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Depression Scores Associate With Chronotype and Social Jetlag in a Rural Population

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In public health, mood disorders are among the most important mental impairments. Patients with depressive episodes exhibit daily mood variations, abnormal patterns in sleep-wake behavior, and in the daily rhythms of several endocrine-metabolic parameters. Although the relationship between the sleep/circadian processes and mood disorders is poorly understood, clock-related therapies, such as light therapy, sleep deprivation, and rigid sleep schedules, have been shown to be effective treatments. Several studies investigated the relationship between circadian phenotype (chronotype) and depression. These focused mainly on urban populations and assessed diurnal preferences (Morningness-Eveningness score) rather than the actual timing of sleep and activity. Here, we used the Beck Depression Inventory (BDI) in an essentially rural population (N = 4051), and investigated its relation to circadian phenotype (chronotype and social jetlag), assessed with the Munich Chronotype Questionnaire (MCTQ). In our study design, we (i) normalized both chronotype and BDI scores for age and sex (MSF_{sas} and BDI_{as}, respectively); (ii) calculated individual social jetlag (misalignment of the biological and social time); and (iii) investigated the relationship between circadian phenotypes and BDI scores in a population homogeneous in respect to culture, socioeconomic factors, and daily light exposure. A 15.65% (N = 634) of the participants showed mild to severe depressive BDI scores. Late chronotypes had a higher BDI_{as} than intermediate and early types, which was independent of whether or not the participants were smokers. Both chronotype and BDI_{as} correlated positively with social jetlag. BDI_{as} was significantly higher in subjects with >2 h of social jetlag than in the rest of the population—again independent of smoking status. We also compared chronotype and social jetlag distributions between BDI categories (no symptoms, minimal symptoms, and mild to severe symptoms of depression) separately for men and women and for four age groups; specifically in the age group 31–40 yrs, subjects with mild to severe BDI scores were significantly later chronotypes and suffered from higher social jetlag. Our results indicate that misalignment of circadian and social time may be a risk factor for developing depression, especially in 31- to 40-yr-olds. These relationships should be further investigated in longitudinal studies to reveal if reduction of social jetlag should be part of prevention strategies. (Author correspondence: karla.allebrandt@med.uni-muenchen.de)

Keywords: Chronotype, Circadian clock, Depression, Mood disorders, Sleep-wake behavior, Social jetlag

INTRODUCTION

The endogenous clock is responsible for the maintenance and coherence of the body's daily program and its synchronization with the light-dark cycle of the environment (Roenneberg & Merrow, 2003; Roenneberg et al., 2003). The relationship between the circadian clock and health as well as daily modulations of symptoms of mood disorders have been extensively documented (Foster & Wulff, 2005; Ramsey & Bass, 2009; Scheer et al., 2009; Selvi et al., 2010; Wulff et al., 2010). Patients with depressive episodes, for example, show daily mood variations and abnormal patterns in sleep-wake behavior, cortisol secretion, adrenocorticotropic hormone (ACTH), and other endocrine-metabolic parameters (Soria & Urretavizcaya, 2009). Interestingly, clock-genes variants have been associated with abnormal sleep timing and mood disorders (for review see Wulff et al., 2010), indicating common pathways.

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One of the first circadian hypothesis for major depressive disorders suggested that depressed subjects sleep at a significantly later circadian phase compared to healthy individuals (Kripke, 1984; Wehr et al., 1979). Several follow-up studies showed that it is the individual circadian timing, itself, that is drastically delayed in patients with bipolar disorders (Giglio et al., 2009; Soreca et al., 2009), seasonal affective disorders (SADs; Elmore et al., 1993), and major depressive disorders (Drennan et al., 1991; Soria & Urretavizcaya, 2009). SAD has also been associated with "internal" circadian misalignment (Lewy et al., 2006). Although the underlying mechanisms are poorly understood, they are clinically and therapeutically relevant, as evidenced by the antidepressant effects of light therapy, sleep deprivation, or rigid sleep schedules (Benedetti et al., 2007; Boivin et al., 1996; Haynes et al., 2005; Lewy et al., 1987; Terman & Terman, 2005; Zeitzer et al., 2000). Circadian misalignment and sleep disruptions in patients with mood disorders have been linked also to abnormal daily pattern of gene expression, hormonal secretion, body temperature, and cognitive and behavioral functions (for review see Wulff et al., 2010). An additional indication of circadian misalignment contributing to depressive symptoms is the finding that individuals living in urban settings are more prone to depressive symptoms (Chelminski et al., 1999; Giannotti et al., 2002; Hidalgo et al., 2002, 2009). The circadian clock in urban populations is delayed compared to rural populations (Roenneberg & Merrow, 2007), accentuating the discrepancies between social and biological time (Wittmann et al., 2006).

Mood disorders, especially those related to depression, are among the most prevalent mental impairments; it is, therefore, important to understand their etiology for improving their therapy and prevention. Even subclinical depressive symptoms, which are predictors of the onset of mood and anxiety disorders (Gentil et al., 2007), correlate with slow information processing, poor memory functioning (Simons et al., 2009), and cardiovascular dysfunction (Taillard et al., 1993; Wassertheil-Smoller et al., 2004). The prevalence of depression appears to be independent of cultural background—Canada 8.2%; Europe 8.6%; United States 8.7%; southern Brazil 10% (Mari & Williams, 1986)—and is higher in urban populations, with a lifetime prevalence estimated to be 25.1% (18.5% for men and 31.5% for women; Patten, 2007).

Given the importance of subclinical depressive symptoms in public health, we screened a general population with the Beck Depression Inventory (BDI; Beck et al., 1996). On the basis of the hypotheses of circadian misalignment and on the proposal that Eveningness (assessed by the Morningness-Eveningness Questionnaire [MEQ]; Horne & Östberg, 1976) may be as a risk factor for depression, we investigated the relationship between depression and circadian phenotype (chronotype and social jetlag) by assessing the BDI scores of a rural population (N = 4051). Most prior studies investigating these relationships have focused on urban populations and assessed circadian timing as subjective daily preferences using MEQ scores (Chelminski et al., 1999; Giannotti et al., 2002; Hidalgo et al., 2009; Kitamura et al., 2010). Here, we investigated chronotype, social jetlag, and depression scores in a rural population homogeneous in respect to culture, socioeconomic factors, and daily light exposure. Characterization of chronotype and social jetlag was based on quantitative assessments of sleep-wake behavior by the Munich ChronoType Questionnaire (MCTQ). All variables were normalized for age and sex.

METHODS

Study Population

Participants were locals of 12 counties in the Taquari Valley (Brazil) of European descents (Germans and Italians) whose ancestors immigrated to this region between 1824 and 1870. The study was performed according to international ethical standards (Portaluppi et al., 2010) between February 2008 and July 2010. Ethics approval was obtained from the local internal review board and all participants signed an informed consent form.

From the initial 6505 participants, 4051 subjects (1340 men and 2711 women; age: 44.1 ± 13.4 yrs [mean ± SD], and age range from 18 to 65 yrs) were included in this study. Exclusion criteria were (1) incomplete information; (2) ages <18 or >65 yrs; (3) night shiftwork; (4) use of an alarm clock on free days; (5) sleep duration <3 h or >14 h; and (6) use of sleep or psychoactive medication (Supplementary Table 1).

The majority of the population works as farmers (N = 1526; 38%), followed by housekeeping (N = 839; 21%) and "informal jobs," defined as irregular, unregistered, temporary, or part-time work (N = 605; 15%). The remaining 26% (N = 1081) are factory workers, sales people, health care or community workers, full-time students, retired, or jobless.

Instruments

Depression scores (BDI) and sleep-wake behavior (MCTQ) were assessed by trained interviewers using questionnaires.

The Beck Depression Inventory

The Beck Depression Inventory (BDI; Beck et al., 1996) is a self-report scale assessing cognitive, affective, and somatic symptoms of depression (Lasa et al., 2000). It consists of 21 items, whereby each question is assigned to a score ranging from 0 (no symptoms) to 3 (severe symptoms of depression), with a final score between 0 and 63. The Portuguese version was validated in Brazil (Gorenstein & Andrade, 1996). The BDI's screening categories are 0–9 = no or minimal depressive symptoms;

TABLE 1. Prevalence of depression symptoms in the study population accordingly to BDI scores

Classification of BDI scores (points)	Men % (N)	Women % (N)	Total % (N)
Minimal or nondepression symptoms (<10)	90.75 (1216)	81.19 (2201)	84.35 (3417)
Mild depressive symptoms (10 to 16)	7.61 (102)	13.72 (372)	11.70 (474)
Moderate depressive symptoms (17 to 29)	1.42 (19)	4.39 (119)	3.41 (138)
Severe depressive symptoms (≥30)	0.22 (3)	0.70 (19)	0.54 (22)
Sum	33.08 (1340)	66.92 (2711)	100 (4051)

BDI = Beck Depression Inventory.

10–16 = mild depressive symptoms; 17–29 = moderate depressive symptoms, and 30–63 ± severe depressive symptoms (Lasa et al., 2000).

The Munich ChronoType Questionnaire

Chronotype was assessed with the Brazilian-Portuguese version of the Munich ChronoType Questionnaire (MCTQ) (http://www.bioinfo.mpg.de/wepcronotipo/). The calculated mid-sleep time on free days (MSF) of the MCTQ correlates well with the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Zavada et al., 2005). The MEQ assesses subjective daily preferences and results in a Morningness-Eveningness score. These preferences are based on when people prefer to be active or to rest. It does not differentiate between workdays and work-free days, and the questions emphasize subjects' rest-activity behavior in relationship to others.

In contrast, the MCTQ assesses actual sleep times (not bed times), separately for work and free days, and results in a time-based variable, the mid-sleep phase on free days (MSF), which correlates well with entrained circadian phase. As a refined chronotype assessment, MSF is corrected for sleep deficits accumulated during the work week (Roenneberg & Merrow, 2007). Subjects are asked to judge their sleep habits over the prior 2 wks. MSF_{sc} (Mid-Sleep phase on Free days Corrected for the Sleep deficit accumulated during the work week) provides a quantitative measure of chronotype as a continuous, time-based variable (Allebrandt & Roenneberg, 2008). The continuous distribution of MSF_{sc}, with extreme early and late types on either end, is population specific. The MCTQ-assessed information allows the calculation of "social jetlag," defined as the discrepancy between social and endogenous time (absolute difference in hours between the uncorrected MSF and mid-sleep on work days; Wittmann et al., 2006). Average weekly outdoor light exposure ("without a roof above your head") was calculated by averaging the information for work and free days over the week. In addition to the BDI and MCTQ questionnaires, we assessed the participants' smoking and alcohol consumption status, as well as pesticide exposure (yes/no).

Data Treatment

Both chronotype and BDI scores are age and sex dependent (Figure 1A and B; Figure 2) and were, therefore, normalized based on the respective curve fits: MSF_{sc}: $y = -(2 \times 10^{-5})x^3 + 0.0036x^2 - 0.2578x + 8.6317$ for men, and $y = -(2 \times 10^{-5})\ x^3 + 0.0038x^2 - 0.2299x + 7.3658$ for women; BDI for the age range 18–29 yrs: $y = 0.014x^2 - 0.654x + 10.8$ for men, and $y = 0.0322x^2 - 1.241x + 16.84$ for women; BDI for the age range 30–65 yrs: $y = -0.0004x^3 + 0.0568x^2 - 2.4935x + 39.117$ for men, and $y = -0.0001x^3 + 0.0164x^2 - 0.6964x + 14.673$ for women. Fits for BDI were more precise when done separately (Figure 1A) for the age groups of 18–29 yrs (women: N = 539, $r^2 = 1$; men: N = 221, $r^2 = 1$), and subjects >29 yrs (women: N = 2172, $r^2 = 0.81$; men: N = 1119, $r^2 = 0.90$). BDI_{as} (BDI adjusted for age and sex) indicated how early or late individuals were in relation to the average population BDI values for a specific sex or age group. BDI_{as} had a slightly skewed distribution and ranged from –35 to 77 and was, therefore, analyzed by nonparametric statistics.

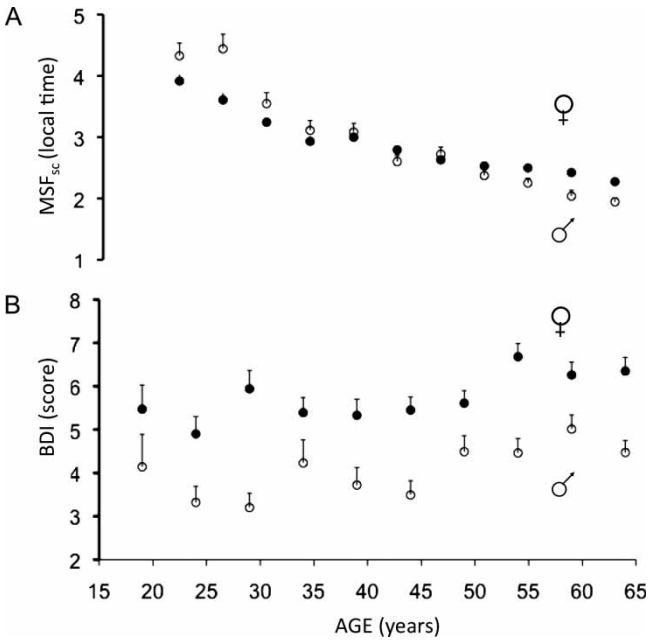

FIGURE 1. Distribution of MSF_{sc} (A) and BDI (B) by age and sex. Filled circles = women; open circles = men. MSF_{sc} = mid-sleep on free days corrected for sleep debt on work days (4-yr bins); BDI = Beck Depression Inventory (5-yr bins). Bars represent the standard error of the mean (SEM).

The distribution of MSF_{sc} times was close to normal, ranging from 23:00 h to 10:15 h (mean ± SD: MSF_{sc} time

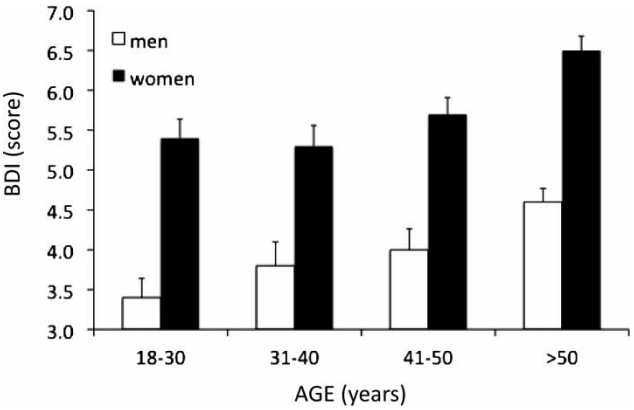

FIGURE 2. BDI average scores for women and men for different age groups in the study population.

= 2.76 ± 1.17 h). Similar to the BDI scores, MSF and MSF_{sc} correlated strongly with age in both women (N = 2711, $r^2 = 0.84$) and men (N = 1340, $r^2 = 0.93$) as shown in Figure 1B. MSF_{sas} (MSF adjusted for the work week sleep deficit, age, and sex) indicated how early or late individuals were in relation to the average population MSF_{sc} values normalized for age and sex, ranging from −4.38 to 6.49 (mean ± SD: −0.21 ± 1.18 h). The distribution of MSF_{sas} values was also close to normal. We conducted the normalizations not only based on means, as shown in the figures, but also based on medians, which produced the same results (data not shown). For comparison purposes, we defined three categories/types of MSF_{sas}, each representing a third of the total population (early: N = 1337; intermediate: N = 1365; and late: N = 1349), as well as three groups of social jetlag (≤2 h: N = 3674; 2–4 h: N = 320; and >4 h: N = 57). Similarly, we analyzed three categories of BDI scores (indicating no symptoms, minimal symptoms, and mild to severe symptoms) in their relationship to chronotype (MSF_{sc}) and social jetlag. Analyses were conducted independently for women and men for the four age groups (18–30 yrs of age: 241 men and 593 women; 31–40 yrs of age: 216 men and 520 women; 41–50 yrs of age: 286 men and 631 women; and >50 yrs of age: 597 men and 967 women). We also assessed individual average daily light exposure and its relation to BDI scores, and the influence of smoking status on the relationships of MSF_{sas} and social jetlag with BDI_{as}.

Statistical Analysis

For comparisons of frequency differences between categorical variables, we used chi-square. Variables with skewed or nearly skewed distributions (BDI_{as}, BDI, social jetlag, light exposure, and MSF_{sas}) were analyzed with the following tests: Spearman's correlations, independent-samples median test, Mann-Whitney *U* test; and Kruskal-Wallis one-way analysis of variance (ANOVA) test. The distribution of BDI_{as} values was compared between chronotype (MSF_{sas}) and social jetlag groups using the Kruskal-Wallis test. The MSF_{sc} and social jetlag distributions were compared between BDI categories with the Kruskal-Wallis test and independent-samples median test. Data were analyzed using SPSS version 18.0 (SPSS, Chicago, IL). For all analyses, statistical significance was $p < .05$.

RESULTS

Approximately 84% of the sample population scored in the lowest category of the BDI scale (≤9 points), and only 3.95% (N = 160) scored ≥17 points (moderate to severe depressive symptoms; Table 1). Alcohol consumption and pesticide exposure were not overrepresented in the group scoring ≥10 points in relation to those with lower BDI scores (total N = 3417 vs. 634; alcohol consumers 42% vs. nonconsumers 52%; and pesticide users 37% vs. nonusers 42%). There were, however, more smokers among subjects scoring ≥10 points than those with lower BDI scores (20% vs. 12%; $\chi^2_{(df = 2)} = 32.5$, $p < .0001$).

As shown in Figure 2, BDI scores significantly increased with age (Mann-Whitney *U* test, $p < .001$) for both sexes up to age 51 yrs, with women scoring on average significantly higher in all age groups (Mann-Whitney *U* test, $p < .01$). BDI scores were independent of average daily light exposure in all age groups except for men >50 yrs, whose scores decreased with increasing light exposure (Kruskal-Wallis test, $p = .006$). We, therefore, normalized the BDI scores for age and sex (BDI_{as}; see Methods).

As shown in Figure 3, upper graph, BDI_{as} showed a positive correlation with the MSF_{sas} ($r = 0.149$, $p < .0001$). The distribution of BDI_{as} values differed significantly for early, intermediate, and late types (Table 2). The significance of these relationships persisted when analyzed separately for smokers and nonsmokers (N = 533, Kruskal-Wallis test $\chi^2_{(df=2)} = 15.6$, $p < .0001$; and N = 3518, Kruskal-Wallis test $\chi^2_{(df = 2)} = 69.8$, $p < .0001$, respectively). The BDI_{as} medians were higher for late chronotypes compared to intermediate and early chronotypes (Table 2; median test $\chi^2_{(df=2)} = 77.7$, $p < .0001$).

As showed in Figure 3, lower graph, social jetlag showed a positive correlation with both MSF_{sas} ($r = 0.381$, $p < .0001$) and BDI_{as} ($r = 0.297$, $p < .0001$). BDI_{as} was significantly higher in subjects with >2 h of social jetlag than in the rest of the population (Table 2), independent of smoking status (Kruskal-Wallis test: for smokers N = 533, $\chi^2_{(df=2)} = 13.8$, $p = .001$; and nonsmokers: N = 3518 $\chi^2_{(df=2)} = 176$, $p < .0001$). The later the chronotype (MSF_{sas}) or greater the social jetlag, the higher the individuals ranked in relation to BDI_{as} means (Table 2). Although the association between BDI_{as} and social jetlag was significant in all three chronotype categories (early: N = 1337; intermediate:

TABLE 2 Independent-sample Kruskal-Wallis one-way ANOVA test

Dependent variable: BDI_{as}		N	BDI_{as} mean ± SD	Mean rank	Chi-square	Significance
Grouping by chronotype (MSF_{sas})						
	Early type	1337	−2.939 ± 18.32	1886	100.27	1.67×10^{-22}
	Intermediate type	1365		1905		
	Late type	1349		2286		
Grouping by social jetlag (h)						
	≤2 h	3674	−2.939 ± 18.32	1945	189.19	8.26×10^{-42}
	>2–4 h	320		2779		
	>4 h	57		2992		
Subpopulations of chronotypes/social jetlag						
Early type	≤2 h	1310	−4.062 ± 19.46	663	16.59	2.49×10^{-4}
	>2–4 h	25		973		
	>4 h	2[a]		905		
Intermediate type	≤2 h	1311	−4.550 ± 17.71	668	46.22	9.15×10^{-11}
	>2–4 h	50		1034		
	>4 h	4[a]		1111		
Late type	≤2 h	1053	−0.196 ± 17.46	624	85.55	2.64×10^{-19}
	>2–4 h	245		841		
	>4 h	51		934		

[a]Number of observations was too small for the statistics, but the groups ≤2 h and >2–4 h were large enough to indicate differences in the BDI_{as} distribution. BDI_{as} = Beck Depression Inventory normalized for age and sex. Groups were defined as described on the methodology. MSF_{sas} = mid-sleep phase on free days adjusted for the sleep deficit accumulated during the work week, age, and sex.

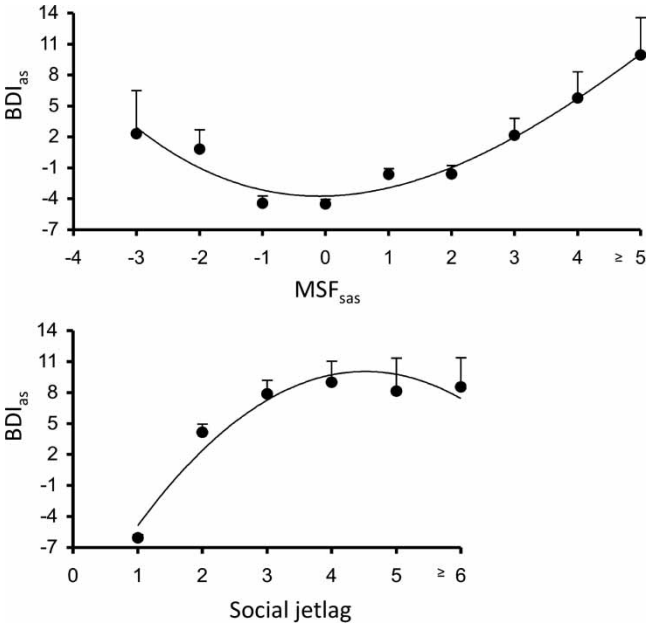

FIGURE 3. MSF_{sas} (1-h intervals) and social jetlag (1-h intervals) plotted against BDI_{as} normalized values. BDI_{as} was higher among late types (upper graph). MSF_{sas} = mid-sleep on free days adjusted for sleep dept of work days, age, and sex; BDI_{as} = Beck Depression Inventory adjusted for age and sex.

N = 1365; late: N = 1349), as shown in Table 2, the association between BDI_{as} and chronotype (MSF_{sas}) was only significant in the lowest of the three social jetlag categories (≤2 h: N = 3674; 2–-4 h: N = 320; >4 h: N = 57; BDI_{as} = 4.08 ± 17.81 [mean ± SD]; Kruskal-Wallis test $\chi^2_{(df=2)} = 47.5$, $p < .0001$).

To complete the differential analysis of BDI, chronotype, and social jetlag, we analyzed three groups of BDI scores (no symptoms: N = 461; minimal symptoms: N = 2956; and mild to severe symptoms of depression: N = 634), separately for men and women and for the four age groups (see Methods), in order to control for age and sex differences. In the highest BDI category, both men and women had a significantly later MSF_{sc} and more severe social jetlag than in the other two BDI categories, specifically in the age group of 31–40 yrs (median test, $p < .05$ for both sexes), as shown in Table 3. Subjects with a social jetlag or MSF_{sc} greater than the population median were overrepresented in the group with mild to severe depression symptoms (Table 3). A comparison for all age groups regarding the distributions of the MSF_{sc} and social jetlag in the different BDI categories, again, only showed significant differences for 31–40-yr-old participants. The distribution of MSF_{sc} was significantly different between BDI categories for both women and men (Kruskal-Wallis test: for women $\chi^2_{(df=2)} = 8.1$, $p = .017$; for men $\chi^2_{(df=2)} = 6.8$, $p = .034$). In this age group, the social jetlag distribution between BDI categories only differed in men (Kruskal-Wallis test: $\chi^2_{(df=2)} = 13.0$, $p = .002$). There were no discrepancies in sample size of the age groups investigated, and the lowest number of observations per BDI categories, for the respective age groups, was 16 for men and 63 for women.

TABLE 3. Independent-samples median test statistics for men vs. women

Dependent variables (medians for men/ women)	Grouping variable BDI scale (points)	Median test statistics: men (women) No symptoms (0)	Minimal symptoms (1–10)	Mild to severe symptoms (>10)	Chi-square (2 *df*)	Asymptotic significance
MSF_{sc} (2.81/2.87)	>Median	14 (26)	83 (185)	11 (49)	7.322/ 6.562	0.026/0.038
	≤Median	28 (40)	75 (188)	5 (32)		
Social jetlag (0.75/0.75)	>Median	9 (26)	86 (158)	9 (47)	14.929/7.389	0.001/0.025
	≤Median	33 (40)	72 (215)	7 (34)		

Median test statistics for men and women from age group 31–40 yrs. Total N of men = 216, and women = 520. MSF_{sc} = mid-sleep phase on free days adjusted for the sleep deficit accumulated during the work week (local time). Social jetlag medians are given in h.

DISCUSSION

In our study population, BDI scores and chronotype correlated positively, as reported before for an urban Brazilian population (Hidalgo et al., 2009). This is the first study, however, to show associations between BDI scores and social jetlag (misalignment of the biological and social time). It is not surprising that both chronotype and social jetlag were found to be related to BDI score, as late chronotypes tend to be misaligned to early work times and sleep at very different times on free days, thus chronically experiencing social jetlag. Uniquely, the dependencies of the circadian phenotypes and BDI scores on age and sex were addressed and incorporated in our analyses. Children are generally early chronotypes, drastically delaying during puberty and adolescence (Roenneberg et al., 2004). Around the age of 20 yrs, people become progressively earlier chronotypes once again, with women being on average of earlier chronotype than men up to the age of 50 yrs (Roenneberg et al., 2004). These general tendencies were also true for our Brazilian study population, but the age when men and women became similar chronotypes, again, was at an earlier age (45 yrs). The prevalence of depressive symptoms increased significantly after the age of 50 yrs in both sexes. But, on average, women had higher BDI scores than men, supporting earlier results (Camozzato et al., 2007). These age dependencies of chronotype (Roenneberg et al., 2004) and depression (Soria & Urretavizcaya, 2009) have been associated with hormonal changes. We, therefore, addressed the confounding effects of age and sex on chronotype and BDI scores by our normalization procedure, or by testing hypotheses independently for women and men of four age groups. The relationship between BDI scores and circadian phenotype (chronotype), or its misalignment (social jetlag), was specifically stronger for subjects 31 to 40 yrs old, indicating these relationships are age dependent.

Additionally, both circadian timing and depression have been shown to depend on light exposure (Benedetti et al., 2007; McClung, 2007; Roenneberg & Merrow 2007; Roenneberg et al., 2007b). We, therefore, also assessed how much time participants spent outdoors in daylight. Average outdoor light exposure of participants was similar for all BDI categories up to the age of 50 yrs, and at older ages only men showed a negative correlation between outdoor light exposure and BDI scores, *i.e.*, could profit from brighter light. Most of our participants either worked as farmers or housekeepers in a small rural community, indicating that they were exposed to more outdoor light throughout the year than urban populations. Indeed, the prevalence of moderate to severe depressive symptoms was less than half that in urban Brazilian populations from equivalent geographic locations (Mari & Williams, 1986). Besides light exposure, the strong social networks and socioeconomic homogeneity, typical for small rural communities, may also play a role in keeping depressive symptoms low.

Smoking and drinking habits were correlated with the manifestation of depression symptoms in cross-sectional studies (Pratt & Brody, 2010; Schneider, 2010; Wittmann et al., 2006). A correlation between social jetlag and well-being was also reported (Wittmann et al., 2006), and a subsequent reanalysis of the same data in relation to substance use indicated that the increased psychological distress of late chronotypes correlated with their smoking and drinking habits (Wittmann et al., 2010). In our study, subjects who scored mild to severe depression symptoms were, indeed, more likely to smoke (but less likely to drink alcohol) compared to subjects having lower BDI scores. However, nicotine consumption status had no impact on the association between BDI_{as} and chronotype or social jetlag. Nevertheless, BDI_{as} increased with social jetlag, independently of chronotype, indicating a relationship between circadian misalignment and mood disorders. Consistent with this finding is the observation that rigid sleep schedules had an antidepressive effect in clinically depressed patients (Boivin et al., 1996; Zeitzer et al., 2000).

Confounders and Exclusion Criteria

First of all, our observations were based on a cross-sectional study, and, therefore, we are limited to report associations found without making causal relationships. Second, mood disorders are complex traits, and a combination of genetic and environmental interactions will contribute to the manifestation of depressive symptoms.

In this essentially rural population, pesticide handling is a common practice, and both acute and chronic pesticide exposure could contribute to the manifestation of depressive symptoms (Beseler et al., 2008). Symptoms of depression were, however, not more prevalent among subjects handling pesticides, indicating that this variable was not a confounder. We had no assessments, however, to quantitatively evaluate the influence of pesticides use or alcohol and nicotine consumption on the manifestation of depression scores, or on their relationship with circadian phenotype.

We applied exclusion criteria for the quality control of phenotype data as follows: (i) for sleep/wake times to reflect endogenous time, subjects must report wakeup times without the use of alarm clock on free days; (ii) too short or too long sleep duration compromises sleep/wake times so that the mid-sleep measure becomes unreliable to estimate chronotype; (iii) night shiftworkers have their sleep/wake times dictated by their work schedule, so that even when having free days within a week, they will still suffer from the aftereffects of being pushed against their endogenous time during the work days; and (iv) chronotype changes strikingly throughout life (Roenneberg et al., 2007a). We excluded very young and elderly subjects to reduce heterogeneity of our sample. Additionally, we excluded subjects using sleep and psychoactive drugs to avoid interference with the sleep-wake cycle. Consequently, we excluded (indirectly) subjects being treated for mood disorders, with minor implications for our study, as our goal was not to have a sample of clinically depressed subjects. We also are aware, however, that interviewing subjects, instead of using self-assessment, could influence the reliability of answers. Nevertheless, interviewers could help with the subject's interpretation of the questions, probably compensating the validity of the interview assessments in relation to self-assessment.

CONCLUSION

In summary, our results indicate that misalignment of the circadian and social timing may be a risk factor for developing depression, especially in 31- to 40-yr-olds. These relationships should be further investigated in longitudinal studies to reveal if the reduction of social jetlag should be part of prevention strategies.

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SUPPLEMENTARY TABLE 1. Pharmacological sleep agents. Drug groups and correspondent ATC codes used as exclusion criteria when selecting phenotyped subjects for this study.

Drug groups	Pharmacological ATC codes
Benzodiazepines	N05CD, N05CF
Barbiturates	N01AF, N01AG, N03AA, N05CA, N05CB, N05CX
Imipramine	N06AA02, N06AA03, N06AA06
Nortriptyline	N06AA10
Neuroleptics	N05AK
Phenothiazines	N05AB, N05AC, N05AA
Fluoxetine	N06AB03
Sertraline	N06AB06
Paroxetine	N06AB05
ß-Blockers, propranolol	C07, S01ED
Theophylline	R03DA04
Amphetamine	N06B