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RESEARCH ARTICLE

Predicting circadian phase in community-dwelling later-life adults using actigraphy data

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Summary

The accurate estimation of circadian phase in the real-world has a variety of applications, including chronotherapeutic drug delivery, reduction of fatigue, and optimal jet lag or shift work scheduling. Recent work has developed and adapted algorithms to predict time-consuming and costly laboratory circadian phase measurements using mathematical models with actigraphy or other wearable data. Here, we validate and extend these results in a home-based cohort of later-life adults, ranging in age from 58 to 86 years. Analysis of this population serves as a valuable extension to our understanding of phase prediction, since key features of circadian timekeeping (including circadian amplitude, response to light stimuli, and susceptibility to circadian misalignment) may become altered in older populations and when observed in real-life settings. We assessed the ability of four models to predict ground truth dim light melatonin onset, and found that all the models could generate predictions with mean absolute errors of approximately 1.4 h or below using actigraph activity data. Simulations of the model with activity performed as well or better than the light-based modelling predictions, validating previous findings in this novel cohort. Interestingly, the models performed comparably to actigraph-derived sleep metrics, with the higher-order and nonphotic activity-based models in particular demonstrating superior performance. This work provides evidence that circadian rhythms can be reasonably estimated in later-life adults living in home settings through mathematical modelling of data from wearable devices.

KEYWORDS
actigraphy, circadian rhythms, dim light melatonin onset, later-life adults, mathematical modeling, wearable data

1 | INTRODUCTION

Circadian timekeeping impacts a variety of physiological systems, with the suprachiasmatic nucleus (SCN) serving as a central clock in the hypothalamus that coordinates peripheral clocks throughout the body (Czeisler & Gooley, 2007; Hastings et al., 2018; Rijo-Ferreira & Takahashi, 2019). While circadian rhythms are internally generated, they become entrained to the external day/night cycle primarily through light input to the retinohypothalamic tract (Czeisler et al., 1981; Duffy & Czeisler, 2009; Duffy & Wright Jr., 2005; Sadun et al., 1984). Disruptions to these rhythms are associated with detrimental health outcomes, including psychiatric disorders, metabolic disorders, sleep disturbances, and cancer (Baron & Reid, 2014; Gale et al., 2011; Haus & Smolensky, 2013; Mason et al., 2020; Walker 2nd

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et al., 2020). To achieve more precise diagnosis and effective treatment of these diseases, for example, through chronotherapeutic interventions (Kim, Byun, et al., 2023; Lévi, 2001; Lévi et al., 2007), an understanding of the circadian timekeeping system of the individual is essential (Lévi, 2001; Lévi et al., 2007).

Given this background, a need exists to assess accurately the properties of the underlying circadian rhythm. Dim light melatonin onset (DLMO), the time at which the endogenous melatonin concentration reaches a certain level in dim light conditions, is a traditional gold-standard marker of the circadian phase in humans (Glacet et al., 2023; St Hilaire & Lockley, 2022). To determine one DLMO measurement, an individual typically spends the evening in dim light and salivary melatonin samples are collected usually every 30 min between evening and bedtime (Lewy, 2007). The saliva samples are later assayed to determine the actual measured DLMO time. The high cost, time-consuming nature, and substantial patient burden have thus hindered the incorporation of this marker into real-world settings or clinical care. Different approaches may therefore be needed to facilitate the translation of valuable laboratory circadian findings into real-world health and medicine.

One promising alternative is to predict circadian information from mathematical models and wearable data, which can be continuously and noninvasively collected in real-world settings (Huang, Mayer, Cheng, et al., 2021; Kim et al., 2022; Kim, Lee, & Forger, 2023; Kim, Mayer, et al., 2023; Song et al., 2023; Stone, Aubert, et al., 2019; Woelders et al., 2017). Mathematical models of the human circadian clock take wearable activity or light measurements as inputs and are simulated to predict circadian biomarkers–in particular circadian phase (Forger et al., 1999; Jewett et al., 1999; Kim, Lee, & Forger, 2023; Mayer et al., 2023; St Hilaire et al., 2007). Four models typically utilised for circadian phase prediction consist of an original van der Pol oscillator-based framework with a degree seven nonlinearity (termed the higher-order model) (Jewett et al., 1999), a simplified model of degree three (the simpler model) (Forger et al., 1999), a revised iteration of the van der Pol framework that considers nonphotic input (the nonphotic model) (St. Hilaire et al., 2007), and a physiologically based model derived from models of neurons within the SCN (the Hannay model). Recent studies have investigated the ability of the models coupled with wearable data to predict circadian phase biomarkers, such as DLMO or aMT6s acrophase (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Kim et al., 2022; Stone, Aubert, et al., 2019; Woelders et al., 2017). For example, the nonphotic model simulated with wearable light data predicted the circadian phase with an approximate accuracy of 1 h in workers on a rotating shift (Stone, Aubert, et al., 2019). A recent study performed by Huang and colleagues has shown that the more commonly available data source of wearable activity data, either from an actigraph or a consumer-grade Apple Watch, can be used as the model input instead of light to predict DLMO in multiple datasets (Huang, Mayer, Cheng, et al., 2021). However, because previous studies have focussed solely on assessing the models' predictive accuracy for DLMO among younger working individuals, there remains a need to explore their predictive capabilities with larger cohorts from different populations (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021).

To further test the approach combining wearable data with mathematical models, it may be promising and necessary to focus on older adults, as the ageing process has a substantial impact on circadian rhythms. Specifically, circadian timing, its relationship to sleep timing, and the effects of stimuli on the circadian system can all change with age (Chen et al., 2016; Duffy et al., 2015; Duncan, 2020; Huang et al., 2002; Turek et al., 1995). Research has revealed that the oldest participants experienced reduced amplitude and increased fragmentation of their circadian rhythms through the use of actigraphic monitoring across various age groups (Huang et al., 2002). Further work demonstrated reduced amplitude (particularly in temperature) and advanced circadian phase in older individuals (Dijk & Duffy, 1999; Weitzman et al., 1982). The effect of light on the circadian system may also become altered with age, although findings are less clear in this area. Several previous studies did not find a significant effect of age on the phase response to light stimuli at various intensities (Benloucif et al., 2006; Duffy et al., 2015; Kim et al., 2014), while another found an effect in the intermediate light range (Duffy et al., 2007). Circadian and sleep interactions may also become modified in older populations, with these individuals being particularly impacted by circadian misalignment (Dijk et al., 1999; Dijk et al., 2000; Dijk & Duffy, 1999; Silva et al., n.d.).

Here, we test the ability of four limit-cycle oscillator models to predict DLMO from actigraphy data in a larger cohort of later-life individuals. We demonstrate that the mathematical models and actigraph data can produce accurate predictions of home DLMO measurements in older adults, particularly when the models were simulated with activity data rather than light data. We further analyse the relationship between the circadian timing and actigraphy-derived sleep metrics in this cohort, and find that the mathematical models improve performance over sleep metrics alone. This study provides a validation and extension of the ongoing work to enable accurate circadian phase predictions in real-world settings.

2 | METHODS

2.1 | Participants and study procedures

The analysis used a dataset from a cross-sectional study investigating the relationship between circadian rhythm characteristics and brain health in older adults (Moon et al., 2024). The study was approved by the University of Iowa Institutional Review Board. The DLMO and actigraphy data were collected from community dwelling later-life adults who were older than the age of 55 and could speak, read, and write in English. The exclusion criteria were (1) shift workers, (2) people who had crossed a time zone in the past 2 weeks, (3) colour blind individuals, (4) individuals with insomnia disorders, (5) individuals with unstable chronic disorders, such as neurological disorders (e.g. dementia, Alzheimer's disease, stroke, traumatic brain injury), uncontrolled cardiovascular conditions (e.g. heart failure, arrhythmia,

uncontrolled hypertension), untreated psychiatric disorders, history of alcohol or substance abuse, or other health conditions that may affect sleep and health (i.e. severe kidney failure, chronic liver failure, uncontrolled cancer, ongoing chemotherapy). For the current study, we additionally excluded individuals (1) without DLMO or actigraphy data and (2) exposed to more than 20 lux during the DLMO session (see Section 2.1.1 below for details). The study team sent out invitation letters to eligible individuals populated through medical record reviews using the University of Iowa Institute for Clinical and Translational Science TriNetX database (https://icts.uiowa.edu/investigators/biomedical-informatics-core/trinetx). Individuals who showed interest in the study were rescreened. The participants completed a telephone screening interview. At the initial visit, participants completed questionnaires and a colour-deficiency test using the Ishihara colour vision test. Participants were asked to wear actigraphy for 14 days with a daily sleep diary, followed by a single home DLMO session.

As a result, of the 52 eligible participants who followed the study protocol and provided both DLMO and actigraphy data, we excluded data from seven participants due to higher light exposure (above 20 lux) during the DLMO assessment (see Section 2.2.1. below for details). Thus, the final dataset consisted of 45 individuals, each with actigraphy data and DLMO measurements.

2.2 | Measures

2.2.1 | DLMO assessment

We utilised a home DLMO kit from previous work (Burgess et al., 2016), which demonstrated a strong correlation ($r = 0.93$, $p < 0.001$) with laboratory DLMO results (Burgess et al., 2016). Study participants were instructed to remain awake and seated in a dimly lit environment in their homes (Burgess et al., 2016). Participants were prohibited from consuming alcohol, caffeine, or non-steroidal anti-inflammatory drugs—except for aspirin as part of a cardiovascular medication regimen—at least 24 h before the DLMO session. Participants collected a total of 13 saliva samples by collecting samples every 30 min for 6 h prior to their habitual bedtime, which was determined by 10 days of actigraphy data (Actiwatch Spectrum Plus, Respironics, Bend, OR). Salivette tubes (Sarstedt AG & Co., Nümbrecht, Germany) with cotton inserts were used to collect saliva samples. Study staff placed the cotton inserts from Salivette tubes into plastic vials equipped with MEMS Track Caps (MWV Healthcare, Richmond, VA, USA), which recorded each time the participants opened the vials for sample collection. Participants were instructed to saturate the cotton inserts by placing them in their mouths and then return the inserts to the Salivette tubes. Next, saliva samples were stored in the participants' home freezers overnight and transferred to our research laboratory the following day. Then, samples were stored in a −80°C freezer. The samples were subsequently sent to Solid-phase Inc. (Portland, ME) for radioimmunoassay (Buhlmann RIA), which has demonstrated high sensitivity for melatonin levels as low as 0.5 pg/mL.

Each participant's DLMO was defined as the point in time (as determined by linear interpolation) when the melatonin concentration exceeded and remained above the threshold for at least 2 h (Molina & Burgess, 2011; Voultsios et al., 1997). The threshold was calculated as twice the mean of the first three low daytime melatonin values. This threshold was used since it calculates DLMO closer to the initial melatonin rise. To ensure the accuracy of the DLMO, all melatonin profiles were visually inspected.

To mitigate the confounding effects of light, participants were asked to wear blue light-blocking sunglasses (Uvex Skyper, Honeywell, Charlotte, NC) during the experiment to reduce the impact of light on melatonin suppression, as done in previous work (Burgess et al., 2016; Sasseville et al., 2006). Participants also wore an actigraph (Actiwatch Spectrum Plus, Respironics, Bend, OR) on their wrist with a photosensor to measure light exposure and were instructed not to cover it to ensure compliance. To reduce the further impact of light exposure on melatonin suppression, the current analysis was done using the data from participants with a maximum light exposure of less than 20 lux during the 30 min between the two points used to calculate DLMO after reviewing the photosensor data (the range of maximum lux = [0 lux, 19.57 lux], Median 1.71 lux).

2.2.2 | Actigraphy data

The participants were asked to wear a wrist actigraph (Actiwatch Spectrum Plus, Respironics, Bend, OR) on their non-dominant wrist for 14 days to obtain at least 10 days of data. Actigraphy was collected for each participant for approximately 10 days with 1 min epoch; the data included date/time, on or off wrist status, activity count, and white, red, green, and blue light exposure in lux. Participants were instructed to press the event marker on the monitor before and after sleep each night. Sleep data were analysed using the Actiware 5.70.1 program (Respironics, Bend, OR). The event markers, light data, and activity levels guided us in setting the nightly rest intervals for analysis including daily metrics for sleep onset time, sleep offset time, sleep midpoint, hours in bed, total sleep time, sleep onset latency, percent sleep efficiency, wakefulness after sleep onset (WASO) minutes, and number of awakenings. We examined summary statistics for these categories. To test the relationship between sleep onset and measured DLMO in this cohort, we compared the sleep onset time on the final day of the study, shifted earlier by 2 h (Burgess et al., 2003), with the measured DLMO. We considered the relationship between activity counts and white light, by determining the light level corresponding to an activity count (increasing in increments of 25 counts/minute) to construct individual activity/light profiles. These profiles (i.e. the light levels corresponding to the activity bin for each individual) were then averaged across individuals, to construct the aggregate curve showing the relationship between activity and white light.

2.3 | Mathematical models of the human circadian clock

2.3.1 | Model background

Four limit-cycle oscillator ODE models (the higher-order, simpler, nonphotic, and Hannay models) were implemented in MATLAB (Forger et al., 1999; Jewett et al., 1999; St Hilaire et al., 2007). The first three of these models were based on a van der Pol oscillator framework, while the Hannay model was derived from higher-dimensional models for neuron populations in the SCN. The higher-order model conceptualises the circadian pacemaker as a degree seven limit cycle oscillator (Jewett et al., 1999), while the simpler model provides a less complex framework by reducing the degree to three (Forger et al., 1999). The nonphotic model extends this approach by considering a sleep/wake indicator in addition to light-based effects (St Hilaire et al., 2007), and the Hannay model utilises a different framework based on coupled oscillators in the SCN. Note that each circadian model has its own mechanism (i.e. distinct differential equations) for processing light stimuli. See Supplemental Information S1 for details of the model equations.

All of the models were originally developed to predict the time of core body temperature (CBT) minimum (CBTmin), from an input time series of light recordings. The model-predicted CBTmin for the van der Pol based models (i.e. higher-order, simpler, and nonphotic) was taken as the time at which the state variable x achieved a minimum. For the Hannay model, the predicted CBTmin corresponded to the time at which the phase output was closest to π. Recently, these models have been adjusted to instead predict CBTmin from an input time series of activity data, with comparable or even greater accuracy than when using light data (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021). These predictions can be shifted to estimate DLMO under the assumption that DLMO occurs 7 h earlier than CBTmin (Benloucif et al., 2005; Berry & Wagner, 2014; Wichniak et al., 2017). Women may generally have an earlier CBTmin and DLMO compared with men (Cain et al., 2010), and older adults may have an earlier CBTmin and DLMO compared with young adults (Duffy et al., 2015; Kennaway, 2023; Kim et al., 2014). Since both CBTmin and DLMO are advanced by approximately 1–1.5 h in these scenarios (Cain et al., 2010; Kim et al., 2014), however, we expected their phase relationship would not change significantly. We therefore used the same 7 h shift across individuals.

2.3.2 | Model implementation

The four models were simulated using inputs of light and activity recordings from an actigraph device. Initial conditions were determined from a limit cycle, generated by simulating the model for 30 days with a fixed schedule of darkness from 12 a.m. to 8 a.m. (8 h) and light from 8 a.m. to 12 a.m. (16 h). A fixed light level of 800 lux was used at all times during the light period, following previous work (Huang, Mayer, Cheng, et al., 2021). The duration of 30 days was more than sufficient to ensure that the models are entrained on this schedule. For example, the norm difference between model states (x,x_c,n) (or (R,ψ,n) in the case of the Hannay model) at a fixed time of the day (12 a.m.) consistently decreased to less than 0.001 after 23 days for the simpler model, 25 days for the higher-order model, 29 days for the nonphotic model, and 27 days for the Hannay model (Figure S1). The resulting limit cycle model output corresponding to the time that most closely matched the individual's start time (i.e. clock time of the start of the actigraphy recording) was then selected as the initial condition for that individual, as in previous work (Huang, Mayer, Cheng, et al., 2021). We simulated the models with the light data, a piecewise step to light function based on the activity data (see Section 2.2.3. below for details), and the raw activity counts (without a scaling factor) (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021). When simulating with the activity data (in the piecewise steps to light function or the raw activity counts), the light data were not utilised in the models. Missing data were replaced with zeros before simulating the models to enable even spacing of the data, based on the assumption that individuals were inactive and in dark conditions during missing data times, as done in previous work (Huang, Mayer, Cheng, et al., 2021). Note that there was a very low amount of missing data (Table S1): specifically, 0.73% missing for activity data, and 0.77% missing for white light. Therefore, no artificial bias towards lower values in the time series is expected. For the nonphotic model, the sleep–wake indicator was taken to be zero if activity was nonzero (indicating sleep/non-activity), and one otherwise (indicating wake/activity). The activity-based simulations were performed with the piecewise function (termed "piecewise activity") unless otherwise specified.

As described above, the model-predicted CBTmin was then converted to predicted DLMO by shifting it 7 h earlier. The simpler model predictions were further shifted 0.97 h later, to account for differences in the reference angle (Forger et al., 1999; St Hilaire et al., 2007). Circular means and standard deviations were implemented in MATLAB and used to compute statistics on the DLMO timing predictions. The final day's predicted DLMO was compared with the measured DLMO to generate a mean absolute (phase) error measurement (MAE). Sleep onset times from the actigraph were shifted 2 h earlier when using sleep timing as a proxy for DLMO, consistent with previous work (Burgess et al., 2003; Burgess & Eastman, 2005; Huang, Mayer, Cheng, et al., 2021; Van Reen et al., 2013).

2.3.3 | Preprocessing of activity data

To simulate the mathematical models, we preprocessed activity counts and estimated light levels, as done in previous studies (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Huang, Mayer, Walch, et al., 2021; Kim, Lee, & Forger, 2023; Kim, Mayer, et al., 2023). Specifically, given that the light measurements are correlated with activity counts (Huang, Mayer, Cheng, et al., 2021), we hypothesised that activity could serve as a suitable proxy for light exposure. We then used a piecewise function $Lt(i)$ to estimate light exposure from activity analytically:

$$Lt(i) = \begin{cases} L_1 & \text{if activity}(i) \le a_1 \\ L_2 & \text{if activity}(i) > a_1 \text{ and activity}(i) < a_2 \\ L_3 & \text{if activity}(i) \ge a_2 \text{ and activity}(i) < a_3 \\ L_4 & \text{if activity}(i) \ge a_3 \text{ and activity}(i) < a_4 \\ L_5 & \text{otherwise} \end{cases}$$

where $L_1 = 0, L_2 = 100, L_3 = 200, L_4 = 500,$ and $L_5 = 2000$ (in lux) for the light levels, and $a_1 = 0, a_2 = 0.1\,\text{m}, a_3 = 0.25\,\text{m},$ and $a_4 = 0.4\,\text{m}$ for $m = \frac{\max_i\{\text{activity}(i)\}}{2}$ (Huang, Mayer, Cheng, et al., 2021). In a previous study, the performance of the piecewise steps-to-light function in predicting circadian phase was compared against more complex machine learning approaches, such as multilayer perceptron, decision tree, and random forest (Huang, Mayer, Cheng, et al., 2021). The performance of the piecewise function was comparable to these methods. Therefore, we adopted this simple yet effective piecewise steps-to-light function for this study.

3 | RESULTS

3.1 | Baseline characteristics of an older adult cohort

The 45 individuals included in the analysis ranged in age from 58 to 86 years (mean = 69.51 years, SD = 5.88) (Table 1, Figure 1a), and included 24 men and 21 women. The home DLMOs ranged from 17:00 to 23:22 (mean = 19:50, SD = 1:22), with men having a mean of 19:31 and SD of 1:22 and women a mean of 20:18 and SD of 1:19 (Figure 1b). There was no significant difference between men and women in the home DLMO (p-value = 0.11, Watson's U2 test). Additionally, sleep metrics from the actigraph were analysed for this cohort (Table 2 and Figure 1c). The phase angle of entrainment for this population (the time interval between measured DLMO and sleep onset) was 2.56 (SD = 1.52) hours. Using actigraphy, activity counts and light levels for each individual were collected. Demographic information and summary statistics derived from the sleep, activity, and light data are shown in Tables 1, 2, and S1.

Examining the binned light levels and activity measurements revealed a clear trend: as activity counts increased, so did the light levels (Figure 1d). These results support the rationale for using activity data in addition to light data when predicting circadian phase, as done previously in our earlier study (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021). When activity levels reached approximately 150 count/min, the light levels were saturated (i.e. different activity counts correspond to approximately the same light levels), matching the previous observations from younger working populations (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021). This plateau pattern was observed regardless of sex. The variance in light levels also increased for higher activity counts: the standard error of the mean was less than 100 lux for all activity count bins less than 475, and an average of 164.24 lux for activity counts >475.

TABLE 1 Demographic and clinical information ($n = 45$). Age is measured in years, and all other values are measured in number (and percentage) of participants. Note that percentages may not sum to 100% due to rounding.

	Mean (SD)
Age (years)	69.51 (5.9)
	Number (percentage)
Gender	
Male	24 (53.3%)
Female	21 (46.7%)
Race	
American Indian/Alaska Native	1 (2.2%)
Asian	1 (2.2%)
Native Hawaiian or other Pacific Islander	0 (0.0%)
Black or African American	0 (0.0%)
White or Caucasian	43 (95.56%)
Hypertension	21 (46.7%)
Hyperlipidaemia	12 (26.7%)
Diabetes	7 (15.6%)
Coronary artery disease	10 (22.2%)
Chronic kidney disease	3 (6.7%)
Chronic obstructive pulmonary disorder	2 (4.4%)
Depression	3 (6.7%)
Antidepressants	5 (11.1%)
Anti-anxiety medications	1 (2.2%)
Beta blockers	5 (11.1%)
Calcium channel blockers	4 (8.9%)
Diuretics	0 (0%)
ACE inhibitors	6 (13.3%)
Aspirin	15 (33.3%)

3.2 | Circadian phase prediction

We examined whether it is possible to predict the DLMOs of later-life adults by analysing their actigraph wearable data using mathematical models. Activity or light recordings were employed as inputs for four circadian models: the higher-order, simpler, nonphotic, and Hannay models (Figure 2 and see Methods and Supplemental Information S1 for details). By simulating the models coupled with the actigraph measurements over time, we generated an oscillatory signal and utilised it to predict a circadian biomarker, DLMO, following the approach used in previous studies (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Stone, Aubert, et al., 2019; Woelders et al., 2017) (see Methods).

We then compared the predicted DLMO of the four models with the measured (i.e. home) DLMO. In general, the models with activity as the input provided reasonable predictions, with higher accuracy than when using light as the input in terms of capturing the measured DLMO (Figure 3 and Table 3). Specifically, for light inputs, the mean

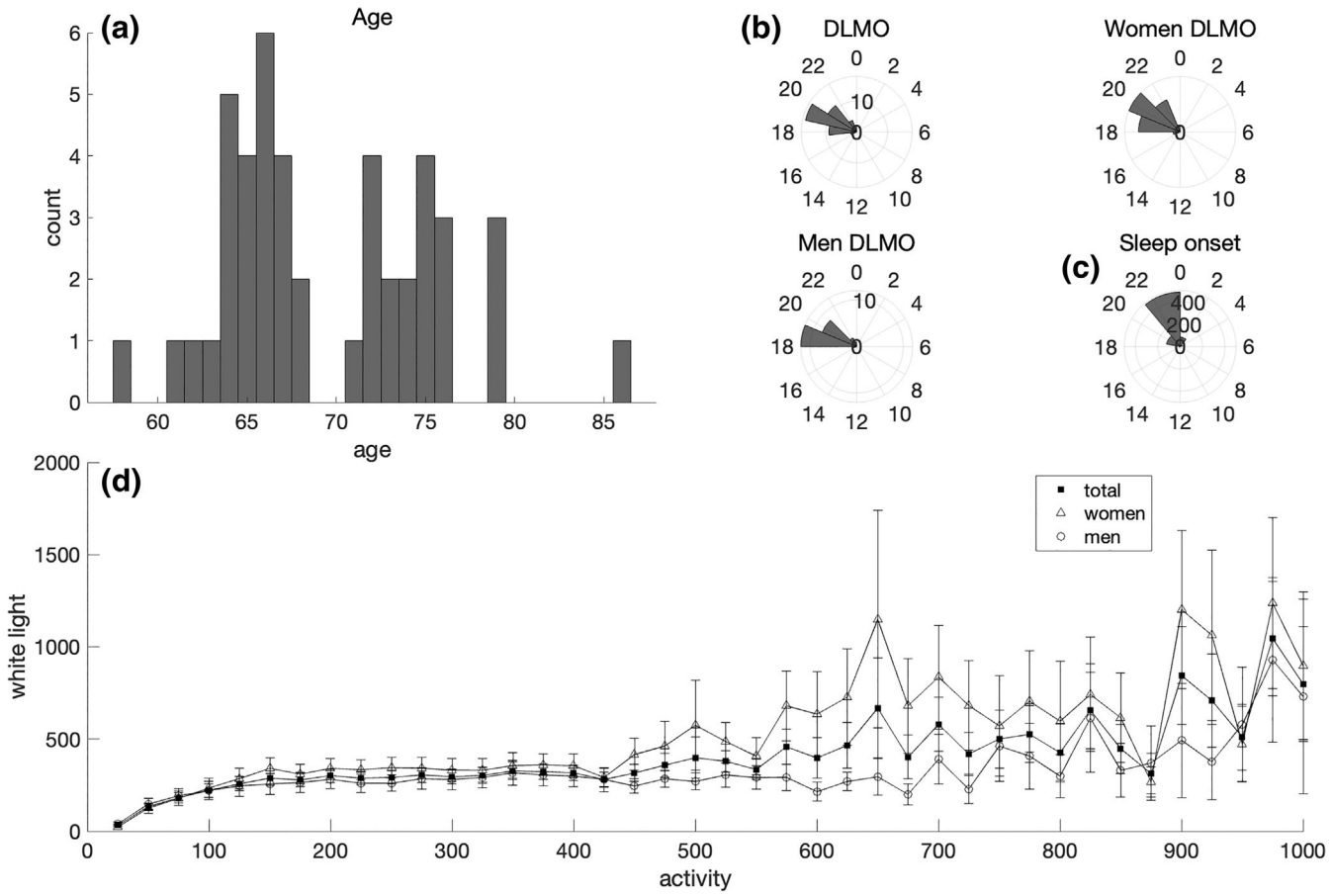


FIGURE 1 Overview of the dataset. (a) Age distribution for the cohort. (b) Circular histogram of measured DLMOs in hours (from 0 to 24), with one measurement per participant. Plots for the total population, women, and men are shown. (c) Circular histogram of actigraph-derived sleep onsets in hours (from 0 to 24), over all the days of the study. (d) White light versus activity, for the total population (filled square), women (open triangle), and men (open circle). Activity was binned in increments of 25 counts, and the corresponding level of white light was assessed. Error bars denote the standard error of the mean (SEM).

	Total	Men	Women
Sleep onset (clock time)	22:40 (1:33)	22:31 (1:37)	22:50 (1:28)
Sleep offset (clock time)	06:56 (1:37)	6:59 (1:40)	6:54 (1:32)
Time in bed (hours)	8.31 (1.42)	8.55 (1.55)	8.06 (1.22)
Total sleep time (hours)	7.03 (1.35)	7.28 (1.36)	6.78 (1.29)
Onset latency (minutes)	20.84 (34.67)	21.34 (35.45)	20.33 (33.92)
Sleep efficiency (percentage)	84.95 (10.50)	85.45 (9.29)	84.44 (11.60)
WASO minutes (minutes)	39.66 (29.88)	40.46 (32.69)	38.85 (26.79)
Number awakenings (counts)	24.78 (12.13)	23.25 (11.74)	26.33 (12.34)

TABLE 2 Summary statistics for sleep metrics. The column quantities were computed across all the days of available data for the relevant individuals. Mean values are shown for the total population, men, and women (note that for some individuals, sex information is not available). Standard deviations are shown in parentheses.

absolute (phase) errors (MAEs) were 1.61, 2.13, 1.25, and 1.57 h for the higher-order, simpler, nonphotic, and Hannay models, respectively. However, when simulated with activity inputs via the piecewise steps to light function following previous studies (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Stone, Aubert, et al., 2019; Woelders et al., 2017), the MAEs decreased to 0.93, 1.41, 0.96, and 1.12 h, respectively. The decrease was statistically significant (higher-order model: p-value = 0.003, paired t-test; Hannay model: p-value = 0.02; simpler model, p-value = 0.02) except for the nonphotic model (p-value = 0.06). This outperformance persisted even when using the raw activity input without any intermediaries (Table 3). Additionally, our results remained consistent even after excluding subjects who were either on antidepressants or beta blockers, which could potentially affect DLMO measurements (Table S2). Moreover, activity generally outperformed light across circadian misalignment levels (quantified as larger phase angles

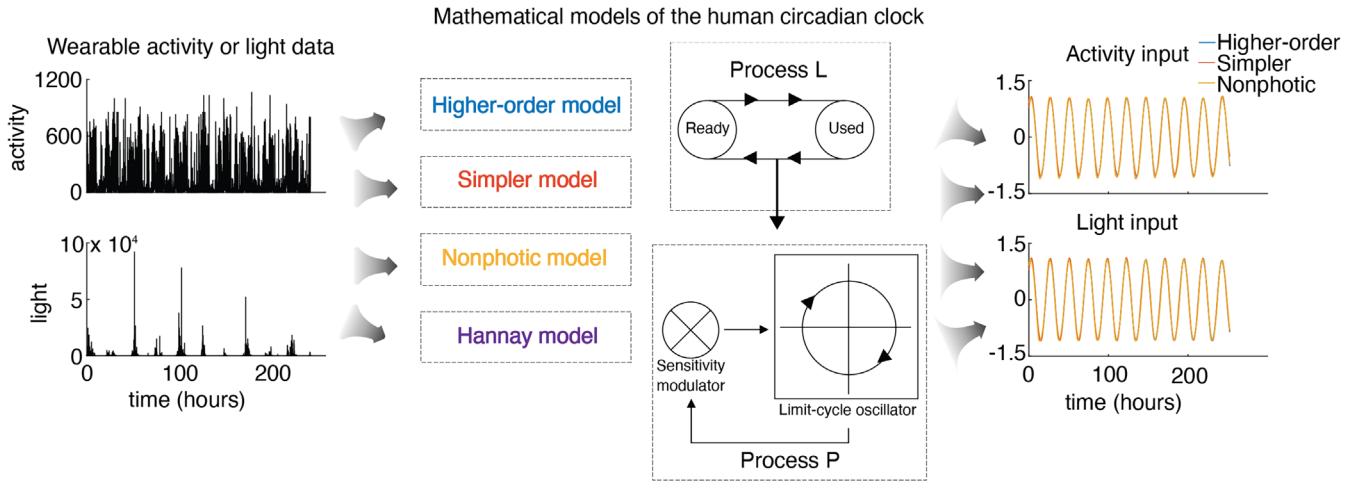


FIGURE 2 Overview of the models and methods. The light or activity input to the model first passes through light processing, termed Process L, wherein photopigments transfer from a ready to a used state based on activation by the light stimulus. This generates an input to the circadian pacemaker, Process P. This input may be further modulated based on timing information (in the sensitivity modulator). The processed input then is used to simulate model equations, either in the van der Pol models or the single population Hannay model. These result in trajectories for the state variable x (plotted), which determines the circadian phase prediction of the model.

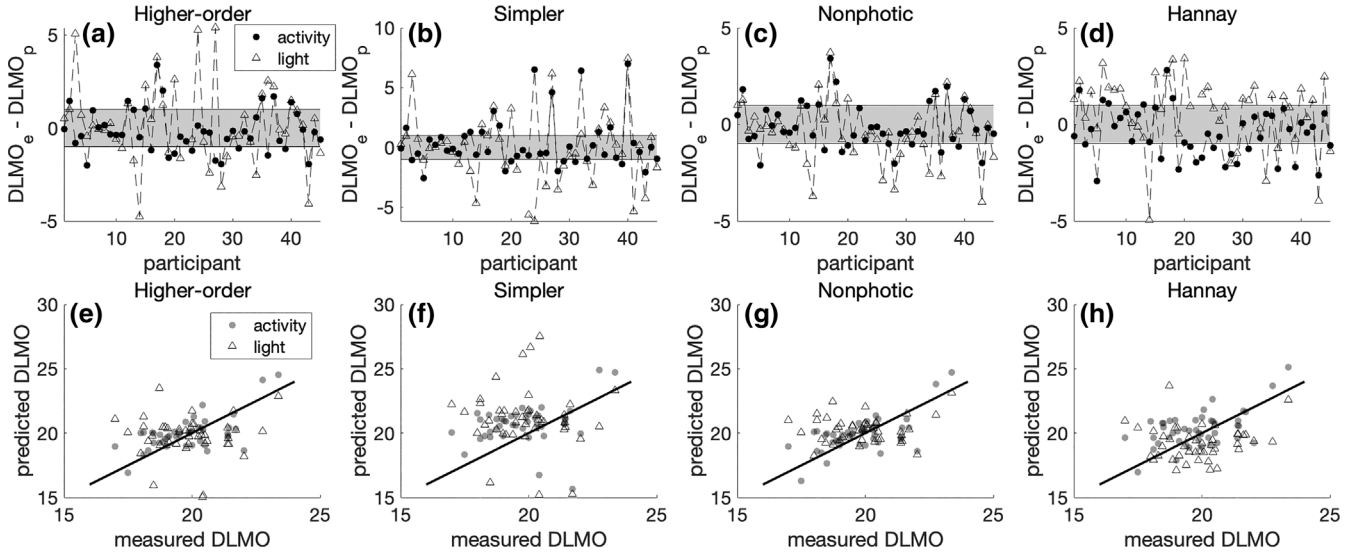


FIGURE 3 Predicted versus experimental (i.e. home) DLMO for the four mathematical models. Models were simulated with activity (piecewise function, dark circles) and light (light triangles), using the higher-order (a), simpler (b), nonphotic (c), and Hannay (d) models. The difference between experimental DLMO ($DLMO_e$) and predicted DLMO ($DLMO_p$) is shown, with the shaded region denoting a prediction error of $\pm$ 1 h. In (e–f), the predicted vs. measured DLMOs are plotted for the four models and the activity (dark circles) and light (light triangles) inputs. A diagonal 45-degree line is plotted.

between sleep onset and DLMO). For example, a high misalignment group (absolute value of phase angle plus 2 h larger than 2 h) had MAEs of 1.31, 1.77, 1.27, 1.53 for activity and 1.88, 2.15, 1.28, 1.38 for light and the higher-order, simpler, nonphotic, and Hannay models, respectively. Individuals with lower levels of misalignment had MAEs of 0.86, 1.23, 0.89, and 1.03 for activity and 1.62, 2.13, 1.30, and 1.64 for light, respectively.

The higher-order and non-photic models showed the best performance overall for the absolute errors, although the performance differences between the models were not statistically significant for the piecewise activity input (p-value = 0.09, Friedman test). They were significant for the light input (p-value = 0.04, Friedman test). Lin's bias corrections and concordance coefficients were assessed: the bias corrections with activity input were 0.992, 0.655, 0.998, and 0.946, with concordance correlation coefficients of 0.609, 0.126, 0.608, and 0.531 for the higher-order, simpler, nonphotic, and Hannay models, respectively. With light input, the bias corrections were 0.956, 0.539, 0.904, and 0.897 with concordance correlation coefficients of 0.050, −0.018, 0.103, and 0.077, respectively.

TABLE 3 Summary of prediction errors in hours for the higher-order, simpler, nonphotic, and Hannay models.

	MAE (hours)	SD of MAE (hours)	Percent within 1 h (percentage)	Percent within 2 h (percentage)
Piecewise activity (Huang, Mayer, Cheng, et al., 2021) input				
Higher-order	0.93*	0.71	57.78	93.33
Simpler	1.41	1.67	55.56	84.44
Nonphotic	0.96	0.70	60.00	91.11
Hannay	1.12	0.79	51.11	82.22
Raw activity input				
Higher-order	0.94*	0.72	60.00	95.56
Simpler	2.05	2.09	46.67	68.89
Nonphotic	0.98	0.72	64.44	95.56
Hannay	1.13	0.82	44.44	88.89
Light input				
Higher-order	1.61	1.50	45.45	70.45
Simpler	2.13	2.13	38.64	65.91
Nonphotic	1.25*	1.25	50.00	77.27
Hannay	1.57	1.10	36.36	75.00

Note: The mean absolute (phase) errors, or MAEs, are shown, with * denoting the best performing model for each input category. The percentage of individuals with absolute error within 1 and 2 h is also shown.

The percentages of individuals with a predicted DLMO within 1 h of their measured DLMO when simulated with light were 45.45%, 38.64%, 50.00%, and 36.36% for the higher-order, simpler, nonphotic, and Hannay models, respectively. When simulated with piecewise activity, the percentages increased to 57.78%, 55.56%, 60.00%, and 51.11%, respectively. The large majority (approximately 82%–93%, depending on the model) of the individuals were able to be predicted within 2 h using activity data (Table 1). These results indicate that the integration of mathematical models with wearable activity data holds potential to provide accurate predictions of circadian phase in older populations.

We next investigated the performance of the circadian models across sex, due to the potential impact of sexual dimorphism in circadian rhythms on the predictive capabilities of the models (Anderson & FitzGerald, 2020; Walton et al., 2022). Indeed, the models reached a satisfactory level of accuracy in both sexes, although the prediction error was lower in men than in women (Table S3). In particular, the MAEs for the higher-order and nonphotic models with piecewise activity were 0.84 for men and 1.04 h for women and 0.85 for men and 1.09 for women, respectively, which were lower than that of the other models. These sex differences were not statistically significant, however (p-values >0.05, t-test), suggesting that our approach can be utilised regardless of the sex of the individual. Up to this point, we used white light when predicting DLMO using the models coupled with light data. However, the prediction performance of the models could vary depending on light colour (i.e. different wavelengths of light) (Duffy & Czeisler, 2009; Morita & Tokura, 1998; Wright & Lack, 2001). To explore this, we tested the home DLMO predictions using the four models and four colours of light, instead of white light alone (Table S4). The raw values in lux were used to simulate the models when using the non-white light colours, in a similar way to when using the white light. Of the light inputs considered, white light provided the best prediction accuracy across the models, supporting the use of white light as the most relevant light colour for model simulation. Indeed, the superior performance of white light could be attributed to the fact that the circadian models were originally built to take photopic illuminance as an input.

3.3 | Comparing sleep metrics and circadian phase

We compared the actigraph-derived sleep metrics with the circadian information, for 40 individuals who had both DLMO measurements and sleep information on the same day. Using sleep onset minus 2 h as a circadian phase proxy provided an MAE of 1.36 h, with 37.50% of individuals having a prediction within 1 h and 75.00% within 2 h (Figure 4). The alternate proxies of sleep midpoint minus 6 h and sleep offset minus 10 h yielded MAEs of 1.21 and 1.45 h, respectively. The DLMO prediction performance using sleep metrics was generally worse compared with that achieved by the models, in terms of both the MAE (e.g. sleep onset vs. the higher-order model with activity: 1.36 vs. 0.93 h) and the percentage of individuals with a predicted DLMO within 1 h (e.g. sleep onset vs. the nonphotic model with activity: 37.50% vs. 60.00%). The absolute phase prediction errors were significantly lower for the higher-order model (p-value = 0.01, paired t-test) and the nonphotic model (p-value = 0.02) than for the sleep onset metrics, but were not significantly different between the sleep onset and the simpler or Hannay models (p-values > 0.05). Notably, the outperformance of the higher-order and nonphotic models with activity input remained consistent even when adjusting the phase angle between sleep onset and DLMO used for the sleep-based prediction (Figure S2). This indicates that the effective processing of actigraph wearable data, such as the application of mathematical models, has the potential to enhance the prediction of circadian metrics based on wearable data in real-world environments.

4 | DISCUSSION

In this study, we assessed the ability of four mathematical models to predict ground truth DLMO for a home-based cohort of 45 later-life adults. This generalises and extends previous work that described the performance of these models in assessing circadian phase (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Stone, Aubert, et al., 2019), showing the applicability of the models in a relatively large cohort of individuals with potential age-related differences in their circadian rhythms. Since prior work has suggested differential effects of light on the circadian system depending on age (Benloucif et al., 2006; Duffy et al., 2007; Kim et al., 2014), the application of light and activity-based modelling to these populations serves as a

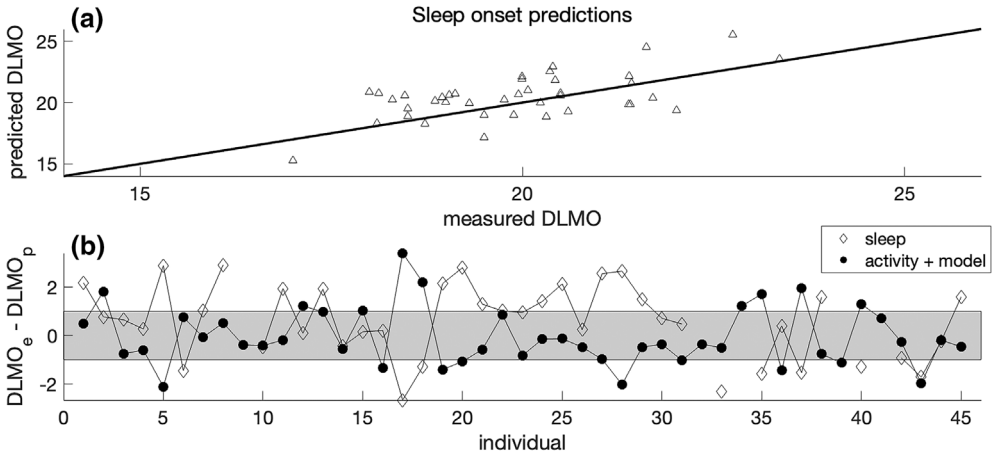


FIGURE 4 Comparison of the accuracy of DLMO predictions between sleep metrics and a mathematical model. (a) DLMO predictions from sleep onset (vertical axis) vs. the measured/experimental DLMO (horizontal axis) plotted as light triangles. A 45-degree diagonal line is shown. (b) The experimental DLMO ($DLMO_e$) minus the predicted DLMO ($DLMO_p$) was computed by either shifting sleep onset 2 h earlier (open diamonds) or simulating the nonphotic model coupled with piecewise activity data (filled circles). A prediction error of plus or minus 1 h is shaded. Individuals without open diamonds (individuals 9, 32, 34, 39, and 41) do not have sleep metrics.

notable advance. The at-home DLMO collection is another novel aspect of this study, as previous studies with the four mathematical models have focussed on predicting laboratory DLMO (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021).

We tested the performance of the higher-order, simpler, nonphotic, and Hannay models when simulated with either light or activity data from a research-grade actigraph device. While light serves as the primary entraining signal to the circadian system (and the models were originally developed with a light input in mind), the growth of wearable activity-collecting devices in recent years makes activity a valuable signal to consider for translating circadian findings into the real-world. When simulating with activity data instead of light, the accuracy improved across all the models tested; this is consistent with previous work (Huang, Mayer, Cheng, et al., 2021). Potential explanations for the improvement include activity being both related to light and capturing nonphotic phase shifting effects, and light measurements not being reflective of true ocular light exposure (e.g. due to individuals wearing long sleeves). Exercise is known to shift the circadian clock (Yamanaka et al., 2006; Youngstedt, Elliott, & Kripke, 2019), so higher levels of activity may be capturing these effects in addition to being related to increased light exposure. Interestingly, the relationship between activity and light displayed little variability across individuals for lower levels of activity, but showed substantially higher variation for activity counts above approximately 475. This demonstrates interindividual differences in the activity/light relationship for higher levels of activity, which could be due to variability in light exposure during typical high activity events like exercise. Indeed, some individuals may primarily exercise in indoor settings with relatively lower light exposure, while others may tend to exercise in brighter outdoor conditions. Future work may be needed to characterise this activity/light relationship across different behavioural categories.

A previous study using the same models with activity found MAEs ranging from 0.61 to 1.22 h for day workers and 2.51–2.79 h for shift workers (Huang, Mayer, Cheng, et al., 2021); here, the MAEs ranged from 0.93 to 1.41 h although, unlike the previous analyses (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Stone, Aubert, et al., 2019), the mean age of our sample was older and had several underlying comorbidities (such as hypertension, diabetes, dyslipidaemia, and coronary artery disease). This suggests that models based on a later-life adult sample can predict circadian phase to a similar or slightly lower degree than for younger day workers, but with much more accuracy than for shift workers. The higher-order and nonphotic models generated the lowest mean absolute phase errors for both activity and light, making them promising candidates for phase prediction in later-life adults, who usually encounter greater disruptions in circadian rhythms compared with young adults. This aligns with the earlier finding that the higher-order and nonphotic models yield superior predictions compared with the other models particularly when analysing rotating shift workers facing heightened circadian disruptions (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Stone, Aubert, et al., 2019).

Substantial interindividual variability existed in the accuracy. This suggests that future work is needed to investigate underlying factors contributing to this discrepancy, to improve the accuracy of estimating sleep and circadian proxies, or to personalise the models. Indeed, the model parameters used here were previously fit at a group level, and may not fully generalise to this older population. Shifted sleep onset can also estimate DLMO relatively accurately in this cohort. However, when simulated with activity data, the higher-order and nonphotic models generated statistically significantly lower errors than sleep onset-based DLMO predictions. This indicates that mathematical modelling of actigraphy data in real-world settings can provide additional key information about underlying circadian rhythms in older adults.

In this study, we used a fixed light schedule to determine the initial conditions. While it is possible to use different light assumptions (e.g. lower but nonzero light in the evening from 7 p.m. to 12 a.m.), as

done in our previous work (Walch, Huang, Forger, & Goldstein, 2019), accurately determining an appropriate light level for every time of day is challenging. It depends on various factors such as geography, time zone, and behavioural patterns. Moreover, varying light levels may not necessarily improve the initial conditions due to individual differences in light exposure. Importantly, we have at least 10 days of actual actigraphy data prior to the DLMO prediction, allowing the models to mitigate the effects of initial conditions by incorporating individual light/activity patterns. Other related studies (e.g. (Mayer et al., 2023; Song et al., 2023; Stone, Aubert, et al., 2019; Woelders et al., 2017)) have employed diverse methods to estimate initial conditions. Notably, Stone, Aubert, et al. (2019) explored the impact of initial values on model estimations and found no significant improvement in predictions. However, developing a systematic approach to identify personalised initial conditions would be an important direction for future research to improve prediction accuracy and support the integration of computational approaches with wearable technology.

Another commonly used method to assess circadian phase from activity data is cosinor analysis, in which a sinusoidal function is fit to the activity profile (Cornelissen, 2014). However, the applicability of these methods to data that do not necessarily have an appropriate oscillatory shape has been questioned (Klerman, Wang, Phillips, & Bianchi, 2017). We avoid this concern by incorporating activity within mathematical models, thereby considering it as a particular input to the circadian timekeeping system. Past research has demonstrated that cosinor analysis does not accurately capture circadian phase, with a mean absolute error of over 3 h in a day worker population (Huang, Mayer, Cheng, et al., 2021). The models we analysed generated phase predictions with average errors on the order of an hour, and therefore appear better suited than sinusoidal fitting of activity for DLMO prediction. Additional methods have used actigraphy data to predict human circadian phase, for example using a neural network-based classification approach (Brown et al., 2021), ARMAX autoregressive models (Gil, Aubert, & Beersma, 2014), or other neural network approaches (e.g. multilayer perceptron) (Kolodyazhniy et al., 2012; Stone, Phillips, et al., 2019). While these methods have demonstrated accuracy particularly in healthy populations, the additional required data types and their unclear generalisability to other populations did not make them suitable to include in this study. Specifically, Kolodyazhniy et al. (2012) predicted human circadian phase utilising neural networks with skin temperature and other inputs from different locations on the body (feet, hand, thorax, shoulders, upper legs, and lower legs). This work achieved a very high accuracy: phase error mean = 12 min, SD = 41 min during a constant routine protocol. The inclusion of skin temperature, however, may make the performance not directly comparable to our modelling framework. Indeed, skin temperature served as one of the most meaningful predictive variables in the neural network models. Another study on shift workers compared the performance of different combinations of inputs, including shift schedule, commute times, and light exposure from an actigraph, on circadian phase prediction (Knock et al., 2021). Depending on the input combination and diurnal or nocturnal shift, the mean absolute errors ranged from 0.87 (SD = 0.83) hours (with the diurnal schedule and shift + commute + light as inputs) to 3.05 (SD = 4.22) hours (with the phase change schedule and shift as input). This study found that actigraphy-based light recordings were key in generating the most accurate predictions (accuracies on the order of 1–1.5 h), but did not assess the performance of activity count-based models as in our work. Future work could compare the performance of these inputs and approaches in predicting human circadian phase across populations.

The reliable estimation of circadian phase from activity patterns sets the stage for the development of circadian-based applications in the real-world. This opens avenues for the longitudinal tracking of circadian phase estimates based on wearable smartwatch activity data, which could provide valuable insights concerning the relationship between circadian metrics and health states over time. Additionally, the costly and time-consuming collection process for traditional laboratory DLMO collection makes it difficult to incorporate into clinical care, while these prediction methods have the potential to enable the consideration of DLMO in medical applications. Indeed, the long-term goal of this research is to enable individualised circadian phase prediction from actigraph and other wearable data. The prediction of circadian phase in less burdensome settings may be particularly relevant for an older population, who may experience increased circadian disruption and struggle to spend nights in a sleep laboratory.

Previous studies have shown large variability in melatonin expression levels among individuals (Arendt, 1988; Scholtens, van Munster, van Kempen, & de Rooij, 2016). For example, it has been shown that older females have lower melatonin levels than older males (Obayashi et al., 2015). Additionally, older individuals typically have lower melatonin expression levels compared with younger individuals (Iguchi, Kato, & Ibayashi, 1982; Sack, Lewy, Erb, Vollmer, & Singer, 1986; Scholtens et al., 2016; Waldhauser et al., 1988). Therefore, using a fixed threshold to measure DLMO across all older participants may result in an abnormal delay in the time to first reach that threshold and fail to capture the interindividual variability. To circumvent this, we utilised a relative threshold instead of a fixed threshold in this study. However, the relative threshold could potentially become too low. Such a low threshold could lead to false positives in detecting DLMO. These false positives typically occur when there is a brief increase in melatonin levels, followed by a decrease below the threshold. To mitigate these false positives, we carefully conducted a visual review of all individual melatonin expression profiles and confirmed a sustained increase after the first touch of the relative threshold. Furthermore, we defined DLMO as the point in time (determined by linear interpolation) when the melatonin concentration exceeded and remained above the threshold for at least 2 h, following previous work (Molina & Burgess, 2011; Voultsios et al., 1997).

We acknowledge that this work has several limitations, including the potentially inaccurate lighting information that may have diminished the accuracy of the light-based simulations. Specifically, a relatively high percentage of the white light data was below 1 or below 5 lux (Table S1), potentially reflecting sensor coverage due to sleeves. One could process and clean the light data further, for example considering light levels below 1 lux during wake periods as artefacts, and

therefore as missing data (Scheuermaier, Laffan, & Duffy, 2010). However, this necessitates missing data imputation to maintain equally spaced data for model simulations, which is not guaranteed to better reflect light exposure. Moreover, the circadian models are responsive to low light levels depending on the state of the circadian pacemaker (Forger et al., 1999; Jewett et al., 1999), which may still allow for accurate simulations even under low light conditions. Given these considerations, we adopted an approach directly using raw light measurements, which was used widely in previous studies (Cheng et al., 2021; Huang, Mayer, Cheng, et al., 2021; Huang, Mayer, Walch, et al., 2021; Kim, Lee, & Forger, 2023; Kim, Mayer, et al., 2023; Mayer et al., 2023). Notably, advancing the current method and developing a systematic approach to identify and address potential artefacts during model simulations is an interesting direction for future research. Additionally, applying these models to data from various light sources (e.g. optical and wrist lighting) in future work could provide valuable insights into the superior performance of activity data. The lack of racial diversity is another limitation of this study, since the cohort was predominantly White/Caucasian (Table 1). As there may be differences in key circadian parameters like the intrinsic period (Smith, Burgess, Fogg, & Eastman, 2009) across races, future work testing model performance in more diverse populations is needed. The range of circadian phases in this population was somewhat limited (Figure 1b), so future model prediction across a wider span of phases and circadian disorders is needed. Furthermore, interindividual differences in model parameters were not considered here. Research has shown that individuals differ substantially in certain circadian parameters, such as sensitivity to light and intrinsic period, and that these differences can greatly impact circadian timing (Mayer et al., 2023; Phillips, Chen, & Robinson, 2010; Phillips et al., 2019; Stone et al., 2020; Wright Jr, Gronfier, Duffy, & Czeisler, 2005). Personalisation of the mathematical models, for example, by fitting parameters on an individual level based on another oscillatory data source such as heart rate or temperature, serves as a promising avenue for future work (Kim, Mayer, et al., 2023). The assumption of a fixed 2 h window between DLMO and sleep onset (based on previous work (Berry & Wagner, 2014; Burgess et al., 2003; Burgess & Eastman, 2005; Huang, Mayer, Cheng, et al., 2021; Van Reen et al., 2013)) may also be improved by considering interindividual differences in this phase relationship. This 2 h window is consistent with previous work; for example, Burgess et al. (2003) found a difference of 1.98 h (SD = 1.42 h) between sleep onset and DLMO, 6.08 h (SD = 1.13 h) between DLMO and sleep midpoint, and 13.83 h (SD = 0.99 h) between wake time and DLMO in a cohort of young healthy adults on a typical schedule. Prior studies have also found comparable phase angles in younger and older adults (Arrona-Palacios, Lee, Czeisler, & Duffy, 2023; Benloucif et al., 2006). In this study, we followed a previously validated protocol for home DLMO assessment (Burgess et al., 2016) to mitigate the confounding effects of light. However, further research may be needed to efficiently and effectively control light exposure on participants' eyes in field settings, given the high sensitivity and interindividual variability of the circadian system in response to light (Phillips et al., 2019). Finally, the data were not captured in a controlled setting, and we therefore do not have information about other potentially confounding variables (e.g. food intake, posture) that impact the circadian system.

Overall, this work has demonstrated the applicability of a set of four mathematical models to the home assessment of circadian phase in later-life adults. This validates and extends previous work in using activity to predict laboratory DLMO via limit cycle oscillator models, and sets the stage for longitudinal and real-world assessments of circadian rhythms using actigraphy and mathematical modelling.

AUTHOR CONTRIBUTIONS

Caleb Mayer: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; visualization; software; data curation; formal analysis. **Dae Wook Kim:** Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis; supervision; visualization. **Meina Zhang:** Writing – review and editing; data curation; resources; project administration; formal analysis. **Minki P. Lee:** Writing – review and editing; formal analysis. **Daniel B. Forger:** Writing – review and editing; methodology; project administration; supervision. **Helen J. Burgess:** Writing – review and editing; funding acquisition; conceptualization; supervision. **Chooza Moon:** Writing – review and editing; conceptualization; investigation; funding acquisition; data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

Financial disclosure: Daniel B Forger (DBF) is the CSO of Arcascope, a company that makes circadian rhythms software. Both he and the University of Michigan own equity in Arcascope. HJB serves on the scientific advisory board for Natrol, LLC and is a consultant for F. Hoffmann-La Roche Ltd.

DATA AVAILABILITY STATEMENT

The computer codes used in this study are accessible from the GitHub repository: https://github.com/ojwalch/predicting_dlmo. Further information and requests for resources should be directed to and will be fulfilled when possible by the lead contact, Chooza Moon (chooza-moon@uiowa.edu).

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SUPPORTING INFORMATION

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

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