RESEARCH ARTICLE

Sleep Problems in Adults With Autism Spectrum Disorder and Intellectual Disability

Pura Ballester, María José Martínez, Auxiliadora Javaloyes, María-del-Mar Inda, Noemí Fernández, Pilar Gázquez, Víctor Aguilar, Agustín Pérez, Luís Hernández, Amanda L. Richdale, and Ana M. Peiró

Sleep problems (SP) are recognized as a common comorbid condition in autism spectrum disorder (ASD) and can influence core autism symptoms and mental and physical health. SPs can be lifelong and have been reported that adults on the autistic spectrum with and without intellectual disability (ID) present SPs (longer sleep latency, frequent night awakenings, and circadian rhythm sleep–wake disorders).

A prospective, objective sleep study was conducted in 41 adults with ASD (33 ± 6 years old) and ID and 51 typically developing adults (33 ± 5 years old) using ambulatory circadian monitoring (ACM) recording wrist temperature, motor activity, body position, sleep, and light intensity. The findings indicated that individuals with ASD presented sleep difficulties including low sleep efficiency, prolonged sleep latency and increased number and length of night awakenings, together with daily sedentary behavior, and increased nocturnal activity. Furthermore, indications of an advanced sleep–wake phase disorder were found in these autistic adults. Examining sleep and markers of the circadian system showed significant differences between adults with ASD and ID and an age-matched, healthy adult population. The sleep disturbances described for this sample of adults with ASD and ID are similar to those of already described for adults with ASD without ID; their relationship with intellectual ability should be further studied. Improving knowledge of sleep patterns in ASD adults with ID might help to designed targeted interventions to improve their functioning and reduce family stress. ***Autism Res*** *2018*. © 2018 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: SPs are very frequent in autism from childhood to adulthood. We recorded sleep with a watch-like device in adults with autism and ID and compared sleep patterns with nonautistic volunteers. Results showed poorer sleep conditions in adults with autism (increased sleep latency and number/length of night awakenings) that resulted in decreased sleep efficiency. Increasing knowledge of the SPs in adults on the autism spectrum will allow to improve their and their families' quality of life.

Keywords: autism spectrum disorder; intellectual disability; sleep problems; circadian rhythm; circadian rhythm sleep–wake disorder

Introduction

Sleep problems (SPs) are common comorbid symptoms in individuals with autism spectrum disorder (ASD) and can impair social behavior [Buck et al., 2014; Cortesi, Giannotti, Ivanenko, & Johnson, 2010; Couturier et al., 2005; Hollway, Aman, & Butter, 2013; Matson, Wilkins, & Ancona, 2008b; Tani et al., 2004], cognitive daytime performance ([Limoges, Bolduc, Berthiaume, Mottron, & Godbout, 2013], and quality of life [Adkins et al., 2012; Kuhlthau, McDonnell, Coury, Payakachat, & Macklin, 2017; May, Cornish, Conduit, Rajaratnam, & Rinehart, 2015]). SPs can be lifelong with a prevalence in childhood ranging up to 86% [Souders et al., 2017], whereas 44.7% of 168 autistic adults with severe intellectual disability (ID) were reported to have SPs using the DASH II questionnaire [Matson et al., 2008a). However, Hare, Jones, and Evershed (2006b) reported that sleep measures in a small group of adults with autism and ID did not differ from adults with ID alone. Similarly, cognitively able autistic adults are reported to have increased insomnia symptoms, including increased sleep latency, poor sleep

From the Department of Health of Alicante-General Hospital, ISABIAL, Neuropharmacology on Pain (NED) Research Unit, Alicante, Spain (P.B., M-.I, A.M.P.); Department of Clinical Pharmacology, Organic Chemistry and Pediatrics, Miguel Hernández University of Elche, Alicante, Spain (P.B., A.M.P.); Chronobiology Lab, College of Biology, Department of Physiology, University of Murcia, IUIE, IMIB-Arrixaca, Murcia, Spain (M.J.M.); Ciber Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain (M.J.M.); EDUCATEA, Education Center for Children and Adolescents with Autism, Mental Health Problems and Behavioral Disorders, Alicante, Spain (A.J.); Angel Rivière Autism Center, Valencia, Spain (N.F.); Infanta Leonor Autism Center, Alicante, Spain (P.G.); San Rafael Autism Center, Santa Faz, Spain (V.A.); Department of Statistics and Financial Resources, Miguel Hernández University of Elche, Alicante, Spain (A.P.); Sleep Unit, Department of Health of Alicante-General Hospital, ISABIAL, Alicante, Spain (L.H.); Olga Tennison Autism Research Centre, School of Psychology and Public Health, La Trobe University, Melbourne, Australia (A.L.R.); Department of Health of Alicante-General Hospital, Clinical Pharmacology, Alicante, Spain (A.M.P.)

Received February 13, 2018; accepted for publication June 18, 2018

Address for correspondence and reprints: Ana M. Peiró, Neuropharmacology on Pain (NED) research group, Hospital General Universitario de Alicante, c/ Pintor Baeza, 12, 03010 Alicante, Spain. E-mail: peiro_ana@gva.es

Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/aur.2000

efficiency, shorter night sleep, and advanced or delayed circadian sleep–wake rhythms [Baker & Richdale, 2015; Baker & Richdale, 2017; Goldman et al., 2017; Hare et al., 2006a, 2006b; Limoges, Mottron, Bolduc, Berthiaume, & Godbout, 2005; Tani et al., 2003). Causes for sleep abnormalities are likely to be multifactorial, such as neurotransmitter abnormalities (e.g., serotonin) [Anderson & Lombroso, 2002; Malow et al., 2006), medical problems (e.g., gastrointestinal disorders [Klukowski, Wasilewska, & Lebensztejn, 2015), epilepsy (Kaleyias et al., 2008]), psychopathology [Nadeau et al., 2015; Richdale, Baker, Short, & Gradisar, 2014] or behavioral etiologies (e.g., poor sleep habits [Malow et al., 2012; Reynolds & Malow, 2011]). In children with ASD, SPs can also be a marker of parental stress and one of the main reasons for pharmacological intervention [Schwichtenberg et al., 2013; Valicenti-McDermott et al., 2015]. However, comparisons of sleep patterns between individuals with ASD and the general population have been performed in only a few studies [Baker & Richdale, 2015; Baker, Richdale, Short, & Gradisar, 2013; Limoges et al., 2005], and studies of sleep in adults with ASD and comorbid ID are lacking.

The sleep–wake cycle is a circadian rhythm. Circadian rhythms are physiologic or behavioral cycles with a recurring periodicity of approximately 24 hr and can be measured as daily oscillations of hormones (melatonin, cortisol), core body temperature, rest-activity cycles or transcriptome patterns [Bhadra, Thakkar, Das, & Pal Bhadra, 2017]. There is good evidence that circadian rhythm sleep–wake disorders (CRSWDs) play a role in many psychiatric illnesses such as depression, posttraumatic stress disorder, and eating disorders, which are often comorbid with ASD [Schuch, Genro, Bastos, Ghisleni, & Tovo-Rodrigues, 2017]. These CRSWDs are characterized by blunted amplitude and altered circadian phase [Boivin, 2000; Wirz-Justice, Bromundt, & Cajochen, 2009]. To date, information concerning circadian sleep–wake cycles in individuals with ASD is scarce. A small number of children with autism are reported to have SPs suggestive of a CRSWD [Souders et al., 2009; Wiggs & Stores, 2004], and in adults, circadian sleep–wake disturbances also have been indicated in a small number of individuals [Hare et al., 2006a, Limoges et al., 2005]. Most recently, Baker and Richdale (2017) reported that 44.4% of cognitively able autistic adults met criteria for a CRSWD, primarily delayed sleep wake rhythm disorder, but nothing is known about adults with ASD and comorbid ID.

Sleep can be assessed using subjective (e.g., questionnaires or sleep diaries) or objective measures (e.g., actigraphy, ambulatory circadian monitoring (ACM), or polysomnography (PSG)). In this study, ACM devices were used, because they are wearable, generally well-tolerated, and able to estimate participants' sleep in the home environment [Anders, Iosif, Schwichtenberg, Tang, & Goodlin-Jones, 2011; Jean-Louis, Kripke, Cole, Assmus, & Langer, 2001]. Furthermore, it has been reported that values obtained with ACM are closer to PSG sleep estimations than actigraphy records [Ortiz-Tudela, Martinez-Nicolas, Albares, et al., 2014a; In addition, ACM is considered as more reliable than sleep diaries and is currently widely accepted [Ancoli-Israel et al., 2003; Tsuchiyama, Nagayama, Kudo, Kojima, & Yamada, 2003]. It can thus provide sleep information that may be otherwise not easily available in individuals with ASD and ID.

Thus, the aim of our study was to compare circadian rhythms and sleep patterns in adults with ASD and ID with those of typically developing adults using ACM. The results from this study will contribute to a better understanding of SPs in adults with ASD across the spectrum and therefore help to prevent or treat sleep difficulties in this population.

Table 1. Participants' Demographic Information.

	ASD	Control
	n = 41	*n* = 51
Gender (*n*)		
Male	31	21
Female	10	30
Age (years old)	33 ± 6	33 ± 5
BMI (Kg/m2)	24.4 ± 1	23.2 ± 0.6

ASD: autism spectrum disorder; BMI: body mass index. Data are expressed as mean ±SD or as counts.

Methods

Participants

Forty-one individuals with ASD and ID (78% male, body mass index (BMI): 24.4 ± 1 Kg/m^2) aged between 27 and 39 years old and 51 adults with normal intellectual functioning and no diagnosis of mental or physical health problems (41% male; BMI: 23.2 ± 0.6 Kg/m^2) with ages from 28 to 38 years old were included in this study. Demographic data are summarized in Table 1.

Procedure

Following Hospital Ethics Review Board approval, all participants, or their legal guardians received information about the design and purpose of the study, and participants or legal guardians' informed consent were obtained. The study was performed in accordance with the principles of the Helsinki Declaration.

Participant recruitment and inclusion criteria. The adults on the autism spectrum were recruited from Spanish autism associations after researchers met with parents and carers (93%), from clinics specializing in adults on the spectrum (5%) and via social media (2%); all participants were resident across three institutions for adults with ID. The control group was composed of typically developing adults recruited from the same

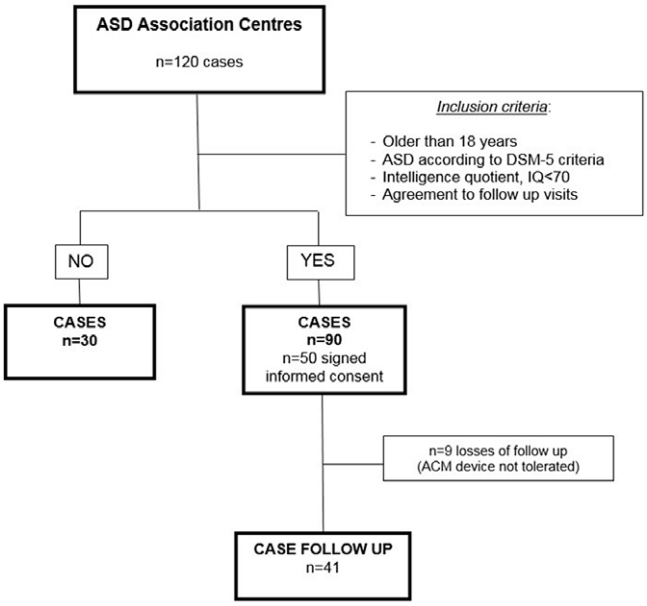

Figure 1. Flow chart of ASD sample selection.

geographical area who were also participating in a longitudinal study being conducted by the Chronobiology group at Murcia University. The study information provided to participants emphasized that no SP was required to participate in this sleep study.

Inclusion criteria for the adults with ASD (Fig. 1) were aged from 18 to 45 years; agreement to an initial clinic visit, and a previous diagnosis of ASD substantiated using the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) criteria for ASD. Diagnosis based on DSM-5 criteria was confirmed by a clinician from the individual's residential facility and by a psychiatrist from our research team. ID (intelligence quotient (IQ) <70) for the adults with ASD was confirmed from medical records of professionals from the Spanish social services. Adults on the autism spectrum continued to take their regular medications during the study, but individuals taking any sleep medication or melatonin were excluded from the study. Either no participant in the control group had a clinically significant medical or psychiatric condition or was taking any psychotropic medications. The inclusion criteria for the control group were age ≥ 18–45 years, agreement to an initial clinical visit and that their data would be included in this study.

Participants in both groups could withdraw from the study at any time. In both groups, those with any medical condition that was incompatible with the study conditions were excluded.

The study was conducted from February 2012 to December 2013, excluding summer (June to –August) because weather could affect the accuracy of the temperature sensor. During the first visit, demographic information (age, sex, body weight, height, and job status) and current medications were ascertained. Thirty-three (80%) participants with ASD reported various comorbid clinical diagnoses (epilepsy, depression, and aggressive behavior) and

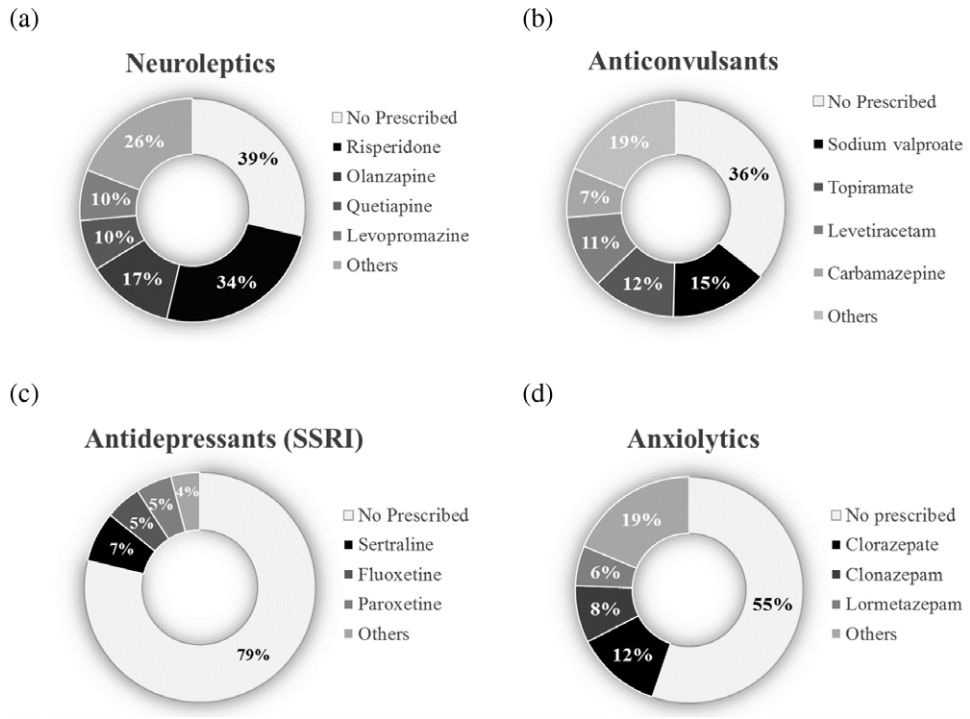

Figure 2. Categorization of medications prescribed to ASD participants with potential effects on sleep: neuroleptics (a), anticonvulsants (b), selective serotonin reuptake inhibitor (SSRI) antidepressants (c), and anxiolytics (d).

were taking medications associated with them. Figure 2 presents the different medications with potential effects on sleep (increasing sleep or somnolence) taken by ASD participants. Other drugs taken by ASD participants but without potential effects on sleep were proton pump inhibitors (17%), anticholinergic agents (22%), ß-agonists (2%), and/or ß-blockers (2%). No participant was receiving cognitive behavioral therapy, so sleep was not influenced by this factor.

Ambulatory circadian monitoring

The ACM device (Kronowise) has three different sensors. The first measures wrist temperature (Thermochron iButton DS1921H, ±°C accuracy, and sampling every 10 min; [Carrier & Monk, 1997]. The second is an actimeter that estimates motor activity using degrees of change in position and body position using the angle between the X-axis of the actimeter (90° verticality) and the horizontal plane (0° maximum horizontality), (HOBO Pendant G Acceleration Data Logger UA- 004-64, three-channel logger (*X*-, *Y*-, *Z*-axes) with eight-bit resolution, programmed to record data every minute; [Edgar & Dement, 1991; Mormont et al., 2000]. The actimeter information was analyzed defining two variables: motor activity and body position [Bonmati-Carrion et al., 2015; Carvalho Bos, Waterhouse, Edwards, Simons, & Reilly, 2003]. The third sensor measures light intensity (HOBO Data Logger UA-002 64, it has a measurement range of 0–320 000 lux, measured in 30-s intervals; [Martinez-Nicolas, Ortiz-Tudela, Madrid, & Rol, 2011].

Van Someren nonparametric indexes and sleep parameters were calculated from the data recordings. The information stored in the Thermochron iButton, the actimeter, and light sensor was transferred to a personal computer using the software provided by the manufacturer through an adapter (DS1402D-DR8; IDC, Spain) or an optical USB Base Station (MAN-BASE-U-4, HOBO). The Circadianware software implemented in the Kronowizard platform (https://kronowizard.um.es/) calculated the single integrated variable, TAP, from the integration of wrist temperature (inverted), motor activity and body position where maximum values should occur at the same time of the day and indicate a high level of activation (values near 1) or complete rest and sleep (around 0) [Lopez, Jaussent, & Dauvilliers, 2014; Ortiz-Tudela, Martinez-Nicolas, Albares, et al., 2014a]. For computing TAP values, motor activity and body position data were added up and averaged, respectively, in 10-min intervals (matching wrist temperature sampling rate). Sleep was inferred from TAP and converted into a binary code, with 1 corresponding to a resting period and 0 to an active period [Ortiz-Tudela, Martinez-Nicolas, Albares, et al., 2014a; Sarabia, Rol, Mendiola, & Madrid, 2008; Scheer, Wright Jr., Kronauer, & Czeisler, 2007].

All participants were asked to follow their usual routines and wore the ACM device on the wrist of their nondominant arm for 7 days. The ACM was removed during showering or any other activity where the ACM might get wet; data were filtered to eliminate erroneous measurements produced by its temporary removal. In addition, control participants, completed a 7-day, sleep–wake diary (mornings and evenings) and in case of the adults with ASD, a parent or caregiver was responsible for completing each participant's sleep diary. Sleep diaries were used as a backup for the ACM recordings if needed.

The sleep parameters calculated were (a) total sleep time (TST, normal value between 420 and 540 min), defined as the number of minutes registered as sleep between sleep onset and sleep offset during the night (similar to PSG sleep period time); (b) time in bed (TIB, normal value from 420 to 569 min), total minutes in bed until sleep offset; (c) sleep onset latency (SoL, normal value <30 min) the time until sleep onset at night; (d) number of awakenings after sleep onset (normal value 0–1 number), number of awakenings during the TST interval; (e) awake period duration after sleep onset duration (WASO, normal value <20 min), the awake period length in minutes during the TST interval; and (f) sleep efficiency (SE, normal value ≥85%), calculated as the ratio of TST/TIB multiplied by 100. The results of the sleep parameters from all participants were classified as normal or abnormal values according to ranges previously described for the general population [Carskadon & Rechtschaffen, 2000; Natale, Plazzi, & Martoni, 2009; Zhang et al., 2011]. In addition, the time that the person was still in bed after the last sleep episode (residual TIB) was calculated by subtracting TST, SoL, and WASO from the TIB.

Circadian sleep–wake rhythm disorders determination

Nonparametric circadian rhythm analysis is a method for extracting circadian characteristics from the rest-activity cycle (Van Someren & Riemersma-Van Der Lek, 2007; Weitzman et al., 1981). Of major interest is the relative amplitude (RA), as it shows how activity is distributed throughout the day compared with night: the higher the RA, the better the consolidation of daytime activity and nighttime sleep. The RA is calculated from the ratio of the most active 10-hr period (M10) to the least active 5-hr period (L5) across the averaged 24-hr profile. A second characteristic is the inter-daily stability (IS), which quantifies the invariability day by day, that is, how well the sleep–wake cycle is synchronized to supposedly stable environmental cues. Third, intraday variability (IV) gives an indication of the fragmentation of the rhythm. Timing information comes from determining the onset of

the 5 hr with least activity (L5 onset) and onset of the 10 hr with most activity (M10 onset). Finally, the circadian function index (CFI), which assesses circadian rhythmicity status, was calculated as (IS+(2-IV) + RA)/3. CFI has proved to be very sensitive to changes in circadian robustness [Ortiz-Tudela, Martinez-Nicolas, Campos, Rol, & Madrid, 2010; Witting, Kwa, Eikelenboom, Mirmiran, & Swaab, 1990].

Statistical analyses

The Shapiro–Wilk normality test was used as the basis for selection of parametric or nonparametric statistical tests. Continuous variables are presented as mean ± standard deviation (SD), mean ± standard error (SEM) or median and interquartile range (IQR, $P_{25,}$ P_{75}) according to assessed normality of the variable. Categorical variables are expressed as percentages. A t-test for independent samples or a Mann–Whitney U test was used to assess group differences; effect sizes (η^2, *r*, respectively) and 95% confidence intervals (CIs) are also reported. Frequencies were compared using the Chi-Square test, with Yate's continuity correction as appropriate and X^2 (df, *n*) were reported. All statistical analyses were carried out with R 3.2.4 software and Graph Pad Prism 5.0. *P*-values of <0.05 were considered to indicate significance for all analyses.

As treatments used by adults on the autism spectrum for their comorbidities (neuroleptics, anticonvulsants, antidepressants or anxiolytics) could have potential effects on sleep, comparison analyses of sleep parameters between typically developing controls and adults with ASD with or without comorbidity treatments were conducted using the Student's *t*-test or Mann–Whitney U-test. Acknowledging that the categories of neuroleptics, anticonvulsants, antidepressants, or anxiolytics could embrace several different molecules that could affect sleep in different ways, further intragroup analysis classifying the molecules according to how they affect sleep (positively, negatively or neutral [Brunton, Chabner, & Knollman, 2011]) were conducted by Kruskal–Wallis test.

Results

The ASD group had a median of three comorbidities ($IQR_{25–75}$: 1–4, 38% epilepsy) and five prescribed medications associated with these comorbidities ($IQR_{25–75}$: 2–6, 61% neuroleptics, 51% anticonvulsants, 22% antidepressants and 32% anxiolytic, 20% without treatment Fig. 2). Control group participants were not medicated. There were no significant differences between ASD and control groups with respect to age, but as may be expected, there were significantly more males in the ASD group (X^2 (1, 92) = 13.27, $P = 0.002$). A comparison analysis showed significant differences for ASD participants with and without anxiolytic treatment only for the number of awakenings only ($P = 0.006$, 95% CI:–2.812 to –0.5072, $r = 0.196$). No significant differences for any sleep parameter were found when drug categories (neuroleptics, anticonvulsants, antidepressants, or anxiolytics) were analyzed by their potential effects on sleep (positive, negative, or neutral).

Sleep parameters determination

Comparison of sleep parameter data between ASD and control groups obtained from ACM recordings is presented in Table 2. Significant differences between ASD and control groups were found for all sleep parameters, except TST. The ASD group showed significantly increased TIB, SoL, number of awakenings and WASO than controls and significantly lower SE. Overall, with the exception of WASO, significantly fewer individuals with ASD had sleep parameters in the normal range compared to those in the control group. In spite of the

Table 2. Sleep Parameters Comparison Obtained From ACM Recordings Between Adults with ASD and ID and Control Participants.

Sleep parameters	ASD	Control	*P*-value	*R* or η^2	95% CI
Total sleep time (min)	478 ± 140	457 ± 77	0.064	0.19	
Time in bed (min)	657 ± 182	540 ± 72	**<0.001**	2.74	
Sleep onset latency (min)	60 ±48	14 ±9	**<0.001**	4.85	
Number of awakenings (n°)	3 (2–5)	2 (1–3)	**<0.001**	0.1746	0.71–1.9
Wake after sleep onset (min)	106 ± 74	50 ± 35	**<0.001**	2.13	
Sleep efficiency (%)	70	85	**<0.001**	2.48	
% From normal population range	ASD	Control	*P*-value	X^2	
Total sleep time (420–540 min)	5	72	**<0.001**	40.01	
Time in bed (420–569 min)	16	75	**<0.001**	31.53	
Sleep onset latency (<30 min)	16	95	**<0.001**	59.92	
Number of awakenings (0–1 n°)	3	33	**<0.001**	12.57	
Wake after sleep onset (<20 min)	0	10	0.073	3.77	
Sleep efficiency (≥85%)	5	67	**<0.001**	34.44	

Sleep parameters derived from ACM recordings in participants expressed as mean ± SD. Statistically significant differences were found by Mann–Whitney test or χ^2 test. The significance values of $P < 0.05$ are highlighted in bold. For all parameters X^2 (df, n) equals to (1, 92).

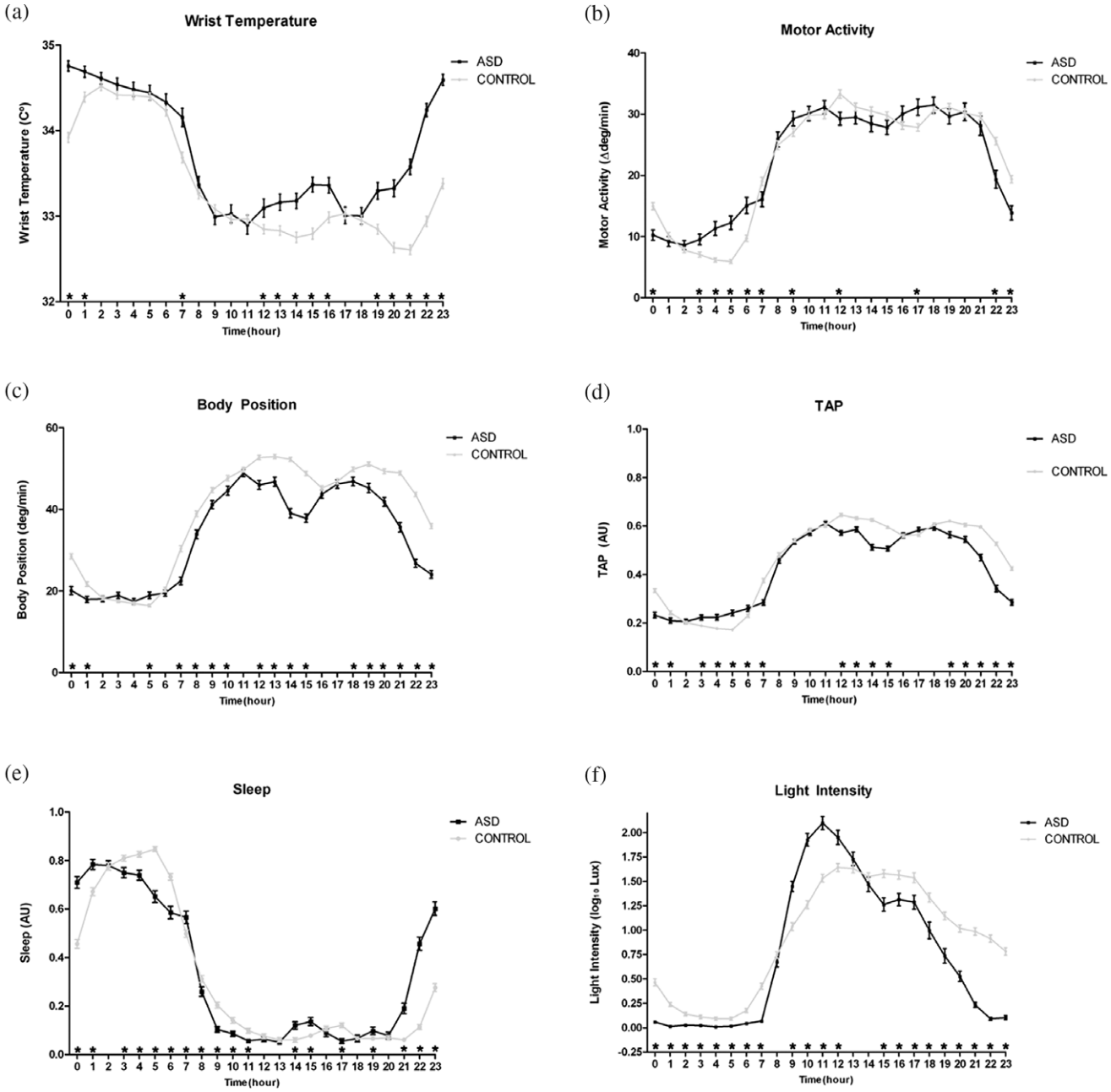

Figure 3. Circadian rhythms from wrist temperature (a), motor activity (b), body position (c), TAP (d), sleep (e), and light intensity (f) in ASD and control subjects.

difference in gender distribution observed between ASD and control groups, differences in sleep parameters were maintained when analyzed by sex ($P \geq 0.05$ only for TST). No differences between males and females within each group were observed ($P \geq 0.05$).

Circadian sleep–wake rhythm disorders determination

Analysis of the circadian rhythms (wrist temperature, motor activity, body position, TAP, sleep, and light intensity) showed significant differences between the ASD and control groups (Fig. 3). The ASD group had higher wrist temperature values with a lower amplitude and a wake maintenance zone (time interval of minimal sleep probability, minimal daily distal temperatures) that appeared earlier than in controls (ASD: 17:00–18:00 hr vs. controls: 20:00–21:00 hr) (Fig. 3a). Lower overall motor activity with less difference between the least (L5) and most active (M10) phases was observed in the ASD group (Fig. 3b). Furthermore, the ASD group showed higher motor activity values between 3:00 and 6:00 hr (Fig. 3b) and body position at 5:00 hr (Fig. 3c). Together, these results point to sedentary daytime behavior in the ASD adults, with nocturnal activation (Fig. 3b,c). As expected,

Table 3. Analysis of Nonparametric Circadian Rhythms Along 24-hr Period in Adults with ASD and ID Compared to Typical Developing Controls.

	Wrist temperature					Motor activity					Body position			
	ASD	Control	*P*-value	*r*		ASD	Control	*P*-value	r		ASD	Control	*P*-value	r
IS	0.44 ±0.04	0.38 ±0.02	**0.048**	0.31	IS	0.29 ± 0.02	0.25 ±0.02	**0.002**	0.69	IS	0.42 ± 0.03	0.41 ± 0.02	0.231	0.04
IV	0.14 ± 0.01	0.21 ± 0.01	**0.001**	0.79	IV	1.02 ± 0.04	1.04 ± 0.02	0.369	0.01	IV	0.42 ± 0.06	0.42 ± 0.02	0.091	0.14
RA	0.28 ± 0.03	0.29 ± 0.02	0.384	0.01	RA	0.72 ± 0.03	0.71 ± 0.02	0.252	0.04	RA	0.49 ± 0.03	0.51 ± 0.02	0.447	0.00
M5	1:07 ± 0:40	4:32 ± 0:38	**<0.001**	1.27	L5	2:37 ± 0:24	3:54 ± 0:11	**0.001**	0.76	L5	2:26 ± 0:39	4:20 ± 0:08	**0.003**	0.61
VM5	34.75 ± 0.16	34.6 ± 0.10	0.208	0.06	VL5	5.42 ± 0.85	5.97 ± 0.55	0.087	0.15	VL5	15.78 ± 1.44	16.92 ± 0.77	**0.035**	0.26
L10	14:35 ± 0:22	18:04 ± 0:31	**<0.001**	0.01	M10	15:58 ± 0:41	15:55 ± 0:30	0.495	0.00	M10	15:12 ± 00:17	15:55 ± 0:13	**0.017**	0.36
VL10	32.79 ± 0.17	32.66 ± 0.13	0.326	0.02	VM10	28.09 ± 2.17	31.56 ± 1.09	**0.024**	0.33	VM10	44.70 ± 1.94	51.52 ± 0.88	**0.001**	0.82
CFI	0.55 ± 0.02	0.52 ± 0.02	0.070	0.18	CFI	0.5 ± 0.02	0.48 ± 0.01	0.128	0.20	CFI	0.58 ± 0.02	0.57 ± 0.01	0.278	0.03
	TAP				**Sleep**					**Light intensity**				
	ASD	**Control**	*P*-value	**r**		**ASD**	**Control**	*P*-value	**r**		**ASD**	**Control**	*P*-value	***r***
IS	0.52 ± 0.03	0.49 ± 0.02	0.133	0.10	IS	0.59 ± 0.03	0.59 ± 0.02	0.352	0.01	IS	0.62 ± 0.06	0.45 ± 0.02	**<0.001**	0.95
IV	0.43 ± 0.04	0.36 ± 0.02	0.139	0.10	IV	0.36 ± 0.03	0.28 ± 0.02	**0.005**	0.54	IV	0.18 ± 0.02	0.29 ± 0.02	**<0.001**	1.64
RA	0.54 ± 0.02	0.56 ± 0.02	0.346	0.01	RA	0.82 ± 0.03	0.89 ± 0.02	**0.028**	0.31	RA	0.97 ± 0.03	0.93 ± 0.02	**0.007**	0.46
L5	2:54 ± 0:19	4:13 ± 0:09	**<0.001**	0.90	M5	00:59 ± 0:55	3:49 ± 0:16	**<0.001**	0.05	L5	2:23 ± 0:13	4:04 ± 0:18	**<0.001**	1.40
VL5	0.18 ± 0.01	0.18 ± 0.01	0.140	0.09	VM5	0.79 ± 0.04	0.85 ± 0.02	0.195	0.31	VL5	0.02 ± 0.01	0.14 ± 0.05	**<0.001**	1.55
M10	14:59 ± 0:20	15:56 ± 0:17	**0.013**	0.40	L10	13:40 ± 0:23	14:56 ± 0:21	0.361	0.12	M10	14:04 ± 0:23	15:25 ± 0:19	**<0.001**	1.57
VM10	0.56 ± 0.02	0.63 ± 0.01	**<0.001**	1.01	VL10	0.12 ± 0.03	0.05 ± 0.01	**0.027**	0.06	VM10	1.43 ± 0.11	1.55 ± 0.09	0.098	0.13
CFI	0.61 ± 0.02	0.63 ± 0.01	0.369	0.00	CFI	0.72 ± 0.03	0.78 ± 0.01	0.051	0.22	CFI	0.80 ± 0.02	0.74 ± 0.01	**<0.001**	**1.35**

IS: inter-daily stability; IV:intra-daily variability; RA: relative amplitude; phase markers: M5 and M10, L5 and L10, indicate consecutive 10- and 5-hr period of maximum and minimum values, respectively, and CFI corresponds to the circadian function index. Non-parametric circadian rhythm analysis values expressed as mean ± SEM. Statistically significant differences were found by Mann–Whitney test. The significance values of $P < 0.05$ are highlighted in bold. For all parameters, *r* refers to size effect.

TAP and sleep values were consistent with the results for motor activity and body position (Fig. 3d,e). Differences in light intensity between both groups were also found. In the morning, individuals with ASD were exposed to higher light levels than control subjects, and from 15:00 to 7:00 hr they experienced lower light levels (Fig. 3f).

Overall, circadian phase advance in the ASD group was suggested by the higher values for wrist temperature and sleep and the lower motor activity and body position during the late afternoon and the first part of the night when compared to controls.

Table 3 shows the nonparametric indexes for the circadian rhythms plotted in Fig. 3a–f. The circadian characteristics of the sleep–wake rhythm showed a consistent phase advance in ASD subjects as evidenced by the four phase markers (L5, L10, M5, and M10). Significant group differences were present in all circadian rhythms studied (wrist temperature, motor activity, body position, TAP, sleep, and light intensity) when compared with controls (Table 3). The ASD group showed significantly higher IS in wrist temperature and light intensity and lower IS in motor activity. Intra-daily variability results were consistent with those found for IS. Lower amplitude was found in sleep records for the ASD group in contrast with light intensity, indicating poor sleep conditions in adults with ASD and ID. Residual TIB significantly correlated with central sleep hour, phase marker M5 ($r = -0.35$, $P = 0.026$) indicating that the time the ASD participants rested awake in bed after sleep influenced their central sleep hour.

Discussion

Similar to previous cross-sectional research from childhood to middle age (Baker & Richdale, 2015; Goldman et al., 2017; Souders et al., 2009), we found significantly poorer sleep quantity and quality in our ASD participants with ID compared to controls, together with daytime sedentary behavior, nocturnal activation and a consistent phase advance in circadian rhythms. The latter has been previously reported in children (Tatsumi et al., 2015) and in a small number of ASD adults [Baker & Richdale, 2017; Hare et al., 2006a; Limoges et al., 2005]. These are consistent with a higher vulnerability to SPs in the ASD population from early childhood through to middle age [Goldman, Richdale, Clemons, & Malow, 2012; Tani et al., 2004]; neither adults with ASD and no ID nor adults with ASD and ID have received much attention in the literature [Baker & Richdale, 2017; Hare et al., 2006a, 2006b; Limoges et al., 2005; Matson et al., 2008a; Wiggs & Stores, 2004]. To the best of our knowledge, our study is the largest study examining objective sleep parameters and circadian markers in ASD adults with ID.

Overall, the findings indicate that adults with ASD and ID have low sleep efficiency, prolonged latency, and increased frequency and length of night awakenings, compared with neurotypical adults. Although they did not show less total sleep on average than controls, total night sleep was highly variable across the ASD group and only 5% of individuals on the spectrum had a TST within the normal range for adults, which differed from controls where 72% were within the normal range. Our results support previous studies in individuals with ASD. Increased sleep onset latency (SoL) and wakes after sleep onset (WASO). SoL and WASO, more frequent nocturnal awakenings, decreased total sleep and lower sleep efficiency are variously reported in cognitively able adolescents and adults on the autism spectrum [Baker & Richdale, 2015; Baker & Richdale, 2017; Goldman et al., 2017; Hare et al., 2006a; Limoges et al., 2005; Tani et al., 2003]. Impaired sleep in adults with ASD and ID also is reported as related to severe challenging behaviors [Matson et al., 2008a].

The longer SoL and TIB and shorter SE described for the adults on the spectrum could be a result of prescribed schedules in their group residences that do not allow flexibility that fits with individual preferences and circadian differences; however some authors did not find a link between different residential conditions and SPs in children with ASD and ID [Cohen et al., 2017]. Anxiety, high physiological arousal, [Hundley, Shui, & Malow, 2016] and problematic daytime behavior [Matson et al., 2008a] may influence SoL length. However, our results showed that those adults with ASD taking anxiolytic medication for co-morbid anxiety disorders only differed from other adults in their number of awakenings.

In our ASD group, the wrist temperature 24 hr rhythm showed an advanced wake maintenance zone (17:00–18:00 hr) when compared with the control group (20:00–21:00 hr); this phase advancement was supported by the phase markers M5 and L10. Misalignment of the wrist temperature rhythm could contribute to the SPs described in our adults [Shekleton et al., 2013]. Furthermore, adults on the spectrum in this study displayed an overall rhythm of increased wrist temperature that could be related to reduced activation of noradrenergic vasoconstrictor tone resulting in a slower sleep onset [Blazquez, Martinez-Nicolas, Salazar, Rol, & Madrid, 2012] and melatonin secretion is strongly influenced by the temperature rhythm [Kräuchi, Cajochen, & Wirz-Justice, 1998].

Vulnerability to SPs can be associated with the functioning of the circadian system. When assessing the circadian system, the most common marker rhythms are core body temperature, motor activity, light intensity, cortisol, and melatonin [Klerman, Lee, Czeisler, & Kronauer, 1999; Van Someren, 2000]. Wrist (skin) temperature is also a consolidated, noninvasive, robust, and reliable tool for assessing circadian system function [Blazquez et al., 2012; Bonmati-Carrion et al., 2014]. Circadian rhythms need to be continuously synchronized with the environment, and the most powerful zeitgeber (environment

time cue that entrains circadian rhythmicity) is the 24-hr light/dark cycle (Wright et al., 2013), but nonphotic zeitgebers such as meal timing and social contacts can also be influential [Kalsbeek, Merrow, Roenneberg, & Foster, 2012]. The wrist temperature rhythm reflects endogenous and exogenous circadian influences, thus presenting considerable advantages for evaluating the effects of synchronizing agents, such as light exposure, on circadian function. Peripheral temperature, as reflected by the wrist temperature, affects sleep-regulating areas in the brain and increases before sleep onset, remaining high overnight until waking and remaining low during the rest of the day [Benloucif et al., 2005; Sarabia et al., 2008]. The time of minimal sleep probability known as "wake maintenance zone," is usually between 20:00 and 22:00 hr in healthy adults and matches with the lowest value of daily peripheral temperature (Ortiz-Tudela et al., 2010), and the dim light melatonin onset [Lewy, Cutler, & Sack, 1999]. Thus it can be used to assess advanced or delayed circadian system timing due to its relation with the intrinsic circadian period [Wright, Gronfier, Duffy, & Czeisler, 2005].

The motor activity 24 hr wave and non-parametric circadian rhythm values from adults on the spectrum are higher during the night (21:00–01:00 hr) and lower during the day (12:00 hr). Those elevated night values could be due to certain SPs such as restless legs syndrome or epilepsy, but authors have described that to detect this, the actimeter should be worn on the leg [Cippà et al., 2013], and there was only one participant who suffered two epileptic seizures during ACM data collection and one of those was during the day. Thus, the results together with the L5 value of motor activity suggest an earlier night-wake activation as previously described for cases of phase advancement [Limoges et al., 2005]. The higher IS and the VM10 values in ASD suggest a stability in physical activity tasks [Iosa et al., 2014] and sedentary lifestyle [MacDonald, Esposito, & Ulrich, 2011; Orsmond & Kuo, 2011].

Motor activity, together with wrist temperature and light intensity, provide a better evaluation of chronobiologic disorders than temperature alone [Klerman et al., 1999] and have been described as a substitute for PSG to test circadian rhythms status in humans [Carvalho Bos et al., 2003]. The body position added information to motor activity records. Lower body position values are described for our sample during the day. As described, body position together with motor activity help to define rest-activity spans properly [Blazquez et al., 2012]. Phase advance in our sample with ASD is also evidenced with phase markers L5 and M10 and lower TAP values registered from midday until midnight. Our TAP rhythm in ASD matched that described for circadian rhythm alterations in mild cognitive impairment [Ortiz-Tudela, Martinez-Nicolas, Díaz-Mardomingo, et al., 2014b]. The light intensity values recorded in the ASD sample were significantly higher in the morning and more robust during the week, according to the greater CFI value found. According to the literature, wrist temperature is a marker of circadian phase, and light applied after night arousal has a phase-advancing effect [Pavlova, 2017] so higher morning values in ASD could be moving the rhythm forward.

The phase advance in adults with autism and ID detected (M5 and L5 at ~01:00 hr AM) was consistent along all the circadian rhythms analyzed, similar to previous results [Baker & Richdale, 2017; Hare et al., 2006a; Limoges et al., 2005; Tatsumi et al., 2015]. Normal timing of M5 and L5 [Ortiz-Tudela et al., 2010] takes place around 04:00 hr, during REM sleep with minimum muscle tone [Madrid & de Lama, 2006] and melatonin reaches its nocturnal peak then [Claustrat, Brun, & Chazot, 2005]. However, as light intensity is a synchronizer of melatonin secretion [Morin & Allen, 2006], melatonin peaks in the adults with ASD from our sample could be happening before the usually described times [Arendt, 1994].

The criteria to diagnose a CRSWD, according to the International Classification of Sleep Disorders (third edition, 2014), require symptoms to be present for at least 3 months and confirmed with 14 days of actigraphy. We have only 1 week of ACM data and thus cannot confirm the presence of a CRSWD. However, the results presented in our paper provide enough information to evaluate the circadian system and its disruptions [Corbalán-Tutau et al., 2011; Cornelissen, Gubin, Halberg, & Milano, 1999; Focan, 1995; Lewy, 1999] and strongly infer the presence of a CRSWD, primarily advanced sleep wake rhythm disorder, in adults with autism and ID.

The phase advance found in this study affected 60% of individuals with ASD, which is higher than in other studies [Baker & Richdale, 2017; Hare et al., 2006a] who reported this advanced sleep wake rhythm disorder in 10% of their ASD participants. This could be due to reasons other than light exposure. All participants with ASD in our study were unemployed, and unemployment has been related to the presence of a sleep disorder in high-functioning ASD [Baker & Richdale, 2017]. However, most unemployed individuals in their study met criteria for delayed sleep wake rhythm disorder [Baker, Richdale, & Hazi, in press]. Nevertheless, adults with ASD in these studies did not have an ID and were not institutionalized [Baker & Richdale, 2017; Hare et al., 2006a] and thus presumably were able to self-select bed and wake times.

Our study presents several limitations. First, as a neurodevelopmental disorder, we acknowledge that the most life critical phase for symptom manifestation of SPs in ASD is in childhood [Humphreys et al., 2014], but they have been documented as life-long conditions [Baker & Richdale, 2015; Hollway et al., 2013; Matson, Mahan,

Hess, & Fodstad, 2010]. Studying the course of SP development across the lifespan is crucial for developing supports and assessing the efficacy of appropriate interventions [Bangerter et al., 2017]. Second, even though, the study information emphasized that no SP was required to participate, it is possible that parents or legal guardians of adults with ASD and ID with disturbed sleep were more likely to participate. Third, ACM has not been validated in ASD to study sleep and this is the first study that has used this device to assess sleep in autistic individuals; however ACM has been shown to give rise to more accurate results than actigraphy [Ortiz-Tudela, Martinez-Nicolas, Albares, et al., 2014a]. Furthermore, this device has shown its effectiveness for assessing sleep in individuals with Parkinson [Madrid-Navarro et al., 2018], mild cognitive impairment [Ortiz-Tudela et al., 2014b], or critically ill confined participants [Madrid-Navarro et al., 2015]. Furthermore, the algorithms used by actigraphy devices to predict sleep periods are sometimes designed for specific populations, which could impair the proper detection of sleep in groups with different conditions [Sadeh & Acebo, 2002; Insana, Gozal, & Montgomery-Downs, 2010]; however, the TAP variable predicts rest-activity periods with high accuracy and independently from conditions that participants may have [Ortiz-Tudela et al., 2010]. Fourth, the comparison group was healthy, nonmedicated adults, but most adults in the ASD group were medicated and polypharmacy was common. As it is well established that some medications can alter levels of neurotransmitters (e.g., serotonin) and change sleep architecture by decreasing arousals or redistributing the REM stage [Esbensen, Greenberg, Seltzer, & Aman, 2009; Seda, Tsai, & Lee-Chiong, 2014] such effects could bias the results in the ASD group. Future research in regard to these effects should consider the study of sleep EEG rhythms [Vakalopoulos, 2014]. However, even though the polypharmacy in our ASD group was defined as "medication not matching diagnosis" [Logan et al., 2015], only anxiolytic medication affected sleep significantly (i.e., number of awakenings). Nevertheless, the impact of polypharmacy is being broadly analyzed in an ongoing study. Although the sample could be considered relatively small, effect sizes were moderate/large and the number of participants was similar to other published studies that used actigraphy to assess insomnia symptoms and CRSWD in adults on the spectrum [Hare et al., 2006a, 2006b; Baker & Richdale, 2015; Goldman et al., 2017]; however, further studies with larger numbers of participants should be performed to validate our results. In addition, the percentage of participants in the control group with normal number and duration of awakenings after sleep onset was low. However, our data are similar to other studies in healthy individuals [Chakar et al., 2017) and could be related to other factors such as occupational status [Kim & Lee, 2015] or raising a child [Reader, Teti, & Cleveland, 2017]. Finally, the group with ASD was only matched on age with the control group, but not on sex, IQ, employment status, or living conditions. However, when we examined sex, no differences were found for sleep. Nevertheless, as other authors have described [Knutsson, 2004; Tudor, Hoffman, & Sweeney, 2012], IQ, employment, and living conditions (e.g., bedtime schedule, light exposure) may impact negatively on some of the sleep parameter values found in this study, but these conditions are the reality for adults on the spectrum with associated ID. We acknowledge that all these factors, including forced bedtime schedules or evening light exposure, could affect our results; however, we are unable to modify living conditions of ASD individuals in those institutions.

In conclusion, examining sleep and markers of the circadian system showed significant differences between adults with ASD and comorbid ID and an age-matched, healthy adult population. In the adults on the autism spectrum, there was a high prevalence of SPs and a predisposition to phase advanced circadian rhythms. The sleep disturbances described for this sample of adults with ASD and ID are similar to those already described for adults with ASD without ID, and in children and adolescents on the spectrum, evidencing that SPs are a life-long condition; their relationship with intellectual ability should be further studied. The ACM device used here provided important information about the status of the circadian system and could be used to achieve a better understanding of sleep in ASD and to examine response to treatment of sleep difficulties.

References

Adkins, K. W., Molloy, C., Weiss, S. K., Reynolds, A., Goldman, S. E., Burnette, C., … Malow, B. A. (2012). Effects of a standardized pamphlet on insomnia in children with autism spectrum disorders. Pediatrics, 130, S139–S144.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: Author.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. (2003). The role of actigraphy in the study of sleep and circadian rhythms. American Academy of Sleep Medicine Review Paper. Sleep, 26, 342–392.

Anders, T. F., Iosif, A.-M., Schwichtenberg, A., Tang, K., & Goodlin-Jones, B. L. (2011). Six-month sleep–wake organization and stability in preschool-age children with autism, developmental delay, and typical development. Behavioral Sleep Medicine, 9, 92–106.

Anderson, G. M., & Lombroso, P. J. (2002). Genetics of childhood disorders: XLV. Autism, part 4: Serotonin in autism. Journal of the American Academy of Child & Adolescent Psychiatry, 41, 1513–1516.

Arendt, J. (1994). Melatonin and the mammalian pineal gland. Springer Science & Business Media.

Arendt, J. (1995). Melatonin and the mammalian pineal gland (1st ed.). London: Chapman & Hall. Springer Science & Business Media.

Baker, E., & Richdale, A. L. (2017). Examining the behavioural sleep-wake rhythm in adults with autism spectrum disorder and no comorbid intellectual disability. Journal of Autism and Developmental Disorders, 47, 1207–1222.

Baker, E., Richdale, A. L., Short, M., & Gradisar, M. (2013). An investigation of sleep patterns in adolescents with high-functioning autism spectrum disorder compared with typically developing adolescents. Developmental Neurorehabilitation, 16, 155–165.

Baker, E. K., & Richdale, A. L. (2015). Sleep patterns in adults with a diagnosis of high-functioning autism spectrum disorder. Sleep, 38, 1765–1774.

Baker, E. K., Richdale, A. L., & Hazi, A. (2018). Employment status is related to sleep problems in adults with autism spectrum disorder and no comorbid intellectual impairment. Autism, 1: 1362361317745857.

Bangerter, A., Ness, S., Aman, M. G., Esbensen, A. J., Goodwin, M. S., Dawson, G., … Pandina, G. (2017). Autism behavior Inventory: A novel tool for assessing core and associated symptoms of autism spectrum disorder. Journal of Child and Adolescent Psychopharmacology, 27, 814–822.

Benloucif, S., Guico, M., Reid, K. J., Wolfe, L., L'Hermite-Balériaux, M., & Zee, P. (2005). Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. Journal of Biological Rhythms, 20, 178–188.

Bhadra, U., Thakkar, N., Das, P., & Pal Bhadra, M. (2017). Evolution of circadian rhythms: From bacteria to human. Sleep Medicine, 35, 49–61.

Blazquez, A., Martinez-Nicolas, A., Salazar, F., Rol, M., & Madrid, J. (2012). Wrist skin temperature, motor activity, and body position as determinants of the circadian pattern of blood pressure. Chronobiology International, 29, 747–756.

Boivin, D. B. (2000). Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. Journal of Psychiatry & Neuroscience, 25, 446–458.

Bonmati-Carrion, M., Middleton, B., Revell, V., Skene, D., Rol, M., & Madrid, J. (2014). Circadian phase asessment by ambulatory monitoring in humans: Correlation with dim light melatonin onset. Chronobiology International, 31, 37–51.

Bonmati-Carrion, M., Middleton, B., Revell, V., Skene, D., Rol, M., & Madrid, J. (2015). Validation of an innovative method, based on tilt sensing, for the assessment of activity and body position. Chronobiology International, 32, 701–710.

Brunton, L., Chabner, B., & Knollman, B. (2011). Goodman and Gilman's the pharmacological basis of therapeutics, London Twelfth Edition: McGraw-Hill Education.

Buck, T. R., Viskochil, J., Farley, M., Coon, H., McMahon, W. M., Morgan, J., & Bilder, D. A. (2014). Psychiatric comorbidity and medication use in adults with autism spectrum disorder. Journal of Autism and Developmental Disorders, 44, 3063–3071.

Carrier, J., & Monk, T. H. (1997). Estimating the endogenous circadian temperature rhythm without keeping people awake. Journal of Biological Rhythms, 12, 266–277.

Carskadon, M. A., & Rechtschaffen, A. (2000). Monitoring and staging human sleep. Principles and Practice of Sleep Medicine, 3, 1197–1215.

Carvalho Bos, S., Waterhouse, J., Edwards, B., Simons, R., & Reilly, T. (2003). The use of actimetry to assess changes to the rest–activity cycle. Chronobiology International, 20, 1039–1059.

Chakar, B., Senny, F., Poirrier, A. L., Cambron, L., Fanielle, J., & Poirrier, R. (2017). Validation of midsagittal jaw movements to measure sleep in healthy adults by comparison with actigraphy and polysomnography. The Sleep Science, 10, 122–127.

Cippà, M. A., Baumann, C. R., Siccoli, M. M., Bassetti, C. L., Poryazova, R., & Werth, E. (2013). Actigraphic assessment of periodic leg movements in patients with restless legs syndrome. Journal of Sleep Research, 22, 589–592.

Claustrat, B., Brun, J., & Chazot, G. (2005). The basic physiology and pathophysiology of melatonin. Sleep Medicine Reviews, 9, 11–24.

Cohen, S., Fulcher, B. D., Rajaratnam, S. M., Conduit, R., Sullivan, J. P., St Hilaire, M. A., … Lockley, S. W. (2017). Behaviorally-determined sleep phenotypes are robustly associated with adaptive functioning in individuals with low functioning autism. Scientific Reports, 7, 14228.

Corbalán-Tutau, M. D., Madrid, J. A., Ordovas, J. M., Smith, C. E., Nicolás, F., & Garaulet, M. (2011). Differences in daily rhythms of wrist temperature between obese and normal-weight women: Associations with metabolic syndrome features. Chronobiology International, 28, 425–433.

Cornelissen, G., Gubin, D., Halberg, F., & Milano, G. (1999). Chronomedical aspects of oncology and geriatrics. In Vivo (Athens, Greece), 13, 77–82.

Cortesi, F., Giannotti, F., Ivanenko, A., & Johnson, K. (2010). Sleep in children with autistic spectrum disorder. Journal of Clinical Sleep Medicine, 11, 659–664.

Couturier, J. L., Speechley, K. N., Steele, M., Norman, R., Stringer, B., & Nicolson, R. (2005). Parental perception of sleep problems in children of normal intelligence with pervasive developmental disorders: prevalence, severity, and pattern. Journal of the American Academy of Child and Adolescent Psychiatry, 44, 815–822.

Edgar, D. M., & Dement, W. C. (1991). Regularly scheduled voluntary exercise synchronizes the mouse circadian clock. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 261, R928–R933.

Esbensen, A. J., Greenberg, J. S., Seltzer, M. M., & Aman, M. G. (2009). A longitudinal investigation of psychotropic and non-psychotropic medication use among adolescents and adults with autism spectrum disorders. Journal of Autism and Developmental Disorders, 39, 1339–1349.

Focan, C. (1995). Marker rhythms for cancer chronotherapy. From laboratory animals to human beings. In Vivo (Athens, Greece), 9, 283–298.

Goldman, S., Alder, M., Burgess, H., Corbett, B., Hundley, R., Wofford, D., et al. (2017). Characterizing sleep in adolescents and adults with autism spectrum disorders. Journal of Autism and Developmental Disorders, 47, 1682–1695.

Goldman, S. E., Richdale, A. L., Clemons, T., & Malow, B. A. (2012). Parental sleep concerns in autism spectrum disorders:

Variations from childhood to adolescence. Journal of Autism and Developmental Disorders, 42, 531–538.
Hare, D. J., Jones, S., & Evershed, K. (2006a). A comparative study of circadian rhythm functioning and sleep in people with Asperger syndrome. Autism, 10, 565–575.
Hare, D. J., Jones, S., & Evershed, K. (2006b). Objective investigation of the sleep-wake cycle in adults with intellectual disabilities and autistic spectrum disorders. Journal of Intellectual Disability Research, 50, 701–710.
Hollway, J. A., Aman, M. G., & Butter, E. (2013). Correlates and risk markers for sleep disturbance in participants of the autism treatment network. Journal of Autism and Developmental Disorders, 43, 2830–2843.
Humphreys, J. S., Gringras, P., Blair, P. S., Scott, N., Henderson, J., Fleming, P. J., & Emond, A. M. (2014). Sleep patterns in children with autistic spectrum disorders: A prospective cohort study. Archives of Disease in Childhood, 99, 114–118.
Hundley, R. J., Shui, A., & Malow, B. A. (2016). Relationship between subtypes of restricted and Repetitive behaviors and sleep disturbance in autism spectrum disorder. Journal of Autism and Developmental Disorders, 46, 3448–3457.
Insana, S. P., Gozal, D., & Montgomery-Downs, H. E. (2010). Invalidity of one actigraphy brand for identifying sleep and wake among infants. Sleep Medicine, 11, 191–196.
Iosa, M., Morelli, D., Nisi, E., Sorbara, C., Negrini, S., Gentili, P., … Fusco, A. (2014). Assessment of upper body accelerations in young adults with intellectual disabilities while walking, running, and dual-task running. Human Movement Science, 34, 187–195.
Jean-Louis, G., Kripke, D. F., Cole, R. J., Assmus, J. D., & Langer, R. D. (2001). Sleep detection with an accelerometer actigraph: Comparisons with polysomnography. Physiology & Behavior, 72, 21–28.
Kaleyias, J., Cruz, M., Goraya, J. S., Valencia, I., Khurana, D. S., Legido, A., & Kothare, S. V. (2008). Spectrum of polysomnographic abnormalities in children with epilepsy. Pediatric Neurology, 39, 170–176.
Kalsbeek, A., Merrow, M., Roenneberg, T., & Foster, R. (2012). Nutrition and the circadian timing system. The Neurobiology of Circadian Timing, 199, 359.
Kim, B. H., & Lee, H.-E. (2015). The association between working hours and sleep disturbances according to occupation and gender. Chronobiology international, 32, 1109–1114.
Klerman, E. B., Lee, Y., Czeisler, C. A., & Kronauer, R. E. (1999). Linear demasking techniques are unreliable for estimating the circadian phase of ambulatory temperature data. Journal of Biological Rhythms, 14, 260–274.
Klukowski, M., Wasilewska, J., & Lebensztejn, D. (2015). Sleep and gastrointestinal disturbances in autism spectrum disorder in children. Developmental Period Medicine, 19, 157–161.
Knutsson, A. (2004). Methodological aspects of shift-work research. Chronobiology International, 21, 1037–1047.
Kräuchi, K., Cajochen, C., & Wirz-Justice, A. (1998). Circadian and homeostatic regulation of core body temperature and alertness in humans: What is the role of melatonin. Circadian Clocks and Entrainment, 7, 131–146.
Kuhlthau, K. A., McDonnell, E., Coury, D. L., Payakachat, N., & Macklin, E. (2017). Associations of quality of life with health-related characteristics among children with autism. Autism, 1:1362361317704420.
Lewy, A. (1999). The dim light melatonin onset, melatonin assays and biological rhythm research in humans. Neurosignals, 8, 79–83.
Lewy, A. J., Cutler, N. L., & Sack, R. L. (1999). The endogenous melatonin profile as a marker for circadian phase position. Journal of Biological Rhythms, 14, 227–236.
Limoges, É., Bolduc, C., Berthiaume, C., Mottron, L., & Godbout, R. (2013). Relationship between poor sleep and daytime cognitive performance in young adults with autism. Research in Developmental Disabilities, 34, 1322–1335.
Limoges, É., Mottron, L., Bolduc, C., Berthiaume, C., & Godbout, R. (2005). Atypical sleep architecture and the autism phenotype. Brain, 128, 1049–1061.
Logan, S. L., Carpenter, L., Leslie, R. S., Garrett-Mayer, E., Hunt, K. J., Charles, J., & Nicholas, J. S. (2015). Aberrant behaviors and co-occurring conditions as predictors of psychotropic polypharmacy among children with autism spectrum disorders. Journal of child and adolescent psychopharmacology, 25, 323–336.
Lopez, R., Jaussent, I., & Dauvilliers, Y. (2014). Objective daytime sleepiness in patients with somnambulism or sleep terrors. Neurology, 83, 2070–2076.
MacDonald, M., Esposito, P., & Ulrich, D. (2011). The physical activity patterns of children with autism. BMC Research Notes, 4, 422.
Madrid, J. A., & de Lama, Á. R. (2006). Cronobiología básica y clínica. Editec@ red, Madrid.
Madrid-Navarro, C. J., Escamilla-Sevilla, F., Mínguez-Castellanos, A., Campos, M., Ruiz-Abellán, F., Madrid, J. A., & Rol, M. A. (2018). Multidimensional circadian monitoring by wearable biosensors in Parkinson's disease. Frontiers in Neurology, 9, 157.
Madrid-Navarro, J. C., Sánchez-Gálvez, R., Martinez-Nicolas, A., Marina, R., Garcia, J. A., Madrid, J. A., & Rol, M. A. (2015). Disruption of circadian rhythms and delirium, sleep impairment and sepsis in critically ill patients. Potential therapeutic implications for increased light-dark contrast and melatonin therapy in an ICU environment. Current Pharmaceutical Design, 21, 3453–3468.
Malow, B. A., Byars, K., Johnson, K., Weiss, S., Bernal, P., Goldman, S. E., … Glaze, D. G. (2012). A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. Pediatrics, 130, S106–S124.
Malow, B. A., Marzec, M. L., McGrew, S. G., Wang, L., Henderson, L. M., & Stone, W. L. (2006). Characterizing sleep in children with autism spectrum disorders: A multidimensional approach. Sleep, 29, 1563–1571.
Martinez-Nicolas, A., Ortiz-Tudela, E., Madrid, J. A., & Rol, M. A. (2011). Crosstalk between environmental light and internal time in humans. Chronobiology International, 28, 617–629.
Matson, J. L., Ancona, M. N., & Wilkins, J. (2008a). Sleep disturbances in adults with autism spectrum disorders and severe intellectual impairments. Journal of Mental Health Research in Intellectual Disabilities, 1, 129–139.
Matson, J. L., Mahan, S., Hess, J. A., & Fodstad, J. C. (2010). Effect of developmental quotient on symptoms of inattention and

impulsivity among toddlers with autism spectrum disorders. Research in Developmental Disabilities, 31, 464–469.

Matson, J. L., Wilkins, J., & Ancona, M. (2008b). Autism in adults with severe intellectual disability: an empirical study of symptom presentation. Journal of Intellectual and Developmental Disability, 33, 36–42.

May, T., Cornish, K., Conduit, R., Rajaratnam, S. M., & Rinehart, N. J. (2015). Sleep in high-functioning children with autism: Longitudinal developmental change and associations with behavior problems. Behavioral Sleep Medicine, 13, 2–18.

Morin, L., & Allen, C. (2006). The circadian visual system, 2005. Brain Research Reviews, 51, 1–60.

Mormont, M.-C., Waterhouse, J., Bleuzen, P., Giacchetti, S., Jami, A., Bogdan, A., … Lévi, F. (2000). Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. Clinical Cancer Research, 6, 3038–3045.

Nadeau, J. M., Arnold, E. B., Keene, A. C., Collier, A. B., Lewin, A. B., Murphy, T. K., & Storch, E. A. (2015). Frequency and clinical correlates of sleep-related problems among anxious youth with autism spectrum disorders. Child Psychiatry & Human Development, 46, 558–566.

Natale, V., Plazzi, G., & Martoni, M. (2009). Actigraphy in the assessment of insomnia: a quantitative approach. Sleep, 32, 767–771.

Orsmond, G. I., & Kuo, H.-Y. (2011). The daily lives of adolescents with an autism spectrum disorder: discretionary time use and activity partners. Autism, 15, 579–599.

Ortiz-Tudela, E., Martinez-Nicolas, A., Albares, J., Segarra, F., Campos, M., Estivill, E., … Madrid, J. A. (2014a). Ambulatory circadian monitoring (ACM) based on thermometry, motor activity and body position (TAP): A comparison with polysomnography. Physiology & behavior, 126, 30–38.

Ortiz-Tudela, E., Martinez-Nicolas, A., Campos, M., Rol, M. Á., & Madrid, J. A. (2010). A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. PLOS Computational Biology, 6, e1000996.

Ortiz-Tudela, E., Martinez-Nicolas, A., Díaz-Mardomingo, C., García-Herranz, S., Pereda-Pérez, I., Valencia, A., … Rol, M. A. (2014b). The characterization of biological rhythms in mild cognitive impairment. BioMed Research International, 2014, 524971.

Pavlova, M. (2017). Circadian rhythm sleep-wake disorders. Continuum (Minneap Minn), 23, 1051–1063.

Reader, J. M., Teti, D. M., & Cleveland, M. J. (2017). Cognitions about infant sleep: Interparental differences, trajectories across the first year, and coparenting quality. Journal of Family Psychology, 31, 453–463.

Reynolds, A. M., & Malow, B. A. (2011). Sleep and autism spectrum disorders. Pediatric Clinics of North America, 58, 685–698.

Richdale, A. L., Baker, E., Short, M., & Gradisar, M. (2014). The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. Sleep Medicine, 15, 1082–1088.

Sadeh, A., & Acebo, C. (2002). The role of actigraphy in sleep medicine. Sleep Medicine Reviews, 6, 113–124.

Sarabia, J. A., Rol, M. A., Mendiola, P., & Madrid, J. A. (2008). Circadian rhythm of wrist temperature in normal-living subjects A candidate of new index of the circadian system. Physiology & Behavior, 95, 570–580.

Scheer, F. A., Wright, K. P., Jr., Kronauer, R. E., & Czeisler, C. A. (2007). Plasticity of the intrinsic period of the human circadian timing system. PLOS One, 2, e721.

Schuch, J. B., Genro, J. P., Bastos, C. R., Ghisleni, G., & Tovo-Rodrigues, L. (2017). The role of CLOCK gene in psychiatric disorders: Evidence from human and animal research. American Journal of Medical Genetics Part B, 177, 181–198.

Schwichtenberg, A. J., Young, G. S., Hutman, T., Iosif, A. M., Sigman, M., Rogers, S. J., & Ozonoff, S. (2013). Behavior and sleep problems in children with a family history of autism. Autism Research, 6, 169–176.

Seda, G., Tsai, S., & Lee-Chiong, T. (2014). Medication effects on sleep and breathing. Clinics in Chest Medicine, 35, 557–569.

Shekleton, J. A., Rajaratnam, S. M., Gooley, J. J., Van Reen, E., Czeisler, C. A., & Lockley, S. W. (2013). Improved neurobehavioral performance during the wake maintenance zone. Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine, 9, 353.

Souders, M. C., Mason, T. B., Valladares, O., Bucan, M., Levy, S. E., Mandell, D. S., … Pinto-Martin, J. (2009). Sleep behaviors and sleep quality in children with autism spectrum disorders. Sleep, 32, 1566–1578.

Souders, M. C., Zavodny, S., Eriksen, W., Sinko, R., Connell, J., Kerns, C., … Pinto-Martin, J. (2017). Sleep in children with autism spectrum disorder. Current Psychiatry Reports, 19, 34.

Tani, P., Lindberg, N., Nieminen-von Wendt, T., von Wendt, L., Alanko, L., Appelberg, B., & Porkka-Heiskanen, T. (2003). Insomnia is a frequent finding in adults with Asperger syndrome. BMC Psychiatry, 3, 12.

Tani, P., Lindberg, N., Nieminen-von Wendt, T., von Wendt, L., Virkkala, J., Appelberg, B., & Porkka-Heiskanen, T. (2004). Sleep in young adults with Asperger syndrome. Neuropsychobiology, 50, 147–152.

Tatsumi, Y., Mohri, I., Shimizu, S., Tachibana, M., Ohno, Y., & Taniike, M. (2015). Daytime physical activity and sleep in pre-schoolers with developmental disorders. Journal of Paediatrics and Child Health, 51, 396–402.

Tsuchiyama, K., Nagayama, H., Kudo, K., Kojima, K., & Yamada, K. (2003). Discrepancy between subjective and objective sleep in patients with depression. Psychiatry and Clinical Neurosciences, 57, 259–264.

Tudor, M. E., Hoffman, C. D., & Sweeney, D. P. (2012). Children with autism: Sleep problems and symptom severity. Focus on Autism and Other Developmental Disabilities, 27, 254–262.

Vakalopoulos, C. (2014). The EEG as an index of neuromodulator balance in memory and mental illness. Frontiers in Neuroscience, 8–63.

Valicenti-McDermott, M., Lawson, K., Hottinger, K., Seijo, R., Schechtman, M., Shulman, L., & Shinnar, S. (2015). Parental stress in families of children with autism and other developmental disabilities. Journal of child neurology, 30, 1728–1735.

Van Someren, E. J. (2000). Circadian rhythms and sleep in human aging. Chronobiology International, 17, 233–243.
Van Someren, E. J., & Riemersma-Van Der Lek, R. F. (2007). Live to the rhythm, slave to the rhythm. Sleep Medicine Reviews, 11, 465–484.
Weitzman, E. D., Czeisler, C. A., Coleman, R. M., Spielman, A. J., Zimmerman, J. C., Dement, W., … Pollak, C. P. (1981). Delayed sleep phase syndrome: A chronobiological disorder with sleep-onset insomnia. Archives of General Psychiatry, 38, 737–746.
Wiggs, L., & Stores, G. (2004). Sleep patterns and sleep disorders in children with autistic spectrum disorders: Insights using parent report and actigraphy. Developmental Medicine & Child Neurology, 46, 372–380.
Wirz-Justice, A., Bromundt, V., & Cajochen, C. (2009). Circadian disruption and psychiatric disorders: The importance of entrainment. Sleep Medicine Clinics, 4, 273–284.
Witting, W., Kwa, I., Eikelenboom, P., Mirmiran, M., & Swaab, D. (1990). Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biological Psychiatry, 27, 563–572.
Wright, K. P., Gronfier, C., Duffy, J. F., & Czeisler, C. A. (2005). Intrinsic period and light intensity determine the phase relationship between melatonin and sleep in humans. Journal of Biological Rhythms, 20, 168–177.
Wright, K. P., McHill, A. W., Birks, B. R., Griffin, B. R., Rusterholz, T., & Chinoy, E. D. (2013). Entrainment of the human circadian clock to the natural light-dark cycle. Current Biology, 23, 1554–1558.
Zhang, J., Ma, R., Kong, A., So, W. Y., Li, A. M., Lam, S. P., … Wing, Y. K. (2011). Relationship of sleep quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in healthy middle-aged adults. Sleep, 34, 225–233.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1: Supplementary data-abbreviation