A. COVER PAGE

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hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: To examine the relationship between pre-conceptional and in utero shift work exposure and growth perturbations in the kids: Children born to women who work night shifts have lower birth weight, adverse early life somatotypes, and higher adult height, waist circumference, and body mass index (BMI) compared to children whose moms did not work night shifts. These effects are stronger if night shift work took place during pregnancy.

Aim 2: To examine the relationship between pre-conceptional and in utero shift work exposure and mood disorders in the kids: Children born to women who work night shifts have a higher risk of developing depression/anxiety. These effects are stronger if shift work took place during pregnancy. Preliminarily, we will also examine the risk of autism spectrum disorders in the offspring of women with night shift work.

Aim 3: To examine the relationship between pre-conceptional and in utero shift work exposure and sleep as well as glucocorticoid signaling in the kids:

a. Sleep duration: Children born to women who work night shifts have a higher rate of too short or too long sleep; these effects are stronger if shift work took place during pregnancy.

b. Timing of sleep: Children born to women who work night shifts (particularly if shift work took place during pregnancy) are more likely evening types than kids of moms without any night work.

c. Biomarkers of sleep: melatonin/cortisol: Morning urinary melatonin levels are lower, and saliva cortisol levels higher (and they decline more slowly throughout the day), in children born to women who work night shifts. These effects are stronger if night shift work took place during pregnancy.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

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Project Title:

Adverse Health Effects of Shift Work

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Table of Contents.

	Page Number
List of Abbreviations	2
Abstract	3
SECTION 1	4
Significant or Key Findings	4
Translation of Findings	4
Research Outcomes/ Impact	4
SECTION 2 – Scientific Report	5
Background	5
Specific Aims	6
Procedures and Methodology	6
Results	9
Aim 1	9
Aim 2	9
Aim 3	10
Discussion and Conclusion	10
Publications	11
Inclusion of gender and minority study subjects	11
Inclusion of children	12
Materials available for other investigators	12
Bibliography	13

List of Terms and Abbreviations.

NHS2	Nurses' Health Study 2
GUTS	Growing Up Today Study
T2DM	Type 2 diabetes mellitus
BMI	Body-mass Index
HPA	hypothalamic-pituitary-adrenal
FFQ	Food frequency questionnaires
SD	standard deviation
RR	Relative risk
MV	Multi-variable
95% CI	95% confidence interval
p_{trend}	P-value for trend test
p_{intx}	P-value for interaction
DoHAD	Developmental Origins of Health and Disease
sAA	salivary alpha amylase

Abstract.

Adverse Health Effects of Shift Work

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Worker groups studied. Almost 15 million Americans regularly work alternate shifts (1). Considerable uncertainty exists about the potential harm that shift work during pregnancy may impose on a mom's child, yet working night shifts during pregnancy is currently an established reality in the US. We have previously linked work schedules, particularly those involving night shifts, with an increased risk of spontaneous abortion and delivering pre-term in the Nurses' Health Study 2 (NHS2) – risks which remained elevated even after adjusting for exposure to antineoplastic drugs and sterilizing agents. Identifying the effects of shift work on health by targeting the "Developmental Origins of Health and Disease" (DOHaD) concept as it relates to prenatal shift work exposure, to examine how exposure of the embryo and fetus to shift work may affect their health and chronic disease risk later in life, remains central to further research.

Approach. Drawing on a worldwide unique resource, which provides critical information on both moms and their offspring, including occupational shift work exposure during pregnancy, existing data from the ongoing NHS2 cohort and Growing Up Today Study (GUTS), i.e. children of the nurses participating in NHS2, and newly collecting urine samples from a subset of GUTS participants, investigated the following 3 major hypotheses: (1) can shift work (prior to conception as well as during pregnancy) induce growth perturbations and altered mental health in the offspring, and how may this influence disease risk across the lifespan? (2) are worsened sleep parameters including lower overnight melatonin production, and higher glucocorticoid signaling in young adulthood associated with such early life exposures? and (3) can we define critical developmental windows (e.g., preconception, embryonic, and fetal periods) during which shift work may influence chronic disease etiology. Data on lifetime shift work history of the NHS2 mothers of all 27,795 children in GUTS, 3,740 children whose mothers additionally provided shift work history during pregnancy, and 621 mom/child pairs where the mom was actually pregnant with the respective GUTS kid during shift work, were available.

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; 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, metabolic syndrome, hypertension, stroke, endometriosis, type 2 diabetes (T2DM). Building on this large body of prior work, in our current project, we were able to show that that children of moms with a history of longer duration of shift work tended to have a higher BMI at age 9-10 than children of moms without any night work. Importantly, adherence to an overall healthy lifestyle before pregnancy was strongly associated with a low risk of offspring obesity in childhood, adolescence, and early adulthood, or for moms who worked night shifts. Additionally, we observed differences in cortisol and sAA patterns suggesting a different stress response (potentially indicative of a more reactive stress system) in offspring of women with night shift work, compared to offspring of women without. Further, we observed a higher risk of depression for offspring of women who worked night shifts before pregnancy and reported being definite morning chronotypes, indicating that maternal chronotype significantly modifies the relationship between maternal night shift work before pregnancy and depression outcomes in their offspring. This is an exciting finding corroborating that the interplay between work hours and internal clock (chronotype) might be of importance for disease outcomes.

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, our research exemplifies the translation of research into practice (r2P) in that it may lead to actual changes in work practice for pregnant women. Ultimately, this is a potentially highly effective prevention practice, which can readily be adopted by any other workplace.

SECTION 1

Significant or Key Findings.

Aim 1: We examined the relationship between pre-conceptional and in utero shift work exposure and growth perturbations in the kids. Specifically, we explored in detail how working night shifts surrounding and during pregnancy affects weight outcomes in the offspring, based on the previous observation that women who had ever worked night shifts were more likely to be obese and consumed more total calories. We found that women's night shift work surrounding pregnancy was associated with a modestly increased risk of obesity/overweight in their offspring, showing that children of moms with a history of longer duration of shift work tended to have a higher BMI at age 9-10 than children of moms without any night work. Importantly, adherence to an overall healthy lifestyle before pregnancy was strongly associated with a low risk of offspring obesity in childhood, adolescence, and early adulthood, or for moms who worked night shifts.

Aim 2: We set out to examine the relationship between pre-conceptional and in utero shift work exposure and mood disorders in the kids. In analyses stratified by maternal chronotype, we observed a higher risk of depression for offspring of women who worked night shifts before pregnancy and reported being definite morning chronotypes, suggesting that maternal morning/evening preference significantly modifies the relationship between maternal night shift work before pregnancy and depression outcomes in their offspring. This is a novel observation, providing further evidence for the potential importance of the interplay between work hours and internal clock (chronotype) for disease outcomes, even in the offspring of night workers. Future work is needed to further corroborate these findings and to provide mechanistic underpinning also in relationship to other disease endpoints.

Aim 3: We examined the relationship between pre-conceptional and in utero shift work exposure and sleep as well as glucocorticoid signaling in the kids. In these analyses, we observed differences in cortisol and sAA patterns suggesting a different stress response (potentially indicative of a more reactive stress system) in offspring of women with night shift work, compared to offspring of women without. Secondarily, we found that larger differences between minimum and maximum photoperiod during maternal pregnancy were related to lower odds of depression; which appeared specific to the 2nd pregnancy trimester, - a critical period of neuronal generation, migration, and organization.

Translation of Findings.

Our findings suggest that exposure of the embryo and fetus to shift work may affect their health and chronic disease risk later in life, as it relates to depression risk and stress markers. These findings were modified by maternal chronotype, e.g. suggesting that chronotype and night shift work of the mom interact in their potential impact on offspring health. Overall, they corroborate a potential effect of shift work on health through the "Developmental Origins of Health and Disease" (DOHaD) concept as it relates to prenatal shift work exposure, and that these early exposures of the embryo and fetus to shift work may in certain subgroups affect their health and chronic disease risk later in life.

Research Outcomes/Impact.

We were funded to comprehensively study the impact of early life exposures to night shift work on offspring outcomes. Because shift work is so central to our multi-tasking high-stress work life, it will likely continue; therefore, defining the most vulnerable populations to possibly exempt them from shift work is critical. One such vulnerable population may be pregnant women, and by extension the unborn. Our novel findings of subtle impacts of early life night work exposure on. offspring health, perhaps particularly among women with mismatched (to their work schedule) chronotype, merit further attention, and warrant future studies to corroborate our findings including their mechanistic underpinning. Ultimately, they could represent a substantial step forward in the aim to improve our understanding of the early life effects of night shift work to better delineate the multi-facetted negative health effects of night work.

SECTION 2

Scientific Report

Background.

Despite the high prevalence of shift work and sleep deprivation among pregnant women in the United States, the question of whether prenatal sleep disturbances at any level or pattern of exposure may enhance the biological risk for chronic diseases later in life remains largely unexplored and warrants further investigation. While obesity and related diseases, sleep problems, and mental illness are on the rise among young Americans, and growing research in both animal models and in humans connects disrupted sleep cycles during pregnancy to adverse health outcomes among the offspring, data regarding the potential long-term effects of rotating night shift work on health in the children of night workers remain largely elusive. Due to the difficulties of associating diseases with past occupational exposure, and particularly relating occupational exposure of the mom to her child's health, no reliable statistics exist. However, there are several lines of evidence suggesting a link between maternal stressors and outcomes in the offspring, which provide the underpinning for our proposal. Overall, alterations of genetic expression or other epigenetic mechanisms, including their effect on the hypothalamic-pituitary-adrenal (HPA) axis, are thought to contribute to heightened disease risk later in life (2, 3).

Today, animal models have largely confirmed that several adulthood health outcomes are, at least in part, programmed during pregnancy.(4-8) Perturbations at critical windows of development have been shown to cause life-long and often irreversible alterations with proven consequences regarding adiposity and heart disease (4, 5). As such, external and maternal influences act through gene x environment interactions or epigenetic programs to shape the developing brain and body, as well as disease vulnerability.(9) They may contribute to heightened risk of mental health disorders later in life as well,(10) – likely through maternal-fetal glucocorticoid signaling (11). In fact, an imbalance between central glucocorticoids and mineralocorticoid receptors predisposes, via dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, to susceptibility to anxiety and other mood disorders.(12-15) Glucocorticoids are vital for the maturation of fetal organs, yet excessive levels of stress hormones on the developing fetus may impact cardiovascular health (16). Moreover, loss of 11beta-hydroxysteroid dehydrogenase (11beta-HSD) – an isozyme that facilitates glucocorticoid action on target tissues and which is widely expressed throughout the body as well as selectively elevated in adipose tissue in obesity, – from the fetus and fetally-derived tissues, results in a life-long phenotype of anxiety, consistent with developmental programming.(17) Selective inhibition of 11beta-HSD, finally, improves several metabolic syndrome parameters in rodent models and human clinical trials (12, 16, 18). In short, the HPA-axis likely plays a major role in the early origins of obesity and mental health.

In addition, the core circadian genes, which control numerous physiologic functions of great relevance to disease risk (e.g. cell cycle control, DNA damage and repair, immunity), appear to be intimately coupled to a variety of epigenetic mechanisms (19, 20). Epigenetic control via chromatin remodeling through post-translational histone modification (e.g. methylation, acetylation) is important for clock function and is coupled to changes in the environment through signaling pathways, particularly e.g. the nicotinamide adenine dinucleotide (NAD+)-dependent SIRT1 histone deacetylase (HDAC), linking clock to intracellular energetic environments.

We, therefore, set out to examine the effect of maternal shift work exposure on the DOHaD paradigm by leveraging the unique resources of two existing large prospective cohorts with critical information on both moms and their offspring, including occupational shift work exposure during pregnancy: using existing data from the ongoing NHS2 and GUTS cohort, i.e. children of the nurses participating in NHS2, and newly collecting urine samples from a subset of GUTS participants, we investigated the following 3 major hypotheses: (1) can shift work (prior to conception as well as during pregnancy) induce growth perturbations and altered mental health in the offspring, and how may this influence disease risk across the lifespan? (2) are worsened sleep parameters including lower overnight melatonin production, and higher glucocorticoid signaling in young adulthood associated with such early life exposures? and (3) can we define critical developmental windows (e.g., preconception, embryonic, and fetal periods) during which shift work may influence chronic

disease etiology. We have complete lifetime shift work history of the NHS2 moms of all 27,795 children in GUTS, 3,740 children whose moms additionally provided shift work history during pregnancy, and 621 mom/child pairs where the mom was actually pregnant with the respective GUTS kid during shift work. Focusing on three interlinked mediators of major health outcomes throughout life – body weight, mental health, and sleep (21), these hypotheses gave rise to the following specific aims:

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

Aim 1: To examine the relationship between pre-conceptional and in utero shift work exposure and growth perturbations in the kids: Children born to women who work night shifts have lower birth weight, adverse early life somatotypes, and higher adult height, waist circumference, and body mass index (BMI) compared to children whose moms did not work night shifts. These effects are stronger if night shift work took place during pregnancy.

Aim 2: To examine the relationship between pre-conceptional and in utero shift work exposure and mood disorders in the kids: Children born to women who work night shifts have a higher risk of developing depression/anxiety. These effects are stronger if shift work took place during pregnancy. Preliminarily, we will also examine the risk of autism spectrum disorders in the offspring of women with night shift work.

Aim 3: To examine the relationship between pre-conceptional and in utero shift work exposure and sleep as well as glucocorticoid signaling in the kids:

a. Sleep duration: Children born to women who work night shifts have a higher rate of too short or too long sleep; these effects are stronger if shift work took place during pregnancy.
b. Timing of sleep: Children born to women who work night shifts (particularly if shift work took place during pregnancy) are more likely evening types than kids of moms without any night work.
c. Biomarkers of sleep: melatonin/cortisol: Morning urinary melatonin levels are lower, and saliva cortisol levels higher (and they decline more slowly throughout the day), in children born to women who work night shifts. These effects are stronger if night shift work took place during pregnancy.

In **secondary analyses**, we explored these associations by trimester and by gender of the kids, and assess whether chronotype (of the moms and kids), season of child's birth, average UV-B flux at residence during pregnancy, and mom's mood and body size modify the relationship between pre-pregnancy shift work and body weight, mental health, and sleep in these kids.

Procedures and Methodology.

Study Population

The NHS2 is a cohort of 116,434 female nurses 25-42 years, who returned a health and lifestyle questionnaire in 1989. Since then, nurses are asked on biennial follow-up questionnaires if they have been diagnosed with various diseases, including cancer, myocardial infarction (MI), stroke, and type 2 diabetes (T2DM). Medical records are obtained to adjudicate affirmative responses. Detailed data is also available about numerous lifestyle factors such as diet (obtained from food frequency questionnaires, FFQ), smoking, physical activity, alcohol intake, height/weight, reproductive history, family history of major chronic diseases, use of medications (including prescriptions as well as non-prescription drugs such as aspirin), hypertension status, and many others. Questionnaire-derived information on these important covariates has been extensively validated. Follow-up has been >90% and our active surveillance for mortality surpasses 98% complete ascertainment of deaths in the cohort. In addition, on the main 2009 questionnaire, all NHS2 participants were asked specifics about each single one of their pregnancies, including the baby's birth weight and gestational age, type of delivery (vaginal delivery, c-section), and pregnancy complications (e.g. gestational diabetes). This questionnaire also assessed whether any of their children had ever been diagnosed with an autism spectrum disorder, a question, which was also posed on the main NHS2 questionnaire in 2005 as well.

Supplemental pregnancy questionnaire in NHS2.

On the 2001 biennial questionnaire, participants were asked whether they had a pregnancy since 1993, worked as a nurse during the most recent of these pregnancies, and would be willing to participate in a

substudy, i.e. a supplemental survey ascertaining specific information surrounding that most recent pregnancy. Of the 101,281 respondents to the 2001 questionnaire, 11,177 (11%) had at least one pregnancy since 1993 during which they worked as a nurse. Of these women, 9,547 (85%) indicated willingness to participate; 654 (6%) declined; and 985 (9%) did not answer the question about the supplemental survey. Of the 9,547 women who, between 2001 and 2003, were mailed the supplemental survey, 8,461 (89%) responses were received, resulting in an overall participation rate of 89%. Study participants lived in the following US states: California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas.

The Growing Up Today Study was first established in 1996 (NIDDK, DK-46834, 1996-2000) to assemble a cohort of young people, ages 9-14 years of age. The overall purpose of the project was to assess diet and other various factors affecting weight change and weight gain in this population of 27,805 subjects. To establish the cohort, we identified mothers from the ongoing NHS2 who had children ages 9 to 14. In total, 53,000 children were in the eligible age range. In October 1996, we mailed letters and baseline questionnaires to the 13,261 girls and 13,504 boys whose mothers had granted us consent to invite them to participate in the Growing Up Today Study (GUTS1). Approximately 68% of the girls (N=9,039) and 58% of the boys (N=7,843) returned completed questionnaires, thereby assenting to participate in the cohort. In 2004, a second cohort was established (GUTS2) using the same procedures. In this mailing, 6,006 girls and 4,917 boys returned completed questionnaires and became part of the second cohort. Follow-up questionnaires have been mailed every two years to each cohort. Considering their overlap with the supplemental pregnancy questionnaire in NHS2, which was mailed between 2001 and 2003, all children included in this study, today, are between the ages 17 and 21 (as of 2014).

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

Shift work history. As part of the NHS2 biennial questionnaires, we have collected detailed information on rotating night shift work in participants. The first questionnaire in 1989 asked about total months during which study participants had worked rotating night shifts for at least 3 days/month, in addition to having worked days or evenings in those months. This information was subsequently updated in 1991, 1993, and regularly thereafter, including items about total hours slept/day. In addition, in 2009, we included detailed questions on occupation, average sleep duration during shiftwork, and shift schedule including rotating nights at various ages (e.g., ages 20-25, 26-35, 36-45, and 45+). In addition to this existing data, we updated information on rotating night shifts on the main questionnaire in 2013. Further, on the supplemental pregnancy survey that was responded to in 2003 by 8,461 women participating in NHS2, trimester-specific occupational exposure to shift work was collected. Specifically, we queried their work schedule (days only, evenings only, nights only, rotating with nights, rotating without nights, other/did not work); number of nights per month (none, 1-2/month, 3-4/month, 2-3 nights/week, 4+nights/week), and average hours worked per week during each trimester (none, 1-20, 21-40, 41-60, 61+ hours/week). Night shift was defined as most of work hours falling between midnight and 8:00am. Thus, we will have full information on history of rotating night shifts including during pregnancy and subsequently (i.e. during breast feeding as well).

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 (22)) and was validated using sleep logs (23).

Body Mass Index. Weight and height are queried 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/m^2).

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, such as 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.

Ascertainment of primary endpoints of interest in GUTS.

a. Growth perturbations / body weight

Birth weight was assessed for each GUTS child on the NHS2 pregnancy supplemental questionnaire; specifically, moms were asked about the birth weight of their baby (in pounds): <5, 5-5.4, 5.5-6.9, 7.0-8.4, 8.5-9.9, 10+ pounds. On all subsequent GUTS questionnaires, weight (in pounds), and height (inches) have been assessed regularly, as well as circumference of waist in 2011. Body shape at age 5 (in 2004) and 10 (in 2006) was assessed in GUTS using 8 different pictograms ranging form thin (1) to obese (8). Both in 2004 as well as 2006, kids were also asked about their current body shape, using the same pictograms. As another scale of physical development, in addition, we also have information on Tanner stage from the 2004 and 2006 questionnaire, using pictograms with varying levels of pubic hear development ranging from 1 (there is no pubic hair) to 5 (the hair is now like that of a grown woman/man). In preliminary analyses we find that in 2004, the average BMI among boys and girls combined was 18.6 kg/m^2 (standard deviation (SD), 3.5) as well as 21.0 (SD, 3.5) in 2008, and their average waist circumference 30.9 inches (SD, 4.7).

b. Mental health

We have several different assessments of mental health in GUTS. In 2011, a question was posed both related to being depressed as well as experiencing anxiety “Which of these questions best describes your own health state today: depression/anxiety not, slightly, moderately, severely, extremely anxious or depressed”. Of all respondents, 62% reported feeling depressed rarely or none of the time, 21% felt depressed some of the time, and 14% occasionally or a moderate amount of time, with 3% reporting being depressed all the time. Further, on the 2013 GUTS questionnaire, we assesses whether kids, since 2006, have ever been told by a heath care provider that they had any of the following diagnoses: anxiety, depression and when (before 2006, or 2006-2008, 2009-2011, 2012+). They were also asked whether they used any SSRI-type antidepressants (e.g. Prozac, Zoloft), or other antidepressants (Elavil, Tofranil). In addition, a separate question akin to the 2011 assessment queried whether they felt anxious or depressed, with the possible answers they could provide being: not, slightly, moderately, severely, extremely. Lastly, the 2009 questionnaire assessed whether any of the nurses’ children had ever been diagnosed with an autism spectrum disorder, a question, which was also posed on the main NHS2 questionnaire in 2005 as well.

c. Sleep

In GUTS2, in 2008 and 2011, the following question was asked – in a typical 24 hours, how many hours of sleep do you get (less than 5, 5, 6, 7, 8, 9, 10, 11+). Further, questions on sleep quality were added to the 2006 and 2008 GUTS2 questionnaire. On these questionnaires, we asked kids how many hours of sleep they get in a typical night before school, and in a typical 24-hour period; how they rate their sleep quality during the past month; how many minutes it usually takes to fall asleep at bedtime; how often, during the past month, they felt overly or excessively sleepy; and how often they used smart phones etc in the hours before sleep (as well as whether they had these in reach during sleep). In preliminary analyses we find that, in 2006, most kids (41%) report sleeping on average 8 hours on school nights, 38% slept 9 hours, and 8% 10 hours or more. 11% slept an average of 7 hours, and the remainder 6 or fewer hours. As they get older, fewer kids report sleeping 8+ hours (e.g., in 2011, 31% sleep 8 hours, 12% 9 hours, and 4% sleep 10+ hours. By contrast, 27% sleep 7 hours and the remaining 12% sleep 6 hours of fewer.

Urine collection in GUTS. As part of this project, we invited all respondents to the 2014 follow-up questionnaire in GUTS (currently 12,122 kids) to provide first morning urine samples. In total, we collected first morning urine samples in our urine substudy of 1,222 kids, following similar protocols as in prior studies for the urine collection. After exclusions of melatonin values that exceeded the upper limit of the assay (n=33) or were identified as outliers (n=10), 1,179 participants were available.

Saliva collection and cortisol measurement. Between 2011 and 2013, a saliva collection was conducted in the GUTS cohort, and of 1,169 kids from GUTS2 who were invited to participate, 774 (66%) returned saliva samples, 768 of which have a mother in NHS2. The initial purpose of this study was to ascertain the effects of stress on hormones, particularly cortisol. Specifically, participants collected five saliva samples, using passive drool into tubes, over the course of the day (at awakening, 45 min, 4 hrs, 8 hrs, and 12 hrs after awakening, and at bedtime) using straws and 2.0 mL sample tubes. Samples were shipped to the Channing Lab, centrifuged, aliquoted, and stored according to established protocols for salivary cortisol. Concentrations of salivary free cortisol were measured at Brandeis University's Laboratory for Biological Health Psychology (under the direction of Nicolas Rohleder), using a commercially available chemiluminescence-immuno assay (CLIA; IBL, Hamburg, Germany) with intra- and inter-assay precision of 11% and 13%, respectively.

Results.

Aim 1:

As part of this aim, we explored in detail how working night shifts surrounding and during pregnancy affects ***weight outcomes*** in the offspring, based on the previous observation that women who had ever worked night shifts were more likely to be obese (OR=1.37, 95%CI, 1.31-1.43) and consumed more total calories (≥1715 kcal/day) (OR=1.09, 95%CI, 1.04-1.13). We included 4,044 mothers of NHS2, who were on average 33.4 (SD=3.6) years old when they gave birth to the children included in this analysis, and 65% of them reported ever having worked night shifts. At enrollment in GUTS2 in 2004, children were on average 11.7 (SD=1.2) years old. Overall, there were only modest differences in terms of maternal and offspring characteristics according to history of night shift work before pregnancy. Mothers who had worked night shifts for six years or more prior to conception of the first considered child were older, more likely to be past or current smokers, more adherent to a healthy diet (AHEI), and more physically active compared to women with no history of working night shifts. Also, offspring born to mothers with longer shift work history were more likely to be delivered by Cesarean section compared to those born to mothers without a history of shift work.

We found that overall, there were no associations of history of shiftwork with birth weight or somatotype at age 5 in the offspring. We did find a significantly higher risk of the offspring having overweight or obesity at any time during follow-up between 2004 and 2013 for mothers with any history of night shift work before pregnancy (MV RR_{any} 1.11, 95% CI, 1.02-1.21) when compared to mothers who never worked any night shifts. The association was slightly more pronounced for the risk of persistently having overweight or obesity (MV RR_{any} 1.25, 95% CI, 1.00-1.56). However, there was no evidence of a dose-response association with increasing number of years of night shift work history (overweight/obese MV $RR_{extreme}$ 1.07, 95%CI, 0.92-1.23; P_{trend} =0.14; persistently overweight/obese MV $RR_{extreme}$ 1.04, 95%CI, 0.71-1.52; P_{trend} =0.17). Longer duration of night shift work was not associated with changes in BMI with age (P_{trend}>0.34), but was associated with greater differences in mean BMI (P_{trend} <0.01) at baseline age (Table 2). I sum, we found that women's night shift work surrounding pregnancy was associated with a modestly increased risk of ***obesity/overweight*** in their offspring,(24) showing that children of moms with a history of longer duration of shift work tended to have a higher BMI at age 9-10 than children of moms without any night work. Importantly, adherence to an overall healthy lifestyle before pregnancy was strongly associated with a low risk of offspring obesity in childhood, adolescence, and early adulthood, or for moms who worked night shifts (25).

Aim 2:

In Aim 2, we examined the impact of shift work surrounding pregnancy on ***mental health*** outcomes in the offspring (26). In analyses stratified by maternal chronotype, we observed a higher risk of depression for offspring of women who worked night shifts before pregnancy and reported being definite morning chronotypes ($OR_{ever\ nightwork}$=1.95; 95%CI, 1.17-3.24 vs. $OR_{ever\ nightwork}$ = 0.93; 95%CI, 0.68-1.28 for any other chronotypes; P_{intx}=0.005). Our results indicate that maternal chronotype significantly modifies the relationship between maternal night shift work before pregnancy and depression outcomes in their offspring. This is an exciting finding corroborating that the interplay between work hours and internal clock (chronotype) might be of importance for disease outcomes. Specifically, these findings also suggest that the social and biological stress

induced by an extreme mismatch of preferred and actual sleeping times might have an impact on offspring mental health. Interestingly, we identified this effect modification only for self-reported physician/clinician-diagnosed depression and not for any of the other considered outcomes, including a broader depression definition that also included antidepressant use and depressive symptoms. Possible explanations are that self-reported physician/clinician-diagnosed depression may capture more severe depression cases, may have higher specificity and precision than the broad definition, or may indicate earlier age-at-onset cases. The longitudinal follow-up of mothers and children, together with detailed information on determinants of maternal lifestyle and social economic status, were unique strengths of our study, whereas limitations included relatively modest power, the self-reported nature of our outcomes. Future studies with more refined exposure assessments and more detailed longitudinal measures of psychiatric outcomes throughout childhood, adolescence, and adulthood are needed to explore these relationships in more detail.

Aim 3:

As part of Aim 3, we investigated the association between maternal rotating night shift work before conception and offspring ***stress markers*** (salivary cortisol and alpha amylase (sAA) patterns) and ***melatonin*** in young adulthood among mothers enrolled in the NHS2 and their offspring participating in the Growing Up Today Study 2 (GUTS 2)(27). Briefly, we observed differences in cortisol and sAA patterns suggesting a different stress response (potentially indicative of a more reactive stress system) in offspring of women with night shift work, compared to offspring of women without. In addition, we examined associations between maternal shift work history before conception, and morning urinary melatonin measures (standardized for creatinine). In multivariable adjusted models, geometric means of melatonin levels did not appear to differ significantly among children whose mothers reported a history of night shift work before conception. Further, we observed higher odds of average shorter (≤6 hours), but not of longer (9+ hours) sleep duration among the children whose mothers worked night shifts before conception for 3 years or longer; and they had slightly shifted timing of sleep depending on whether their mothers had shorter (<3 years) shift work history i.e. offspring more likely to be evening chronotypes; versus if their mothers had 3+ years of night work history before conception, i.e. offspring were less likely to be evening types; though these odds did not reach significance.

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 (28). A growing body of literature provides evidence linking night-shift work with increased risk of several malignancies including breast cancer (29-38), endometrial cancer (39), prostate cancer (40, 41), colorectal cancer (42), and lymphoma (43). Night-shift work is also believed to be associated with other health problems such as cardiovascular disease, diabetes, gastro-intestinal disorders, and sleep disorders (44-46). One hypothesis is that night shift work impacts the health of shift workers through disruption of circadian rhythm (47). Further, we have previously linked work schedules, particularly those involving night shifts, with an increased risk of spontaneous abortion(48) and delivering pre-term in the Nurses' Health Study 2 (NHS2),(49) – risks which remained elevated even after adjusting for exposure to antineoplastic drugs and sterilizing agents.(50)

Some countries in the developed world exclude women from working at night if they become pregnant. By contrast, currently, it is acceptable for women in the United States to work night shifts throughout their pregnancy until shortly before they give birth. Until recently, no study had yet examined the effects of shift work during pregnancy on health in the offspring, making our analyses highly novel; we conducted the first large-scale prospective study of rotating night shiftwork in nurses during pregnancy to evaluate which effect this may have on their children. A major advantage compared to retrospective evaluations of health in kids born to moms who report having worked night shifts is that associations controlling for a multitude of potential confounders both in the mom as in the kid is necessary (e.g., sleep habits, coffee consumption, chronotype, diet, history of mental health as well as other diseases, medication intake – also during pregnancy, etc etc) and our resource put us into a unique position to be able and do so as we have collected most known disease risk factors repeatedly and over a long time in both the moms and the kids.

The findings from this work provide support for potential intergenerational effects of maternal night shift work exposure before and during pregnancy on offspring weight and mental health outcomes and some indication for altered stress response in these children. These findings have the potential to inform research on early pregnancy risk in broader populations, beyond nurses: by establishing a possible link between shift work during pregnancy and health outcomes in the offspring, our findings may suggest new pathways for preserving health in the offspring and truly identify new frontiers for early means of reducing obesity/mental disease/sleep problems in adolescents via occupational, lifestyle, and health interventions, thereby laying the foundation for healthier aging in these kids.

Publications.

Journal Articles

1. Strohmaier S, Devore EE, Vetter C, et al. Night Shift Work Before and During Pregnancy and Offspring Weight Outcomes Through Adolescence. *Obesity (Silver Spring).* 2018;26(9):1491-1500. (Aim 1)
2. Devore EE, Chang SC, Okereke OI, McMahon DG, Schernhammer ES. Photoperiod during maternal pregnancy and lifetime depression in offspring. *J Psychiatr Res.* 2018;104:169-175. (Aim 1 and secondary aim)
3. Strohmaier S, Devore EE, Vetter C, et al. Night shift work before and during pregnancy in relation to depression and anxiety in adolescent and young adult offspring. *European journal of epidemiology.* 2019;34(7):625-635.(Aim 2)
4. Dhana K, Haines J, Liu G, et al. Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: results from two prospective cohort studies of mother-child pairs in the United States. *Bmj.* 2018;362:k2486.(Aim 1)
5. Strohmaier S, Devore EE, Huang T, et al. Maternal rotating night shift work before pregnancy and offspring stress markers. *Physiol Behav.* 2019;207:185-193.(Aim 3)
6. Devore E, Chang SC, Okereke OO, McMahon DG, Schernhammer ES. Photoperiod During Maternal Pregnancy and Risk of Lifetime Depression in Offspring. *J Psychiatr Res* 2018;104:169-175. (secondary aim)

Proceedings

1. Devore E et al. Photoperiod during maternal pregnancy and lifetime depression risk in offspring. *25th EPICOH and X2016 Conferences*, Barcelona, Spain - September 2016
2. Strohmaier S Devore E, Vetter C, Missmer S, Eliassen AH, Rosner B, Okereke O, Schernhammer ES. Nightshift work before and during pregnancy and offspring mental health disorders in adolescence. *Society of Epidemiology Research (SER) 2018*, Baltimore, USA
3. Strohmaier S, Devore E, Vetter C, Missmer S, Eliassen AH, Rosner B, Okereke O, Schernhammer ES. Night shift work before and during pregnancy and offspring mental health disorders in adolescence. *Psycho EPA Section of Epidemiology and Psychiatry*, Vienna, Austria (April 2018)

Inclusion of gender and minority study subjects.

This proposal takes advantage of the existing NHS2 cohort, only including women, as well as of GUTS, which include both boys and girls.

That all subjects in NHS2 are women 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 GUTS, both boys and girls were allowed into the study.

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) (51). 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.

Our proposal studied the effects of exposure to shift work of the mom during and before pregnancy on the health of their offspring – children enrolled in GUTS. Hence, the inclusion of children (ages 8-21 per NIH definition) is critical, although the majority of our participants are 19 years and older at study start. No children were included in the NHS2. Cohort participants were a minimum of 25 years old in 1989 and currently range in age from 50 to 68.

Participants in the GUTS cohort were all children at the time of enrollment. NHS2 participants provided consent for their children's enrollment in the GUTS cohort. The first wave of recruitment enrolled children aged 9-14 years in 1996 (who are currently aged from 27 to 32 years old), while the second wave enrolled children aged 9-14 years in 2004 (who are currently aged from 19 to 24 years old). Therefore, questionnaire data from children were included in this study to understand how early life shift work could impact the health of the NHS2 women's offspring.

Materials available for other investigators.

The analytic methods and models are in detail summarized in the peer-reviewed literature and further details available upon request.

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C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Lawson CC, Whelan EA, Lividoti Hibert EN, Spiegelman D, Schernhammer ES, Rich-Edwards JW. Rotating shift work and menstrual cycle characteristics. Epidemiology (Cambridge, Mass.). 2011 May;22(3):305-12. PubMed PMID: 21364464; PubMed Central PMCID: PMC5303197; DOI: 10.1097/EDE.0b013e3182130016.
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N/A: Not NIH Funded	Johnson CY, Tanz LJ, Lawson CC, Howards PP, Bertone-Johnson ER, Eliassen AH, Schernhammer ES, Rich-Edwards JW. Anti-Müllerian hormone levels in nurses working night shifts. Archives of environmental & occupational health. 2020;75(3):136-143. PubMed PMID: 30945620; PubMed Central PMCID: PMC6776712; DOI: 10.1080/19338244.2019.1577210.
N/A: Not NIH Funded	Shi Y, Liu L, Hamada T, Nowak JA, Giannakis M, Ma Y, Song M, Nevo D, Kosumi K, Gu M, Kim SA, Morikawa T, Wu K, Sui J, Papantoniou K, Wang M, Chan AT, Fuchs CS, Meyerhardt JA, Giovannucci E, Ogino S, Schernhammer ES, Nishihara R, Zhang X. Night-Shift Work Duration and Risk of Colorectal Cancer According to *IRS1* and *IRS2* Expression. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2020 January;29(1):133-140. PubMed PMID: 31666286; PubMed Central PMCID: PMC6954315; DOI: 10.1158/1055-9965.EPI-19-0325.
N/A: Not NIH Funded	Johnson CY, Tanz LJ, Lawson CC, Schernhammer ES, Vetter C, Rich-Edwards JW. Night shift work and cardiovascular disease biomarkers in female nurses. American journal of industrial medicine. 2020 March;63(3):240-248. PubMed PMID: 31828843; PubMed Central PMCID: PMC8572536; DOI: 10.1002/ajim.23079.
N/A: Not NIH Funded	Ziobrowski HN, Buka SL, Austin SB, Sullivan AJ, Horton NJ, Simone M, Field AE. Using latent class analysis to empirically classify maltreatment according to the developmental timing, duration, and co-occurrence of abuse types. Child abuse & neglect. 2020 September;107:104574. PubMed PMID: 32531618; PubMed Central PMCID: PMC7494521; DOI: 10.1016/j.chiabu.2020.104574.
N/A: Not NIH Funded	Ziobrowski HN, Buka SL, Austin SB, Duncan AE, Simone M, Sullivan AJ, Horton NJ, Field AE. Child and adolescent maltreatment patterns and risk of eating disorder behaviors developing in young adulthood. Child abuse & neglect. 2021 October;120:105225. PubMed PMID: 34352683; PubMed Central PMCID: PMC8493560; DOI: 10.1016/j.chiabu.2021.105225.
N/A: Not NIH Funded	Zhang Y, Song M, Yuan C, Chan AT, Schernhammer ES, Wolpin BM, Stampfer MJ, Meyerhardt JA, Fuchs CS, Roberts SB, Rimm EB, Willett WC, Hu FB, Giovannucci EL, Ng K. Unrestrained eating behavior and risk of mortality: A prospective cohort study. Clinical nutrition (Edinburgh, Scotland). 2021 November;40(11):5419-5429. PubMed PMID: 34653818; PubMed Central PMCID: PMC8571025; DOI: 10.1016/j.clnu.2021.09.014.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
ESS123	Y	SCHERNHAMMER, EVA S	MPH,MS,DRPH,MD	PD/PI	4.8	0.0	0.0			NA
AHE123	Y	Eliassen, A. Heather	AB,MS,SCD	Co-Investigator	1.0	0.0	0.0			NA
	N	Devore, Elizabeth		Research Analyst Assistant	1.2	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

NOTHING TO REPORT

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT
No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE
Not Applicable
G.11 PROGRAM INCOME
Not Applicable
G.12 F&A COSTS
Not Applicable

I. OUTCOMES

I.1 What were the outcomes of the award?

In this project, we examined the relationship between pre-conceptional and in utero shift work exposure and growth perturbations as well as mental health, sleep, and glucocorticoid signaling in the offspring. Specifically, we explored in detail how working night shifts surrounding and during pregnancy affects these outcomes in the children of nurses participating in the Nurses' Health Study, based on the fact that – despite the high prevalence of shift work and sleep deprivation among pregnant women in the United States – the question of whether prenatal sleep disturbances at any level or pattern of exposure may enhance the biological risk for chronic diseases later in life remains largely unexplored and warrants further investigation

Some of our key findings were:
• Women's night shift work surrounding pregnancy was associated with a modestly increased risk of obesity/overweight in their offspring, showing that children of moms with a history of longer duration of shift work tended to have a higher BMI at age 9-10 than children of moms without any night work. Importantly, adherence to an overall healthy lifestyle before pregnancy was strongly associated with a low risk of offspring obesity in childhood, adolescence, and early adulthood, or for moms who worked night shifts.
• In analyses stratified by maternal chronotype, a higher risk of depression for offspring of women who worked night shifts before pregnancy and reported being definite morning chronotypes was observed, suggesting that maternal morning/evening preference significantly modifies the relationship between maternal night shift work before pregnancy and depression outcomes in their offspring. This is a novel observation, providing further evidence for the potential importance of the interplay between work hours and internal clock (chronotype) for disease outcomes, even in the offspring of night workers. Future work is needed to further corroborate these findings and to provide mechanistic underpinning also in relationship to other disease endpoints.
• We observed differences in cortisol and sAA patterns suggesting a different stress response (potentially indicative of a more reactive stress system) in offspring of women with night shift work, compared to offspring of women without.

Translation of Findings.

Our findings suggest that exposure of the embryo and fetus to shift work may affect their health and chronic disease risk later in life, as it relates to depression risk and stress markers. These findings were modified by maternal chronotype, e.g. suggesting that chronotype and night shift work of the mom interact in their potential impact on offspring health. Overall, they corroborate a potential effect of shift work on health through the "Developmental Origins of Health and Disease" (DOHaD) concept as it relates to prenatal shift work exposure, and that these early exposures of the embryo and fetus to shift work may in certain subgroups affect their health and chronic disease risk later in life.

Research Outcomes/Impact.

We were funded to comprehensively study the impact of early life exposures to night shift work on offspring outcomes. Because shift work is so central to our multi-tasking high-stress work life, it will likely continue; therefore, defining the most vulnerable populations to possibly exempt them from shift work is critical. One such vulnerable population may be pregnant women, and by extension the unborn. Our novel findings of subtle impacts of early life night work exposure on. offspring health, perhaps particularly among women with mismatched (to their work schedule) chronotype, merit further attention, and warrant future studies to corroborate our findings including their mechanistic underpinning. Ultimately, they could represent a substantial step forward in the aim to improve our understanding of the early life effects of night shift work to better delineate the multi-facetted negative health effects of night work.