

More variable circadian rhythms in epilepsy: a retrospective cross-sectional study using long-term heart rate recordings from wearable sensors

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Abstract

Background: The circadian rhythm aligns physiology and behaviour with the 24-hour light-dark cycle, and its disruption is linked to neurological disorders such as epilepsy. However, how to best quantify circadian disruption remains unclear, as it can manifest across various properties and timescales. A promising but under-explored approach is to assess the intra-individual variability in circadian rhythms over timescales of weeks to years. This is yet to be studied in epilepsy.

Methods: We retrospectively used wearable smartwatch data (Fitbit) from 143 people with epilepsy (PWE) and 31 controls. For each participant, we extracted the circadian oscillation underlying their heart rate time series and analysed the intra-individual variability of three circadian properties: period, acrophase, and amplitude.

Findings: We found increased intra-individual variability in period (77 min *vs.* 62 min, $z = 3.32, p < 0.001$) and acrophase (68 min *vs.* 54 min, $z = 2.97, p = 0.003$) for PWE compared to controls, but not in amplitude (1.98 bpm *vs.* 2.05 bpm, $z = -0.66, p = 0.51$). For PWE, we did not find any correlations between seizure frequency and intra-individual variability in circadian properties, or any difference between weeks with and without seizures.

Interpretation: This finding indicates that the circadian rhythm of heart rate is more variable for people with epilepsy and that this can be detected using a wearable device. However, we were unable to find any associations with seizure frequency or occurrence, suggesting intra-individual variability could be another manifestation of epilepsy aetiology. Future work should investigate the combined role of anti-seizure medications, demographics, co-morbidities, and health behaviours in driving the increased intra-individual variability of circadian properties in epilepsy.

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1 Introduction

The circadian rhythm aligns our physiology and behaviour to the 24-hour environmental light-dark cycle. A stable circadian rhythm is thought to be important for overall health, and disruptions to the circadian rhythm have been associated with various conditions, including sleep disorders (Burgess et al., 2017; Fishbein et al., 2021), psychiatric disorders (Ali et al., 2023; Carr, 2018; Song et al., 2024), and neurological disorders (Logan and McClung, 2019). However, it remains unclear how circadian disruption should be assessed over the long term, with different suggestions across different contexts (Asgari-Targhi and Klerman, 2019; Vetter, 2018).

One promising and easy-to-interpret approach is to assess the intra-individual variability of some circadian rhythm properties, such as amplitude, measured across multiple days. This approach has also been referred to as ‘day-to-day variability’ (Fossion et al., 2017; García-Iglesias et al., 2023) or ‘circadian variability’ Carr (2018). Intra-individual variability is designed to detect persistent irregularities in circadian rhythms over long-term physiological recordings. Such data are most easily obtained from peripheral measures using wearable devices (such as heart rate, physical activity, and skin temperature), making this approach a cost-effective and scalable methodology to study circadian disruption, complementary with existing methods.

Epilepsy is a neurological disorder characterized by recurrent seizures (Devinsky et al., 2018), which are influenced by sleep patterns (Bazil, 2003; Degen, 1980; Dell’Aquila and Soti, 2022; Derry and Duncan, 2013; Grayson and DeWolfe, 2018) and the circadian rhythm (Bazhanova, 2022; Gascoigne et al., 2023; Hofstra and de Weerd, 2009; Karoly et al., 2021; Stirling et al., 2023; Thornton et al., 2024). However, the impact of persistent, long-term circadian disruption on epilepsy remains unstudied. We propose using an intra-individual variability assessment on data from people with epilepsy (PWE), which could provide valuable insights for clinical applications, such as enhancing wearable seizure prediction and guiding chronotherapeutic treatments (Bazhanova, 2022), including ASM alert systems. Additionally, demonstrating the effectiveness of variability in circadian patterns as a measure of disruption in epilepsy could support its broader use as a clinical biomarker in wearable devices.

Here, we measure the intra-individual variability of three descriptive properties of the circadian

rhythm of heart rate (CRHR) using long-term wearable-derived heart rate recordings from 143 PWE and 31 controls. We seek to establish whether variability is greater in epilepsy and, if so, whether a relationship exists between variability and seizure frequency and occurrence.

2 Methods

2.1 Participant Data

Wearable smartwatch data from people with epilepsy (PWE) and controls were used retrospectively, sourced from the observational “Tracking Seizure Cycles” study (Karoly et al., 2021). Adults with epilepsy were recruited to this study by referral from collaborating epilepsy specialists in tertiary referral epilepsy clinics. Inclusion criteria were diagnosis of epilepsy from a specialised epileptologist, uncontrolled/partially controlled seizures as determined by their neurologist, and that they were deemed capable of keeping a reliable seizure diary. Additionally, Karoly et al. (2021) recruited control participants without epilepsy from their colleagues, friends and relatives, with no randomisation or blinding performed. Their study was approved by the St Vincent’s Hospital Human Research Ethics Committee (HREC 009.19). All participants provided written informed consent.

For both PWE and controls, data were collected via a wearable smartwatch (Fitbit), continuously measuring heart rate via photoplethysmography (PPG) at 5 s resolution. PWE participating also used a mobile device to manually report clinically-apparent seizures using the freely-available Seer App for either the entirety, or a subset of, the study period.

Before processing, data was available for n=164 PWE and n=36 controls.

Our retrospective analysis of this data was approved by the Newcastle University Ethics Committee (40679/2023).

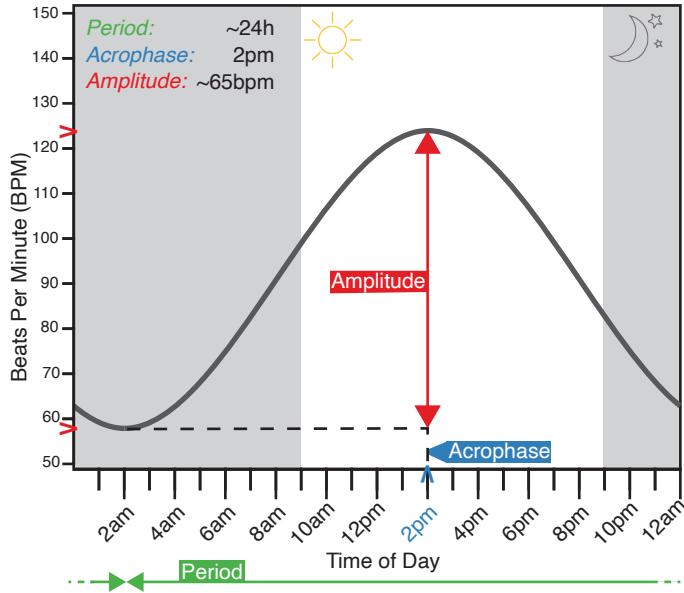


Figure 1: An illustrative schematic of one ‘cycle’ of the circadian rhythm of heart rate (CRHR) with the 3 descriptive properties used in this study labelled. Period reflects the duration of one cycle of the modelled CRHR (approximately 24 hours). Acrophase is defined as the time-of-day at peak cycle magnitude, reflecting rhythm ‘timing’. Amplitude is a measure of circadian ‘strength’, defined as the difference in magnitude between cycle peak and previous trough.

2.2 Measuring circadian disruption using physiological time-series: the ‘intra-individual variability’ approach

Capturing the intra-individual variability of the circadian rhythm involves the daily measurement of three descriptive circadian properties, which are illustrated in Figure 1. For each participant, the circadian rhythm of heart rate (CRHR) was extracted from their wearable recording. Three circadian properties were then computed for each daily cycle in the CRHR. Finally, estimates of the average (statistical mean) and variability (statistical standard deviation) of each property over the recording were produced. Figure 2 provides an overview of this process, and further details are provided below and in Supplementary S1.

2.2.1 Accounting for gaps in recording

To calculate the circadian properties of the heart rate, a continuous signal was required. Any gaps shorter than 8 hours were linearly interpolated, and the signal was split up into ‘runs’ of data

between remaining gaps (Figure 2B). 26 participants (21 PWE, 5 control) without any ‘runs’ longer than 7 days were excluded from further analysis. A more detailed explanation and justification for this approach is provided in Supplementary S1.3.

2.2.2 Extracting the circadian rhythm

For each ‘run’ of data, singular spectrum analysis (SSA) was applied to decompose the continuous raw heart-rate time series into components of distinct frequency (Figure 2C-E(i)). SSA was found to be the best-performing algorithm from a set of similar methods (see Supplementary S1.1). To determine which component represented the CRHR, Fourier analysis was performed on each component to determine its central frequency. The component with period (inverse of frequency) closest to 24 hours was selected as the circadian component (Figure 2E(i)).

2.2.3 Computing circadian properties

The extracted CRHR was then split-up into the individual (approximately daily) circadian cycles (Figure 2E), and the period, acrophase and amplitude were computed for each cycle (Figure 2G). To achieve this, the Hilbert transform was applied to the extracted CRHR, producing a complex-valued analytic signal, from which the circadian “phase series” (Supplementary S1.2), a measure of circadian cycle progression, was derived (Figure 2E(ii)). The rhythm was then split into daily cycles at each trough in the phase-series. For each individual cycle, *period* was computed from the duration between the first and last time point of the cycle, *acrophase* as the time of day at zero cycle phase, and *amplitude* as the difference between magnitude at acrophase and trough (Figure 1).

2.2.4 Calculating the intra-individual variability of circadian properties

Circadian properties for each cycle were grouped into consecutive, non-overlapping segments of seven days. The standard deviation was calculated across all seven days in each segment and property (Figure 2G), and the summary *intra-individual variability* was calculated from the average

of the standard deviations across all segments. The *intra-individual average* of circadian properties, only used for reference later, was calculated in the same way from the average of the means across segments. The fixed segment size of seven days prevents any bias introduced by varying recording duration and ‘run’ length between participants when calculating the mean and standard deviation (see Supplementary S1.3 for more detail).

2.3 Statistical Analysis

We calculate p-values for reference only, and all reported values are raw, uncorrected by FDR. A two-sided Wilcoxon rank-sum test was used to compare the intra-individual average and variability of each circadian property between PWE and controls. To account for the imbalance between PWE and control sample sizes, a random sub-sampling test was performed over 10,000 iterations where the whole control sample was compared to a random sub-sample of 28 PWE using the same statistical method as above. Sampling was without replacement within an iteration, but with replacement across iterations.

Pearson’s correlation was used to test whether an individual’s seizure frequency was correlated with their intra-individual variability calculated over segments occurring between the start and end of their seizure diary. Seizure frequency was defined in terms of the average number of seizures per week of recording data post-segmenting. The distribution of seizure frequency was highly skewed, so a log10 transformation was applied for the correlation analysis.

To test whether having one or more seizures in a seven-day period was associated with greater intra-individual variability, we classified each 7-day segment as either seizure-containing or seizure-free according to the seizure diary. We then calculated the Area Under the Curve (AUC) from the receiver operator characteristic (ROC) curve to compare the variability distributions in seizure-containing versus seizure-free segments for each individual. The AUC score indicates the separability of these two distributions: a value of 0.5 shows no difference in variability between seizure-containing and seizure-free weeks, values from 0.5 to 1.0 suggest higher variability in seizure-containing weeks, and values from 0 to 0.5 indicate greater variability in seizure-free weeks. Thus, each circadian property yields a single AUC value, representing its association with seizure activity.

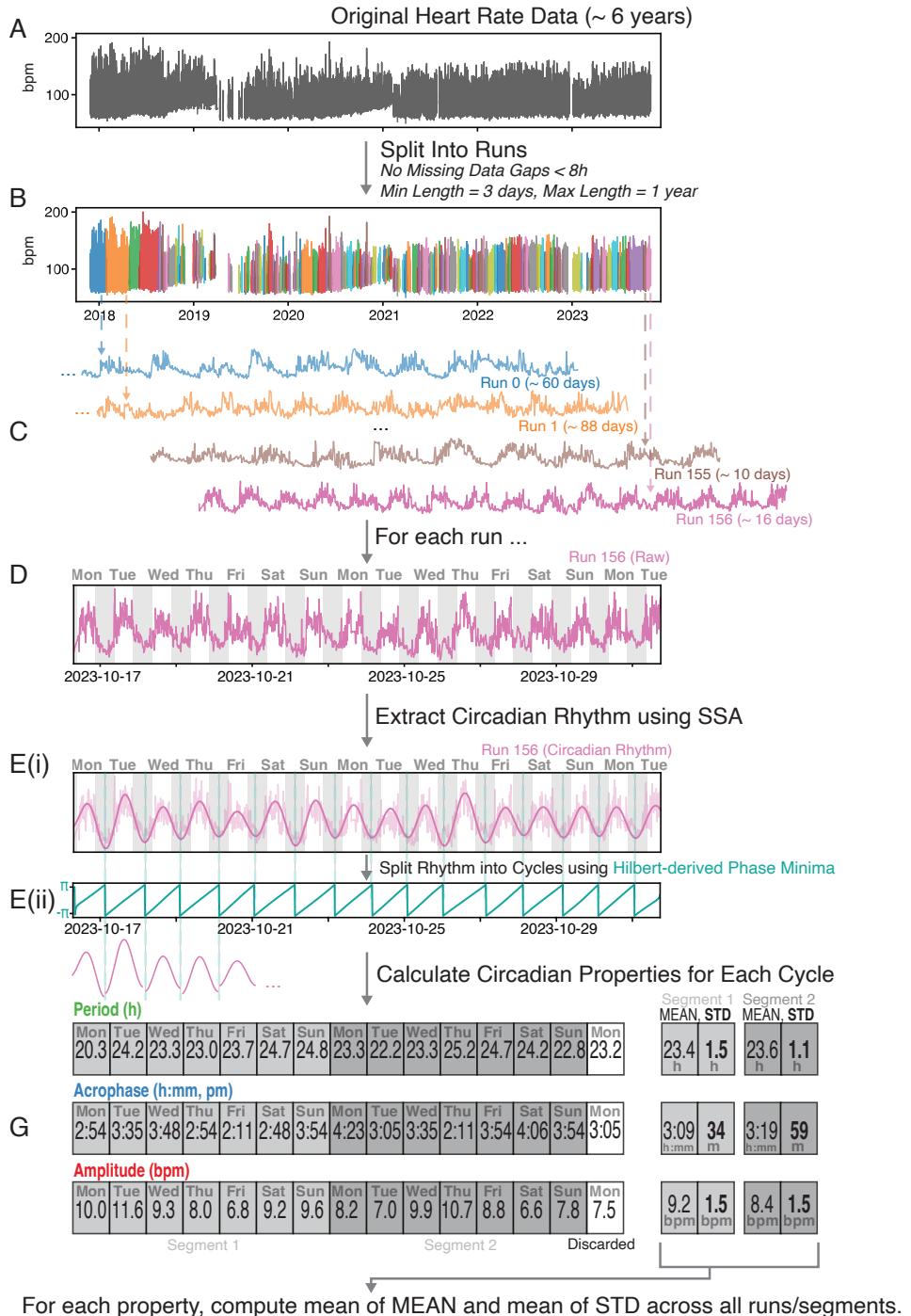


Figure 2: Participant heart rate data (A) was split into runs between >8h gaps of missing data (B). SSA extracted the CRHR from each run (C to E(i)). Troughs in the circadian phase (E(ii)) were used as reference points for splitting the extracted CRHR into individual cycles. Circadian properties were calculated for each cycle and grouped into segments of seven days (G). The mean and standard deviation of each property was then calculated within each 7-day segment. The mean across all segments in a subject produces the final intra-individual average and variability values. The intra-individual variability of acrophase across the two example segments would be $(34 + 59)/2 = 46.5$ minutes.

3 Results

143 people with epilepsy (PWE) and 31 controls remained after processing. Table 1 lists the demographics and other metadata of this cohort. An average of 163 hours ($sd = 183$) were discarded for each subject, resulting in an average recording duration of 443.9 days ($sd = 530.9$) for PWE and 221.7 days ($sd = 257.0$) for controls. There was no relationship between (post-segmenting) recording duration and intra-individual variability in any circadian property (Supplementary S2). There were no age ($t = -0.215, p = 0.84$) or sex ($\chi^2 = 2.777, p = 0.427$) differences between PWE and controls, and there was no association between intra-individual variability in any circadian property and age or sex (see Supplementary S4).

	Controls	Epilepsy	Statistic	p-value
N	31	143		
Age mean (years)	37.0	38.6		
Age sd (years)	16.9	13.3	-0.215	0.84
Age unavailable	26	39		
Sex female	15	87		
Sex male	13	39		
Sex other	0	1		
Sex unavailable	3	16		
Recording Duration mean (days)	221.7	443.9		
Recording Duration sd (days)	257.0	530.9	1685	0.037
Focal		41		
Generalised		13		
Mixed		3		
Total Number of Seizures		6110		
Average Number of Seizures		42.7		

Table 1: Demographic and clinical characteristics of the cohort. The distribution of age was compared between PWE and controls using the independent two-sided Welch's t-Test. Sex comparison was performed using the Chi-square test of independence. Duration comparison was performed using the two-sided Mann-Whitney U test.

3.1 The circadian rhythm of heart rate is more variable for people with epilepsy

The intra-individual variability in period (77min *vs.* 62 min, $z = 3.32, p < 0.001$) and acrophase (68 min *vs.* 54 min, $z = 2.97, p < 0.001$) was increased for PWE compared to controls (Figure 3).

However, there was no difference in intra-individual variability of amplitude between PWE and controls ($\sim 2\text{bpm}$, $z = -0.66$, $p = 0.51$).

For reference, we also present the results for intra-individual average in Figure 3, but found no substantial difference between PWE and controls (period: $z = 0.36$, $p = 0.72$; acrophase: $z = 0.95$, $p = 0.34$; amplitude: $z = -1.52$, $p = 0.13$).

All results held after applying random sub-sampling to equal numbers of PWE and controls (see Supplementary S3).

3.2 Intra-individual variability of circadian properties does not correlate with increased seizure frequency

Next, the correlation between seizure frequency and intra-individual variability was investigated. PWE without seizures recorded, or with outlying intra-individual variability (absolute z-score > 3) in any property were removed. We found that intra-individual variability was not correlated with seizure frequency ($R^2 << 0.1$).

3.3 The intra-individual variability of circadian properties does not differ between weeks with and without seizures

Finally, we investigated whether either seizure-containing or seizure-free weeks contributed more to intra-individual variability of circadian properties. An AUC was calculated between variability in seizure-containing and seizure-free weeks for each property, resulting in three AUC values (period, acrophase, amplitude) for each participant. Figure 5A shows the AUCs and the distributions they were calculated from for an example participant. Figure 5B shows the AUC values for each property across all participants. The distributions are centered around 0.5 indicating that, at the population level, the circadian period, acrophase and amplitude variability does not differ in weeks where seizures occur.

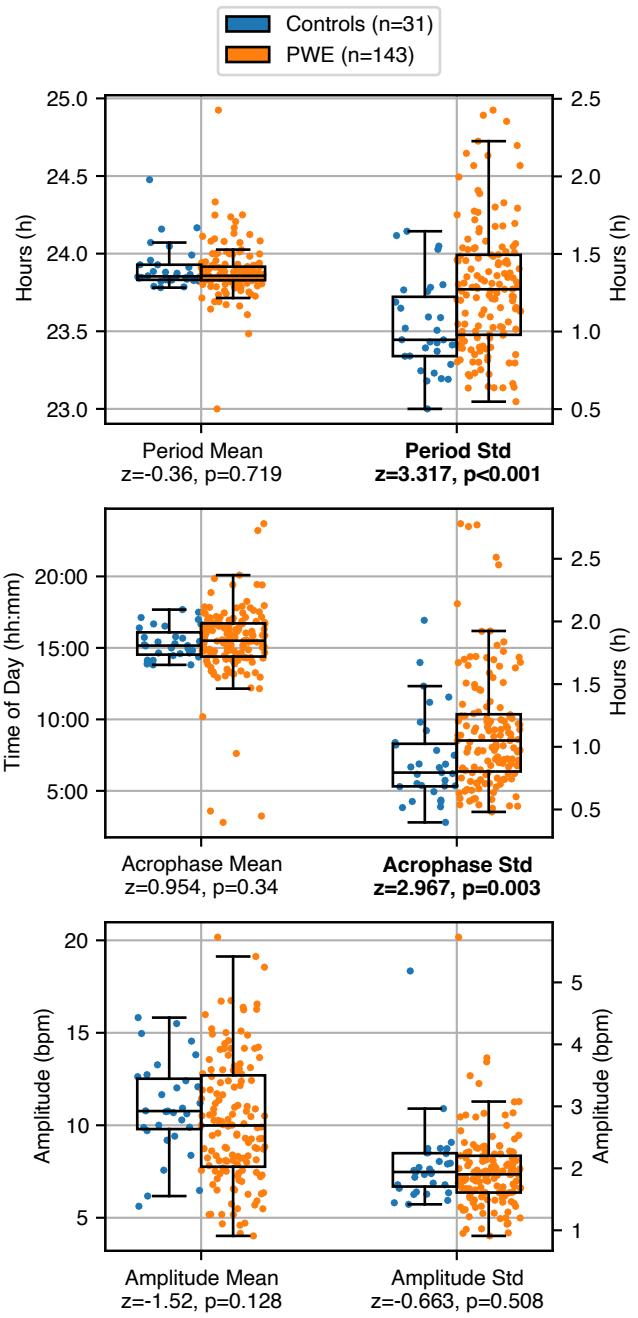


Figure 3: Comparison of the distribution of the intra-individual average and variability of circadian properties between PWE and controls. Period, acrophase and amplitude are defined in Figure 1. The two-sided Wilcoxon rank-sum test was used for comparison between PWE and Controls.

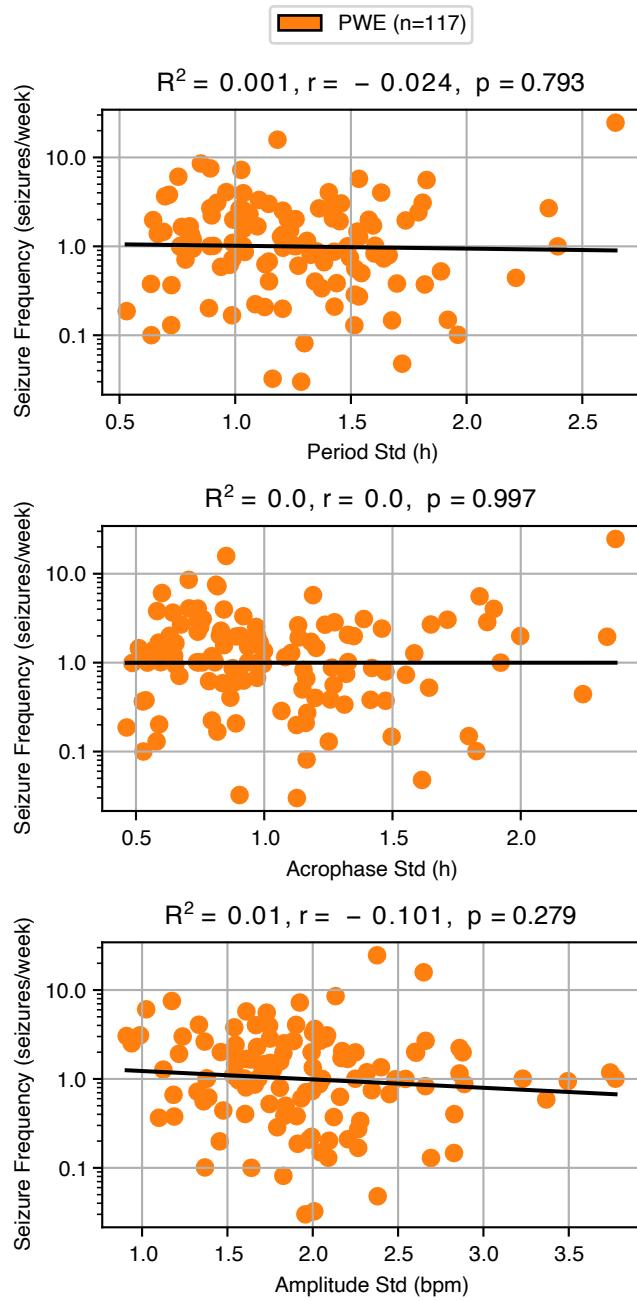


Figure 4: Scatter plots between intra-individual variability of circadian properties and seizure frequency. Seizure frequency is in units of seizures per week on log10 scale.

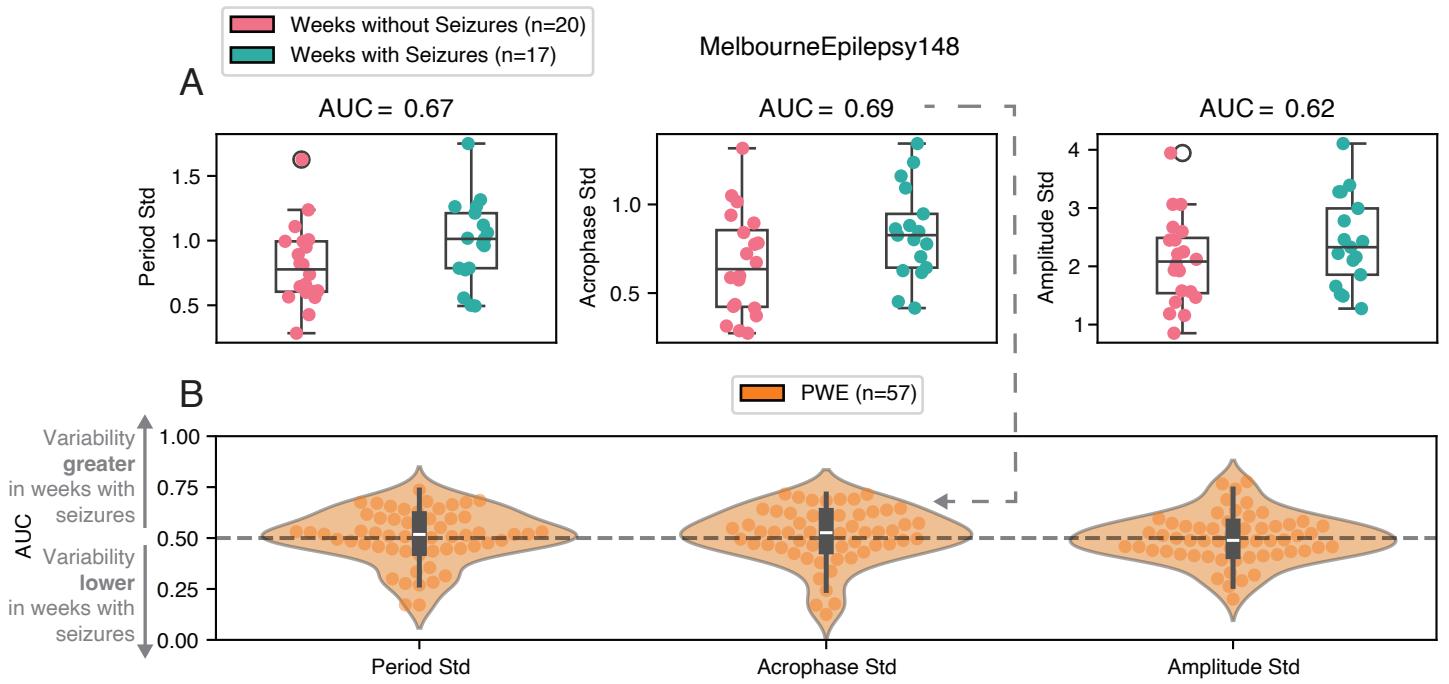


Figure 5: Comparison of the variability in each circadian property in seizure-containing weeks *vs.* seizure-free weeks. (A): Box and scatter plots comparing the distribution of variability in each circadian property in seizure-containing segments (turquoise) *vs.* seizure-free segments (pink), for one example participant. Each *segment* corresponds to 1-week of data (Figure 2). The AUC was calculated between the distributions of variability in each circadian property. (B): The distribution of AUC values across all participants for each circadian property. For visual clarity, a dotted line joins the AUC of one comparison (acrophase variability) for one participant in (A) to its approximate corresponding position in (B).

4 Discussion

This study analysed the intra-individual variability in three properties of the circadian rhythm using long-term wearable heart rate data from 143 PWE and 31 controls. We found an increased variability in circadian period and acrophase for PWE, providing initial evidence of circadian disruption in epilepsy. However, we found no evidence of an association between intra-individual variability and seizure frequency, or occurrence at the population level.

Circadian disruption has a bi-directional relationship with health (Abbott et al., 2020) and is associated with mortality over the long term (Zuurbier et al., 2014). It is therefore likely to have compounding health implications for PWE, so the results presented here should motivate the development of interventions to reduce the co-morbidities associated with circadian disruption in PWE (Latreille et al., 2018).

We found no evidence of any link with seizures but consider a link with epilepsy aetiology possible. Evidence from ex vivo tissue (Wu et al., 2021), and intracranial EEG (Thornton et al., 2024) indicates that tissue associated with epilepsy pathology may have an impaired circadian ‘clock’, which could also have downstream effects on the expression of the circadian rhythm in heart rate. Co-morbidities of epilepsy such as anxiety and depression (Keezer et al., 2016; Leidy et al., 1999) are also themselves associated with circadian disruption (Walker et al., 2020), and so also may contribute to the observed difference. Within the epilepsy cohort we found that intra-individual variability has a wide range and considerable overlap with the control distribution. Future work should investigate the extent to which the co-morbidities mentioned above can explain these findings.

Our approach has some key limitations. Firstly, while heart rate follows a strong circadian cycle (Vandewalle et al., 2007), bouts of activity such as exercise or stress can cause ‘behavioural masking’, interfering with measurement of the circadian state (Cui et al., 2023). Secondly, our analysis does not include some key variables that may play a role in the intra-individual variability we observe. Anti-seizure medications (ASMs) have been reported to both stabilise and disrupt sleep (Bazil, 2003; Derry and Duncan, 2013), and so could explain the increased intra-individual variability we see in PWE as well as variability between subjects. Demographics such as age and

sex are also known to associate with circadian parameters (Logan and McClung, 2019; Natarajan et al., 2020). We did observe a correlation between age and intra-individual averages of acrophase and amplitude as expected based on previous literature, but not with variability in any property. We did not find any sex differences with respect to circadian average or variability. Despite the noise- and accuracy-associated problems of wearable measures (such as PPG-derived heart rate), their clinical ubiquity and relative convenience arguably justifies their usage in this context. Future work should take advantage of multi-modal wearables, integrating heart rate with activity and temperature for circadian state estimation, for example.

y, the role of sleep disruption in epilepsy is well noted (Bazhanova, 2022; Daley and DeWolfe, 2018; Derry and Duncan, 2013; Foldvary-Schaefer and Grigg-Damberger, 2006; Grayson and De-Wolfe, 2018; Hofstra and de Weerd, 2009; Touchon et al., 1991), and while a distinct process physiologically (Hofstra and de Weerd, 2009; Meyer et al., 2022; Vetter, 2018), it is intrinsically tied to the circadian rhythm. As the circadian behaviour of heart rate is tied to sleep, its variability may primarily driven by sleep disruptions. Future studies should incorporate sleep quality questionnaires and wearable sleep tracking to distinguish between sleep-related variability *vs.* more broad intra-individual variability of the circadian rhythm.

In conclusion, we found increased variability of the circadian rhythm of heart rate in epilepsy, which may be indicative of a pathological circadian rhythm disruption in epilepsy as detected using a commercial wearable device. The driving effect of this remains unclear; we were unable to detect any relationship with seizures, so we instead propose that co-morbidities, ASMs, sleep disruption or some other confounds may be involved, or that it is an additional effect - alongside seizures - of the cellular dysfunction underlying the aetiology found in some epilepsies. We hope our findings encourage further research of this phenomenon and whether it has application in seizure prediction and chronotherapy in epilepsy, and further encourage use of intra-individual variability of circadian properties as a wearable biomarker for disruption in other conditions.

5 Data Availability

All wearable heart rate recordings and seizure metadata are available upon request to PK (`karoly.p@unimelb.edu.au`). A subset of this data is already publicly available on Figshare ([DOI10.26188/15109896](https://doi.org/10.26188/15109896)) from a previous publication (Karoly et al., 2021). We would like to acknowledge and thank the participants of this study.

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Supplementary

S1 Methodological Details

S1.1 Comparison of circadian rhythm extraction methods

Approaches for computational modelling of the circadian rhythm broadly fall into two categories: dynamic modelling, where the behaviour of the circadian system is represented within a set of equations, and statistical modelling, where a periodic function approximating an underlying core circadian fluctuation is fit to, or derived from, the data (Asgari-Targhi and Klerman, 2019). Here, we apply the latter statistical modelling methods.

The simplest statistical modelling approach involves the fitting of a sinusoid wave. The rhythm produced is fixed in period, acrophase and amplitude. However, it can often be empirically observed (especially in uncontrolled conditions) that these properties vary over time from one circadian cycle to the next (Asgari-Targhi and Klerman, 2019), potentially as the result of challenges to the circadian system (e.g inconsistent night shift working), variation in lifestyle and behaviour (e.g occasional late nights), or perhaps even disease (e.g the change between mood states in bipolar disorder, or seizure occurrence in epilepsy).

Bandpass-filtering of the signal around 24 hours derives a circadian rhythm where amplitude is able to vary across cycles, but the other parameters remain somewhat fixed. More sophisticated methods exist, such as wavelet-based analysis (the continuous and discrete wavelet transform), signal decomposition techniques (such as empirical mode decomposition) and others such as singular spectrum analysis (SSA) (Figure 2E(i)). An overview these methods can be found in (Eriksen and Rehman, 2023). These methods are more flexible and produce a rhythm that fits the data better, capturing variation in all three properties across cycles. García-Iglesias et al. (2023) evaluated these, as well as other, methods to extract a circadian rhythm from various physiological parameters, including heart rate. They compared the goodness-of-fit of the rhythm extracted by each method with the original data in each case. While certain methods performed better for some measures, SSA was the best all-rounder across measures.

S1.2 Deriving circadian cycles for computing circadian properties

We split the rhythm into the individual circadian cycles (Figure 2E(ii)), and compute the daily period, acrophase and amplitude (Figure 2G). To do so, the Hilbert transform is applied to the extracted circadian rhythm, producing a complex-valued analytic signal, from which the circadian “phase series” can be derived (Figure 2E(ii)). The phase series is a periodic triangular waveform with bounds of $-\pi$ to π . It is aligned with the input circadian rhythm, and can be thought of as a measure of circadian progression; at $-\pi$ the rhythm is at trough, and reaches its peak as phase increases to 0. As phase increases further from 0 to π , the cycle falls again before it reaches the next trough at π , where it wraps back around to $-\pi$. Using this, we can robustly split the rhythm at each phase trough ($-\pi$) into the daily circadian cycles. Once we have collected individual cycles, the circadian properties (Figure 1) are calculated for each cycle.

S1.3 Accounting for gaps in recording and variability in recording duration between participants

As shown in Table 1, the recording duration for both PWE and controls in this cohort is uniquely long, and there is substantial variation in recording duration between participants. These factors necessitated two additional steps in the calculation of intra-individual variability: the splitting of a participant’s recording into “runs” between missing gaps prior to extraction of the circadian rhythm, and the grouping of extracted per-cycle circadian property values into “segments” prior to computation of mean and standard deviation.

Missing data gaps in the recording were most likely caused by device charging or removal of the device by the participant for whatever other reason. As the heart rate recordings were computed by a proprietary Fitbit algorithm from raw PPG, it is possible that periods of noisy data (for example, due to poor device contact with skin) were excluded also. SSA, and other modelling methods, cannot handle missing data in the input recording, so interpolation (e.g linear) is required. However, there are occasionally very long (days-months) gaps of missing data for some participants, so we opted to avoid running the algorithm over very long interpolations of data, as

this wasted computational resources and interfered with results. As such, the raw heart rate data was split into ‘runs’ between missing gaps larger than 8 hours. Within each run, any remaining gaps (which must be below 8 hours) were linearly interpolated.

As stated previously, the intra-individual variability approach involves computation of a mean and standard deviation for each of the circadian properties (period, acrophase, amplitude) for each participant. However, given the variation in recording duration between participants (and especially between PWE and controls) in this dataset, and given that estimation of mean and standard deviation become more reliable as sample size increases, it would not be fair to compare the intra-individual variability between a participant with, for example, a recording duration of a month to a participant with multiple years worth of data. Therefore, once the circadian properties have been calculated for each cycle, rather than calculating the mean and standard deviation of each property across *all* cycles, we group cycles into consecutive non-overlapping seven-day ‘segments’.

Grouping occurred within runs; for example, a run that contained 17 circadian cycles would produce 2 segments (14 cycles), with 3 cycles discarded. We opted to perform the segmenting within runs rather than across the cycles of all runs as, given the minimum 8 hour gap between runs, there may be a considerable gap of time between two consecutive runs.

For each seven-day segment, the standard deviation of each property (Figure 2G) was calculated, reflecting the variability of that property during the corresponding week. Therefore, for each participant, a distribution of standard deviation values is produced for each property, reflecting differences in variability across weeks. To summarise these distributions for each participant, three summary values - circadian *period variability*, *acrophase variability* and *amplitude variability* - were calculated by taking the mean of the standard deviation values of each property across the segments distribution. Three additional summary values: *period average*, *acrophase average* and *amplitude average*, were calculated in a similar manner, using the mean of each property across all segments.

Calculating the mean and standard deviation separately for each segment ensures that they are always calculated on samples of data of the same length (7 cycles), reducing the problem of varying recording duration between participants. Taking the mean across all segments allows for comparison of circadian average and variability between participants.

A visualisation of our implementation of the intra-individual variability method, with the addition of the segmenting step, can be found in Figure 2.

S2 Recording duration does not affect intra-individual variability estimates

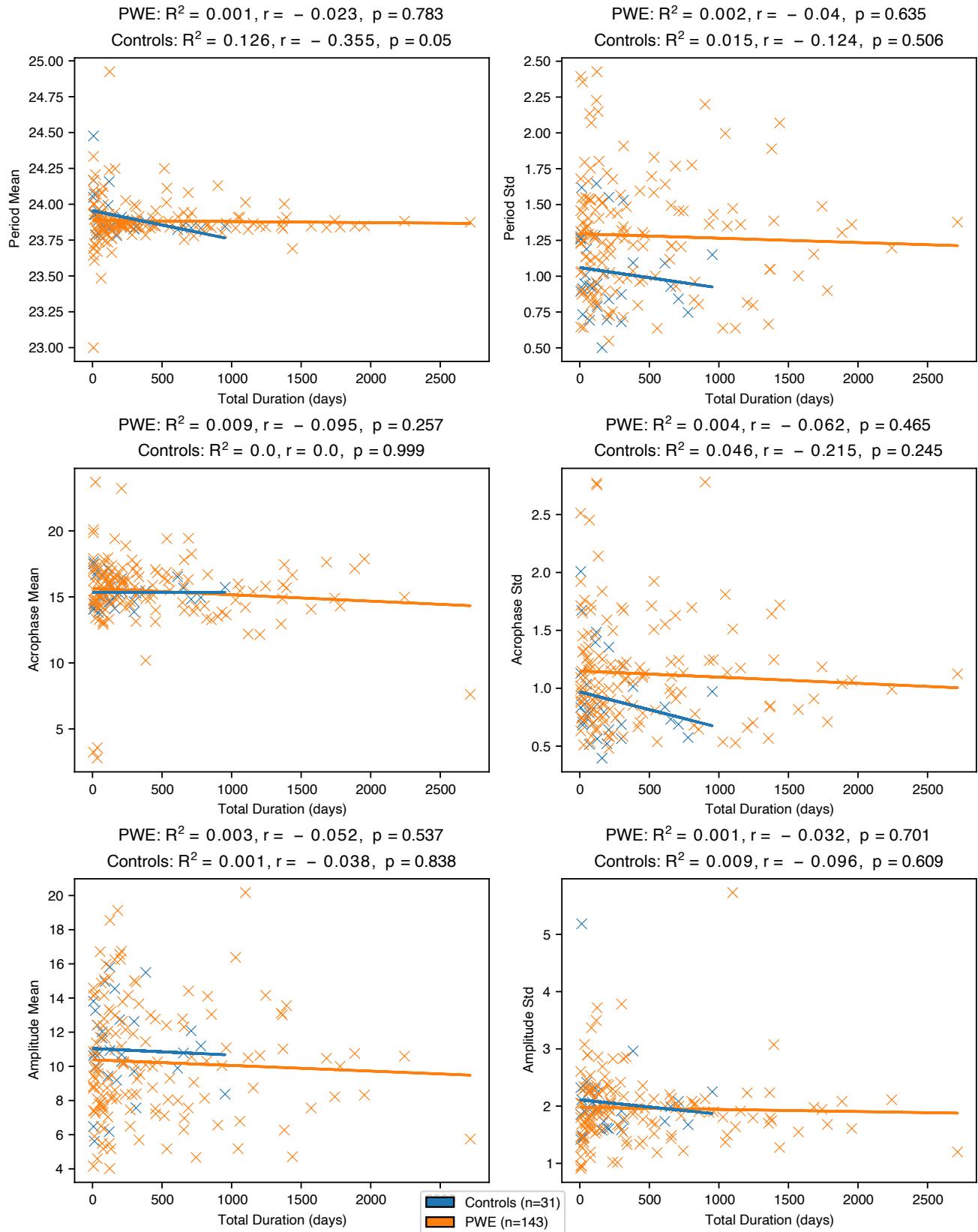
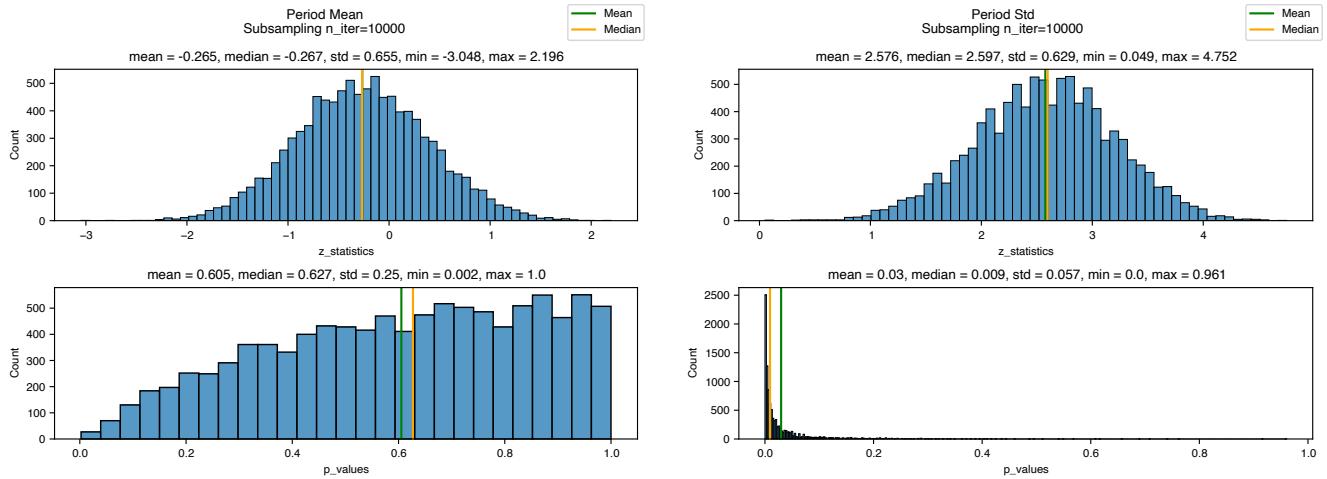


Figure S2.1: The relationship between intra-individual variability of circadian properties and total duration.

S3 Results hold when we resample to account for unbalanced samples



	median z	median p
Period Mean	-0.267	0.627
Period Std	2.597	0.009
Acrophase Mean	0.753	0.426
Acrophase Std	2.316	0.021
Amplitude Mean	-1.19	0.234
Amplitude Std	-0.514	0.531

(c) Table of random sub-sampling median p-values and z-statistics

Figure S3.1: Overview of the random sub-sampling correction to Figure 3. (a) and (b) show the distribution of the z-statistic and p-value over 10,000 iterations of the Wilcoxon rank-sum test using the entire Control cohort and a randomly selected sub-sample of 31 PWE. (a) shows this distribution for Period Mean, which was not originally different between PWE and controls. This result holds after applying random sub-sampling as the z-statistic is normally distributed around ~ 0 (no effect) and the p-value distribution is uniform. (b) shows this distribution for Period Std, which was originally different between PWE and controls. This result also holds after applying random sub-sampling, as the z-statistic is normally distributed around 2.5 (moderate effect) and the p-value distribution is extremely skewed with a median < 0.05 . (c) shows the median z-statistic and p-values across each property average and variability.

S4 Increased intra-individual variability of circadian properties is not age or sex dependent

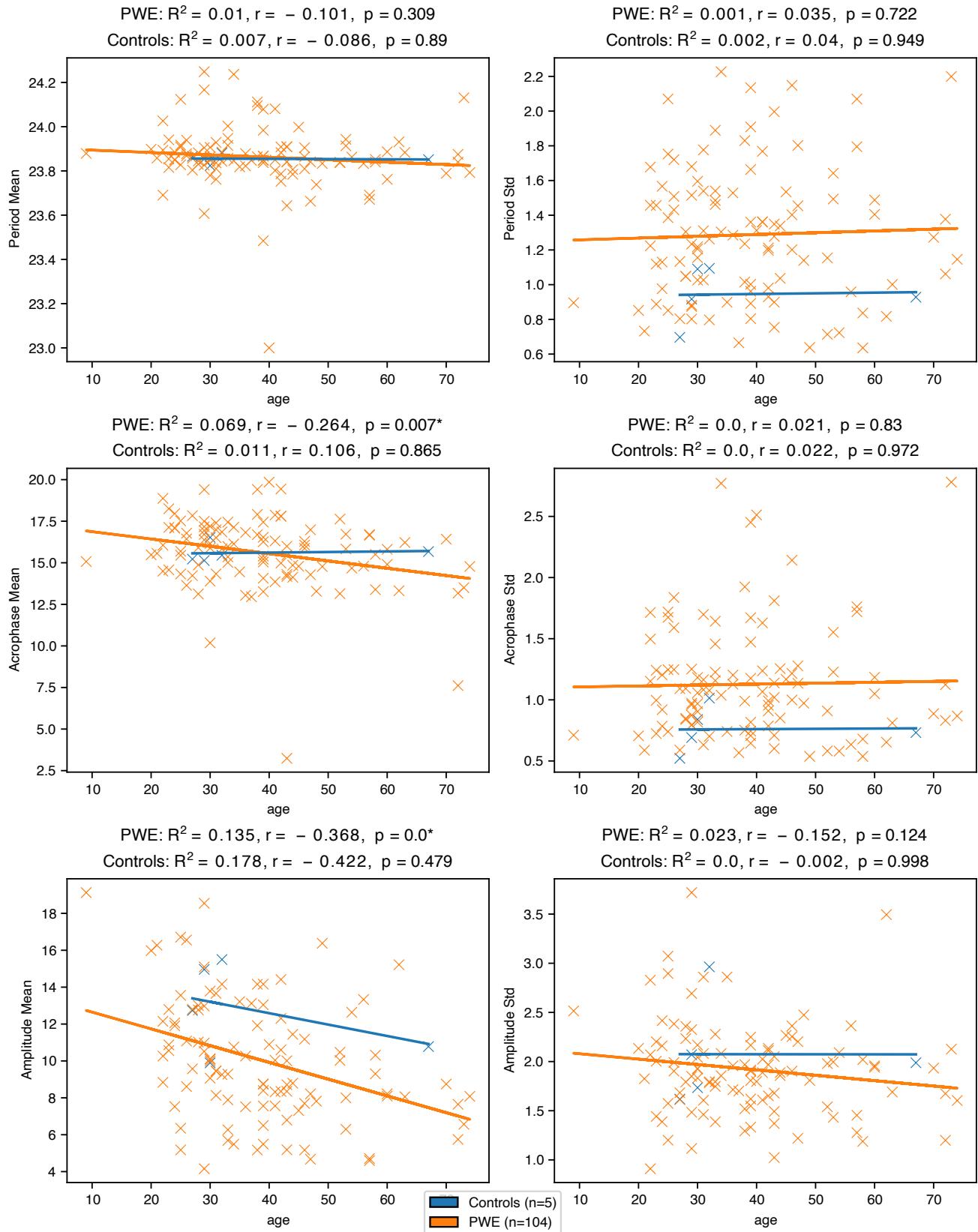


Figure S4.1: The relationship between intra-individual variability of circadian properties and averages and age.

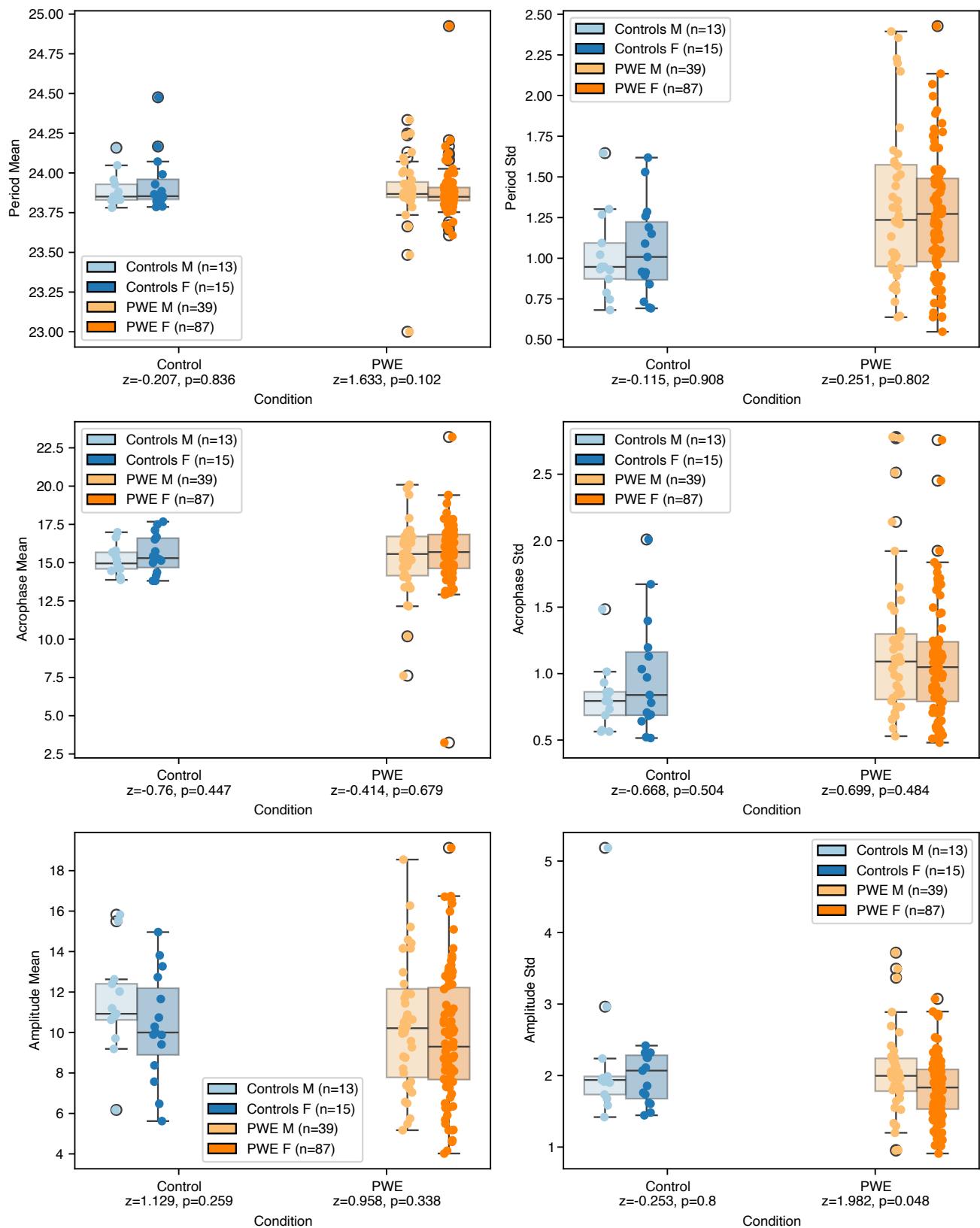


Figure S4.2: Comparison of the distribution of the average and variability in each circadian property between PWE and controls, split by sex. Two-sided Wilcoxon rank-sum test used to compare circadian average and variability between males and females within either PWE or controls.