Research Article

CHRONOTYPE ASSOCIATIONS WITH DEPRESSION AND ANXIETY DISORDERS IN A LARGE COHORT STUDY

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Background: ***The chronotype, being a morning or an evening type, can influence an individual's psychological health. Studies have shown a link between depressed mood and being an evening type; however, most studies have used symptom scales and not diagnostic criteria, and confounding factors such as sleep patterns and somatic health factors have often not been considered. This study aims to examine the association between chronotype and depressive (major depressive disorder (MDD), dysthymia) and anxiety (generalized anxiety disorder, panic disorder, agoraphobia, and social phobia) disorders diagnosed using clinical interviews, while taking into account relevant sociodemographic, clinical, somatic health, and sleep parameters.*** **Methods:** ***Data from a large cohort, the Netherlands Study of Depression and Anxiety were used (n = 1,944), which included 676 currently depressed and/or anxious patients, 831 remitted patients, and 437 healthy controls. Chronotype was assessed using the Munich Chronotype Questionnaire.*** **Results:** ***Our results showed that current depressive and/or anxiety disorders were associated with a late chronotype (β = .10, P = .004) even when adjusting for sociodemographic, somatic health, and sleep-related factors (β = .09, P = .03). When examining each type of disorder separately, MDD only, but not dysthymia or specific anxiety disorders, was associated with the late chronotype. The late chronotype also reported significant diurnal mood variation (worse mood in the morning).*** **Conclusions:** ***Our findings show a clear association between MDD and late chronotype (being an evening type), after controlling for a range of pertinent factors. A late chronotype is therefore associated with a current status of MDD and deserves the relevant clinical attention when considering treatments. Depression and Anxiety 00:1–9, 2015.*** *© 2015 Wiley Periodicals, Inc.*

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INTRODUCTION

Circadian rhythms vary across individuals. Circadian typology consists of three chronotypes: morning type, evening type, and intermediate type.[1] People in either extreme category prefer to perform physical and mental activities at the respective time of day, i.e. morning types in the morning and evening types in the evening. About 40% of the population can be classified as either morning or evening type.[1] The "biological clock" (suprachiasmatic nuclei (SCN) and its network) is involved mainly in the regulation of the timing of both sleep and wakefulness,[2] and is influenced by many factors like genes, peripheral hormones, and peptides as well as environmental factors like light and stress.[3] The biological clock network affects wake-behavior and consequently a person's chronotype.[4] In order to assess chronotypes, the most used measure is the Morningness-Eveningness Questionnaire (MEQ),[5] but more recently, the Munich Chronotype Questionnaire (MCTQ) has been developed, which distinguishes sleep behavior in the work days and free days.[6] The MCTQ correlates with the MEQ ($r = -0.73$).[7]

There is accumulating research showing that circadian rhythmicity influences a person´s psychological health. Specifically, the evening type has been associated with depression in a number of studies. Drennan et al.[8] initially showed that depressed patients showed more eveningness than controls and a number of studies thereafter have demonstrated an association between eveningness and depressive mood.[9–12]

Sleep disturbances, often present in depressive disorders, have also been associated with chronotypes. Hypersomnia is more common in the evening chronotype[13] and eveningness and insomnia were recently found to predict nonremission in depressed patients.[14] However, sleep problems may not be the sole factor explaining the link between circadian typology and depression. A study designed to examine whether sleep problems (daytime sleepiness, insomnia) mediate the association between eveningness and negative emotionality, found that eveningness was an independent risk factor.[15] Eveningness was also associated with increased severity and suicidal thoughts in depressed patients ($n = 100$), whereas no association was found with sleep parameters in this group.[16] Another study showed that eveningness was associated with an increased risk of suffering from depressive states (OR = 1.96), even after adjusting for sleep-related factors.[10]

Diurnal mood variation is one of the characteristics of the melancholic subtype of depression and like many physiological variables it has a circadian pattern and is influenced by sleep.[17] In the STAR*D trial, diurnal mood variation was reported by approximately one-fourths of depressed participants and was not attributed to environmental factors for the majority of subjects.[18] Morning and evening worsening of mood were the most common features, and both related to additional melancholic symptoms in that sample.[18] Chronotype information was not reported so we lack information in large cohorts about how mood varies according to diagnostic status and chronotype. Other studies have reported irregularity and variation in frequency of mood fluctuations in depressed samples[19,20] with a delay in a positive affect increment during the day compared to healthy controls.[20,21] In an insomniac sample, evening types also reported lower positive affect than morning types, and differences were more pronounced in the morning and afternoon hours.[22]

Less is known about the association between chronotypes and anxiety disorders and results are mixed. In college samples, evening types reported more anxiety symptoms.[23,24] In a large in-patient sample ($n = 1468$), anxiety was associated with eveningness.[25] However, in an adolescent sample the evening chronotype was not associated with anxiety disorders,[26] and also in a large cohort of adult fibromyalgia patients, chronotype was not related to anxiety.[27]

Other factors that have been related to chronotypes and often also to psychopathology include somatic health factors, such as dietary intake, body mass index (BMI), smoking behavior, and alcohol use.[1,28,29] Evening types have been associated with an increased BMI[30–32] but also with lower BMI[33] and no differences between groups have also been reported[34] Increased smoking and alcohol behaviors are also observed in evening types compared to morning ones.[35–38] Increased smoking among late (evening) types has been suggested to be a consequence of "social jetlag," namely, the discrepancy between biological and social rhythms (work day vs. free day schedules),[39] emphasizing the need to adjust these schedules in order to reduce such maladaptive behaviors.

In sum, people's chronotype may influence their vulnerability to psychopathology. Although a number of studies show an association between depression-related outcomes and the evening chronotype, large representative samples are lacking to confirm this association and only few studies have examined anxiety disorders. Most studies have based their findings on symptom checklists rather than clinical diagnoses[9–12], [27] and many lack information on additional factors that are known to influence chronotypes, such as somatic health factors, sleep parameters, or medication use. This study aims to examine the association between chronotypes and the presence of depressive and anxiety disorders (using clinical diagnostic instruments) in a large cohort, while taking into account relevant sociodemographic, somatic health, and sleep factors. Moreover, we examined whether

chronotypes are associated with a remitted state of these disorders, as well as with which specific type of depressive or anxiety disorder an association can be observed.

METHODS

PARTICIPANTS

Participant data for the present study came from the Netherlands Study of Depression and Anxiety,[40] a longitudinal cohort study, which follows the course of depressive and anxiety disorders ($n = 2{,}981$ at baseline). A detailed description of the study's rationale, methods, and recruitment strategies has been described elsewhere.[40] In brief, participants were recruited from the general community ($n = 564$), from general practice (primary care) ($n = 1{,}610$), and from mental health organizations ($n = 807$), this way composing a representative sample from different settings and developmental stages of psychopathology. From primary care, data from 65 general practitioners were obtained and a three-stage screening procedure was followed (including a questionnaire and phone screenings). The community sample was built from two cohorts that were already available from prior studies (the Netherlands Mental Health Survey and Incidence Study which used a multistage, stratified sampling procedure of a random sample of private households in 90 Dutch municipalities and the Adolescents at Risk for Anxiety and Depression study). Recruitment from mental health care included outpatient clinics, where participants were mainly selected on the basis of structured intake interviews. Recruitment of the baseline assessment took place from September 2004 and ended in February 2007. In September 2006 the two-year assessment began. The main inclusion criterion was an age of 18 through 65 years. The study had few exclusion criteria: a primary diagnosis of psychotic, obsessive compulsive, bipolar, or severe addiction disorder and not being fluent in Dutch.The ethical committees of all participating institutes approved the research protocol and all respondents provided written informed consent.

Data from participants who participated at both baseline and the 2-year follow-up assessments were included for this study. Of the 2,981 participants assessed at baseline, 2,596 (87.1%) participated in the 2-year follow-up; nonresponders were more likely to be younger, with lower education and with a depressive disorder.[41] The chronotype measurement and all covariates were assessed at the 2-year measurement and lifetime status of psychopathology was determined using baseline and 2-year follow-up data (data from both time points were required to classify psychopathology and healthy groups).

MEASURES

Chronotype. Chronotype was assessed with the Munich Chronotype Questionnaire (MCTQ, [6]). The MCTQ is a self-report questionnaire, which contains 29 questions about times of waking up and falling asleep on work days and on free days. Chronotype has been defined as the midpoint in time between falling asleep and waking up on free days (Mid Sleep on Free Days (MSF)), since it is most likely to be accurate when one's natural circadian rhythm can be observed, without the interference of work schedules and alarm clocks.[6,42] Therefore, the measure relies only on the sleep-wake cycle (wake-onset and sleep-onset), which is in turn dictated by circadian clock processes such as body temperature.[43] A higher time point on the MSF implies a later chronotype (evening type) and a lower time point implies an earlier chronotype (morning type). However, for late chronotypes, sleep duration during the workdays may be decreased due to working schedule demands and compensated for during the free days, therefore a "sleep debt" is accumulated, leading to a much higher MSF. An improved measure has been developed, namely, the midsleep on free days corrected for the sleep-debt accumulated during the work week (MSFsc).[6] This is calculated by subtracting from the MSF half of the difference between sleep duration on free days and average total sleep duration (see supplement of[44] for correction algorithm). For our analyses, we used this more sophisticated outcome (MSFsc) to measure chronotype as a continuous trait; the correlation between MSF and MSFsc was $r = .91$, $P < .001$ in our sample. We also performed some exploratory analyses using categories ("early," "intermediate," or "late" chronotypes) for descriptive purposes. Categorization was based on quintiles of the MSFsc score, where early chronotype was the first quintile (lowest score), intermediate chronotype consisted of the 2nd, 3rd, and 4th quintiles, and the late chronotype was the fifth quintile (highest score) (as previously reported).[27,29]

Psychopathology. Depressive (major depressive disorder (MDD) and dysthymia) and anxiety (social phobia, generalized anxiety disorder, panic disorder, and agoraphobia) disorders were determined using the Composite International Diagnostic Interview (both at baseline and 2-year follow-up) (CIDI; version 2.1), a standardized diagnostic psychiatric interview that uses DSM-IV criteria to establish diagnoses.[45] Participants were categorized as follows: no lifetime depressive or anxiety disorder (as derived from baseline and 2-year measurement), current depressive and/or anxiety disorder (diagnosis present during the past six months, as derived from the 2-year measurement) or remitted disorder (past depressive and/or anxiety disorder, no current disorder in past six months) (as derived from baseline and 2-year measurement).

Other Clinical Characteristics. At the 2-year measurement, severity of depressive symptoms was measured with the Inventory of Depressive Symptoms (IDS), a 30-item self-report questionnaire.[46] Diurnal mood variation (DMV) was measured with the IDS item 9a: "Mood in relation to the time of day": (i) "There is no regular relationship between my mood and the time of day"; (ii) "my mood often relates to the time of day because of environmental events (e.g. being alone, working)"; (iii)"in general, my mood is more related to the time of day than to environmental events"; (iv) "my mood is clearly and predictably better or worse at a particular time each day." Participants who chose (iii) or (iv) were subsequently asked item 9b: Is your mood typically worse in the morning, afternoon or night? We coded diurnal mood variation as: (1) mood not related to time of day; (2) mood worse in the morning; (3) mood worse in the afternoon/night. Severity of anxiety symptoms was measured with the Beck Anxiety Inventory (BAI).[47] Antidepressant and benzodiazepine use in the past month was classified according to the World Health Association's Anatomical Therapeutic Chemical Classification System (ATC). Antidepressants were categorized as selective serotonin reuptake inhibitors (SSRIs, ATC code NO6AB), tricyclic antidepressants (TCAs, ATC code NO6AA), and other antidepressants (ATC codes N06AF and N06AX). For benzodiazepines ATC codes NO5BA, NO5CF, NO5CD, and NO3AE were used if indicated use was frequent (≥50% of the days during past month).

Covariates. Sociodemographic factors (assessed at the 2-year measurement) that were associated with both chronotype and with psychiatric disorders included age, gender, education (in years), working status, having a partner and having children living in the household. Somatic health factors such as BMI, smoking, alcohol intake, and chronic diseases have been associated with chronotypes[1,28] and were also considered in our analyses. BMI was calculated as weight in kilograms divided by height in meters squared. Smoking was based on self-report (currently smoking: yes/no). For alcohol consumption, we used the Alcohol Use Disorder Identification Test (AUDIT), which consists of 10 items measuring frequency and quantity of drinking as well as dependency symptoms.[48] The following self-reported chronic diseases for which participants received treatment were assessed: chronic nonspecific lung disease, heart condition, diabetes, stroke, arthritis, cancer,

hypertension, intestinal disorders, and thyroid gland disease; a total number of diseases was recorded. Insomnia and sleep duration were taken into account in our analyses, since both have been linked to depressive and anxiety disorders in NESDA.[49] Insomnia was measured with the Women's Health Initiative Insomnia Rating Scale (IRS)[50] that consists of five questions concerning sleep (trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up and sleep quality) during the past four weeks. Average sleep duration in hours per night was calculated from the MCTQ and was used as a continuous measurement.

Statistical Analyses. Data were analyzed using IBM SPPS Statistics 21.0 (SPSS Inc, Chicago, Illinois). Sociodemographic and clinical characteristics were compared between chronotype categories (early, intermediate, and late). Correlations between MSFsc and sleep duration were calculated using Pearson's Correlation coefficient. Linear regression analyses were performed with MSFsc (continuous score) as the outcome variable and psychopathology (categories) as main predictor variables. First, we adjusted for sociodemographic variables (age, gender, education, and employment, having a partner and having children in the household). Second, in addition to previous covariates, we adjusted for somatic health factors (BMI, chronic diseases, smoking, and alcohol) and for sleep variables (insomnia and sleep duration). In a regression model, we also examined to what extent diurnal mood variation and specific type of depressive/anxiety disorder are associated with chronotype, considering other covariates (age, gender, and psychotropic drugs).

RESULTS

PARTICIPANT FLOW

Of the 2,596 individuals participating in the 2-year interview, 269 did not fill out the MCTQ. Of the remaining 2,327 participants, 1,944 participants had sufficient data for the computation of our main outcome: midsleep on free days, adjusted for sleep-deficit on working days (MSFsc).

SAMPLE DESCRIPTION

The total sample ($n = 1{,}944$) had a mean age of 42.8 $\pm$ 12.7, with a range from 19 to 68 years old, and 66.3% ($n = 1{,}289$) were females. The mean MSFsc was 4.03 $\pm$ 1.03, with a range from 0.91 to 9.81. For descriptive purposes, Table 1 shows the baseline characteristics of the sample stratified by chronotype groups: early (MSFsc range: 0.91–3.25), intermediate (MSFsc range: 3.26–4.79), and late chronotypes (MSFsc range: 4.80–9.81). Late chronotypes were younger, less likely to be female, had more years of education, were less likely to be working and less likely to have a partner or children. With regard to psychopathology, late types were more likely to belong to the currently depressed and/or anxious group and depression and anxiety severity were higher in the late group. With regard to diurnal mood variation, the late chronotype was more likely to state that their mood was related to the time of day, reporting worse mood in the morning. Use of antidepressant medication did not differ between the three chronotype groups. Early types were more likely to frequently use benzodiazepines compared to the intermediate and late chronotype groups. Differences in sleep problems were also found between chronotype groups, with lower prevalence of insomnia in the late type group compared to the early type. Average sleep duration was slightly higher in the late group. Of note, correlations between MSFsc and sleep duration were weak ($r = .09$) indicating that the two constructs can be seen as independent. BMI was slightly lower in late types, and the morning type had a higher mean number of chronic diseases. Late types were more likely to be smokers and scored higher on the alcohol use measure (AUDIT).

ASSOCIATION BETWEEN CHRONOTYPE AND PSYCHOPATHOLOGY

Multiple regression analyses with MSFsc as continuous outcome were performed (Table 2). In model 1, we examined the association between chronotype and psychopathology status, adjusting for socio-demographic variables. All sociodemographic characteristics were significant predictors. Individuals with current depressive and/or anxiety disorders had a later chronotype; results for individuals with remitted disorders were similar but did not reach statistical significance. In model 2, additional somatic health factors and sleep factors were entered as competing predictors. Current smokers and alcohol users had a later chronotype, whereas insomnia was less likely as chronotype increased. Current depressive and/or anxiety disorders remained a significant predictor of a later chronotype in the adjusted model (Table 2), which was not the case for remitted depressive and/or anxiety disorders. We briefly examined demographic and clinical differences between the current psychopathology group, remitted group, and healthy group (Supporting Information Table S1). In short, there were no age differences between the groups (which is important to note, since age is strongly related to chronotype).[42,51] As expected, the current psychopathology group also reported higher depressive and anxiety symptoms, as well as more diurnal mood variation compared to the other groups.

We subsequently examined which specific depressive and anxiety disorders are associated with chronotype (Table 3). A regression model, with age and gender as covariates showed that only MDD ($\beta = .07$, $P = .006$) was a significant predictor of chronotype; individuals with current MDD had an increased chance of having a later chronotype. Dysthymia and all anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, and generalized anxiety disorder) were not significant predictors of chronotype (P's $> .05$). In a second model, we also added diurnal mood variation and psychotropic drug use indicators to the model. Current MDD remained the only significant type of disorder predicting chronotype ($\beta = .05$, $P = .04$). Psychotropic medication was not associated with chronotype. Diurnal mood variation was predictive of chronotype, specifically, those who reported worse mood in the morning had a later chronotype ($\beta = .12$, $P < .001$).

TABLE 1. Socio-demographic, clinical, and health characteristics according to chronotype groups (n = 1,944)

	"Early" Chronotype (n = 409)	*"Intermediate" Chronotype* (n = 1,148)	*"Late" chronotype* (n = 387)
Chronotype (MSFsc), range (hours)	0.91–3.25	3.26–4.79	4.80–9.81
Chronotype (MSFsc) (mean ± SD)	2.81 ± 0.42	3.96 ± 0.41	5.59 ± 0.81
Socio-demographics			
Age (M years ±SD)	45.8 ± 11.9	43.2 ± 12.5	38.3 ± 13.2
Female gender, N (%)	67.0%	68.6%	58.7%
Education (M years ±SD)	11.9 ± 3.3	13.2 ± 3.2	13.1 ± 3.2
Currently working, N (%)	295 (73.2%)	840 (74.7%)	253 (66.8%)
Partner present, N (%)	301 (88.8%)	685 (81.5%)	164 (71.6%)
Presence of children in the household, %	183 (54.0%)	400 (47.6%)	67 (29.3%)
Clinical characteristics			
Psychopathology status N(%)			
-no lifetime depression or anxiety	99 (24.2%)	272 (23.7%)	66 (17.1%)
-remitted depression or anxiety	171 (41.8%)	510 (44.4%)	150 (38.8%)
-current depression or anxiety (past six months)	139 (34.0%)	366 (31.9%)	171 (44.2%)
Depression severity (total IDS; M ± SD)~	15.66 ± 12.37	13.97 ± 10.73	16.85 ± 12.24
Anxiety severity (BAI; M ± SD)	8.51 ± 8.94	7.37 ± 7.49	9.09 ± 8.82
Diurnal Mood Variation			
Mood not related to the time of day	313 (77.9%)	841 (74.9%)	244 (64.4%)
Mood worse in the morning	39 (9.7%)	146 (13.0%)	88 (23.2%)
Mood worse in the afternoon/evening	50 (12.4%)	136 (12.1%)	47 (12.4%)
Use of antidepressants, N (%)			
-SSRI	46(11.2%)	152(13.3%)	62 (16.1%)
-TCA	9 (2.2%)	29 (2.5%)	9 (2.3%)
-Other antidepressants	25 (6.1%)	55 (4.8%)	16 (4.1%)
Frequent use of benzodiazepines, N(%)	23 (5.6%)	28 (2.4%)	15 (3.9%)
Presence of insomnia, N (%)	183 (44.7%)	388 (33.8%)	120 (31.1%)
Insomnia score (M ± SD)	7.91 ± 4.85	6.87 ± 4.54	6.74 ± 4.23
Average sleep duration (M hours ± SD)	7.65 ± 1.09	7.74 ± 0.98	7.84 ± 1.18
Somatic health factors			
BMI (M ± SD)	26.22 ± 4.72	25.53 ± 4.64	24.71 ± 4.72
Nr. of chronic diseases (M ± SD)	0.77 ± 0.97	0.59 ± 0.82	0.55 ± 0.80
Currently smoking, N(%)	96 (34.2%)	301 (38.2%)	176 (56.4%)
Alcohol use disorder identification test (M ± SD)	3.61 ± 4.14	4.67 ± 4.32	6.61 ± 5.67

IDS, inventory of depressive symptoms; BAI, beck anxiety index; BMI, body mass index; MSFsc, midsleep on free days; adjusted for sleep-deficit on working days, M, mean; SD, standard deviation.

~IDS: removal of 4-sleep items from the total score showed same pattern of difference in symptoms: early CT 12.87 ± 11.29, intermediate CT 11.58 ± 9.81, late CT 14.22 ± 11.25, $P < .001$.

DISCUSSION

In the present study, we found an association between current MDD and a late chronotype, whereas associations with dysthymia or anxiety disorders were not maintained when looking at each specific type of disorder separately. In addition, persons with remitted disorders did not show such a strong association with chronotype. Our main findings are in line with prior literature showing an association between later (or evening) types and depression levels.[10–12], [52] We have extended these findings by showing that this association holds when psychiatric diagnoses are considered (not just symptom scales) and when a number of clinical, sleep and somatic health factors have been controlled for.

The association with MDD is in line with the observed link between diurnal mood variation and chronotype. Late types were more likely to report worse mood in the morning than the other groups. Diurnal mood variation could also explain the stronger association found between the current psychopathology group and chronotype, since remitted patients were less likely to report diurnal mood variation (supplementary data). In line with our observations, studies using ecological momentary assessments have shown lower positive affect in the morning for evening types, suggesting that this group may be more susceptible to depression due to their likelihood to have a delayed and blunted positive affect rhythm.[53,54] Similarly, self-reported arousal has been found to be lower in evening types in the morning compared to the evening hours (opposite pattern is found for morning types).[55] Apart from diurnal mood variation as a potential explaining factor linking the late chronotype with depresssion, the association could arise from multiple other sources and interactions. For example, lower exposure to light could influence the biological clock and mood[56] and evening types

TABLE 2. Results of associations between chronotype (MSFsc outcome) and sociodemographic, sleep, and somatic health factors*

	Model 1		Model 2	
	β	*P*	*β*	*P*
Demographics				
Age	−.15	<.001	−.11	.002
Female gender	−.06	.02	−.02	.57
Education (years)	.10	<.001	.09	.009
Currently working	−.05	.049	−.06	.07
Partner present	−.12	<.001	−.11	.001
Presence of children in household	−.17	<.001	−.16	<.001
Somatic health factors				
BMI			−.007	.82
Number of chronic diseases			−.02	.51
Currently smoking			.14	<.001
Alcohol use disorder identification test			.18	<.001
Sleep factors				
Insomnia rating scale			−.08	.02
Average sleep duration			−.01	.72
Psychopathology				
-no lifetime depressive or anxiety disorders	Ref.	Ref.	Ref.	Ref.
-remitted depressive or anxiety disorders	.05	.16	.02	.61
-current depressive and/or anxiety disorders	.10	.004	.09	.03

*Multiple linear regression analyses.
Model 1: Socio-demographics and psychopathology as predictors of chronotype.
Model 2: Model 1+ somatic health factors and sleep factors as predictors of chronotype.
MSFsc, midsleep on free days; adjusted for sleep-deficit on working days; BMI, body mass index; Ref, reference category.

may be less likely to be exposed to light due to their social rhythms; light therapy has been associated with a shift in the circadian phase.[57,58] Furthermore, the evening type has been associated with personality traits known to be risk factors for psychopathology, such as neuroticism, novelty seeking, and harm avoidance,[23], [59–61] (for the latter two traits mixed findings have been reported,[23,59,62]) as well as increased sensation seeking attitudes and impulsivity.[24,63,64] Other traits more closely related to depression, such as ruminative thinking remain to be explored in relation to chronotypes.

We also found that a range of sociodemographic, clinical, and somatic health characteristics were related to a later chronotype. Specifically, we found that being younger and male having higher education and having no partner or children in household were associated with a later chronotype, suggesting to a certain extent that social/family obligations may play a role. With regard to gender, prior studies have also found an evening preference to be associated with the male gender,[65,66] however the opposite pattern (evening type more prevalent among women) has also been reported in a Finnish cohort[67] and no differences between the two sexes have also been found.[68] Eveningness has been previously linked to poor educational performance in adolescent and university samples,[69,70] but not in older adults,[71] as in our study. With regard to somatic health factors, a higher BMI and a higher number of chronic diseases was observed in the early chronotype, however these factors were not significant predictors in the adjusted regression models. Prior literature has shown that evening types have increased body fat and BMI[30,31] but also lower BMI in another study[33] and null associations have also been reported.[34] We found increased number of smokers and alcohol users among late chronotypes in our sample, and these factors were also predictive of chronotype. This is in line with prior research showing increased smoking and alcohol behaviors in evening types in university samples [35–37] and in older adult samples.[38] Interestingly, monozygotic twin differences in chronotypes have been found in relation to educational attainment and smoking (but not alcohol), indicating that these behaviors may be more environmentally determined than genetically.[72] Increased smoking in late chronotypes has been described as a possible reaction to social jetlag, namely the difficulty to adapt to work day schedules in contrast to free day schedules.[39] Although a prior study showed that only those late types who smoked and used alcohol were likely to suffer from psychological distress,[73] our study showed that the association between the late chronotype and MDD remains, even after controlling for smoking effects.

In relation to sleep parameters we observed that insomnia levels decreased in later chronotypes whereas average sleep duration was not predictive of chronotype. In prior research, eveningness and insomnia were shown to be independent predictors of depression and its nonremission.[14] Evening types seem to report more total sleep time or time in bed,[74] however, studies have also underlined that evening types are also more likely to report poor sleep quality overall [75,76] and hypersomniacs are also more likely to be evening

TABLE 3. Regression analysis with MSFsc (as outcome) and each type of depressive and anxiety disorders as predictors of chronotype (n = 1,937)

	Model 1		Model 2	
	β	P	β	P
Age	−0.22	**<.001**	−0.22	**<.001**
Female	−0.09	**<.001**	−0.09	**<.001**
Diurnal mood variation				
Mood not related to the time of day			Ref.	Ref.
Mood worse in the morning			.12	**<.001**
Mood worse in the afternoon/night			−.01	.64
Psychotropic drug use				
- SSRI			0.03	0.19
- Other antidepressants			−0.03	0.28
- TCA			0.02	0.30
- Benzodiazepines			−0.02	0.44
Psychopathology[a]				
Dysthymia	−0.02	0.34	−0.02	0.36
Major depression	0.07	**0.006**	0.05	**0.04**
Social phobia	0.03	0.19	0.03	0.25
Panic with agoraphobia	0.01	0.72	0.004	0.87
Panic without agoraphobia	−0.01	0.61	−0.02	0.48
Agoraphobia	−0.01	0.57	−0.02	0.49
Generalized anxiety disorder	0.02	0.40	0.02	0.43

Model 1 adjusted for age and gender.
Model 2: Model 1 + psychotropic drug use and diurnal mood variation.
[a]Diagnosis present (past 6 months).
SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

types.[13] Our findings point out that the association between depression and a later chronotype cannot be solely explained by sleep factors such as insomnia or sleep duration (in line with prior literature.[10])

Our study has several strengths. The large sample size with DSM-IV clinical diagnoses of depressive and anxiety disorders make it the first one to show associations with each specific disorder and chronotypes. In addition, we could adjust for a number of confounding factors (sociodemographic, clinical, somatic health, and sleep) and get more insight in the diurnal mood variation in that sample. Limitations of the study include the use of self-report for chronotype and sleep measures. It may be the case that patients have a distorted perception of times of going to sleep and waking up, however, even if this is the case, the associations remain informative. Finally, this is a cross-sectional analysis, allowing no inference about the direction of causality underlying the chronotype—psychopathology association.

In conclusion, this study showed an association between current MDD and the late chronotype, which remains after controlling for a number of sociodemographic, clinical, somatic health, and sleep factors that are also associated with chronotype, indicating an independent association between depression and a late chronotype. Insight into the link between MDD and eveningness can shed light on the potentially disturbed circadian rhythms in MDD patients, which could prove useful when selecting more tailored treatments or prevention methods. For example, light therapy and sleep deprivation are well-established chronotherapies for mood disorders, which could be further indicated as first-line treatments in evening type patients.[77,78]

Conflict of interest. Prof. Brenda Penninx is the principal investigator of The Netherlands Study of Depression and Anxiety (NESDA). The infrastructure for the NESDA study (www.nesda.nl) has been funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and participating universities (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen). All other authors (N.A., N.V., Y.M., R.S.) have nothing to disclose.

REFERENCES

1. Adan A, Archer SN, Hidalgo MP, et al. Circadian typology: a comprehensive review. Chronobiol Int 2012;29(9):1153–1175.
2. Kondratova AA, Kondratov RV. The circadian clock and pathology of the ageing brain. Nat Rev Neurosci 2012;13(5):325–335.
3. McClung CA. Circadian rhythms and mood regulation: insights from pre-clinical models. Eur Neuropsychopharmacol 2011;21(Suppl 4):S683–S693.
4. Goel N, Basner M, Rao H, Dinges DF. Circadian rhythms, sleep deprivation, and human performance. Prog Mol Biol Transl Sci 2013;119:155–190.
5. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4(2):97–110.

6. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: Daily temporal patterns of human chronotypes. J Biol Rhythms 2003;18(1):80–90.
7. Zavada A, Gordijn MC, Beersma DG, et al. Comparison of the Munich Chronotype Questionnaire with the Horne-Ostberg's Morningness-Eveningness Score. Chronobiol Int 2005;22(2):267–278.
8. Drennan MD, Klauber MR, Kripke DF, Goyette LM. The effects of depression and age on the Horne-Ostberg morningness-eveningness score. J Affect Disord 1991;23(2):93–98.
9. Chelminski I, Ferraro FR, Petros TV, Plaud JJ. An analysis of the "eveningness-morningness" dimension in "depressive" college students. J Affect Disord 1999;52(1–3):19–29.
10. Kitamura S, Hida A, Watanabe M, et al. Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. Chronobiol Int 2010;27(9–10):1797–1812.
11. Merikanto I, Lahti T, Kronholm E, et al. Evening types are prone to depression. Chronobiol Int 2013;30(5):719–725.
12. Hidalgo MP, Caumo W, Posser M, et al. Relationship between depressive mood and chronotype in healthy subjects. Psychiatry Clin Neurosci 2009;63(3):283–290.
13. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. Sleep 2009;32(6):753–759.
14. Chan JW, Lam SP, Li SX, et al. Eveningness and insomnia: independent risk factors of nonremission in major depressive disorder. Sleep 2014;37(5):911–917.
15. Simor P, Zavecz Z, Palosi V, et al. The influence of sleep complaints on the association between chronotype and negative emotionality in young adults. Chronobiol Int 2015;32(1):1–10.
16. Gaspar-Barba E, Calati R. Cruz-Fuentes CS, et al. Depressive symptomatology is influenced by chronotypes. J Affect Disord 2009;119(1–3):100–106.
17. Wirz-Justice A. Diurnal variation of depressive symptoms. Dialogues Clin Neurosci 2008;10(3):337–343.
18. Morris DW, Rush AJ, Jain S, et al. Diurnal mood variation in outpatients with major depressive disorder: implications for DSM-V from an analysis of the Sequenced Treatment Alternatives to Relieve Depression Study data. J Clin Psychiatry 2007;68(9):1339–1347.
19. Gordijn MC, Beersma DG, Bouhuys AL, et al. A longitudinal study of diurnal mood variation in depression; characteristics and significance. J Affect Disord 1994;31(4):261–273.
20. Peeters F, Berkhof J, Delespaul P, et al. Diurnal mood variation in major depressive disorder. Emotion 2006;6(3):383–391.
21. Murray G. Diurnal mood variation in depression: a signal of disturbed circadian function? J Affect Disord 2007;102(1–3):47–53.
22. Hasler BP, Allen JJ, Sbarra DA, et al. Morningness-eveningness and depression: preliminary evidence for the role of the behavioral activation system and positive affect. Psychiatry Res 2010;176(2–3):166–173.
23. Hsu CY, Gau SS, Shang CY, et al. Associations between chronotypes, psychopathology, and personality among incoming college students. Chronobiol Int 2012;29(4):491–501.
24. Prat G, Adan A. Relationships among circadian typology, psychological symptoms, and sensation seeking. Chronobiol Int 2013;30(7):942–949.
25. Lemoine P, Zawieja P, Ohayon MM. Associations between morningness/eveningness and psychopathology: an epidemiological survey in three in-patient psychiatric clinics. J Psychiatr Res 2013;47(8):1095–1098.
26. Alvaro PK, Roberts RM, Harris JK. The independent relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence. Sleep Med 2014;15(8):934–941.
27. Kantermann T, Theadom A, Roenneberg T, Cropley M. Fibromyalgia syndrome and chronotype: late chronotypes are more affected. J Biol Rhythms 2012;27(2):176–179.
28. Urban R, Magyarodi T, Rigo A. Morningness-eveningness, chronotypes and health-impairing behaviors in adolescents. Chronobiol Int 2011;28(3):238–247.
29. Sato-Mito N, Sasaki S, Murakami K, et al. The midpoint of sleep is associated with dietary intake and dietary behavior among young Japanese women. Sleep Med 2011;12(3):289–294.
30. Lucassen EA, Zhao XC, Rother KI, et al. Evening chronotype is associated with changes in eating behavior, more sleep apnea, and increased stress hormones in short sleeping obese individuals. Plos One 2013;8(3):e56519.
31. Soreca I, Fagiolini A, Frank E, et al. Chronotype and body composition in bipolar disorder. Chronobiol Int 2009;26(4):780–788.
32. Arora T, Taheri S. Associations among late chronotype, body mass index and dietary behaviors in young adolescents. Int J Obes 2015;39(1):39–44.
33. Merikanto I, Lahti T, Seitsalo S, et al. Behavioral trait of morningness-eveningness in association with articular and spinal diseases in a population. PLoS One 2014;9(12):e114635.
34. Harb A, Levandovski R, Oliveira C, et al. Night eating patterns and chronotypes: a correlation with binge eating behaviors. Psychiatr Res 2012;200(2–3):489–493.
35. Kabrita CS, Hajjar-Muca TA, Duffy JF. Predictors of poor sleep quality among Lebanese university students: association between evening typology, lifestyle behaviors, and sleep habits. Nat Sci Sleep 2014;6:11–18.
36. Whittier A, Sanchez S, Castaneda B, et al. Eveningness chronotype, daytime sleepiness, caffeine consumption, and use of other stimulants among Peruvian University students. J Caffeine Res 2014;4(1):21–27.
37. Randler C. Differences between smokers and nonsmokers in morningness-eveningness. Soc Behav Pers 2008;36(5):673–679.
38. Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. Addiction 1994;89(4):455–462.
39. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int 2006;23(1–2):497–509.
40. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 2008;17(3):121–140.
41. Lamers F, Hoogendoorn AW, Smit JH, et al. Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). Compr Psychiatry 2012;53(1):63–70.
42. Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. Sleep Med Rev 2007;11(6):429–438.
43. Kawato M, Fujita K, Suzuki R, Winfree AT. A three-oscillator model of the human circadian system controlling the core temperature rhythm and the sleep-wake cycle. J Theor Biol 1982;98(3):369–392.
44. Roenneberg T, Kuehnle T, Pramstaller PP, et al. A marker for the end of adolescence. Curr Biol 2004;14(24):R1038–R1039.
45. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28(1):57–84.
46. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26(3):477–486.

47. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56(6):893–897.
48. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption–II. Addiction 1993;88(6):791–804.
49. vanMill JG, Hoogendijk WJ, Vogelzangs N, et al. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. J Clin Psychiatry 2010;71(3):239–246.
50. Levine DW, Kripke DF, Kaplan RM, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess 2003;15(2):137–148.
51. Broms U, Pitkaniemi J, Backmand H, et al. Long-term consistency of diurnal-type preferences among men. Chronobiol Int 2014;31(2):182–188.
52. Park CI, An SK, Kim HW, et al. Relationships between chronotypes and affective temperaments in healthy young adults. J Affect Disord 2015;175C:256–259.
53. Hasler BP, Germain A, Nofzinger EA, et al. Chronotype and diurnal patterns of positive affect and affective neural circuitry in primary insomnia. J Sleep Res 2012;21(5):515–526.
54. Miller MA, Rothenberger SD, Hasler BP, et al. Chronotype predicts positive affect rhythms measured by ecological momentary assessment. Chronobiol Int 2015;32(3):376–384.
55. Watts C, Cox T, Robson J. Morningness-eveningness and diurnal variations in self-reported mood. J Psychol 1983;113(2d Half):251–256.
56. Bedrosian TA, Nelson RJ. Influence of the modern light environment on mood. Mol Psychiatry 2013;18(7):751–757.
57. Elmore SK, Dahl K, Avery DH, et al. Body temperature and diurnal type in women with seasonal affective disorder. Health Care Women Int 1993;14(1):17–26.
58. Terman JS, Terman M, Lo ES, Cooper TB. Circadian time of morning light administration and therapeutic response in winter depression. Arch Gen Psychiatry 2001;58(1):69–75.
59. Adan A, Lachica J, Caci H, Natale V. Circadian typology and temperament and character personality dimensions. Chronobiol Int 2010;27(1):181–193.
60. Caci H, Robert P, Boyer P. Novelty seekers and impulsive subjects are low in morningness. Eur Psychiatry 2004;19(2):79–84.
61. Tonetti L, Fabbri M, Natale V. Relationship between circadian typology and big five personality domains. Chronobiol Int 2009;26(2):337–347.
62. Muro A, Goma-i-Freixanet M, Adan A. Morningness-eveningness, sex, and the alternative five factor model of personality. Chronobiol Int 2009;26(6):1235–1248.
63. Muro A, Goma-i-Freixanet M, Adan A. Circadian typology and sensation seeking in adolescents. Chronobiol Int 2012;29(10):1376–1382.
64. Russo PM, Leone L, Penolazzi B, Natale V. Circadian preference and the big five: the role of impulsivity and sensation seeking. Chronobiol Int 2012;29(8):1121–1126.
65. Adan A, Natale V. Gender differences in morningness-eveningness preference. Chronobiol Int 2002;19(4):709–720.
66. Natale V, Di Milia L. Season of birth and morningness: comparison between the northern and southern hemispheres. Chronobiol Int 2011;28(8):727–730.
67. Merikanto I, Kronholm E, Peltonen M, et al. Relation of chronotype to sleep complaints in the general Finnish population. Chronobiol Int 2012;29(3):311–317.
68. Paine SJ, Gander PH, Travier N. The epidemiology of morningness/eveningness: influence of age, gender, ethnicity, and socioeconomic factors in adults (30–49 years). J Biol Rhythms 2006;21(1):68–76.
69. Besoluk S, Onder I, Deveci I. Morningness-eveningness preferences and academic achievement of university students. Chronobiol Int 2011;28(2):118–125.
70. Preckel F, Lipnevich AA, Boehme K, et al. Morningness-eveningness and educational outcomes: the lark has an advantage over the owl at high school. Br J Educ Psychol 2013;83(Pt 1):114–134.
71. Diaz-Morales JF, Sanchez-Lopez MP. Morningness-eveningness and anxiety among adults: a matter of sex/gender? Pers Indiv Diff 2008;44(6):1391–1401.
72. Barclay NL, Eley TC, Parsons MJ, et al. Monozygotic twin differences in non-shared environmental factors associated with chronotype. J Biol Rhythms 2013;28(1):51–61.
73. Wittmann M, Paulus M, Roenneberg T. Decreased psychological well-being in late 'chronotypes' is mediated by smoking and alcohol consumption. Subst Use Misuse 2010;45(1–2):15–30.
74. Ong JC, Huang JS, Kuo TF, Manber R. Characteristics of insomniacs with self-reported morning and evening chronotypes. J Clin Sleep Med 2007;3(3):289–294.
75. Barclay NL, Eley TC, Maughan B, et al. Associations between diurnal preference, sleep quality and externalizing behaviours: a behavioural genetic analysis. Psychol Med 2011;41(5):1029–1040.
76. Lehnkering H, Siegmund R. Influence of chronotype, season, and sex of subject on sleep behavior of young adults. Chronobiol Int 2007;24(5):875–888.
77. Benedetti F, Colombo C. Sleep deprivation in mood disorders. Neuropsychobiology 2011;64(3):141–151.
78. Dallaspezia S, Benedetti F. Chronobiological therapy for mood disorders. Expert Rev Neurother 2011;11(7):961–970.