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Biological rhythms, health, and gender-specific differences

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Summary. Biological rhythms exist at any level in living organisms and, according to their cycle length, are classified into a) circadian (from the Latin *circa dies*, period of ~24 hours), b) ultradian (period <24 hours), and c) infradian (period >24 hours) rhythms. Circadian rhythms are the most widely studied. The central circadian clock is located within the suprachiasmatic nucleus of the hypothalamus, and is entrained by light-dark alternation. Moreover, peripheral circadian clocks are present in many other cells. Although circadian information is inherited with DNA, an individual circadian preference (chronotype) exists. Three main chronotypes can be identified: Morning-type, Evening-type, and Neither-type. A growing body of research indicates that Evening-type may be associated with a series of unfavorable conditions, also in the presence of gender-specific differences. Moreover, organization of circadian rhythms may be disrupted by desynchronizing factors, such as exposure to light at night, jet lag, shiftwork, and daylight saving time. This article will review the available evidence of possible gender-specific differences related to the individual chronotype, as well as to the above indicated desynchronizing factors. Most studies on adolescents found an association between evening chronotype and unhealthy habits, such as reduced physical activity, higher consume of chocolate, soft drinks, smoking and alcohol. In adults, Evening-type was significantly associated with diabetes (in men), and metabolic syndrome (in women), and with sleep disturbances and psychopathology, such as impulsivity, anger, depression and anxiety disorders (the latter especially in women). A more-in-depth knowledge of individual circadian organization could also help in obtaining more effective patient care in the view of a personalized precision medicine.

Key words. Chronobiology, circadian rhythms, biological clocks, chronotype, desynchronization, light, jet lag, shiftwork, daylight saving time, sex, cardiovascular diseases.

Ritmi biologici, salute e differenze genere-specifiche

Riassunto. I ritmi biologici sono presenti in ogni organismo vivente sulla terra e, a seconda della lunghezza del loro ciclo, vengono classificati in (a) circadiani (dal latino *circa dies*, periodo di circa 24h), (b) ultradiani (periodo <24h) e (c) infradiani (periodo >24h). Di questi, i ritmi circadiani sono quelli più studiati. L'orologio biologico centrale si trova nel nucleo soprachiasmatico dell'ipotalamo e l'alternanza luce/buio è il suo sincronizzatore principale. Inoltre, esiste tutta una serie di altri orologi, definiti periferici, scoperti in molte altre cellule. Anche se l'informazione circadiana è trasmessa geneticamente con il DNA, esiste comunque una preferenza circadiana individuale, definita cronotipo. Esistono tre principali tipologie di cronotipo, il mattutino ('allodola'), l'intermedio, e il nottambulo ('gufo'). Tutta una serie di studi sembra associare il cronotipo gufo con quadri anche patologici e spesso con caratteristiche genere-specifiche. Inoltre, l'organizzazione dei ritmi circadiani può essere disturbata da alcuni fattori desincronizzatori, quali l'esposizione notturna alla luce, la sindrome da fuso orario, il lavoro a turni e il cambio dell'ora legale. Questo articolo intende passare in rassegna le attuali evidenze relativamente alle differenze genere-specifiche sulla base sia del cronotipo individuale che dei fattori desincronizzanti di cui sopra. Ad esempio, numerosi studi condotti su adolescenti hanno rivelato una associazione fra il cronotipo 'gufo' e le abitudini di vita scorrette, elevati consumi di cioccolato e di bevande zuccherine, fumo e alcol. Negli adulti il cronotipo gufo è stato associato al diabete (nei maschi) e sindrome metabolica (nelle femmine), oltre a disturbi del sonno e psicopatologici, come impulsività, ira, depressione e disturbi d'ansia (questi ultimi specialmente nel genere femminile). Una conoscenza più approfondita dell'organizzazione circadiana individuale potrebbe essere di aiuto nell'ottica di una più efficace medicina di precisione individualizzata.

Parole chiave. Cronobiologia, ritmi circadiani, orologio biologico, cronotipo, desincronizzazione, esposizione notturna alla luce, sindrome da fuso orario, lavoro a turni, sindrome dell'ora legale, sesso, malattie cardiovascolari.

Chronobiology, biological systems and circadian rhythms

Chronobiology is a biomedical discipline devoted to the study of biological rhythms. Biological rhythms exist at any level of living organisms and, according to their cycle length, are classified into three main types: a) circadian rhythms (from the Latin *circa-dies*, characterized by a period of ~24 hours), b) ultradian rhythms (period <24 hours, eg, hours, minutes), c) infradian rhythms (period >24 hours, eg, days, weeks, seasons).[1]

Circadian rhythms are the most commonly and widely studied biological rhythms. At a search on PubMed (accessed March 12, 2020), there are 99,826 and 70,049 papers, respectively, with the MeSH terms 'chronobiology phenomena' and 'circadian rhythm', so far. The 2017 Nobel Prize in Medicine and Physiology was attributed to three US scientists, Jeffrey Hall, Michael Rosbash, and Michael Young, for their discoveries on the biological mechanisms underlying the circadian clock. As far as the late 80's, in fact, they first isolated in *Drosophila melanogaster* a gene (period) encoding a protein (PER) produced during daytime and degraded during nighttime.[2] The mechanism is very complicated, and a fine machinery is needed. In mammals, circadian clocks can be classified into two major entities, central and peripheral. The central circadian clock (masterclock) is located within the suprachiasmatic nucleus (SCN) of the hypothalamus, and consists of approximately 20,000 neurons.[3] It is entrained by information on the light-dark alternation received from selected cells (intrinsically photosensitive retinal ganglion cells or ipRGCs), not involved in vision, which contain the photopigment melanopsin.[4] Moreover, peripheral circadian clocks are present both in other regions of the central nervous system and in many other cells, and regulate the expression of numerous clock-controlled genes (CCGs). The primary role for the circadian clock is to allow the cell to anticipate extracellular stimuli prior to their onset, so enhancing the possibility to prepare the cell for a stimulus that does not occur under a given set of conditions.[5]

Individual circadian preference (chronotype)

Chronotype is an individual difference closely linked to biological and psychological variables. Horne & Ostberg first proposed a self-assessment of individual circadian preference, evaluated by means of a Morningness-Eveningness Questionnaire (MEQ).[6] Three main chronotypes can so be identified: Morning-type (MT), Evening-type (ET), and Neither-type (NT). MT achieve peak activation in the first part of the day, and ET reach their best during the second half of the day. Thus, MT and ET subjects are nowadays widely defined by the definition of 'lark' (early riser) and 'owl' (late sleeper), respectively. MT, for example, show higher salivary cortisol levels in the first hour after awakening, not explained by differences in awakening time or sleep duration.[7] Circadian individual preference has a genetic basis, and large-scale genome-wide association studies have identified several genes as far, some of them previously unknown.[8] Rough data seem to indicate a Gaussian distribution of different chronotypes (10% MT, 10% ET, 80% NT).[9]

According with a recent review (164 studies, 186,289 participants, 59% women), individual chronotype exhibits differences by sex and age. In fact, men are on average more evening-oriented than women. However, the differences between men and women reduce with time: young women are more morning-orientated than young men, but older women are less morning-orientated than older men.[10]

Chronotype and health

A growing body of research indicates that evening chronotype may be associated with a series of unfavorable conditions. A review from our group analyzed the available literature to evaluate the relationships between chronotype, gender, and different aspects of health.[11]

As for general health, in adolescents most studies found an association between ET and unhealthy habits, such as reduced physical activity, higher consume of chocolate, soft drinks, fats and sucrose, and higher likelihood of smoking and alcohol drinking. In adults, ET was significantly associated with diabetes (in men), and metabolic syndrome (in women). Again, findings of several studies, mainly conducted in adolescents and young subjects, reported an association between ET and later bedtime and wake-up time, especially on weekends, irregular sleep-wake schedule, subjective poor sleep. ET had also a lower sleep efficiency and lower health-related quality of life.

As for psychological health, several studies documented an association between ET and impulsivity and anger, depression (especially in women) and anxiety disorders, nightmares (especially in young women), use of alcohol, coffee and stimulants, psychopathology and personality traits.[11] Among psychopathologic traits, a particular aspect is given by risk-taking, a complex form of decision-making that involves a calculated assessment of potential costs and rewards, immediate or delayed. Although it is known that males show higher propensity for risk-taking, ET females significantly take more risk than female IT and MT.[12]

According to the results of a study conducted on a cohort of women in the United States (American Heart Association Go Red for Women Strategically-Focused Research Network), ET compared with IT/ET, was associated with higher odds of having poor cardiovascular health (OR 2.41), not meeting AHA diet (OR 2.89) and physical activity guidelines (OR 1.78), and having short sleep (OR 2.15) or insomnia 2.69). The ET compared to MT was also associated with being a current smoker (OR 2.14) and having poor sleep quality (OR 2.35), and long sleep onset latency (OR 1.89).[13] Evening chronotype seems to be associated also with greater odds of comorbidities and mortality. A large study by UK Biobank (>400,000 adults) found that being a definite ET was significantly associated with a higher prevalence of all comorbidities. Compared to definite MT, in fact, the associations were strongest for psychological disorders (OR 1.94), diabetes (OR 1.30), neurological disorders (OR 1.25), gastrointestinal/abdominal disorders (OR

1.23), and respiratory disorders (OR 1.22). Moreover, definite ET showed significantly increased risk of all-cause mortality (HR 1.10), compared with MT.[14]

We will review the most common examples of biological rhythms disruptions and some aspects of gender-specific differences (Table 1).

Biological rhythms disruption

Light at night (LAN)

Environmental

Light pollution is the alteration of night natural lighting levels caused by exaggerated sources of light secondary to human activity (anthropogenic). Nocturnal natural lighting levels depend on natural sources, eg, moon, stars and Milky Way. At today, more than 80% of the world and more than 99% of the US and European populations live under light-polluted skies, and ~60% of Europeans and ~80% of North Americans cannot see the Milky Way.[15]

It has been shown that adolescents living in brightly illuminated urban districts, have a stronger ET orientation than those living in darker and rural municipalities, independently from sex and duration of electronic screen media usage.[16] Studies based on satellite images of night-time illumination, provided by the U.S. Defense Meteorological Satellite Program, combined with data on overweight and obesity prevalence rates, indicated the exposure to artificial light-at-night (LAN) as a statistically significant positive predictor of overweight and obesity either in the United States, and in Korea.[17,18] The Korean study showed also a highly significant difference by sex in the prevalence of obesity (women 47% vs men 39%, p <0.001).[18]

Domestic

Many people spend an increasing amount of time in front of computer screens equipped with light-emitting diodes (LED) emitting a short wavelength (blue range). For most people, this includes the evening hours close to bedtime, and this adversely affects circadian timing, sleep, and alertness. It is known that evening exposure to white LED screen can elicit significant suppression of the rise in endogenous melatonin, delays in self-selected bedtimes, sleep problems with poor sleep quality and sleep deprivation, and impaired next-morning alertness due to excessive daytime sleepiness.[19-21] Gender differences have been reported in young generations also in the use of mobile phone and smartphones, with evening and night girls' calls being significantly longer than boys' calls.[22] Moreover, many studies seem to indicate that women are more frequently involved. In fact, diurnal subjective sleepiness has been associated with a large number of negative outcomes, such as anxiety symptoms, and this association was more important in females than in males.[23]

Obesity is a major risk factor for several chronic diseases, such as cardiovascular diseases, type 2 diabetes, but also psychosocial problems.[24] ET and social jet lag are associated with greater adiposity, i.e., waist circumference and fat mass index in adolescent girls but not adolescent boys, with potential impact on emotional health of adolescent females.[25] In fact, girls are likely to have a poorer self-esteem than boys, and global self-esteem has

Table 1. Common desynchronization of the circadian rhythms and sex-specific differences

	Women	Men	Ref. no.
Light-at-night (LAN)	Overweight and obesity		17, 18, 27
	Diurnal subjective sleepiness and anxiety		23
Jet lag	Poor sleep efficiency (FAs)		30
	Irregular menstrual cycles, insomnia, sleep disorders (FAs)		31
Shift work (SW)	Metabolic disorders		34
		↑ HPA axis activation	37
	↑ Depressive symptoms		34
	Alteration of sleep parameters and melatonin rhythm, ↑ leptin, ↓ estradiol, ↑ IL-1β and IL-6		38
	Evening-oriented W, ↑ sleep disorders, insomnia, fatigue, and anxiety vs M and morning-oriented W		39
Daylight saving time (DST)	↑ MI incidence after spring shift, more in W		42
	↑ MI incidence after spring shift, no sex-differences	↑ MI incidence after spring shift, no sex-differences	43
	↑ AF hospitalizations after spring shift		46

AF: atrial fibrillation, FA: flight attendant, HPA: hypothalamic-pituitary-adrenal, IL: interleukin, M: men, MI: myocardial infarction, W: women.

more influence on the level of depressive mood in girls than in boys.[26] The exposure to nocturnal light has a negative impact even while sleeping. A recent study on more than 43,000 women in the US (35-74 years of age) showed that exposure to LAN while sleeping was a risk factor for overweight or obesity. Compared with no LAN, sleeping with a television or a light on in the room was associated with gaining 5 kg or more (+17%), BMI increase of 10% or more (+13%), incident overweight (+22%), and incident obesity (+33%).[27]

Jet lag

Air travel is a common mode of transportation in our modern society, particularly for individuals traveling long distances. Rapid air travel across several time zones exposes the individual to a shift in the internal biological clock. This gives raise to a transient rhythms desynchronization, lasting until the rhythm is adapted to the new environmental conditions. The most commonly experienced symptoms include sleep disorders, difficulties with concentrating, irritability, depression, fatigue, disorientation, loss of appetite, and gastrointestinal disturbance.[28] Sleep disturbances frequently result in (i) acute sleep deprivation, with reduced attention/vigilance, alteration in mood states, diminished memory processing, alteration in executive function, (ii) insomnia or even (iii) excessive daytime sleepiness associated with physical or mental impairment.[29]

Moreover, traveling is a job for many people. Flight attendants (FAs) may experience circadian disruption due to travel during normal sleep hours and through multiple time zones, and are more likely to have poor sleep efficiency.[30] It is already known that up to 20% of FAs may be exposed to irregular menstrual cycles, especially in those with a length of work >5 years and more than 14 routes a week. Sleep disturbances, in particular insomnia, are very frequent (>40%) and women with sleep disturbances are more likely to complain on dysmenorrhea.[31]

Shiftwork

Light is the strongest synchronizer for the synchronization of the human circadian timing system. Thus, shift work (SW) with night work, due to the alteration of daily light profiles, is a cause of disruption of the normal circadian sleep-wake cycle. An altered phase misalignment between the internal clockwork and the external environment is cause of physiological dysfunction and of SW-associated pathologies.[32] Even under stable light/dark environments, phase misalignment favors decreased metabolic efficiency and disrupted cardiac function.

Night shift workers sleep less hours, have higher weight, BMI, and almost three times higher association with abdominal obesity compared to day shift workers.[33] However, circadian misalignment and its consequences on metabolism seems to show sex-specific differences independent of behavioral and/or environmental factors. The 24-h average levels of the satiety hormone leptin exhibit a ~7% decrease in females and an ~11% increase in males, whereas only in females the hunger hormone ghrelin increased by ~8% during wake periods.[34] In addition to metabolic disturbances, SW is associated in women with increased overall risk of mental health disorders, in particular depression. A meta-analysis study on >28,000 participants showed that SW females are more likely to experience depressive symptoms than non-SW ones.[35]

On-call work is a stressor factor, frequently associated with negative outcomes, with sex-specific differences on impact and coping strategies. A web survey study showed that females were more likely to be responsible for running their household, and reported that being on call was a significant disturb for leisure, domestic and non-domestic activities. When managing on-call work, males and females adopted somewhat different coping styles, with most males using "problem solving" and most females "talking about their feelings".[36] Health-system workers are particularly exposed to SW, and night shifts certainly represent major stressor. Moreover, gender and individual chronotype play a role. As for male physicians, it seems that the hypothalamic-pituitary-adrenal axis is more activated. In fact, evaluating on-duty (24-h shift) and off-duty (free weekend) effects, women showed lower glucocorticoid excretion rates (GER) compared to men, with the ratio GERs on duty/GERs off duty significantly higher in males.[37] Women working half-night shifts (16:00-24:00 hours) had disturbed sleep parameters and melatonin rhythm, and increased leptin levels compared with day-time workers (08:00-16:00 hours). But women working whole-night shifts (16:00-08:00 hours) had even additional problems, such as suppressed estradiol, and increased interleukin (IL1β, IL6) levels.[38] Again, evening-oriented female nurses are more likely to show sleep disorders, insomnia, fatigue, and anxiety than males and morning-oriented females.[39]

Daylight saving time

In the European Union, clocks are changed twice per year to take the best of the available daylight in a given period. Clocks are advanced by one hour in the morning of the last Sunday of March and set back by one hour in the morning of the last Sunday of October to return to standard time (Daylight Saving Time or DST). Although such arrangements were first adopted by Germany and France during the first World War for economic reasons, nowadays the effect on overall savings effect is somewhat marginal. On the other hand, there is evidence of a series of health problems secondary to the transition shifts, especially driven by negative effects on the human circadian rhythms.[40] Thus, the system of bi-annual clock changes has been questioned by the European Northern Countries citizens, and even some international experts were against.[41]

Among the growing body of scientific evidence, we here limit to some aspects dealing with cardiovascular system. Researchers from the Karolinska Institutet, Sweden, first reported a significant increase in the incidence of myocardial infarction (MI) for the first days after the transition to DST in the spring, with a more pronounced effect in women.[42] A further meta-analysis on the available studies, found a significantly higher risk of MI (OR 1.03) during the two weeks following spring or autumn DST transitions. However, although MI risk increased significantly after the spring shift (OR 1.05), the incidence during the week after winter DST transition was comparable with control periods. No substantial differences were observed between women and men.[43] A study in the Veneto region of Italy on 10,387 circulatory deaths (years 2000 to 2015) confirmed a statistically significant excess of deaths on Tuesday only in the spring ($p = 0.011$), but not in the autumn post-transitional weeks, and without differences by sex.[44] Possible explanations include several favoring factors or triggers, such as circadian rhythm disruption, changes in sleep quantity and quality, sympathetic activity overdrive, increase in pro-inflammatory cytokine levels, and heart rate and blood pressure rise.[45] The European Parliament adopted a resolution to definitely stop the bi-annual change in 2021, with Member Countries free to choose between permanent solar or standard time. A recent US study found a significant increase in mean atrial fibrillation admissions over either the Monday to Thursday period and entire week following the DST spring transition compared to the yearly mean, but only in women.[46] Given also previous studies demonstrating a relationship between DST and stroke onset,[47] some US neurologists have called for the DST abolition.[48]

Temporal pattern of cardiovascular diseases

Many medical disorders exhibit predictable-in-time diurnal and 24 h patterning in their signs or symptoms, and nonfatal and fatal events.[49] In particular, the occurrence of cardiovascular (CV) acute events is not randomly distributed during the 24 h, but exhibits evident temporal patterns, as the final result of cyclic variation of either pathophysiologic mechanisms and environmental triggers.[50] However, the underrepresentation of women in cardiovascular research is still a barrier to generating knowledge and developing clinical practice guidelines.[51] This is true also for chronobiologic studies. We made a review on worldwide studies dealing with the definition of time of occurrence of acute cardiovascular diseases ($n = 64$, years 1996-2015, >650,000 cases), and found that only 44% provided separate analysis by gender.[52] Nevertheless, since these studies included the great majority of available cases (85%), the final results can be considered statistically robust, and we can assume that morning hours represent critical time for onset of acute cardiovascular diseases in both men and women. Similarly, seasonal and day-of-week patterns exist, and winter and Monday seem also to exhibit a higher frequency of events, with no sex-specific differences.[53]

Knowledge of temporal patterns of acute cardiovascular diseases and of their underlying endogenous mechanisms, could help in obtaining more effective patient care by using a temporized approach. Chronotherapy, i.e., therapy adapted to time of day, is collecting a growing body of successful studies. Nevertheless, it still remains at the fringes of clinical practice and drug-development studies due to a series of reasons.[54] On one hand, chronotherapy needs to be personalized, since internal circadian time is different for each individual and also influenced by genetic predisposition, age, sex, and environment. Based on this, attempts to obtain blood-based biomarkers for a personalized circadian determination have been proposed.[55] On the other hand, we need for the availability of solid data, especially taking into account possible sex and gender-specific differences, with particular reference to differences in drug responses. The main gender-related variables affecting drug response are weight, body surface area, height, fat mass, plasma volume and total body water. Gender differences can also greatly influence drug safety profile, and it is known that women experience greater incidence and severity of adverse drug reactions compared to men.[56] Something is available for cardiovascular medications, for example acetylsalicylic acid (ASA), a drug usually taken in single dose in the morning. However, when comparing morning versus evening administration, a significant reduction in platelet aggregation was obtained in the evening group. However, for morning administration the response to ASA was dif-

Key messages

- Biological rhythms exist at any level of living organisms, and circadian (period of ~24 hours) rhythms are the most widely studied.
- Circadian information is inherited, but individual circadian preference (chronotype) exists: Morning-type, Evening-type, and Neither-type.
- Circadian rhythms may be desynchronized factors by exposure to light at night, jet lag, shiftwork, and daylight saving time.
- Evening chronotype is associated with unhealthy habits and diet, reduced physical activity, smoking and alcohol, metabolic disturbances, sleep disturbances, and psychopathology.
- Knowledge of individual circadian organization could help precision medicine.

ferent between sexes. Platelet reactivity decreased in men, but increased in women. Thus, women could take greater benefit by shifting ASA administration from the morning to the evening.[57] On the contrary, no difference was found between morning and evening dosing of aspirin administered to pregnant women to prevent eclampsia.[58]

In the next future, according to the objectives of the Center for Gender-Specific Medicine of the Italian National Institute of Health, strategic points will be identifying gender-specific diagnostic and prognostic markers and the most appropriate therapies for each individual.[59] The 'new world' of biological rhythms is now part of this exciting challenge, and we need now a great effort and coalition between basic and clinical sciences to investigate more-in-depth the complex relationships between organization/desynchronization of biological rhythms and individual circadian preference, in the view of sex/gender differences, to achieve a more effective, tailored and personalized medicine for all patients.

References

1. Manfredini R, Salmi R, Malagoni AM, Manfredini F. Circadian rhythm effects on cardiovascular and other stress-related events. In: Encyclopedia of stress. George Fink (Editor-in-Chief). 2nd ed. 2007. vol. 1. p. 500-5.
2. Bargiello TA, Jackson FR, Young MW. Restoration of circadian behavioural rhythms by gene transfer in Drosophila. Nature. 1984;312:752-4.
3. Hastings MH, Herzog ED. Clock genes, oscillators, and cellular networks in the suprachiasmatic nuclei. J Biol Rhythms. 2004;19:400-3.
4. Do MT, Yau KW. Intrinsically photosensitive retinal ganglion cells. Physiol Rev. 2010;90:1547-81.
5. Young ME, Bray MS. Potential role for peripheral circadian clock dyssynchrony in the pathogenesis of cardiovascular dysfunction. Sleep Med. 2007;8:656-67.
6. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97-110.
7. Kudielka BM, Federenko IS, Hellhammer DH, Wüst S. Morningness and eveningness: the free cortisol rise after awakening in 'early birds' and 'night owls'. Biol Psychol. 2006;72:141-6.
8. Kalmbach DA, Schneider LD, Cheung J, Bertrand SJ, Kariharan T, Pack AI, et al. Genetic basis of chronotype in humans: insights from three landmark GWAS. Sleep. 2017; 40(2).
9. Ashkenazi IE, Reinberg AE, Motohashi Y. Interindividual differences in the flexibility of human temporal organization: pertinence to jet lag and shiftwork. Chronobiol Int. 1997;14:99-113.
10. Randler C, Engelke J. Gender differences in chronotype diminish with age: a meta-analysis based on morningness/chronotype questionnaires. Chronobiol Int. 2019;36:888-905.
11. Fabbian F, Zucchi B, De Giorgi A, et al. Chronotype, gender and general health. Chronobiol Int. 2016;33:863-82.
12. Gowen R, Filipowicz A, Ingram KK. Chronotype mediates gender differences in risk propensity and risk-taking. PLoS One. 2019;14:e0216619.
13. Makarem N, Paul J, Giardina EV, Liao M, Aggarwal B. Evening chronotype is associated with poor cardiovascular health and adverse health behaviors in a diverse population of women. Chronobiol Int. 2020;37(5):673-85.
14. Knutson KL, von Schantz M. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. Chronobiol Int. 2018;35:1045-53.
15. Falchi F, Cinzano P, Duriscoe D, et al. The new world atlas of artificial night sky brightness. Sci Adv. 2016;2:e1600377.
16. Vollmer C, Michel U, Randler C. Outdoor light at night (LAN) is correlated with eveningness in adolescents. Chronobiol Int. 2012;29:502-8.
17. Rybnikova NA, Haim A, Portnov BA. Does artificial light-at-night exposure contribute to the worldwide obesity pandemic? Int J Obes (Lond). 2016;40:815-23.
18. Koo YS, Song JY, Joo EY, et al. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. Chronobiol Int. 2016;33:301-14.
19. Cajochen C, Frey S, Anders D, et al. Evening exposure to a light-emitting disordes (LED)-backlit computer screens affects circadian physiology and cognitive performance. J Appl Physiol (1985). 2011;110:1432-8.
20. Chinoy ED, Duffy JF, Czeisler CA. Unrestricted evening use of light-emitting tablet computers delays self-selected bedtime and disrupts circadian timing and alertness. Physiol Rep. 2018;6:e13692.
21. Bruni O, Sette S, Fontanesi L, Baiocco R, Laghi F, Baumgartner E. Technology use and sleep quality in preadolescence and adolescence. J Clin Sleep Med. 2015;11:1433-41.
22. Aledavood T, López E, Roberts SG , et al. Daily rhythms in mobile telephone communication. PLoS One. 2015; 10:e0138098.
23. Pereira-Morales AJ, Adan A, Bussi IL, Camargo A. Anxiety symptomatology, sex and chronotype: the mediational effect of diurnal sleepiness. Chronobiol Int. 2018;35:1354-64
24. Dal Prà C, Fabris R. Obesity and gender differences. Ital J Gender-Specific Med. 2020;6:3-14.
25. Cespedes Feliciano EM, Rifas-Shiman SL, Quante M, Redline S, Oken E, Taveras EM. Chronotype, social jet lag, and cardiovascular risk factors in early adolescence. JAMA Pediatr. 2019;173(11):1049-57.
26. Bolognini M, Plancherel B, Bettschart W, Halfon O. Self-esteem and mental health in early adolescence: development and gender differences. J Adolesc. 1996;19:233-45.
27. Park YM, White AJ, Jackson CL, Weinberg CR, Sandler DP. Association of exposure to artificial light at night while sleeping with risk of obesity in women. JAMA Intern Med. 2019;179(8):1061-71.
28. Manfredini R, Manfredini F, Fersini C, Conconi F. Circadian rhythms, athletic performance, and jet lag. Br J Sports Med. 1998;32:101-6.
29. Weingarten JA, Collop NA. Air travel: effects of sleep deprivation and jet lag. Chest. 2013;144:1394-401.
30. Grajewski B, Whelan EA, Nguyen MM, Kwan L, Cole RJ. Sleep disturbance in female flight attendants and teachers. Aerosp Med Hum Perform. 2016;87:638-45.
31. Radowicka M, Pietrzak B, Wielgoś M. Assessment of the occurrence of menstrual disorders in female flight atten-

dants: preliminary report and literature review. Neuro Endocrinol Lett. 2013;34:809-13.
32. West AC, Smith L, Ray DW, Loudon ASI, Brown TM, Bechtold DA. Misalignment with the external light environment drives metabolic and cardiac dysfunction. Nat Commun. 2017;8:417.
33. Brum MCB, Dantas Filho FF, Schnorr CC, Bertoletti OA, Bottega GB, da Costa Rodrigues T. Night shift work, short sleep and obesity. Diabetol Metab Syndr. 2020;12:13.
34. Qian J, Morris CJ, Caputo R, Wang W, Garaulet M, Scheer FAJL. Sex differences in the circadian misalignment effects on energy regulation. Proc Natl Acad Sci USA. 2019;116:23806-12.
35. Torquati L, Mielke GI, Brown WJ, Burton NW, Kolbe-Alexander TL. Shift work and poor mental health: a meta-analysis of longitudinal studies. Am J Public Health. 2019;109:e13-e20.
36. Roberts B, Vincent GE, Ferguson SA, Reynolds AC, Jay SM. Understanding the differing impacts of on-call work for males and females: results from an online survey. Int J Environ Res Public Health. 2019;16:E370.
37. Boettcher C, Hartmann MF, Zimmer KP, Wudy SA. High glucocorticoid response to 24-h-shift stressors in male but not in female physicians. Front Endocrinol (Lausanne). 2017;8:171.
38. Cakan P, Yildiz S. Effects of half- or whole-night shifts on physiological and cognitive parameters in women. Am J Med Sci. 2019;S0002-9629(19)30426-4.
39. López-Soto PJ, Fabbian F, Cappadona R, et al. Chronotype, nursing activity, and gender: a systematic review. J Adv Nurs. 2019;75:734-48.
40. Proposal for a directive of the European Parliament and of the Council discontinuing seasonal changes of time and repealing directive 2000/84/EC - COM/2018/639 final [Internet]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52018PC0639
41. Meira e Cruz M, Miyazawa M, Manfredini R, et al. Impact of daylight saving time on circadian timing system: an expert statement. Eur J Intern Med. 2019;60:1-3.
42. Janszky I, Ljung R. Shifts to and from daylight saving time and incidence of myocardial infarction. N Engl J Med. 2008;359:1966-8.
43. Manfredini R, Fabbian F, Cappadona R, et al. Daylight saving time and acute myocardial infarction: a meta-analysis. J Clin Med. 2019;8:E404.
44. Manfredini R, Fabbian F, De Giorgi A, Cappadona R, Capodaglio G, Fedeli U. Daylight saving time transitions and circulatory deaths: data from the Veneto region of Italy. Intern Emerg Med. 2019;14:1185-7.
45. Manfredini R, Fabbian F, Cappadona R, Modesti PA. Daylight saving time, circadian rhythms, and cardiovascular health. Intern Emerg Med. 2018;13:641-6.
46. Chudow JJ, Dreyfus I, Zaremski L, et al. Changes in atrial fibrillation admissions following daylight saving time transitions. Sleep Med. 2020;69:155-8.
47. Sipilä JO, Ruuskanen JO, Rautava P, Kytö V. Changes in ischemic stroke occurrence following daylight saving time transitions. Sleep Med. 2016;27-28:20-4.
48. Malow BA, Veatch OJ, Bagai K. Are daylight saving time changes bad for the brain? JAMA Neurol. 2020;77(1):9-10.
49. Smolensky MH, Portaluppi F, Manfredini R, et al. Diurnal and twenty-four hour patterning of human diseases: cardiac, vascular, and respiratory diseases, conditions, and syndromes. Sleep Med Rev. 2015;21:3-11.
50. Manfredini R, Boari B, Salmi R, et al. Twenty-four-hour patterns in occurrence and pathophysiology of acute cardiovascular events and ischemic heart disease. Chronobiol Int. 2013;30:6-16.
51. Norris CM, Yip CYY, Nerenberg KA, et al. State of the science in women's cardiovascular disease: a Canadian perspective on the influence of sex and gender. J Am Heart Assoc. 2020;9:e015634.
52. Manfredini R, Salmi R, Cappadona R, Signani F, Basili S, Katsiki N. Sex and circadian periodicity of cardiovascular diseases: are women sufficiently represented in chronobiological studies? Heart Fail Clin. 2017;13:719-38.
53. Manfredini R, Fabbian F, Pala M, et al. Seasonal and weekly patterns of occurrence of acute cardiovascular diseases: does a gender difference exist? J Womens Health (Larchmt). 2011;20:1663-8.
54. Peeples L. Medicine's secret ingredient: it's in the timing. Nature. 2018;556:290-2.
55. Wittenbrink N, Ananthasubramaniam B, Münch M, et al. High-accuracy determination of internal circadian time from a single blood sample. J Clin Invest. 2018;128:3826-39.
56. Di Mauro G, Zinzi A, Vitiello F, et al. Adverse drug reactions and gender differences: what changes in drug safety? Ital J Gender-Specific Med. 2019;5:114-22.
57. Krasińska B, Paluszkiewicz L, Miciak-Lawicka E, et al. The effect of acetylsalicylic acid dosed at bedtime on the anti-aggregation effect in patients with coronary heart disease and arterial hypertension: a randomized, controlled trial. Cardiol J. 2019;26:727-35.
58. Shanmugalingam R, Wang X, Münch G, et al. A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy. Am J Obstet Gynecol. 2019;221:255.e1-9.
59. Carè A. The center for gender-specific medicine of the italian national institute of health is facing new challenges: research, training and dissemination. Ital J Gender-Specific Med. 2019;5:3-4.

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