwards J, Chavarro JE, Schernhammer ES: [2019] Circadian Strain and Obesity in the Nurses' Health Study 3. In preparation. (Aim 1 and 2)

Vetter C, Chang SC, Devore EE, Rohrer F, Okereke OI, Schernhammer ES: [2018] Prospective study of chronotype and incident depression among middle- and older-aged women in the Nurses' Health Study II. J Psychiatr Res. 2018 May 25;103:156-160. doi: 10.1016/j.jpsychires.2018.05.022. [Epub ahead of print] PubMed PMID: 29860110. PMCID PMC6016366. (Aim 2)

Vetter C. [2018] Circadian disruption – what do we actually mean? Eur J Neurosci Nov 7. doi: 10.1111/ejn.14255. [Epub ahead of print]. PMCID: PMC6504624. (Aim 1)

Proceedings

Vetter C, Gaskins AJ, Lawson CC, Rich-Edwards J, Chavarro JE, Schernhammer, ES: [2018] Developing exposure metrics using a prospective repository of work hours, sleep and circadian phenotypes: the Nurses Health Study 3. Abstract presented at the 23rd International Symposium on Shiftwork and Working Time, Uluru, Australia. (Aim 1)

Inclusion of gender and minority study subjects.

All subjects in NHS2 are women. This is appropriate because the cohort is already established and was originally limited to women as breast cancer was the primary interest; breast cancer in men is very rare while breast cancer is a leading cause of death among U.S. women. The population is also predominantly white, reflecting the ethnic background of women entering nursing in the U.S. in the 1970's and 1980's. There were no exclusions based on race in the original enrollment. In NHS3, men were also allowed into the study, though they are still vastly underrepresented (<500), and were not considered in our analyses

According to the May 1997 supplement to the Current Population Survey (CPS), a greater proportion of blacks (20.9 percent) worked alternative shifts than either whites (16.1 percent) or Hispanics (16.0 percent) (85). Furthermore, even on the same job, it is usually the case that more blacks than whites work on alternative shift. Thus, despite the lack of minorities within this cohort, our research will serve to a great extent members of minority groups, particularly blacks, based on the assumption of no ethnic differences in the underlying patho-physiology.

Inclusion of children.

By the nature of this project, only adults were eligible to participate. Because individuals with work schedules were at the center of this project, children were not considered as part of the scientific aims.

Materials available for other investigators.

The derivation of novel metrics is in detail summarized in the peer-reviewed literature (publication in preparation).

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