HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

J Psychiatr Res. 2018 August ; 103: 156–160. doi:10.1016/j.jpsychires.2018.05.022.

Prospective study of chronotype and incident depression among middle- and older-aged women in the Nurses' Health Study II

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Abstract

Background—Prior cross-sectional studies have suggested that being a late chronotype is associated with depression and depressive symptoms, but prospective data are lacking.

Methods—We examined the association between chronotype and incident depression (defined as self-reported physician/clinician-diagnosed depression or antidepressant medication use) in 32,470 female participants of the Nurses' Health Study II cohort who self-reported their chronotype (early, intermediate or late) and were free of depression at baseline in 2009 (average age: 55 yrs). Women updated their depression status on biennial questionnaires in 2011 and 2013. We used multivariable (MV)-adjusted Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) for incident depression across chronotype categories (i.e., early, intermediate, and late chronotypes).

Results—Across a follow-up period of 4 years, we observed 2,581 cases of incident depression in this cohort. Compared to intermediate chronotypes, early chronotypes had a modestly lower risk of depression after MV adjustment (MVHR=0.88, 95%CI=0.81–0.96), whereas late chronotypes

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had a similar risk of 1.06 (95%CI=0.93–1.20); the overall trend across chronotype categories was statistically significant (ptrend<0.01). Results were similar when we restricted analyses to women who reported average sleep durations (7 to 8h/day) and no history of rotating night shift work at baseline.

Conclusions—Our results suggest that chronotype may influence the risk of depression in middle- to older-aged women. Additional studies are needed to confirm these findings and examine roles of both environmental and genetic factors to further our understanding of the role of chronotype in the etiology of mood disorders.

Keywords

morningness–eveningness; circadian rhythms; sleep; mood; mental health; shift work

Introduction

The past decade has provided increasing evidence for links between the circadian system and mood, including data linking non-visual photoreception pathways in rodents to impaired mood (LeGates et al., 2012), and the beneficial role of timed light exposure therapy and sleep deprivation on mood, likely by resetting circadian rhythms (McClung, 2007, 2013, 2015; A Wirz-Justice, 2003). Circadian rhythms regulate physiology and behavior – from gene expression and immune function to sleep and cognition – and the disturbance of those rhythms has also been put forward as one of the correlates of mood disorders (Wirz-Justice, 2006). The circadian system entrains to the light/dark cycle of the 24h day (Duffy & Wright, 2005; Pittendrigh, 1981; Roenneberg & Merrow, 2007) and thereby gives rise to an individual's chronotype, with genetic variation being at least in part contributing to inter-individual differences in chronotype (Roenneberg, Kuehnle, et al., 2007). This phenotype has also been shown to be associated with e.g. the period length of circadian clock gene expression in human fibroblasts (Brown et al., 2008). And while the implications of the circadian system and circadian photoreception pathways with mood seem established, it is unclear to what extent inter-individual differences in chronotype per se are linked to depression.

Previous work has mainly relied on cross-sectional data sets, with limited information on potential confounding factors. One of the largest datasets, FINRISK, included behavioral information on an established scale of Morningness/Eveningness (Horne & Ostberg, 1976) that correlates well with other proxies for chronotype, such as sleep timing (Kitamura et al., 2014; Zavada et a., 2005) or dim light melatonin onset (Kantermann et al., 2015; Megdal & Schernhammer, 2007; the key circadian phase marker; Arendt, 2006); the FINRISK analysis showed that morningness was associated with lower levels of depressive symptoms, and lower odds of diagnosed depression and anti-depressant medication use (Konttinen et al., 2014; Merikanto et al., 2013, 2015). Studies around the world, in adult and adolescent populations have reported similar findings (Alvaro et al., 2014; Chan et al., 2014; de Souza & Hidalgo, 2014; Hidalgo et al., 2009; Jeong Jeong et al., 2015; Kitamura et al., 2010; Levandovski et al., 2011; Pabst et al., 2009), independent of whether they used sleep timing or morningness/eveningness as a proxy for chronotype. Patients with major depressive disorder have been reported to be more likely to be late chronotypes, as compared to

individuals suffering from dysthymia or anxiety disorders. Those results suggest that depression might also alter an individual's chronotype (Antypa et al., 2016; Lemoine et al., 2013; Müller et al., 2015; Selvi et al., 2010), or possibly that changes in chronotype is related to depression severity. Indeed, recent findings in adolescents show no significant differences in chronotype between healthy controls and patients with remitted depression (Keller et al., 2017). Prospective analyses are crucial to to better understand the directionality of the association of chronotype with depression, and the present study addresses this gap. We hypothesized that late chronotypes would be at higher risk and early chronotypes would be at lower risk for incident depression as compared to intermediate chronotypes.

Methods

The Nurses' Health Study II (NHSII) is a large, prospective cohort study of women's health, which started in 1989 when 116,434 registered US nurses (aged 25 – 42 years) responded to a baseline questionnaire. Biennial follow-up questionnaires have since been mailed to obtain updated information on medical history, lifestyle factors, and newly diagnosed diseases. Follow-up rates are high with approximately 90% participation at each two-year cycle (Schernhammer et al., 2011). This study was approved by the Brigham and Women's Institutional Review Board (IRB), and responding to the self-administered questionnaire was considered to constitute informed consent.

Chronotype Assessment

Chronotype was queried with a single question on the NHSII main questionnaire in 2009 using question 19 from the Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976): 'One hears of morning and evening types of people. Which one of these types do you consider yourself to be?' Response categories included: 'Definitely a morning type', 'Rather more a morning than an evening type', 'Rather more an evening than a morning type', 'Definitely an evening type' and 'Neither'. This single-item measure of chronotype correlates well with the overall score of the MEQ (r=0.72) (Megdal & Schernhammer, 2007), sleep timing (Kitamura et al., 2014; Zavada et al., 2005) and dim light melatonin onset (Kantermann et al., 2015) – the gold standard of human circadian phase markers (Arendt, 2006).

Ascertainment of Depression Cases

In this study, depression assessment in the NHSII relies on self-report of antidepressant medications and/or physician/clinician diagnosis. Questions on regular antidepressant use were assessed biennially since 1997. In 2001, women were asked if they ever had physician-diagnosed depression, with subsequent biennial updates. Incident depression was defined as the first occurrence of self-reported clinical indicators of depression (i.e., physician/clinician-diagnosed depression or regular antidepressant use) as in previous work (Pan et al., 2012). We only included selective serotonin reuptake inhibitors (SSRIs) in our outcome definition, as prior work had shown that tricyclic antidepressants are more likely prescribed for other indications during this period (Okereke et al., 2015).

Assessment of Covariates

Women were asked every two years from 1989 onwards to provide updated information on their medical history and chronic disease risk factors, such as body weight, physical activity, diet, smoking, and menopausal status. Alcohol consumption was calculated based on a food frequency questionnaire collected in 2007, and updated in 2011. Habitual sleep duration was ascertained in 2001 and 2009. Rotating night shift work (i.e., duration that women worked ≥3 night shifts/month) exposure was assessed at baseline in 1989, and was then continuously updated throughout follow-up. In 2009, women responded to a retrospective assessment of work schedules, so that we could identify ever and current permanent night shift workers.

Population for Analysis

We excluded all women from the analyses who i) did not answer the chronotype question, and ii) reported physician/clinician-diagnosed depression or antidepressant medication use prior to or in 2009. In addition, we also assessed depressive symptoms using five-item Mental Health Inventory (MHI-5), a subscale of the Short-Form 36 Health Status Survey (Ware & Sherbourne, 1992, Ware et al., 1994), in 1993, 1997, and 2001. Thus, for this analysis of incident depression, we also excluded all women who either reported having symptoms prior to baseline (i.e., below the validated cutoff for clinical depression, Berwick et al., 1991) or were missing MHI-5 information. After exclusions, our sample for analyses comprised 32,470 women. Follow-up started in 2009 and ended in 2013.

Statistical Analyses

We defined definite morning types as ‘early chronotypes’, definite evening types as ‘late chronotypes’, and others as ‘intermediate chronotypes’, and used Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (95%CI) across the three chronotype categories. Intermediate chronotypes served as the referent group in all analyses. We included the following covariates in multivariable (MV) adjusted models: menopausal status (pre/post-menopausal), marital status (never married, married or with partner, previously married), living situation (alone or with partner/kids), census-tract household income (in tertiles), retirement status (yes or no), smoking status (never smoker, past light/moderate smoker [1–24 cigarettes/day], past heavy smoker [≥25 cigarettes or unknown/day], current light/moderate smoker [1–24 cigarettes/day], current heavy smoker [≥25 cigarettes or unknown/day]), physical activity (MET-hours/week; in quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, ≥15g/day), body mass index (kg/m2, ≤25, 25–29.9, ≥30), sleep duration (in h/day, ≤5, 6, 7, 8, ≥9), and predicted vitamin D levels (in quintiles, (Bertrand et al., 2012)). Secondary analyses used a stricter case definition that required individuals to report both physician/clinician-diagnosed depression and antidepressant medication use (Lucas et al., 2011). To address concerns of reverse causation, we restricted sensitivity analyses to women who i) remained within a healthy range of habitual sleep duration of 7–8 hours; ii) never reported rotating night shift work with three of more night shifts per month; iii) MHI-5 scores lower than 75 in 2009. The shift work sensitivity analysis was additionally restricted to women who did not report current or past permanent night shifts work. We thereby aimed to minimize the number of women in the analyzes with unreported depression.

We report trends across chronotype categories on an ordinal scale (from earlier to later) based on the Wald statistic, and consider p-values of 0.05 as thresholds for statistical significance. All analyses were conducted with SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Across four years of follow-up, we observed 2,518 cases of incident depression. Table 1 shows the baseline characteristics of women free of depression and depressive symptoms at baseline in 2009. Late chronotypes were less likely to be married, and more likely to live alone, to be smokers, and more frequently reported extreme sleep durations.

In age-adjusted models, early chronotypes had a significantly reduced risk of depression as compared to intermediate types (Table 2, HR=0.86, 95%CI=0.79–0.93), which remained similar after MV adjustment (MV HR=0.88, 95%CI=0.81–0.96). In contrast, late chronotypes were at slightly higher risk of depression (HR=1.13, 95%CI=1.00–1.29), but this estimate was attenuated such that their risk was no longer different from intermediates chronotypes (MVHR=1.06, 95%CI=0.93–1.20). Overall, there was a significant linear trend of increasing depression risk across early, intermediate, and late chronotype categories (MV-adjusted p-trend=0.0009). When we adopted a stricter case definition (i.e., physician/clinician-diagnosed depression and anti-depressant medication use, 570 cases), results were similar for late chronotypes (MVHR=1.08, 95%CI=0.82–1.42), but attenuated for early chronotypes (MVHR=0.99, 95%CI=0.82–1.18, MV-adjusted ptrend=0.61).

In sensitivity analyses, we first restricted the analytic sample to women who had a history of sleep durations in the healthy range of 7 or 8 hours (N=17,702, Table 2). Patterns were consistent with the main analyses, although statistical tests did not reach significance in MV models. Finally, we also excluded women with a history of rotating night shift work (i.e., any duration that women worked at least three night shifts per month in addition to morning and evening shifts). In this small sample of 9,701 women, in which power was expected to be reduced, definite early chronotypes had a 27% lower risk of depression as compared to intermediate chronotypes (MVHR= 0.73, 95%CI=0.62–0.86), whereas definite late chronotypes were comparable to intermediate types in their risk of incident depression (MVHR=0.94, 95%CI=0.72–1.21, ptrend=0.002). Additional exclusion of ever or current permanent night shift workers did not change our results. Finally, we also excluded women with an MHI-5 score ≤75, implementing a more conservative baseline exclusion criterion. In the resulting sample of 15,669 women (884 cases), results were similar to our main analysis; specifically, compared to intermediate chronotypes, early chronotypes had a reduced depression risk (MVHR=0.86, 95%CI=0.74–1.00) and late chronotypes had an elevated risk (MVHR=1.15, 95%CI=0.92–1.44). Although statistical tests comparing early and late chronotypes with intermediate chronotypes were not significant, the continuous trend across chronotype categories was statistically significant (MV-adjusted ptrend=0.007).

Discussion

In this study of more than 30,000 middle-aged and older women, chronotype was associated with incident depression, even after accounting for potential confounders of the association. Sensitivity analyses excluding women with potentially disturbed circadian rhythms, such as shift workers or women who had a history of extreme sleep durations, similarly showed that early chronotypes were at lower risk of newly-occurring depression, as compared to intermediate. Thus, our findings indicate that chronotype may be related to the development of mid- to later- life depression independent of other health and lifestyle factors.

Our study contributes to the existing literature in several ways: First, the majority of the conducted studies have relied on cross-sectional examinations of the association between chronotype and depressive symptoms (Alvaro et al., 2014; Levandovski et al., 2011; Merikanto et al., 2013, 2015; Pabst et al., 2009). As for all cross-sectional study designs, this approach bears a risk of reverse causation, i.e. depressive symptoms could influence chronotype. Thus, the advantage of our prospective approach is that – while we cannot establish causal relationships with observational data – we could exclude all women at baseline that already had reported depressive symptoms or physician-diagnosed depression and thereby examine the temporal association of chronotype with depression. In addition, we conducted a series of sensitivity analyses further designed to minimize the likelihood of reverse causation bias. Second, estimates in this study were only slightly attenuated when we included potential confounders of the association between chronotype and depression in our models. This suggests, that at least in middle- to older age women, individual variation in chronotype per se is associated with depression. This novel finding points towards a potential overlap in genetic pathways, which could be explored in future work. Indeed, chronotype is heritable (12–42%), as has been reported by twin and family studies (Gottlieb et al., 2007; Heath et al., 1990; Klei et al., 2005, Von Schantz et al., 2015), and candidate gene association studies reported that diurnal preference measures were associated with CLOCK, PER1, PER2 and PER3 genes (Allebrandt & Roenneberg, 2008). Furthermore, a recent study in more than 2,000 older adults reported that clock gene variants in PER3 and RORA were associated with depressive symptoms (Maglione et al., 2015). However, field and population studies have shown that photoperiod and its changes across season and geographical locations, as well as work- and outdoor-light exposure are associated with circadian phenotypes and sleep timing (Keller et al., 2017, Leocadio-Miguel, et al., 2017, Roenneberg et al., 2007, Stothard et al., 2017, Vetter et al., 2011); such findings suggest that chronotype is at least in part modifiable. The observation that earlier chronotypes have lower risk of depression also indicates that interventions that can advance individual phase of entrainment, such as timed bright light exposure, might be considered for prevention and intervention studies.

While this is the first and largest study of chronotype and incident depression so far, our study also has several limitations. First, we only examined associations in middle to older age, as chronotype was only collected in 2009 in NHSII. Prevalence of depression however is higher in women as compared to men, and case rates are still high in this age group (Kessler et al., 2005). Second, no objective measures of chronotype were available in this cohort, although the assessment used here has been shown to correlate well with sleep

timing and dim light melatonin onset (Kitamura et al., 2014; Megdal & Schernhammer, 2007), a key marker of the human circadian system. Finally, while depression was self-reported, rates were comparable to those reported in other large patient registries and cohort studies (Moore et al., 2009, Norton et al., 2006). While misclassification might still be possible, it is not likely to differ by chronotype, and would therefore bias towards the null.

Overall, our findings suggest that chronotype is a predictor of depression among mid-life and older women, independent of environmental and lifestyle factors. Future studies are warranted, especially to further elucidate the interrelationship between circadian phenotypes, genetics, and mood disorders.

Acknowledgments

Funding: This work was supported by Center for Disease Control and Prevention/The National Institute for Occupational Safety and Health grants 5R01OH009803 and 5R21OH011052. The Nurses' Health Study II is supported by the National Cancer Institute grant UM1CA176726.

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Table 1

Age and age-adjusted characteristics of 32,470 women in the Nurses' Health Study II by chronotype at baseline (2009). yr = year, h=hour, MET = Metabolic Equivalent of Task. Values are either mean (standard deviation) or percentages.

	Early type	Intermediate type	Late type
Sample Size	12,261	17,073	3,136
Age, yr	55.0 (4.6)	55.0 (4.7)	55.0 (4.7)
Married or with partner	85	84	78
Living alone, %	9	9	14
Household income (census-tract level)	66,626 (24,545)	66,413 (24,127)	66,135 (23,392)
Retired (yes), %	18	17	20
Smoking status, %			
Never smoker	70	70	66
Past smoker	26	26	27
Current smoker	4	4	7
Pack-years of smoking[1]	29.1 (15.2)	27.9 (14.8)	32.0 (16.5)
Physical activity, MET-hr/week	28.9 (32.6)	24.3 (27.8)	26.5 (11.8)
Alcohol consumptions, g/d	6.7 (10.1)	6.3 (9.6)	5.7 (10.0)
Body mass index, kg/m^2	26.3 (5.6)	27.0 (6.0)	28.6 (6.8)
Cumulative night shift work, yrs	3.2 (4.3)	3.3 (4.4)	4.1 (5.1)
Usual sleep duration, h/day			
5	4	4	6
6	20	20	25
7	40	41	34
8	30	28	24
≥ 9	3	3	6
Post-Menopausal, %	69	68	68
Predicted 25-hydroxyvitamin D (ng/ml)[2]	32.0 (4.0)	32.5 (4.1)	30.5 (4.1)
History of cancer, %	10	9	9
History of myocardial infarction, %	1	1	1
History of type 2 diabetes, %	4	5	8

[1] Among past and current smokers.

[2] Betrand et al. (2012). British Journal of Nutrition, Volume 108(10), pp. 1889–1896.

Table 2

Association of Chronotype and Incident Depression in the Nurses' Health Study II (N=32,470, 2009–2013). HR= Hazard Ratios, 95%CI= 95% confidence intervals. MV=multivariable, HR=Hazard Ratio, CI=confidence interval.

	Cases	Person/years	Age-adjusted Model		MV Model*	
			HR	95% CI	HR	95% CI
Chronotype						
Early type	872	44,483	0.86	0.79, 0.93	0.88	0.81, 0.96
Intermediate type	1,419	61,411	1.00 (ref)		1.00 (ref)	
Late type	290	11,164	1.13	1.00, 1.29	1.06	0.93, 1.20
			p_{trend}# < 0.0001		p_{trend}# = 0.0009	
Sensitivity analysis restricting to women who usually slept 7–8h/day in 2001 and 2009 (N=17,702, 2009–2013)						
Early type	510	25,296	0.92	0.82, 1.03	0.94	0.84, 1.06
Intermediate type	756	33,967	1.00 (ref)		1.00 (ref)	
Late type	126	4,862	1.19	0.98, 1.44	1.13	0.93, 1.37
			p_{trend}# = 0.02		p_{trend}# = 0.08	
Sensitivity analysis restricting to women, who never worked shiftwork (N=9,701)						
Early type	231	13,330	0.73	0.62, 0.85	0.73	0.62, 0.86
Intermediate type	440	18,749	1.00 (ref)		1.00 (ref)	
Late type	71	3,021	1.00	0.78, 1.29	0.94	0.72, 1.21
			p_{trend}# = 0.0003		p_{trend}# = 0.002	

*Adjusted for menopausal status (pre/post-menopausal), marriage (never married/married or partnership/was married), living situation (living alone/living with partner or kids), census-tract based household income (in tertiles), retirement status (retired, yes/no), smoking status (never smoker, past light/moderate smoker [1–24 cigs per day], past heavy smoker ≥ 25 cigs per day, past smoker with unknown no. of cigs, current light/moderate smoker [1–24 cigs per day], current heavy smoker [≥25 cigs per day] or current smoker with unknown no. of cigs), physical activity (in quintiles), body mass index (≤25, >25 but <30, ≥30 kg per m^2), sleep duration (≤5/6/7/8/≥9h per day), predicted Vitamin D levels (in quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, ≥15g/day), cancer (yes/no), myocardial infarction (yes/no), type 2 diabetes (yes/no).

#P-values for trends are based on a linear trend test using chronotype continuously (early =1, intermediate=2, and late =3).