It's about time: implications of chronoactivity on health and disease

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General introduction

Circadian rhythms

Essentially, almost all living organisms have a circadian (originating from the Latin words ‘circa’ and ‘dies’ meaning ‘about’ and ‘day’, respectively) rhythm. This rhythmicity originates and is sustained by the earth’s rotation which lasts approximately 24 hours per cycle. This alternation of daylight and darkness, but also seasonal changes due to the earth’s orbit around the sun in a stable tilt of its rotational axis, have a big influence on physiology, metabolism and behavior in microorganisms, plants, animals, and humans. Biological clocks (i.e., an internal timekeeping system that produces and orchestrates the whole internal circadian system) function to allow organisms to anticipate rather than react to changes in the environment, including the earths’ light-dark cycle. When an event happens every day at the same time, most organisms will adjust and learn that the event will occur accordingly. This physiological adjustment to external stimuli brings forth a superior evolutionary-conserved strategy of survival.(1) Although our surroundings and the earth seem to play a crucial role in establishing circadian rhythms, fundamental evidence shows that circadian rhythms are entrained rather than solely driven by the earth’s cycle in our solar system.(1) More specifically, circadian rhythms are endogenously and autonomously generated in most organisms. This was first discovered by the French researcher Jean-Jacques d’Ourtous de Mairan in 1729. He described that the opening and closing of the leaves of the Mimosa Pudica was not dependent on light exposure as its daily leaf oscillation continued in constant dark conditions.

In 2017, the Nobel prize in medicine was awarded to doctors Michael Rosbash, Michael W. Young, and Jeffrey C. Hall for their discoveries of the fundamental molecular mechanisms controlling the biological clock.(1) They found that the PER protein inhibits the expression of the Period gene, discovered in the 1970’s by Seymour Benzer and Ronald Konopka, by an inhibitory feedback loop and thereby regulating its own level in a cyclic rhythm with a period of approximately 24 hours.(2)

In humans, the suprachiasmatic nucleus (SCN) that is located in the anterior hypothalamus, functions as the master clock. This master clock is the pacemaker of the circadian rhythm of innumerable physiological processes (**figure 1**). The neurons located in the SCN operate through a daily transcriptional-translational negative feedback loop involving key clock genes and proteins (e.g., Per1/2, Cry1/2, Bmal1, Clock). This central rhythm in neuronal activity is communicated to the rest of the brain and the body.(3) Perhaps the most prominent example of a physiological process coordinated by the circadian rhythm is our sleep-wake cycle in which melatonin and cortisol levels together with blood pressure are timed optimally to facilitate a stable sleep-wake cycle. To be an effective conductor, the master clock must be entrained to solar time which is achieved by direct retinal innervation (exposure to light through the eyes).(4) Through neuronal, endocrine, metabolic and behavioural pathways, the SCN coordinates downstream processes throughout the body. Our circadian rhythms are not only regulated in a top-down manner, as cellular clocks from different tissues also provide bottom-up feedback to the central clock which further helps entrainment.(5) Alignment of circadian rhythms across the body, or in other words; 'a good running clock' has been shown to be crucial for overall health.(6)

Zeitgebers

In the 1950's a physician named Jürgen Aschoff studied the sensitivity of endogenous circadian systems to environmental stimuli in birds and mammals at the Max Planck institute in Munich. During his studies, he introduced a new concept: Zeitgebers (i.e., 'Time givers'). This term refers to regular cyclic environmental, behavioural or social cues that can influence endogenous rhythms and can help to synchronize the biological clock.(7, 8) To be classified as a Zeitgeber, a cue should have (at least one of) the following properties:(9)

1. If the Zeitgeber is removed, the circadian rhythm should fade out or gradually drift away from a strict 24-hour cycle.(9, 10)
2. Reversing or shifting a regular Zeitgeber, such as the light-dark cycle, should cause a corresponding reversal or shift in the circadian rhythms.(9, 10)
3. Changes in the frequency of the Zeitgeber (e.g., how often it occurs) should lead to predictable adjustments in the circadian rhythm, depending on how strongly the Zeitgeber influences the system.(9, 10)

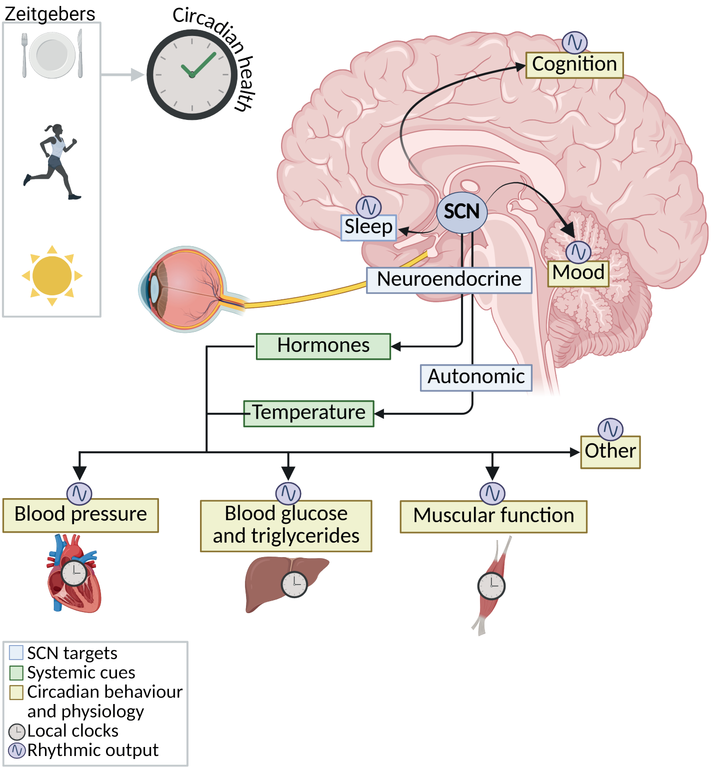

Figure 1. Graphical overview of the human circadian system tailored to the output discussed in this thesis. Figure created in BioRender (https://BioRender.com)

Following these criteria, light exposure is seen as the 'chief Zeitgeber' because of its direct and strong influence on the SCN via the retina. Next to light, food intake and physical activity are the main Zeitgebers.(11) Regularity in the circadian cues from these Zeitgebers as well as synergy with each other is essential for maintaining health. Furthermore, the timing at which these Zeitgebers occur, strongly influences the phase of circadian rhythms. For example, it is well known that exposure to a surge of light in the morning can advance sleep timing and have a positive influence on mental performance whereas exposure to (blue emitting) light in the evening can suppress melatonin production, postpone sleep onset, and affect sleep architecture.(12-14) Additionally, it is known that later timing of food intake (i.e., 'chrononutrition') negatively affects metabolic health(15) and even though evidence is not conclusive yet, recommendations about timed or time restricted eating are trending.(16)

Circadian health and ageing

Ageing affects our biological clock on various levels. Firstly, the circadian phase has been shown to shift forward (i.e., advance).(17) A phase advance is visible in important circadian-driven processes such as core body temperature(18), melatonin and cortisol secretion.(17, 18) Secondly, the amplitude of overall electrical activity in the SCN weakens leading to alterations in output rhythm which in turn causes a reduced amplitude of various hormones and core body temperature.(17, 19) Thirdly, evidence from animal and human studies showed that the expression of clock genes dampens (PER1, PER2 and BMAL1) or becomes arrhythmic (CRY1) with increasing age.(20-22) In addition, the rhythmic oscillations generated by the SCN weaken and signalling becomes increasingly disorganized throughout the system, resulting in disturbances of the circadian clock. This misalignment of SCN output can contribute to a wide range of cellular dysfunctions, many of which are currently poorly understood, but are thought to play an important role in the development of several age-related pathologies.(23) These changes mainly seem to affect the sleep-wake cycle. For example, experimental studies have shown that sleep is more susceptible to disruption due to weakened circadian regulation in older adults compared to younger individuals.(17) Animal studies also demonstrate that aging alters locomotor activity rhythms, with observed changes including reduced amplitude, increased fragmentation, and shifts in the free-running period.(24) Importantly, the age-related changes of the biological clock are sex-specific. This might explain the observation that insomnia and sleep disruption are most prevalent among older women.(25, 26) Conversely, a good functioning biological clock is a hallmark for healthy ageing. For example, evidence from the Switchbox study showed that people enriched for familial longevity are characterized by a more pronounced circadian rhythmicity and strong amplitude of serum non-HDL cholesterol as compared to their partners.(27) As the biological clock becomes more vulnerable with increasing age, the strategic utilization of Zeitgebers becomes increasingly important to reinforce circadian alignment and support overall health.

Circadian misalignment and disease

It has been established that a ‘good running clock’ is important for good health, while it’s disruption has been increasingly recognized to be crucial in the development of multiple diseases.(6) Most notably, circadian misalignment has been associated with metabolic disease, cardiovascular disease, poor mental health, and sleep problems.(6) These diseases are currently among the most common or burdensome non-communicable diseases worldwide.(28-33)

Metabolic disease

It is well-established that the circadian system has a direct effect on metabolism. The central clock regulates metabolism directly through diffusible factors (mainly cortisol and melatonin) and synaptic projections (via the autonomic nervous system).(34) The interplay between the central clock and peripheral clocks in for example the liver, muscle tissue, and adipose tissue influence a wide spectrum of metabolic targets such as glucocorticoids which in turn affect an array of metabolic processes.(34) Consequently, these processes, that include insulin sensitivity and secretion, cholesterol synthesis, fat oxidation and energy expenditure, all follow a 24-hour rhythm.(35) Evidence from animals and humans shows a direct and strong effect of the circadian system on metabolism. Experiments done in humans and mice showed the negative impact of circadian misalignment on metabolism.(36-38) They observed that participants having circadian misalignment (i.e., when sleep and activity occur out of sync with the internal biological clock) had considerably higher plasma glucose level and lower insulin sensitivity. Moreover, levels of the satiety hormone leptin decreased by 17% which during circadian misalignment, which is indicative of a higher risk of hyperphagia and weight gain.(36) In line, the majority of rhythmic metabolites were misaligned relative to the endogenous clock.(38)

Cardiovascular disease

Peripheral clocks in essentially all cardiovascular cell types regulate key physiological functions, including endothelial activity, blood pressure, heart rate, responsiveness to extracellular signals, and heart regeneration.(39) A well-known example is blood pressure which fluctuates throughout the day being low during rest and peak in the morning. Disruption of circadian rhythms affects cardiomyocyte-specific clock cells. It has been shown that circadian misalignment, for example caused by shift work, can lead to a significant increase of mean blood pressure, especially during sleep, but also to higher lipid levels, inflammation, and higher risk of obesity.(36, 40) Moreover, not only shift work but also irregular daily routines have been associated with increased risk of incident stroke and coronary artery disease in women.(41)

Sleep

There are two main sleep-inducing processes in humans. The first is homeostatic sleep drive which refers to the accumulation of sleep pressure throughout the day. It is the mechanism by which the body maintains a balance between sleep and wakefulness. This homeostasis ensures that the need for sleep increases the longer a person is awake, and decreases during sleep.(42) The second process is the circadian pacemaker. The sleep-wake cycle is one of the most prominent circadian outputs. The direct input of sunlight signals the SCN. Subsequent output triggers the production or suppression of melatonin and cortisol which are important sleep regulating hormones.(5) Especially timing of sleep but also sleep duration and sleep quality are influenced by the circadian system. When the circadian system is disrupted, decreased sleep quality and duration or even sleep disorders can occur which subsequently detrimentally impact overall health.(42) Shift work, which has become essential in our 24/7 society causes sleep displacement and gravely disturbs circadian rhythms. Consequent circadian misalignment caused by shift work, and thus disrupted sleep, increases the risk of metabolic diseases, cancer, cardiovascular diseases and mood disorders.(43, 44) Appropriate timing of the three main Zeitgebers has been reported as a potential non-pharmacological approach to improve sleep outcomes mainly in individuals working nightshifts.(45)

Mental health

There is a strong bidirectional relationship between the biological clock and mental health.(33) Mood disorders such as major depression, anxiety disorder, or seasonal affective disorder are frequently linked to disturbances in processes regulated by circadian output like sleep and cortisol secretion. Conversely, disruptions of circadian rhythms caused by factors such as jet lag, night-shift work, or exposure to artificial light at night, can precipitate or worsen affective symptoms and mood disorders.(33) These disturbances can impair the regulation of mood-related neurotransmitters and affect the hypothalamic-pituitary-adrenal (HPA) axis, which governs the stress responses. More recent studies have started to uncover the interaction between the circadian system and mood regulation.(33) Circadian disruption was found to directly and indirectly alter the function of brain areas involved in emotion and mood regulation through altered neurotransmission and plasticity.(46)

Maintaining stable circadian rhythms has been shown to support emotional resilience and improve therapeutic responses to interventions such as light therapy.(47) Circadian interventions like (timed) light therapy that focus on re-establishing general sleep/wake and social rhythms, are utilized increasingly to treat mood disorders.(33, 47) Understanding the bidirectional relationship between circadian timing and mental health is essential for developing effective and personalized strategies that promote psychological well-being through circadian alignment.

Physical activity and health implications

Not only have circadian rhythms been well established in our physiology from an evolutionary perspective, so has the importance of physical activity.(48) It is therefore not surprising that physical activity plays an essential role in healthy ageing. Being physically active can provide, among many other health benefits, preservation of bone strength and muscle mass, a healthy cardiovascular and metabolic system, good mental health, and good sleep quality.(49) Concurrently, sedentary behaviour (i.e., any waking behaviour characterized by an energy expenditure of less than 1.5 Metabolic Equivalent of a Task (METs, which equals to 3.5 ml.kg maximum volume of oxygen, VO2 max−1.min−1) while sitting, reclining, or lying(49)) or insufficient physical activity can lead to an abundance of negative health outcomes such as increased risk of non-communicable diseases, such as cardiovascular disease, overweight, diabetes type 2, Alzheimer's disease, depression, and even all-cause mortality. People who are insufficiently active have a 20% to 30% increased risk of death compared to people who meet the current physical activity guidelines.(50)

In November 2021, at the start of this PhD project, the World Health Organization (WHO) published the latest physical activity guideline which states that adults should perform at least 150 to 300 minutes of moderate intensity aerobic physical activity per week or 75 to 150 minutes of vigorous aerobic physical activity per week, limit their sedentary time, and do at least two days of muscle strengthening activities for additional health benefits.(49) For older adults (aged 65 years and older) the guidelines additionally recommend varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity at least three times a week.(49) Population data from the Netherlands shows that only 47.1% of adults aged 18-64 years and only 38.9% of older adults (65 years and older) met the physical activity guidelines in 2024, leaving a big part of the population at increased risk of morbidity and mortality attributable to insufficient amounts of physical activity.(51)

The current WHO guideline and derivative national guidelines focus on type, duration, intensity, and frequency of physical activity. These dimensions together form the total volume of physical activity.(52) The importance of each of these dimensions seems to differ per outcome of interest. Yet, from a chronobiology perspective, one could argue that there is another, uncharted dimension of physical activity lacking from current guidelines: *timing*.

Introducing a new concept: chronoactivity

The attention given to physical activity as a Zeitgeber has been far less than that devoted to light and food intake. At the start of this PhD project, only few studies had examined the effects of physical activity on circadian rhythms and circadian-related health and physiological outcomes, and even fewer had investigated the potential impact of its timing.(53-61) When the timing of physical activity would be a significant factor in circadian alignment in the same way timing of light exposure and food intake are, it could represent a low-cost, accessible, and non-pharmacological strategy to enhance (circadian) health. To address this gap, I propose in this thesis the use of the term ‘chronoactivity’ to describe the daily timing of physical activity in relation to the circadian system. This concept underscores the hypothesis that it not only matters how much or how intensively active we are, but also *when* we are active. When validated, chronoactivity could become a powerful tool in the optimization of circadian rhythms and, by extension, overall health.

Measurement of physical activity

Until around 15 years ago, all studies on the potential health benefits of physical activity were based on data from activity logs and questionnaires. This subjective data is considered to be unreliable because of recall bias and social desirability bias easily leading to overestimation of physical activity levels, in particular in certain subgroups. Most of our knowledge about the importance of physical activity for health and also the foundation of current guidelines comes from questionnaire data. Around the 2000s, new technologies arose to objectively measure physical activity patterns. Accelerometery through triaxial measurement on the hip, thigh or wrist is perhaps the most frequently used and most developed measurement tool currently available. Nowadays, smart watches translating accelerometery technology to laymen usage as well as accelerometers with advanced raw data available to scientists are well established and widely used. With the development of user friendly, inexpensive accelerometery technology, there has also been a positive development in open-source algorithms to process accelerometery data.(62)

The caveat of this development is that there is little consensus and great variety of the methodology in the current state.

Most accelerometers register acceleration of the body part on which the sensor is worn on three axes in space (X, Y, and Z). Raw acceleration is mostly presented in gravity (g) or milligravity (mg) where 1 g is equal to the gravity of the earth.(63) The properties of this data highly depend on the sample rate, range and resolution.(52) Most accelerometers sample by default with a frequency of 87 Hz or 100 Hz. Accelerometers are usually worn about five to ten days depending on the goal of the sampling. A validation study has shown that a measurement period of seven days gives a good representation of one’s physical activity behaviour for multiple years.(64)

This novel device-based method of measurement has opened many doors and the development has been vastly advanced over the past decade. For example, intensity, fragmentation, exact timing of physical activity and rest-activity patterns as a whole can now be monitored continuously in a highly detailed manner.

Aim and outline of this thesis

The overall aim of this thesis is to investigate the impact of physical activity timing on cardiometabolic health, sleep, and mental health outcomes. To do so, we have investigated the association with and the effect of chronoactivity on multiple common diseases and outcomes. We have done this by using various study designs; through cross-sectional and prospective observational studies and through a randomized cross-over study. This thesis is structured in three parts in which we explore implications of chronoactivity on cardiometabolic health, sleep health, and mental health.

Part I – Chronoactivity and Cardiometabolic Health

In **chapter 2**, I describe the study on the association between physical activity timing and various metabolic health outcomes, such as body mass index (BMI), venous glucose and insulin levels, and insulin resistance in sedentary older adults from the Actief en Gezond Oud (AGO) study.

Chapter 3 describes a prospective cohort study on the association between physical activity timing and cardiovascular disease (specifically coronary artery disease and stroke) incidence in the UK Biobank, a population based prospective cohort study.

Part II – Chronoactivity and Sleep Health

In **chapter 4**, I introduce the ON TIME study. We have conducted this trial to examine the effect of chronoactivity, using time-based sports activities in groups, on various circadian outcomes with insomnia severity as the primary outcome. This protocol paper gives an elaborate description of the methodology of this randomized cross-over trial.

In **chapter 5,** I describe the primary results of the effect of chronoactivity from the ON TIME study. Most notably, we examined the effect of morning and evening physical activity on insomnia severity, measures of objective and subjective sleep outcomes, and dim light melatonin onset (DLMO).

Part III – Chronoactivity and Mental Health

In this part of the thesis, I discuss the implications of chronoactivity on mental health. In **chapter 6** we examined the association between different diurnal patterns of physical activity timing and depression disorder incidence. Here, I describe an observational analysis in the UK Biobank population accelerometery subgroup with a similar design as used in **chapter 3**.

In **chapter 7**, I further test this hypothesis within the ON TIME study. Here, we collected continuous information on positive and negative affectivity, cognition and feelings of energy and fatigue through ecological momentary assessment (EMA) and examined how morning vs. evening physical activity affected these mood related outcomes.

Finally, in **chapter 8**, I discuss all findings from this thesis. Important considerations for research as well as challenges of clinical and societal implementation of the results are reported. Moreover, I discuss my views on future directions in the field of chronoactivity.

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