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Citation

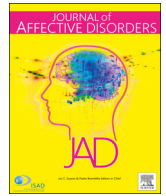
Druiven, S. J. M., Knapen, S. E., Penninx, B. W. J. H., Antypa, N., Schoevers, R. A., Riese, H., & Meesters, Y. (2019). Can chronotype function as predictor of a persistent course of depressive and anxiety disorder? *Journal Of Affective Disorders*, 242, 159-164.
doi:10.1016/j.jad.2018.08.064

Version: Publisher's Version

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Downloaded from: <https://hdl.handle.net/1887/3630588>

Note: To cite this publication please use the final published version (if applicable).



Research paper

Can chronotype function as predictor of a persistent course of depressive and anxiety disorder?

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ARTICLE INFO

Keywords:

Depressive disorder
Anxiety disorder
Chronotype
Circadian rhythm
Chronobiology

ABSTRACT

Background: The role of chronotype, the individual timing of sleep/activity, has been studied in relation to depressive and anxiety disorders. A cross-sectional association between a depressive episode and evening-type has been identified. However, until now the predicting capacity of chronotype concerning persistence of psychiatric disorders remains unclear. Our aim is to examine whether a later chronotype in patients with a depressive and/or anxiety disorder can serve as a predictor of a persistent course.

Methods: A subsample of patients with a depressive and/or anxiety disorder diagnosis and chronotype data of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) was used. Diagnosis of depressive and anxiety disorders (1-month DSM-IV based diagnosis) were determined at baseline ($n = 505$). From this group persistence was determined at 2-year (FU2) (persistent course: $n = 248$, non-persistent course: $n = 208$) and 4-year follow-up (FU4) (persistent course: $n = 151$, non-persistent course: $n = 264$). Chronotype was assessed at baseline with the Munich Chronotype Questionnaire.

Results: A later chronotype did not predict a persistent course of depressive and/or anxiety disorder at FU2 (OR (95% CI) = 0.99 (0.83–1.19), $P = 0.92$) or at FU4 (OR (95% CI) = 0.94 (0.77–1.15), $P = 0.57$).

Limitations: Persistence was defined as having a diagnosis of depressive and/or anxiety disorder at the two-year and four-year follow-up, patients may have remitted and relapsed between assessments.

Conclusion: Chronotype, measured as actual sleep timing, of patients with a depressive or anxiety disorder did not predict a persistent course which suggests it might be unsuitable as predictive tool in clinical settings.

1. Introduction

Depressive and anxiety disorders are highly prevalent in Western societies (Hirschfeld, 2001). Their courses are often of a chronic or recurrent nature. They cause an enormous burden to patients, to those close to them and involve high societal costs (Creed et al., 2002; Penninx et al., 2011). A disturbed timing of the circadian rhythm is found in patients suffering from these disorders (Wirz-Justice, 2006). Circadian rhythmicity is controlled by the suprachiasmatic nucleus (SCN), an area of the brain located in the hypothalamus (Roenneberg et al., 2007). The free-running rhythm, without cues from the environment, of humans is slightly longer than 24 h (Roenneberg and Merrow, 2007). Entrainment is the process that

adapts the internal rhythm to that of our environment through the SCN so that we are synchronized with a 24-hour day. Although the rhythm follows the day and night cycle closely, there are individual differences. The individual timing in which persons perform best mentally and physically is called chronotype (Roenneberg et al., 2003; Urbán et al., 2011). Chronotype can be categorised into either of the following three categories: morning-type (early to bed, early to rise), intermediate-type, or evening-type (late to bed, late to rise) (Roenneberg et al., 2003).

A cross-sectional association between evening-type, measured by a questionnaire, and a clinical depressive disorder has been described in 1991 by Drennan et al. (1991). Subsequent studies also reported this association (Hidalgo et al., 2009; Kitamura et al., 2010; Levandovski et al., 2011; Merikanto et al., 2015). One study found evening-type not

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<https://doi.org/10.1016/j.jad.2018.08.064>

Received 31 March 2018; Received in revised form 12 June 2018; Accepted 12 August 2018

Available online 22 August 2018

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only to be associated with a depressive disorder diagnosis, but also with a higher severity of the disorder, represented by having more suicidal thoughts, paranoid symptoms, impaired work ability, and impaired activities (Gaspar-Barba et al., 2009). Because evening-type is also associated with poor sleep quality, Chan et al. (2014) studied the confounding effect of insomnia on the cross-sectional association between depressive disorder and evening-type (Chan et al., 2014). They found that the association exists independent of insomnia, which reinforces the importance of studying the role of chronotype in depressive disorder.

The association between chronotype and anxiety disorder is largely unexplored. Studies that did examine this, usually combined patients with anxiety disorder and/or depressive disorder in their sample and present mixed results. One study reported an association between higher symptom severity of anxiety disorder and evening-type (Pabst et al., 2009). An earlier study in the Netherlands Study of Depression and Anxiety (NESDA) of Antypa et al. (2016) found a cross-sectional association between evening-type and a depressive and/or anxiety disorder diagnosis. However, when examined separately, this association was only found between evening-type and a Major Depressive Disorder (MDD) diagnosis and not between evening-type and an anxiety disorder diagnosis.

The cross-sectional association between evening-type and a depressive and/or anxiety disorder diagnosis described in previous research (Antypa et al., 2016; Chan et al., 2014; Drennan et al., 1991; Gaspar-Barba et al., 2009), has led to interpretations of the role of chronotype in these disorders. Being an evening-type has been suggested to be an underlying trait that causes vulnerability for both the development and persistence of a depressive disorder (Drennan et al., 1991). In children, a prospective association has been reported between chronotype and depressive disorder during childhood (Haraden et al., 2017). They found that those who were evening-type, assessed as preferred times to perform certain activities, were more likely to have a depressive disorder diagnosis 1 year later (Haraden et al., 2017). Until now however, studies have not examined longitudinal patterns of chronotype and depression diagnoses in adults (Knapen et al., 2017).

The aim of this article is to examine whether chronotype predicts a persistent course of depressive and/or anxiety disorder over time. The prospective association of chronotype in depressed/anxious patients will be examined by determining the course of the disorders, defined as persistent (diagnosis at baseline and follow-up) or non-persistent (diagnosis at baseline but not at follow-up) at two and four-year follow-up. Associations will be examined while relevant sociodemographic and somatic health factors are considered. Additionally, depressive and anxiety disorders will be examined together as outcomes, as well as separately, to study the unique contribution of each disorder.

2. Material and methods

2.1. Study sample

Data are derived from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008). NESDA is a Dutch ongoing multi-center (Groningen, Leiden, Amsterdam), longitudinal cohort study. It examines the course and consequences of depressive and anxiety disorders. A detailed method and rationale have been described elsewhere (Penninx et al., 2008). In short, the sample consists of 1701 patients with a current (present in the 6 months prior to interview) diagnosis of depression and/or anxiety disorder, 907 participants with life-time diagnoses or with increased risk of at risk because of a family history or subthreshold depressive or anxiety symptoms, and 373 healthy controls. In total, 2981 participants (age 18–65 years) were included at baseline through mental healthcare organizations ($N = 807$), the general community ($N = 564$), and primary care ($N = 1610$). The two exclusion criteria applied by NESDA were having a primary clinical diagnosis of a psychiatric disorder that is not part of

NESDA's primary interest (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder) and not being fluent in Dutch.

Baseline inclusion began in 2004 and ended in 2007. The response-rates at the follow-up assessments after two, four and six-year follow-up were relatively high with 87%, 81% and 76% respectively. The ethical committees of participating universities approved the study protocol and participants provided written informed consent (Penninx et al., 2008). The current study will use data from NESDA's two-, four- and six-year follow-up because chronotype was only assessed at FU2. Therefore, the original FU2 will be called "baseline" from here onwards.

2.2. Chronotype assessment

Chronotype was assessed at baseline using the Munich Chronotype Questionnaire (MCTQ) (Roenneberg et al., 2003). This is a self-report questionnaire composed of questions about the timing of sleep on free days and workdays separately. Participants were asked to answer the questions in a way that displayed their current situation (Roenneberg et al., 2003). For factors that might vary over days, like the time to start work, they were asked to give answers that best reflected the most common situation. The MCTQ can be used to calculate the Midpoint of Sleep on Free days (MSF), i.e. the midpoint in time between falling asleep and waking up on free days. For individuals with a late MSF (evening-type), sleep duration during weekdays is often reduced as the result of work schedules. MSF results in an estimation of chronotype that does not take into account the average weekly sleep duration and any sleep debt that is accumulated in the free days resulting in oversleep. Therefore, MSF is corrected for oversleep on free days. This is done by subtracting from MSF half of the difference between sleep duration on free days and average weekly sleep duration (Roenneberg et al., 2012). The corrected MSF measure (MSFsc) is an established, validated measure to estimate chronotype and is used in this study as a continuous variable (Zavada et al., 2005). During the selection of participants, only those with valid MSFsc data were selected. As shown in Fig. 1, from 2596 participants at baseline, 711 patients did not fill out the MCTQ or did not fill out the sufficient amount of questions to calculate their MSFsc.

In this study the baseline characteristics of the patients selected at FU2 and FU4 were compared between categorical chronotype groups, for descriptive reasons. To create these chronotype groups, quintiles were formed from all chronotype data available from baseline ($N = 1885$). In a population, chronotypes mainly group around the mean but can show a great time range between extreme morning and extreme evening-types (Roenneberg et al., 2007). By including more participants in the intermediate group, the more extreme morning-types and evening-types are captured (Roenneberg et al., 2003). Therefore, the first quintile represents the morning-type group, the second, third and fourth quintiles represent the intermediate-type group, and the fifth quintile represents the evening-type group. The ranges were used to categorise the patients selected at FU2 and FU4 between the different chronotypes. This method is previously used for creating chronotype groups (Antypa et al., 2016; Sato-Mito et al., 2011).

2.3. Persistent and non-persistent course

The course of the disorders was defined as persistent or non-persistent at FU2 and FU4. The diagnosis of a depressive (MDD and dysthymia) or anxiety (panic disorder, social phobia, generalized anxiety disorder, and agoraphobia) disorder was established using the Composite International Diagnostic Interview (CIDI), version 2.1 (World Health Organization, 1997). Specific phobia was not assessed by the CIDI and therefore not included in our study. The CIDI is a validated instrument created in accordance with DSM-IV criteria (Wittchen, 1994). For this study, the one-month CIDI diagnosis was

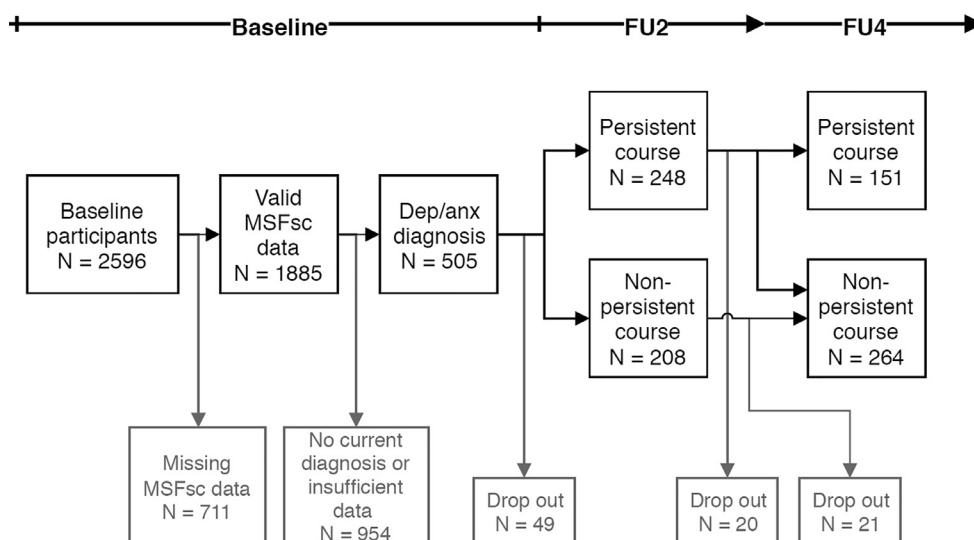


Fig. 1. Flow-chart of the selection of patients at baseline, two-year and four-year follow-up. The timeline is pictured at the top of the flow-chart showing baseline, FU2 (2-year follow-up) and FU4 (4-year follow-up). The drop out between Baseline and FU2 and FU2 and FU4 are the result of patients who did not continue with the study or had missing data at that follow-up. Patients with a non-persistent course at FU2 and a diagnosis at FU4, were not included in the group with a persistent course at FU4. Dep/ans: depressive and/or anxiety disorder.

used, meaning the diagnosis was present in the month prior to the interview. Our rationale for using the one-month CIDI diagnosis is based on reported symptomatology from one month before assessment. This is in line with both the DSM-IV criteria as is used in clinical setting for establishing a depressive disorder diagnosis and the psychological knowledge on recall bias, since a retrospective method is used (American Psychiatric Association, 2000).

Patient selection was performed using two different methods. The first selection was based on a diagnosis of depressive and/or anxiety disorder ('dep/ans', baseline $n = 505$), this method is shown in Fig. 1. The second selection was based on the diagnoses of the two separate disorders, while still including participants with a comorbidity of the two diseases: depressive disorder ('dep', baseline $n = 267$) and anxiety disorder ('ans', baseline $n = 389$).

The selection resulted in the following groups: persistent course at FU2 (diagnosis at baseline and FU2; dep/ans: $n = 248$, dep: $n = 101$, ans: $n = 164$) and non-persistent course at FU2 (dep/ans: $n = 208$, dep: $n = 143$, ans: $n = 186$). From the participants in these categories, persistence was determined once more at FU4, (persistent course at FU4: diagnosis at baseline, FU2 and FU4; dep/ans: $n = 151$, dep: $n = 55$, ans: $n = 91$ and non-persistent course at FU4: dep/ans: $n = 264$, dep: $n = 168$, ans: $n = 226$).

2.4. Baseline covariates

Sociodemographic and somatic health factors that were associated with depressive and anxiety disorder and chronotype included age, gender, body mass index (BMI), years of education, smoking status, alcohol use, antidepressants use, and benzodiazepines use (Arora and Taheri, 2015; Bjelland et al., 2008; Bjørngaard et al., 2015; Díaz-Morales and Pilar Sánchez-López, 2008; Wittmann et al., 2010). Having a child in the household and employment status are factors that may affect chronotype, as participants cannot completely follow their own natural chronotype, and these were also included as covariates. All covariates were assessed at baseline. Standard questions were used to measure the sociodemographic factors. BMI was calculated by dividing body mass (in kg) by the square of the height (in meters). Education level was determined by asking the highest level of established education. The Dutch institute: Standard Classification of Education (Standaard Onderwijsindeling (SOI) of the Office of Statistics (Centraal Bureau voor de Statistiek (CBS)) was used to score level of education (Centraal Bureau voor de Statistiek, 2006). From these categories, the number of years of education was calculated. Smoking status (currently smoking yes/no), employment status (currently employed yes/no), and having a child in the household (yes/no) was determined by self-report.

Alcohol use, frequency and quantity, was determined by the World Health Organization (WHO) Alcohol Use Disorder Identification Test (AUDIT) (World Health Organization, 2001). This test consists of 10 questions which each can be scored from 0 to 4 (range 0–40). As recommended by the WHO, a score of 8 or higher indicates hazardous alcohol use (World Health Organization, 2001). The scores were divided into three categories: no drinking (0), moderate drinking (1–7) and hazardous drinking (≥ 8). Antidepressants and benzodiazepines use in the past month were classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification (Norwegian Institute of Public Health, 2013).

2.5. Statistical analyses

Data were analysed in the Statistical Package for Social Science (SPSS Inc, Chicago, IL version 23.0 for Windows). P -values < 0.05 were considered statistically significant. Baseline differences in socio-demographic and somatic health characteristics were tested between chronotype groups (morning, intermediate and evening-type) for all patients at FU2 and FU4. A Pearson's chi-square test was used to compare dichotomous and categorical variables (gender, smoking, alcohol use, employment, having a child in the household, antidepressant use, benzodiazepine use) between chronotype groups. A one-way analysis of variance (ANOVA) was used for comparing continuous variables (age, BMI, education) between chronotype groups.

The prospective association between chronotype and persistence at FU2 and FU4 was examined using binomial logistic regression analyses. Persistence at FU2, for dep/ans and for dep and ans separately, was used as the outcome variable. These analyses were repeated with the course at FU4. The continuous chronotype measure, MSFsc, was used as the main predictor variable in all analyses.

All analyses were first conducted with entering only MSFsc (model 1). Second, adjustments for age and gender were added (model 2). Third, the covariates: education, employment status, child in household, BMI, smoking status and alcohol use were added (model 3). Finally, use of antidepressants and benzodiazepines were added to the model (model 4).

3. Results

3.1. Baseline characteristics

For descriptive purposes, categorical chronotype groups were formed to compare baseline characteristics. The following MSFsc ranges for each chronotype group were defined from data of all participants at

Table 1

Baseline characteristics of the patients at two and four-year follow-up compared between categorical chronotype groups.

Characteristics	Morning-type		Intermediate-type		Evening-type		P-value ^a	
	FU2	FU4	FU2	FU4	FU2	FU4	FU2	FU4
	(N = 88)	(N = 77)	(N = 254)	(N = 233)	(N = 114)	(N = 105)		
Gender (n (%), women)	62 (70.5)	53 (68.6)	175 (68.9)	161 (69.1)	76 (66.7)	69 (65.7)	0.840	0.819
Age (in yrs, M (SD))	48.09 (9.9)	48.65 (9.9)	43.15 (11.9)	43.15 (12.0)	41.40 (12.7)	40.95 (12.8)	<0.001 ^b	<0.001 ^b
Education (in yrs, M (SD))	11.33 (3.3)	11.32 (3.4)	12.63 (3.5)	12.64 (3.4)	12.92 (3.0)	12.89 (3.0)	0.002 ^c	0.003 ^c
Employment status (n (%), yes)	58 (65.9)	50 (64.9)	176 (69.3)	160 (68.7)	73 (64.0)	68 (64.8)	0.581	0.712
Child in household (n (%), yes)	25 (28.4)	23 (29.9)	94 (37.0)	88 (37.8)	22 (19.3)	20 (19.0)	0.003	0.003
BMI (in kg/m ² , M (SD))	26.04 (4.7)	25.89 (4.2)	25.50 (4.7)	25.39 (4.7)	25.17 (4.9)	25.28 (5.0)	0.437	0.659
Smoking status (n (%), yes)	22 (25.0)	17 (22.1)	77 (30.0)	66 (28.3)	56 (49.1)	51 (48.6)	<0.001	<0.001
Alcohol use:							0.084	0.090
No drinking (n (%))	20 (22.7)	17 (22.1)	35 (13.8)	32 (13.7)	21 (18.4)	19 (18.1)		
Mod. drinking (n (%))	54 (61.4)	49 (63.6)	167 (65.7)	153 (65.7)	62 (54.4)	57 (54.3)		
Haz. drinking (n (%))	14 (15.9)	11 (14.3)	52 (20.5)	48 (20.6)	31 (27.2)	29 (27.6)		
Antidepressants (n (%), yes)	27 (30.7)	25 (32.5)	89 (35.0)	79 (33.9)	44 (38.6)	40 (38.1)	0.505	0.681
Benzodiazepines (n (%), yes)	27 (30.7)	25 (32.5)	45 (17.7)	40 (17.2)	23 (20.2)	21 (20.0)	0.035	0.016

Note: FU2 = 2-year follow-up, FU4 = 4-year follow-up, M = mean, SD = standard deviation.

^a Pearson's chi-square test was used for the dichotomous and categorical variables (gender, employment status, child in household, smoking status, alcohol use, antidepressants and benzodiazepines), one-way analyses of variance (ANOVA) was used for the continuous variables (age, body mass index (BMI) and education).

^b Post-hoc test (Tamhane): Mt > I, Mt > E.

^c Post-hoc test (Tukey HSD): Mt < I, Mt < E; Mt = Morning-type, I = Intermediate-type, E = Evening-type.

baseline: MSFsc = 0.76–3.13 (morning-type, $n = 377$), MSFsc = 3.13–4.68 (intermediate-type, $n = 1132$) and MSFsc = 4.68–8.54 (evening-type, $n = 376$) (total: $N = 1885$; mean (M) = 3.94; standard deviation (SD) = 1.01) (Sato-Mito et al., 2011). These ranges resulted in the following categorical chronotype groups for the patients selected in the study at FU2: morning-type, $n = 88$, intermediate-type, $n = 254$ and evening-type, $n = 114$, and FU4: morning-type, $n = 77$, intermediate-type, $n = 233$, and evening-type, $n = 105$.

Baseline characteristics of the patients at FU2 and FU4 are compared and presented in Table 1: morning-types were older, had less years of education and were more likely to use benzodiazepines than intermediate- and evening-types. Intermediate-types were more likely to have a child in the household and more evening-types were current smokers. FU2 and FU4 characteristics of the patients compared between the chronotype groups are shown in the supplemental information (SI2). Using the baseline sample, the cross-sectional association between a later chronotype (evening-type) and a current depressive and/or anxiety disorder diagnosis was confirmed (data available upon request) which is already described in a previous NESDA article (Antypa et al., 2016).

3.2. Predictor of persistent course

The prospective associations between chronotype, as a continuous variable, and a persistent course at FU2 and FU4 tested in the model with all covariates (model 4) are given in Table 2. The tables with complete statistical results for models 1–4 are given in the Supplemental Information. A later chronotype was not associated with a persistent course of depressive and/or anxiety disorder at FU2 and FU4 compared to a non-persistent course at FU2 and FU4 (model 1–4). Additionally, a later chronotype was also not associated with a persistent course of depressive disorder or anxiety disorder separately (model 1–4).

4. Discussion

In this study, no prospective association was found between a later chronotype and a persistent course of depressive and/or anxiety disorder at two and four-year follow-up. These were robust findings as this association was also not found with a persistent course of depressive or anxiety disorder separately.

Table 2

Selected results of binomial logistic regression analyses with the persistence (persistent or non-persistent course) at FU2 and FU4 as outcome variable and chronotype as predictor variable.

Outcome measure (model 4 ^a)	Main predictor	Persistence at FU2		Persistence at FU4	
		OR (95% CI)	P	OR (95% CI)	P
		Dep/anx	MSFsc	0.99 (0.83–1.19)	0.916
Dep	MSFsc	0.95 (0.75–1.21)	0.689	0.91 (0.68–1.23)	0.539
Anx	MSFsc	0.93 (0.74–1.15)	0.490	0.91 (0.70–1.18)	0.489

Note: Full results are given in the Supplemental Information; ^aModel 4: adjusted for age, gender, education in years, employment status, child in household, smoking status, alcohol use, antidepressants use, and benzodiazepines use (see method section for more details); Dep/Anx = Depressive and/or anxiety disorder, Dep = Depressive disorder, Anx = Anxiety disorder, OR = odds ratio, CI = confidence interval.

The results presented in this article are important for the discussion concerning the underlying mechanisms of chronotype in depressive and anxiety disorders. Previous studies have reported the cross-sectional association between evening-type and depressive disorder (Hidalgo et al., 2009; Kitamura et al., 2010; Levandovski et al., 2011). This association was also found in the NESDA cohort which is described in the study of Antypa et al. (2016). However, as shown here, a later chronotype does not predict a persistent course. There are studies that did find sleep-related variables predictive of a persistent course of depressive and anxiety disorder. The study of van Mill et al., also conducted on NESDA data, used sleep duration instead of chronotype as predictive variable. They showed that both long (≥ 10 hours) and short sleep duration (≤ 6 h) were predictive of a two-year persistent course of depressive and anxiety disorder (van Mill et al., 2014).

Based on our results it is tempting to speculate that chronotype is a factor that is influenced by lifestyle factors. Take for example adults who have a young child in the household. Young children wake up early, and subsequently make the parent wake up earlier which will result in the parents having an earlier chronotype (Schmidt et al., 2007). Suffering from a current depressive or anxiety disorder might also be a changing lifestyle factor affecting their chronotype. The

question here would be whether patients actually shift towards a later chronotype during a depressive episode, which needs to be examined more clearly by using repeated measurements in prospective studies.

Another hypothesis is that chronotype predisposes to a certain lifestyle and not the other way around. For example, a prospective association between evening-type, assessed as preferred and actual bed times, was associated with a higher level of substance use (Hasler et al., 2017; Tavernier et al., 2015). A suggested explanation for this finding was that adolescences who are evening-types were more prone for substance use, as this is mostly done in the evening (Tavernier et al., 2015).

Our results should be interpreted considering the following strengths and limitations. A strength of this study is that both depressive and anxiety disorder diagnoses have been taken into account, together and separately, because of the high comorbidity of these disorders (Hirschfeld, 2001). Other strengths are the large number of participants with a DSM-IV clinical diagnoses and the long follow-up period (4 years) we incorporated in our study. A possible limitation of the study was using MSFsc as the chronotype variable because this variable depends on self-report (Roenneberg et al., 2003). It is possible that participants did not fill-out the correct information about their sleep timing, in this way introducing a discrepancy in their MSFsc scores and actual chronotype. Also, the MCTQ only assesses actual sleep times from which chronotype is estimated by calculating the MSFsc. Yet, chronotype encompasses more than only sleep timing. Chronotype is the individual timing in which persons perform best mentally as well as physically and are most alert (Urbán et al., 2011). The MSFsc does not include these aspects but is validated with the onset of melatonin secretion when measured in dim light conditions which is considered a highly reliable representation of the internal chronotype (Kantermann et al., 2015). Nevertheless, the reliability and long-term consistency of chronotype as measured with MCTQ remains to be determined. Another limitation was the determination of persistence at the fixed assessment point at baseline, FU2 and FU4. A persistent course at follow-up was defined as having a one-month diagnosis of depressive and/or anxiety disorder at the assessment. In this design no information of the prevalence of psychopathologies during the time between the follow-up assessments were taken into account.

To conclude, in this study, a later chronotype did not predict a persistent course of depressive and/or anxiety disorders over time. This suggests it might be unsuitable to use chronotype, assessed with actual sleep times, as a predictive tool in clinical settings.

Contributors

Data was collected by the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl). All authors have contributed significantly and agree with the content of the manuscript. SD, SK, HR and YM drafted the manuscript, SD conducted statistical analysis and all authors contributed to the finalisation of the paper.

Role of the funding source

For this manuscript, data from the Netherlands Study of Depression and Anxiety (NESDA) was used. The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum). The funding sources had no involvement in analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Funding

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum).

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Signed by all authors as follows:

3-31-2018
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Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.08.064.

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