



Photoperiod during maternal pregnancy and lifetime depression in offspring

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ABSTRACT

Experimental studies indicate that perinatal light exposure has enduring effects on affective behaviors in rodents; however, insufficient research has explored this hypothesis in humans. We examined photoperiod (i.e., day length) metrics during maternal pregnancy in relation to lifetime depression in the longitudinal Nurses' Health Study (NHS) and NHS II. 160,723 participants reported birth date and birth state (used to derive daily photoperiod based on published mathematical equations), and clinician-diagnosed depression and antidepressant use throughout adulthood. Logistic regression was used to estimate odds ratios (OR) (and 95% confidence intervals [CI]) for depression (defined as clinician diagnosis and antidepressant use) across quintiles of two exposures during maternal pregnancy: 1) total photoperiod (total number of daylight hours) and 2) differences between minimum/maximum photoperiod; each trimester of pregnancy was examined separately. Total photoperiod during maternal pregnancy was not associated with depression overall or by trimester of pregnancy. However, larger differences between minimum/maximum photoperiod during maternal pregnancy were related to lower odds of depression (multivariable [MV]-adjusted OR: 0.86, 95% CI: 0.83, 0.90 comparing extreme quintiles of exposure; p-trend < 0.0001); this association appeared specific to the second trimester of pregnancy (MV-adjusted p-trends = 0.03, < 0.0001, and 0.3 across the three trimesters, respectively). In addition, birth at higher latitude (where larger differences in minimum/maximum photoperiod exist) was associated with a significant reduction in the lifetime risk of depression. These findings are consistent with an emerging hypothesis in which perinatal light exposure may influence risk of depression, and they might be understood through the conceptual framework of adaptive developmental plasticity.

1. Introduction

Early-life factors, particularly during sensitive periods of brain development, influence the risk of neurodevelopmental disorders (Andersen, 2015; Bale et al., 2010). Historically, epidemiologic studies have identified birth season as an early-life factor with a modest association to psychiatric disorders, including depression (Disanto et al., 2012; Foster and Roenneberg, 2008; Joiner et al., 2002; Pfaff et al., 2006; Torrey et al., 1996, 1997); however, mechanisms underlying a potential association have remained elusive (Schnittker, 2018). Meanwhile, research in rodents has uncovered a link between perinatal day length (i.e., photoperiod) and subsequent risk of depressive phenotypes (Ciarleglio et al., 2011), leading to an emerging hypothesis that early-

life photoperiod may be an important predictor of depression and other psychiatric disorders.

In mice and hamsters, perinatal exposure to short, winter-like photoperiods produced more depressive- and anxiety-like behaviors than exposure to long, summer-like photoperiods (Green et al., 2015; Pyter and Nelson, 2006). Intriguingly, in mice, these effects were accompanied by changes in serotonin signaling in the brain, which represents a key element in the neurobiology of depression (Charney, 1998). Moreover, both signaling and behavioral effects were dependent on the melatonin 1 (MT1) receptor (Ciarleglio et al., 2011; Green et al., 2015), where the agonist melatonin is a hormonal regulator and primary molecular marker of the circadian system; melatonin secretion is entrained to the environmental light-dark cycle and acutely suppressed

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by light (Arendt, 2005). Maternal melatonin is known to freely cross the placenta during gestation (Tamura et al., 2008), in turn regulating the establishment of the fetal circadian system (Goldman, 2003) and development of the fetal adrenal gland and glucocorticoid signaling (Torres-Farfan et al., 2004, 2011), which are thought to play an important role in the programming of emotional behaviors (Ikeda et al., 2013). More recently, in mice, changes in photoperiod during the perinatal period have been shown to have enduring effects on serotonin signaling into adulthood (Siemann and McMahon, unpublished data). Taken together, accumulating evidence suggests that perinatal photoperiod may act through melatonin signaling to influence serotonergic pathways related to emotional behaviors, with implications for long-term risk of affective disorders.

In humans, recent epidemiologic studies of birth season and depression have produced less consistent evidence of an association compared to older studies (Park et al., 2016; Schnittker, 2018; Talarowska et al., 2018), and the vast majority of studies have ignored the potential influence of birth latitude (Disanto et al., 2012; Foster and Roenneberg, 2008; Joiner et al., 2002; Pfaff et al., 2006; Torrey et al., 1996, 1997). Indeed, there has been a specific call to evaluate the combined effects of birth season and birth latitude in relation to psychiatric disorders in large epidemiologic studies (Erren et al., 2012). Thus, in the present study, we examined photoperiod during maternal pregnancy (combining information on birth date and birth latitude) in relation to lifetime depression in the participant-offspring, utilizing existing information on > 160,000 women in the Nurses' Health Studies.

2. Methods and materials

2.1. Study population

The Nurses' Health Study (NHS) was established in 1976, when 121,701 U.S. female nurses, aged 30–55 years, returned a mailed questionnaire with information on demographics, health, lifestyle, and medication use (Colditz, 1995). In 1989, the NHS II was initiated among a younger generation of 116,430 female nurses, aged 25–42 years, using a similar questionnaire to obtain information about participants (Rich-Edwards et al., 1994b). These cohorts were established at Harvard, and their purpose is to evaluate risk factors for chronic conditions in women. Biennial questionnaires were used to update this information in both cohorts since their inception, and the response rate was $\geq 90\%$ at each questionnaire cycle. The Institutional Review Board of Brigham and Women's Hospital approved both studies, and informed consent was implied by participants' return of the cohort questionnaires.

2.2. Ascertainment of perinatal photoperiod

Participants reported their date of birth on the initial questionnaire in each cohort, and they subsequently reported their state of birth on the 1992 questionnaire in NHS and the 1993 questionnaire in NHS II. Based on this information, we estimated the day length (i.e., photoperiod) during the presumed maternal pregnancy period (i.e., beginning 280 days prior to the participant's birth date, as this represents the average length of human pregnancy) using mathematical equations published by the National Oceanic and Atmospheric Administration (Earth System Research Laboratory). We used the longitudinal coordinates of the center of population density for a participant's birth state to represent the location of the participant during gestation. With these assumptions, we created two main exposures of interest: total photoperiod during maternal pregnancy (a proxy for total duration of light exposure, in hours, of the participant's mother during pregnancy), which was calculated by summing the lengths of all 280 days across the pregnancy; and extreme differences in photoperiod during maternal pregnancy (a proxy for variation in light exposure during pregnancy),

which was calculated by subtracting the longest and shortest day lengths during gestation.

2.3. Ascertainment of depression

In NHS, women reported regular use of antidepressant medication for the first time in 1996, and their history of clinician-diagnosed depression in 2000; this information was updated on each subsequent biennial questionnaire. In NHS II, data collection was similar for these variables: antidepressant use was first assessed in 1997, and history of clinician-diagnosed depression was assessed in 2001, with updated information obtained on each follow-up questionnaire. Consistent with previous studies in NHS (Chocano-Bedoya et al., 2014; Lucas et al., 2014), we utilized this information to define depression in two ways: a strict definition (primary outcome) included women who reported clinician-diagnosed depression *and* regular use of antidepressant medication, and a broader definition (secondary outcome) included women who reported either clinician-diagnosed depression or regular use of antidepressant medication. Based on these definitions, the primary outcome should maximize specificity of the case definition and may reduce potential bias in risk estimates, whereas the secondary outcome should have greater sensitivity and detect a higher number of cases (e.g., as described in Lucas et al. (2011b)).

2.4. Ascertainment of suicide

We obtained most information on participant deaths from relatives and postal authorities, as well as by a search of the National Death Index for non-responders after each questionnaire cycle; these methods have been shown to identify approximately 98% of participant deaths in NHS (Rich-Edwards et al., 1994a). Study physicians who were unaware of exposure status reviewed death certificates to determine each participant's cause of death. Suicide was defined as all cases of suicide and self-inflicted injury or harm, as described by International Classification of Disease codes E950-E959 (United States Department of Health, 1965).

2.5. Ascertainment of covariates

Participants reported information on race, hair color (as a proxy for skin tone), and early-life socioeconomic indicators (mother's smoking status during pregnancy, parents' home ownership at time of participant birth, participant birth weight and history of being breastfed, and each parent's occupation during the participant's childhood) on biennial questionnaires.

2.6. Population for analysis

For these analyses, we focused on 224,974 women (116,911 in NHS and 108,063 in NHS II) who were born full term. We excluded 20,912 women (16,600 in NHS and 4312 in NHS II) who never reported information on depression status, and an additional 43,325 women (22,003 in NHS and 21,322 in NHS II) who did not report their state of birth; this left 160,737 participants (78,308 in NHS and 82,429 in NHS II) for our analysis of photoperiod during maternal pregnancy and lifetime depression in the participant-offspring.

2.7. Statistical analysis

We used birth year- and multivariable (MV)-adjusted logistic regression models to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for lifetime depression (defined according to both the stricter and broader definitions described above) across quintiles of total photoperiod and extreme differences in minimum/maximum photoperiod during maternal pregnancy; these exposures were also examined by trimester of maternal pregnancy. For each

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