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

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General discussion

Preface

The main objective of this thesis was to investigate the impact of physical activity timing on cardiometabolic health, sleep, and mental health. The circadian clock is responsible for the coordination and synchrony of multiple different rhythms within the body and also prepares the body for states fitting to the earth's light/dark cycle (e.g., sleep and wakefulness). Disruption of the complex circadian physiology greatly affects health. Finding ways to entrain the biological clock and thereby decrease the incidence of many common non-communicable diseases, would be of significant clinical and societal importance. In this chapter, I explain why it is important to consider physical activity timing in optimizing health strategies. Furthermore, the main findings of this thesis and their scientific, clinical, and societal implications will be discussed. Finally, important considerations of the presented findings will be addressed and future directions for the field of chronoactivity and Zeitgeber research in general will be outlined.

Why look at the time?

Since the industrial revolution, the contrast between day- and night time has become progressively blurred. Nowadays, we live in a 24/7 society. Through (social) media and modern forms of communications, we can connect to all parts of the world at any given moment of the day and night. Additionally, through increased (international) economic demands, a rising number of people work in nightshifts. While these social, economic, and technological developments have made many aspects of life easier and more pleasant, they have also introduced increased exposure to artificial light and subsequently an increased risk of circadian misalignment. Satellite data from 2000 already showed that 75% of the US and European population is exposed to artificial light at night (ALAN).(1) In 2016, 80% of the world's population and even 99% of the US and European population lived under light polluted skies.(2) Exposure to ALAN desynchronizes our internal clock with the environment which consequently disrupts the sleep/wake pattern and is associated with many adverse health outcomes, such as affective disorders, different types of cancer, metabolic disease and cardiovascular disease.(3)

Social jetlag is a common phenomenon that is also a consequence of our modern society. It refers to a discrepancy of sleep timing on working days compared to weekend days due to social activities. As a consequence, sleep timing becomes more variable and there is chronic misalignment which can disrupt molecular clock mechanisms in peripheral cells.(4) Social jetlag is a risk factor for various short- and long-term health problems, including sleep disturbances, reduced cognitive performance, unhealthy behaviours (such as snacking, less physical activity, and increased alcohol and tobacco use), as well as metabolic, cardiovascular, and psychiatric disorders.(5) In industrialized countries, it is thought that 70% of the population has a social jetlag ranging from one hour to more than 2 hours.(5, 6)

Circadian health (i.e. synchronisation of our internal rhythms with the environment) has become endangered due to our modern society. Consequently, there is an increasing demand for more attention for healthier routines and interventions to strengthen and synchronise our clock. Luckily, the circadian system is remarkably sensitive to environmental cues that synchronize internal rhythms to external cycles. Therefore, behavioural, non-invasive interventions such as timed physical activity could tap into these input circuits and align internal and external rhythms in individuals with disrupted circadian systems.(7)

Summary of the main findings

Chronoactivity and cardiometabolic health

At the time we conducted the research described in **chapter 2**, knowledge on the relation between the amount of physical activity at different times of the day and metabolic health outcomes was limited. However, cardiometabolic health, circadian rhythms and physical activity are all intricately linked with each other. The attention that has since been given to cardiometabolic health outcomes in the field of Zeitgeber research is therefore not surprising. In **chapter 2**, we examined how timing and change in timing of physical activity was associated to different measures of metabolic health in sedentary older adults. Cross-sectional analyses showed that higher physical activity in the morning was associated with lower fasting glucose, fasting insulin, and insulin resistance, while late afternoon and early evening physical activity was associated with lower body mass index (BMI) and fat percentage. In contrast, night-time activity was associated with higher BMI, and higher levels of fasting glucose and HbA1c, suggesting that being active during the night, when the body is programmed to sleep, may reflect circadian misalignment.

The prospective analyses, based on changes in activity timing over a 3-month follow-up, provided additional insights into the directionality of these associations. Most notably, participants who increased their morning activity showed significant improvements in fasting insulin and insulin resistance, while those who became more active in the evening experienced reductions in BMI.(8) Although these findings do not imply causality, they merely suggest that shifts in activity timing may coincide with favourable changes in metabolic health.

A strength of this study is that it was one of the first to use a data-driven approach to analyse physical activity patterns. Since this study was published, the field has grown incredibly fast. It is therefore appropriate to provide an update on current knowledge. Despite growing interest in the relationship between the timing of physical activity and metabolic markers, and the publication of multiple studies addressing the question of physical activity timing in different cohorts, the evidence remains inconclusive to this day. Two recently-published systematic reviews and meta-analyses(9, 10) examined 16 studies(11-26) and reported highly heterogeneous findings: some studies suggested that morning activity was most effective, others favoured afternoon or evening activity, and several found no additional benefit of timing at all. This heterogeneity was probably due to variation of methodology. The authors additionally reported that the quality of most included papers was very low. Consequently, both reviews concluded that there is no clearly identifiable time of day for physical activity that consistently improves metabolic outcomes. Nevertheless, a paradigm grounded in the well-established mechanistic link between skeletal muscle circadian clocks and metabolic health has been proposed linking skeletal muscle clock genes to metabolic regulation.(27) According to this paradigm, the timing of physical activity could directly influence the skeletal muscle clock, thereby modulating circadian physiology in ways that support metabolic health.(10, 27, 28) The improvements in insulin-related markers that we observed in **chapter 2** following increased morning activity align with evidence that insulin sensitivity is highest in the morning. Prior research in normoglycemic older adults showed lower postprandial glucose responses in the morning, suggesting more efficient insulin action.(29, 30) Additionally, a recently published meta-analysis suggested that morning exercise in the fasting state in individuals with type 2 diabetes improved 24-hour glucose profiles, likely due to enhanced insulin sensitivity and better utilization of endogenous energy stores for the rest of the day.(31, 32) Our findings have been supported further by a recent cross-sectional study from NHANES that showed that late morning physical activity and afternoon physical activity was associated with lower odds of type 2 diabetes(33) and a recently-published prospective cohort study within the UK Biobank that found that participants most active in the morning had a 12% lower risk of incident type 2 diabetes.(34) These findings support the hypothesis that morning physical activity may be particularly effective for improving insulin dynamics and glucose regulation.

Chapter 3 describes the association between timing of physical activity and cardiovascular disease outcomes. We observed several distinct physical activity timing subgroups in the UK Biobank population, resembling participants with distinct daily patterns of chronoactivity. We observed that participants who were most active in the morning (especially activity during late morning), independent of their total mean daily physical activity level, had a lower risk of incident coronary artery disease (CAD) and (ischemic) stroke. These results align with a previous study that showed that morning physical activity is associated with increased cardiorespiratory fitness, particularly in individuals with type 2 diabetes.(35)

We observed that the results were more explicit in women compared to men which may reflect sex-specific physiological differences in circadian regulation(36) and cardiovascular risk profiles(37), although the underlying mechanisms remain unclear and will require additional research.

Similar to metabolic outcomes, literature on physical activity timing is also still quite ambiguous when it comes to cardiovascular outcomes. Our study was the first large-scale prospective cohort study to focus on cardiovascular events as endpoint rather than on surrogate markers of cardiovascular health such as blood pressure, LDL cholesterol, and BMI. While these surrogate markers can be measured more easily and over shorter periods, they do not always reliably predict the occurrence of clinical outcomes such as coronary artery disease of stroke.(38) As a result, findings based solely on surrogate markers may overestimate or underestimate the true impact of physical activity timing on cardiovascular disease risk, limiting their clinical relevance and the ability to inform prevention guidelines.(38) This study stands out due to its data-driven clustering approach, which allowed us to capture naturalistic patterns of behaviour independent to the overall daily amount of physical activity. These strengths support the robustness of our observations and underscore the potential of chronoactivity as a novel behavioural target to be further investigated as a CVD prevention strategy. Ideally, to prove a causal relation between physical activity timing and incidence of cardiometabolic disease, large scale intervention studies are required but simultaneously nearly impossible to carry out due to the number of confounders, the large sample sizes needed and the long duration and low acceptability of the intervention. Researchers should consider using other methodological approaches to clarify a causal relationship. For example, Mendelian randomization can leverage genetic variants associated with chronotype or activity timing as proxies, allowing researchers to investigate whether these traits have a causal effect on cardiometabolic disease risk(39), but would require genetic variants for chronoactivity that can be used as instrumental variables that are currently unavailable.

Chronoactivity and sleep health

In **chapter 4**, we described the study design of the ON TIME study. A randomized cross-over trial in which we assessed the effect of morning versus evening physical activity on sleep quality and multiple other circadian related outcomes in older adults with sleep problems. This approach, although unfeasible to conduct in very large sample sizes, can provide further evidence for potential causality. This protocol paper comprises all details and considerations of performing a behavioural intervention study using timing of physical activity as a Zeitgeber. The vast majority of studies in this field are observational in nature, likely due to the inherent complexity and susceptibility to confounding in intervention studies targeting Zeitgebers. Nevertheless, there is a clear need for well-designed intervention studies to establish more causal relationships required for optimal translation into clinical practice. In this context, the publication of this protocol represents an important contribution to the transparency and methodological quality of chronoactivity research.

Chapter 5 described the primary results of the ON TIME study. We observed no change in insomnia severity, subjective, or objective sleep quality between the active morning and active evening intervention. The absence of any observed difference could be explained either by a lack of effect or a limitation of the study method. As with many clinical trials, we had difficulties to include the required number of participants and some people dropped out during the trial.

In line with our research hypothesis, we observed that morning activity led to an earlier sleep/wake schedule whereas evening physical activity caused a later sleep/wake schedule (as compared to the sedentary period) which is in line with current literature.(7, 40-42) Additionally, our observation from exploratory analyses that individuals with an evening chronotype were overrepresented among those whose insomnia symptoms improved following morning activity suggests that chronotype may moderate the effectiveness of the intervention. Although exploratory in nature and not sufficiently powered for subgroup analyses, our observation of individual variability in response to the timing of physical activity suggests that intervention effects may differ across individuals and could be influenced by the chronotype of the individual.

In the observational studies described in **chapter 3** and **6**, we observed that morning physical activity was beneficial regardless of chronotype. Prior evidence suggests that evening chronotypes are more susceptible to circadian misalignment.(43) Morning physical activity may therefore be particularly beneficial in promoting circadian alignment for evening chronotypes.(7) The ambiguity of results highlights the need for further investigation in larger, well-powered studies to assess the potential of more personalized intervention strategies.

Chronoactivity and mental health

Given the strong bidirectional relationship between the biological clock and mental health(44, 45), identifying the optimal timing for physical activity, which is known to influence both, could be of great clinical importance. In **chapter 6**, we studied the association between chronoactivity and depression risk using a prospective analysis in UK Biobank. We observed that participants most active in the late morning had a 21% lower risk of incident depression compared to people who were most active during midday. Conversely, we observed an association between physical activity at night and an increased risk of depression incidence.

Despite the clear relation between physical activity, the biological clock and mental health, there is little evidence on the impact of specific timing of physical activity on depression risk. A systematic review from 2022 included five observational studies with small sample sizes and concluded that low physical activity in the morning and high physical activity late in the evening or at night was associated with an increased risk of depression and depressive symptoms.(46) None of these studies however were performed using a prospective study design. The findings from our prospective cohort study, in which we performed sensitivity analyses where we excluded participants with a depression diagnosis within one year after accelerometery assessment to minimize the chance of reverse causation, build on these cross-sectional findings and add substantial knowledge to the field. Yet the need for intervention studies to add further evidence of a causal relationship remains.

In line with the need for intervention evidence, we used data from the experimental ON TIME study to further explore the relationship between chronoactivity and affect and energetic arousal in **chapter 7**. In this study, we focused on subjective energy levels and positive and negative affect, the latter serving as surrogate markers for incident depression and being particularly well suited for investigation in a short-term intervention design.(47) We found that two weeks of morning physical activity increased positive affect and feelings of energy and decreased negative affect and fatigue compared to two weeks of evening physical activity. Furthermore, we observed fluctuations in affect and energy outcomes throughout the day and that morning physical activity improved subsequent affectivity and energy levels. These findings provided evidence that mood has a circadian rhythm and lend support to the hypothesis that morning physical activity can positively influence affect and energy levels.

General considerations

In this thesis, we have observed evidence for a relation between timing of physical activity and some important health outcomes. Specifically, our work showed a potential protective implication of morning physical activity.

The existing physical activity guidelines are now fairly general, with a few age-related nuances.(48) For the vast majority of people, the recommendation is: at least 150 minutes of moderate intensity physical activity per week to become and stay healthy. However, when it comes to timing, this seems to be different. Scientific developments within the chronoactivity field during my PhD teach us that a number of factors first need to be thoroughly investigated further in future studies and in the long term will probably need to be taken into consideration when timing is included as an additional component in the current recommendations and activity-related interventions.

First, the potential differentiation of chronoactivity versus chronoexercise needs to be studied. The terms physical activity and exercise are often used interchangeably, also in Zeitgeber research, despite the fact that they are conceptually and physiologically distinct constructs. Exercise typically refers to structured, intentional, and repetitive bodily movements typically performed in leisure time to improve or maintain physical fitness, whereas physical activity encompasses all bodily movements (performed for leisure or work) that result in energy expenditure above 1.5 METs, including light to moderate activities such as walking, riding a bike or household chores. This distinction becomes particularly important in chronoactivity research, where the timing appears to differentially affect health outcomes depending on the intensity of the activity. The discrepancies and heterogeneity in research findings in the published literature might be due to the fact that the optimal timing for engaging in general, overall physical activity may differ from that of structured exercise. A clear example can be found in the different results observed in **chapter 2** and the study of van der Velde et al.(49) The two studies included similar populations and used similar measurements of physical activity yet in **chapter**

2, decreased insulin resistance was associated with morning physical activity while van der Velde observed that decreased insulin resistance was associated with exercise (moderate to vigorous physical activity, MVPA) in the afternoon.(49) This nuance complicates the interpretation and comparability of studies in the field, but may also help reconcile conflicting results in existing literature. By (re)incorporating activity intensity, and potentially other dimensions such as duration or type of activity, into analyses and interpretation of timing effects, researchers may uncover more consistent patterns and advance our understanding of chronoactivity and chronoexercise. Being able to distinguish specific health outcomes of timed physical activity and exercise is essential to provide tailored interventions in clinical practice. Indeed, when the study on chronoactivity timing on incident type 2 diabetes mellitus was repeated for MVPA timing in the UK Biobank and NHANES study (Feng et al, unpublished results), similar patterns were observed as in the study from the Netherlands Epidemiology of Obesity Study.(49)

Second, sex differences may play a critical role. In **chapter 3**, we observed that the associations were particularly pronounced in women, which could be explained by sex-specific aetiology of cardiovascular disease. Evidence also suggests that circadian output in the heart and other physiological systems differs between men and women, potentially amplifying the role of the biological clock in disease development among women.(36, 50)

Third, chronotype may influence the optimal timing of physical activity. Two opposing perspectives exist: one argues that individuals should align activity with their endogenous circadian rhythm to minimize misalignment, implying that evening chronotypes might benefit from later physical activity. Conversely, evening chronotypes have a higher risk of circadian misalignment, and accompanying health risks, since many obligations are in the early morning (especially for children and working adults).(43, 51) Physical activity earlier in the day is known to advance the clock(7) (**chapter 5**) and could therefore be especially important for individuals with evening chronotypes.

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Fourth, disease- and outcome-specific considerations seem important. Circadian rhythms may be differentially involved in the onset of various diseases, suggesting that recommendations about physical activity timing for individuals with depression or sleep disorders (**chapters 5 and 6**) might differ from those suffering from high blood pressure.(52) Moreover, differentiation between short-term and long-term goals is important. While our observational studies focused on long-term disease incidence, the ON TIME study examined short-term effects. Furthermore, studies suggest aligning training strategies with the circadian rhythm.(53, 54) This could be important when specific performance must be effectively built (e.g. during rehabilitation), such as muscle mass, bone density, or endurance. In line with this, physical performance generally peaks later in the day, favouring afternoon or evening exercise for athletic performance goals(55), whereas morning activity may be more beneficial for certain long-term circadian-related health outcomes, like the outcomes studied in this thesis.

Finally, it is very important to remember that physical activity does not occur in a vacuum. Other zeitgebers and behaviours such as meal timing, light exposure, but also medication schedules may interact with the effects of physical activity timing. Unfortunately, we did not have this data available in our studies. Key questions remain, including whether being physically active before or after meals is preferable and how light exposure interacts with effects of physical activity timing. Addressing these questions will be crucial for developing comprehensive, evidence-based implementation strategies.

Challenges for future implementation

A word of caution is warranted here: the majority of the Western population does not currently meet the WHO guidelines for sufficient physical activity.(56) Introducing an additional timing component may risk discouraging individuals, making physical activity appear even more unattainable than it already is. Therefore, timing should be positioned as an opportunity to further enhance the benefits of existing efforts helping individuals achieve certain health outcomes with the same or, ideally even less, effort.

Moreover, the field of chronoactivity research is still relatively young. As mentioned above, critical steps in research remain to be taken. Once stronger evidence is available to incorporate timing into interventions and recommendations, the next and arguably greater challenge will be to induce behavioural change.(57)

While this thesis provides indications that morning activity may be beneficial for several health outcomes, most adults face work or social obligations during the morning hours. Although for some an active commute to work (e.g., riding a bike or walking) might offer opportunities. For many, simply finding any time to exercise during the day is already a challenge. Implementing timing-based recommendations and change in behaviour will therefore require collaboration beyond (behavioural) scientists; it may necessitate structural changes in society since both the individual and their environment need to be addressed for optimal behavioural change.(58-60) This includes targeting affective judgement in individual participation (i.e., feelings of motivation, pleasure, and enjoyment)(60), but also engaging employers, policymakers, and healthcare systems to normalize practices such as allowing physical activity during working hours. Governments and health insurers could also play a pivotal role by prioritizing prevention and recognizing circadian health as a key component of overall well-being.

Future directions

The studies described in this thesis offer several recommendations for future studies and practical implementation. First, larger and longer-duration intervention studies are required to establish causal relationships and assess the long-term timing effects. Researchers should not underestimate the practical challenges of such intervention trials, as we have encountered as well when executing the ON TIME study. These include accounting for possible confounders and finding a sufficient number of participants willing to change their daily routines for longer periods of time. In addition, prospective analyses in large cohorts can provide further evidence on the associations with diverse health outcomes and should therefore be further utilized in which important details about the intensity and mode of physical activity are described accurately. These large cohort can also be used for Mendelian randomization studies to study causality if a genetic variant would be identified. Future research should also examine the interplay between the different zeitgebers by combining multiple assessment methods (e.g., light sensors, accelerometers and food diaries) in both observational and experimental designs. Special attention should be given to populations at high risk of circadian disruption, including shift workers, individuals with depression, and older adults.

When the efficacy of timed physical activity is clear, there are different ways this could be implemented in clinical practice. For the general population, technological innovations such as wearable devices could integrate chronoactivity principles by estimating circadian status from physiological and behavioural signals and provide personalized, real-time recommendations to promote circadian health and prevent circadian misalignment. In clinical practice, the development of a conceptual framework would help healthcare professionals incorporate timing into existing interventions, stratify evidence by population and outcome, and identify key moderators (such as medication use). Such an overview would provide actionable guidance, advancing personalized (circadian) medicine. To facilitate behavioural change, it is essential to conceptualize barriers and facilitators for implementation of physical activity at a specific time in real-world settings. A qualitative approach could be fitting here, for example by conducting interviews or focus groups with individuals or stakeholders. Ultimately, a theoretical framework could be developed similar to those that exist for physical activity. Finally, I would like to offer some general advice. Currently, the biological clock is still given far too little consideration in research and healthcare. Consideration of time-of-day as a biological variable is nearly non-existent in most areas of research.(36, 61) Given its complex intertwining within so many physiological processes, for example in the cardiovascular system, immune function, and glucose metabolism, I would like to call on researchers in basically all fields of (bio) medical research to think about how the biological clock might play a role within their area of interest.

Conclusion

The circadian timing of physical activity is an important factor to consider. We observed that morning physical activity was associated with better metabolic health, and decreased risks of cardiovascular disease and depression in the general population. We also observed that timing of physical activity was able to shift sleep timing and that morning physical activity had a positive effect on mood and subjective levels of energy. Current literature is still ambiguous and there is no consensus about the most optimal timing and many important questions remain to be answered. Nevertheless, these findings underscore the clinical potential of incorporating timing into physical activity interventions and recommendations. When validated in large-scale trials, and causality has been ascertained, chronoactivity-based interventions could become a low-cost strategy to enhance treatment efficacy and prevention across multiple health domains.

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