KU LEUVEN

STADIUS
Center for Dynamical Systems, Signal Processing and Data Analytics

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Author contact	Carolina.varon@esat.kuleuven.be your phone number *+ 32 (0)16 32 64 17*
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Purpose: That children with nocturnal enuresis ('bedwetting') are deep sleepers is a fact that their parents often state when asking for advice. However, until today no clear difference in sleep has been observed between children who do and do not wet the bed. This study investigates the difference in sleep parameters and heart rate variability (HRV) between enuretic and control children in their home setting by using a wearable sleep tracker during a long observation period.

Methods: 21 enuretic and 18 control children, aged 6 to 12 years old, slept with a wearable sleep tracker device, a Fitbit® Charge2, for fourteen consecutive days. In addition, nocturnal urine production (voided volumes and/or weight of the diaper) were measured. The heart rate variability (HRV) was calculated using the standard time and frequency domain parameters. Kruskal-Wallis test was applied to evaluate the differences in the sleep and HRV parameters between both groups.

Results: Compared to healthy controls, enuretic children showed a higher standard deviation ($p= 0.0209$) of minutes spent in REM sleep among the different nights. In addition, they showed the tendencies to fewer awakenings ($p=0.1161$), although this was not significant. Analyzing the wet nights of the enuretic children, they showed a higher autonomic activity, a lower sleep efficiency and a higher restlessness compared to their dry nights and to the control group.

Conclusion: This 2-weeks sleep-study, using a wrist-worn sleep tracker device Fitbit® Charge2, in normal home environment has shown that enuretic children have a larger variation in their REM sleep and sleep less efficiently during a wet night when compared to non-bedwetting children.

INTRODUCTION

'Primary' Nocturnal Enuresis is defined as wetting the bed while asleep, since birth, that persists beyond the age of 5 in a child, without being dry for more than six months.(1) It is one of the most common sleep disorders in childhood, affecting 3-15% of school children(2). It is further categorized as 'monosymptomatic' primary enuresis, if there are no daytime symptoms, no anatomic causes, no comorbidities and no specific urological history, in contrast to secondary nocturnal enuresis.(3)

Nocturnal enuresis has a complex pathophysiology based on a mismatch in different domains: a higher arousal threshold, combined with either an excessive nocturnal urine production, an overactive bladder, an inhibition deficit of the central nervous system causing failure to suppress detrusor contractions during sleep or combinations of the foregoing.(4) Since failure to arouse in response to auditory stimulations has been demonstrated in enuretic children(5), the hypothesis is that these children experience a deeper sleep. However, this observation could not be substantiated after polysomnographic (PSG) studies that showed no difference in sleep architecture and number of arousals with children who do not wet their bed.(6),(7),(8)

Polysomnography, the golden standard for evaluating sleep, has however several limitations: it has a high cost, a limited availability and is labor intensive.(9) In addition, due to lab recordings, it is impractical and not representative as these children are removed from their familiar environment and providing data for only one or two nights, which makes it inappropriate for long-term recordings.

Bearing in mind these limitations, an alternative might be the use of wearable devices that claim to analyze sleep, provided that they have been validated. This approach could be a child-friendly way of analyzing sleep, without withdrawing children from their familiar surroundings, minimizing interference with the natural sleeping habits and facilitating long-term measurements. Therefore, several recent studies have validated a wrist-worn activity and sleep tracker and confirm clinical and scientific value (10),(11),(12), also in a child and adolescent population.(9),(13),(14) These studies showed comparable results in measuring total sleep duration, number of awakenings and sleep efficiency compared to polysomnography.(15)

New functions such as sleep structure including light, deep, and Rapid Eye Movement (REM) sleep detection by integrating heart rate (HR) data have only recently become available.(15)

A wrist-worn sleep tracker, Fitbit® charge 2 uses a PurePulse™ LED light to measure the heart rate. Most studies validating heart rate recordings compared to continuous electrocardiographic (cECG) and continuous pulse oximetry (SpO_2) monitoring, show the tendency to underestimate the heart rate. Inaccuracies occur mainly in non-sinus rhythms.(16) Only a slight underestimation, with a median difference of 1 bpm(16), is described in sinus-rhythm patients.

. Our goal was to find new insights in the complex pathogenesis of nocturnal enuresis, more specific regarding the eventual difference in sleep between enuretic and non-enuretic children, as this could improve the understanding of treatment mechanisms and open new treatment options in the future. In this study, we explored whether a Fitbit® Charge 2 could bring us these new insights, by comparing sleep parameters and heart rate variability (HRV) of enuretic children detected by the Fitbit to those of matched controls. This is, to our knowledge, the first time that a wearable sleep tracker device is used to measure heart rate variability and sleep parameters in enuretic children over multiple nights in a home setting.

MATERIALS AND METHODS

The Research Ethics Committee of the University Hospital and the University granted ethical approval. The signed informed consent and assent forms of each participant were obtained prior to their enrollment and participation in the study. All study data were pseudonymized and safely stored.

Sample and sampling techniques

This prospective observation study was performed between May 1st 2018 till December 15th 2018.

All children and their parents that were seen at the Pediatric Urology Department university hospital, Gasthuisberg Leuven, presenting with nocturnal enuresis, underwent history, physical examination, renal and bladder ultrasound, uroflowmetry and filled out a frequency-volume chart. If the diagnosis of 'Primary Monosymptomatic Nocturnal Enuresis' was confirmed following the updated International Children Continence Society criteria, and if they were between 6-12years old, they were asked to participate in the study.(3)

During the same period, healthy, 6 to 12-year-old, non-enuretic control children were recruited from a primary school by distributing an open invitation to anonymous participation. Those families who were interested, contacted us. There was no reward promised beforehand, as not to induce any bias.

To ensure the comparability of both study groups, children suffering from lower urinary tract symptoms (LUTS), incontinence, behavioral or sleep disorders, acute illness and disabilities that interfere with mobility were excluded. Previously or currently treated patients and children with psychopharmaceutical drug use were also excluded.

Materials

A Fitbit® Charge 2 (Fitbit®, San Francisco, CA), measuring cup, voiding diary, information letter with clear instructions and contact details were given and explained to the child and their parents once the informed consent was acquired. After completing the experiment, the devices were returned and cleaned. To obtain minute-by-minute measures of heart rate and sleep state, which is a higher time resolution than what is offered in the Fitbit® app itself, the third-party research platform 'Fitabase®' (Small Steps Labs LLC, https://www.fitabase.com) was involved. This data platform, especially designed for clinical studies collecting data from the Fitbit®, guarantees safe and anonymous storage.

Design

Participants installed the free Fitbit® app on their smartphone, using an in advance created anonymous account. For 2 weeks, subjects slept with a Fitbit, well-fitted to the non-dominant hand.

In addition, after every night that the child had slept with the Fitbit, the parents measured the voided volume on awakening. In the group of enuretic children, the weight of the full diaper was also registered. The different parameters collected for each participant are listed in Table 1.

Methods

In all patient and control children, individual average values (μ) and the standard deviations (σ) were calculated for each parameter. Individual means were pooled to one value (μ±σ) per group. The variation of

each parameter was evaluated using the Kruskal-Wallis test with α = 0.05, meaning that p-values <0.05 were considered statistically significant. In order to determine the statistical power (i.e. Power = 1-β) of each evaluation, a post hoc power analysis was performed. This analysis was based on a one-tailed non-parametric test and α = 0.05. The effect size was computed using minimum dispersion in the means and the asymptotic relative efficiency factor. Data analyses were carried out using MatLab.

Analysis of the heart rate variability (HRV), which is the variation in the time interval between consecutive beats, was performed using the classical time and frequency domain parameters, as described by Malik et al.(17) These features allow us to assess the ANS as indicated in Table 2. In order to calculate the frequency parameters, the data was resampled at 4 Hz, this means one sample each 0.25 seconds. At this point, our analysis was restrained by the insufficient time resolution of our device whereby only the SDNN (time domain parameter) and the LF (frequency component) could be computed.

After comparison between enuretic children and controls, comparative analysis using Kruskal-Wallis test of the sleep and HR parameters was carried out between dry and wet nights within the enuresis group. A dry night was defined as no loss of urine in bed and thus a dry diaper. As soon as weight gain of the diaper owing to urine collection was detected, the sleep record was tagged as a wet night. Due to insufficient dry nights per patient, means and standard deviations of dry versus wet nights were compared without differentiating between patients. For completion, the enuretic group was after this subdivision once again compared to the control group. Given the three groups, a multicomparison test with Bonferroni correction was needed with a corresponding significance level of α/3, so a p-value <0.016 indicating significance.

RESULTS

Our sample included 39 participants, consisting of 21 patients and 18 controls, aged 6 to 12 years old, with 24 males and 15 females. Characteristics of the study population are described in Table 3. Data of one enuretic patient was removed due to acute illness. The dataset consisted of 4 273 557 records of data. A typical recording provided by Fitabase is shown in figure 1. All values ($\mu \pm \sigma$) are listed in Table 4 for the healthy controls (HC) and nocturnal enuresis patients (NE) respectively.

Subsequently, group comparison between these parameters was performed, as can be seen in Table 4. From this analysis, only the variation of minutes in REM was significantly different between both groups. Enuresis subjects showed a higher standard deviation ($p = 0.0209$), as shown in Figure 2. The statistical power equal to $1-\beta = 0.52$, which means that there is still a 48% probability of a Type II error. Interestingly, the mean Classic Awake Count showed a tendency, though non-significant, of lower awakenings in enuretic patients ($p=0.1161$). This might suggest a higher arousal threshold in enuretic patients. Further, no additional significant correlations were found.

Focusing on the enuresis group, our data pool contained 225 wet and 40 dry nights. Comparison of wet (WN) and dry nights (DN) within the enuresis group showed significant differences in sleep efficiency ($p= 0.005$), time in bed ($p= 0.039$), restless count ($p= 0.012$) and restless duration ($p= 0.001$) as shown in Figure 3. The complete data set is displayed in Table 5. After adding the control group (227 nights), no differences were seen regarding these parameters with dry nights, while in all these cases, significant differences ($p <0.01$) with wet nights were found. After applying the multicomparison test, the difference between DN and WN was kept for all cases, except for Time in Bed (Figure 4).

Turning now to the HRV, only the SDNN and the LF could be computed, which will be clarified further in the discussion section. As presented in Table 6, no significant difference in the HRV parameters between controls and bedwetters was found but there was a tendency to higher autonomic nervous system activation in enuresis patients (SDNN $p = 0.3$; LF $p = 0.1$). Likewise, no relationship between the amount of urine produced during the night and the different HRV parameters was found. However, after subdivision in wet and dry nights and comparing them to the controls, HRV during dry nights turned out very similar to HRV of controls, whereas SDNN and LF were found to be significantly higher during wet nights ($p=0.004$ and $p=0.0017$ respectively; Figure 5).

DISCUSSION

The tendency of lower awakenings observed in the enuretic participants suggests that enuresis patients might have a higher arousal threshold, supporting previously reported findings.(18) However, since the differences are not significant (p = 0.11) and the statistical power equals $1-\beta = 0.31$, these results need to be interpreted with caution.

The higher restlessness during wet nights is consistent with the earlier finding of higher periodic limb movements in enuresis patients reported by Dhondt et al.(19) This may explain their higher standard deviation of minutes spent in REM sleep, which means that they present a greater intra-personal variation despite the same average of time in REM sleep, among enuretics, knowing that the Fitbit® uses movement-based algorithms to detect REM episodes. Combining the recordings of both dry and wet nights might clarify why the sleep is not uniform in those children. Due to the more disorganized sleep architecture, these children might not recover as they should, possibly leading to a tired feeling and distracted learning. These behaviors were not investigated or questioned during this study, but could be subject in future studies.

Another hypothesis is that such an unstable sleep cycle leads to a sleep deprivation in the long term. Thereafter the brain suppresses the body from awakening by the signal of a full bladder, in an attempt to let the body rest by raising the arousal threshold. This is why these children fail to wake up despite their demonstrated increased number of arousals.

Besides the sleep parameters, the nocturnal heart rate variability was also analyzed, for which enuretic patients showed significantly higher total autonomic activity during wet nights. Normally, mean heart rate decreases from wake to sleep, during REM sleep, in which variability is high. (20) Even though there are previous studies that have assessed HRV in the population of healthy 6 to 12 year old's, only some of them have reported nocturnal HRV measurements(21),(22),(20). These studies demonstrated minimal high frequency values and maximal low frequency values consistent with sympathetic nervous system activation during REM sleep.(23) Opposite changes were found for HF, which increases with sleep onset and reaches the highest values during deep sleep.(23) LF/HF reflecting the sympathovagal balance shifts towards sympathetic predominance during REM and parasympathetic predominance during deep sleep,(23) despite a decrease of total ANS activity.(24)

However, the intention to assess all these HRV parameters was limited as Fitabase®, the data platform that was used, achieves a time resolution of variable sampling with readings every 3 to 15 seconds. This resulted in inconsistent values ranging from a value every 5, 10, or 15 second. Due to the inability to observe faster variations in the heart rate, HF could not be accurately measured with this setup. To measure the RMSSD, the time differences between each heartbeat are needed, which were not provided by this device neither. In addition, multiple artefacts were found in the data. For these reasons, it was unachievable to evaluate whether the enuresis patients had a higher vagal activity, though the data could still be used for analyzing long-term variations of HRV caused by sympathetic activation. With this in mind, only the SDNN and the LF were computed, quantifying respectively the total activation of the ANS and the sympathetic activity.

No significant difference was found between the HRV parameters of bedwetters and healthy controls but there is a tendency to higher total ANS activation in enuresis patients (SDNN p=0.3; LF p=0.1). Only

taking into account the wet nights, total autonomic activity was found to be significantly higher during wet nights relative to controls (SDNN p=0.004; LF p=0.0017). This less-performing fall in the ANS from day to night could possibly be an explanation for higher restlessness and bladder hyperactivity in these patients.

Due to the lack of the other HRV parameters, it is impossible to attribute this increased total autonomic activity to a predominant parasympathethic or orthosympathetic activity. Desk research was inconclusive.

Yeung et al. have, based on the hypothesis that enuretic children would have a different sleep and arousal pattern than non-enuretic children, performed several studies in which he investigated children with enuresis using continuous natural filling cystometry and simultaneous electroencephalogram monitoring during sleep at night. He was able to demonstrate a significant number of children with nighttime overactive bladder, a parameter that we have not addressed in this study (25,26).

CONCLUSION

This study has shown that enuretic children sleep different when compared to control children, by having a greater intra-personal variation of minutes spent in REM sleep, demonstrating how important it is to study sleep over more than one night. In addition, enuretic children showed a higher autonomic activity, a decreased sleep efficiency and a higher restlessness activity during their wet nights, compared to their dry nights and to the control group. The small samples sizes, the lack of a medical device and the resolution restriction of the Fitbit should be mentioned. However, the strength of this study is to observe children in their normal sleep environment, and in addition during multiple nights by using an easily-available device, providing non-invasive and non-disturbing but accurate measurements.

Conflicts of interests

The study did not receive funding from the device manufacturer or from any other source. All funding was done by the principal investigator. The authors alone are responsible for the content and writing of this article.

FIGURE 1. A typical overnight recording of the heartbeat and sleep architecture by the fitbit, abstracted from Fitabase.

FIGURE 2. Compares the standard deviation of total minutes send in REM sleep for healthy controls and nocturnal enuresis patients. The variation in REM sleep duration over the multiple nights was significant higher in enuretic patients ($p = 0.0209$).

FIGURE 3. Comparison of wet (WN) and dry nights (DN) within the enuresis group showed significant differences in sleep efficiency [95.2±2.6% (DN) and 93.7±2.9% (WN), $p= 0.004$], time in bed [566±63 (DN) and 584±87 (WN), $p= 0.039$], restless count [15±7 (DN) and 18±7 (WN), $p= 0.012$] and restless duration [25±13 (DN) and 34±16 (WN), $p= 0.001$].

FIGURE 4. A multicomparison test was performed on control (Controls), dry (DN) and wet (WN) nights with Bonferroni correction. Significances are indicated in the boxplots using the asterisks, corresponding to a P-value < 0.01. Dry nights of enuretic patients turned out not significantly different from controls, in contrast to the dry nights, in which all cases were different from controls. Most of the times, the difference between DN and WN was kept, except for Time in Bed. All control nights (227 night recordings) were compared against WN (225 night recordings) and DN (40 night recordings), implying the necessary caution in interpretation, given the unbalance in number between DN and the other groups.

FIGURE 5. Shows comparison of SDNN and LF HRV parameters between healthy controls (Controls) versus dry (DN) and wet (WN) of enuretic patients. Significances are indicated in the boxplots using the asterisks, corresponding to a P-value < 0.01. SDNN and LF were found to be significantly higher during wet nights relative to controls ($p=0.004$ and $p=0.0017$ respectively).

TABLE 1. The collected parameters for each participant, and its description, as defined by Fitabase®.

Only the analyzed parameters are listed below. A complete overview can be consulted at https://www.fitabase.com/media/1748/fitabasedatadictionary.pdf

TABLE 2. Selected time-domain and frequency-domain measures of HRV and their definition by Malik et al.[17] These features allow us to assess the autonomic nervous system.

TABLE 3. The demographic information of our participants, at the time of their participation.

TABLE 4. the sleep parameters for healthy controls and nocturnal enuresis patients, as captured by the Fitbit® Charge 2.

TABLE 5. The sleep parameters for nocturnal enuresis patients as captured by the Fitbit® Charge 2, after subdivision in wet (WN) and dry nights (DN).

TABLE 6. The time and frequency dependent analysis of heart rate variability (HRV) for healthy controls (HC) and nocturnal enuresis patients (NE).
Data are expressed as mean ± standard deviation. Due to the limited time resolution of the heart rate values, captured by the Fitbit® Charge 2, it was not possible to calculate the RMSDD, VLF, HF and total power.

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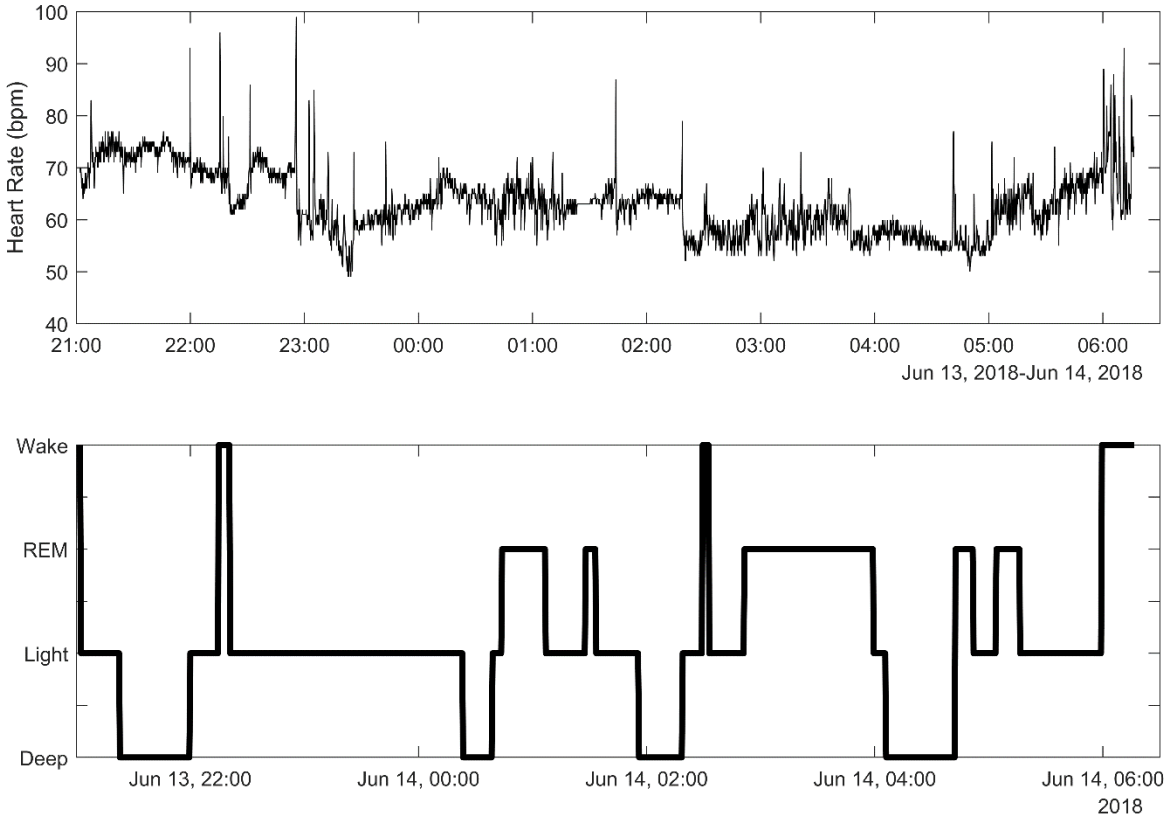


Figure 1

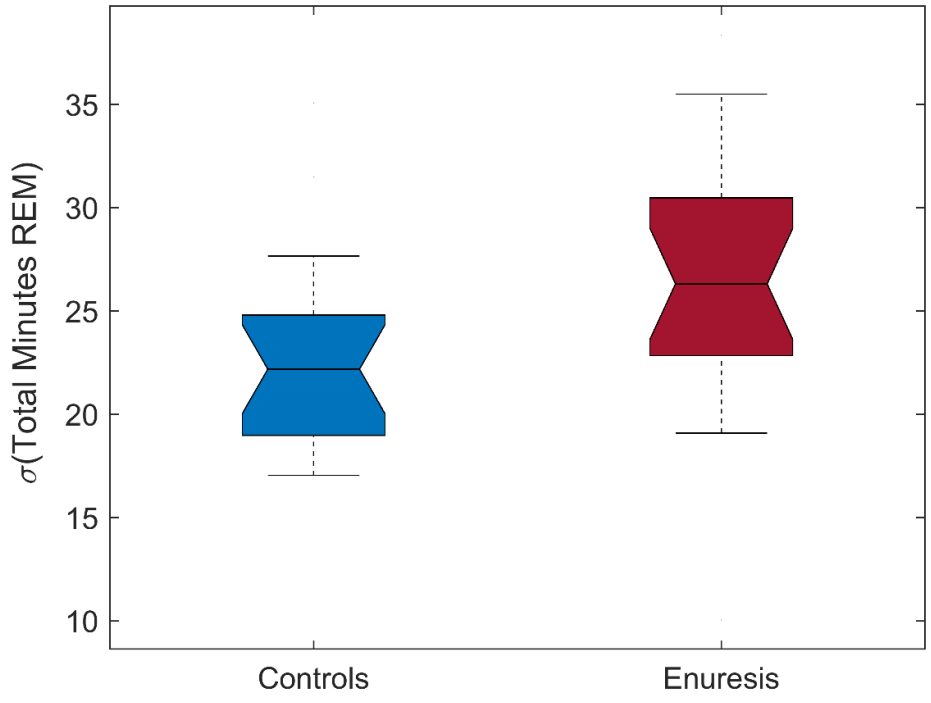


Figure 2

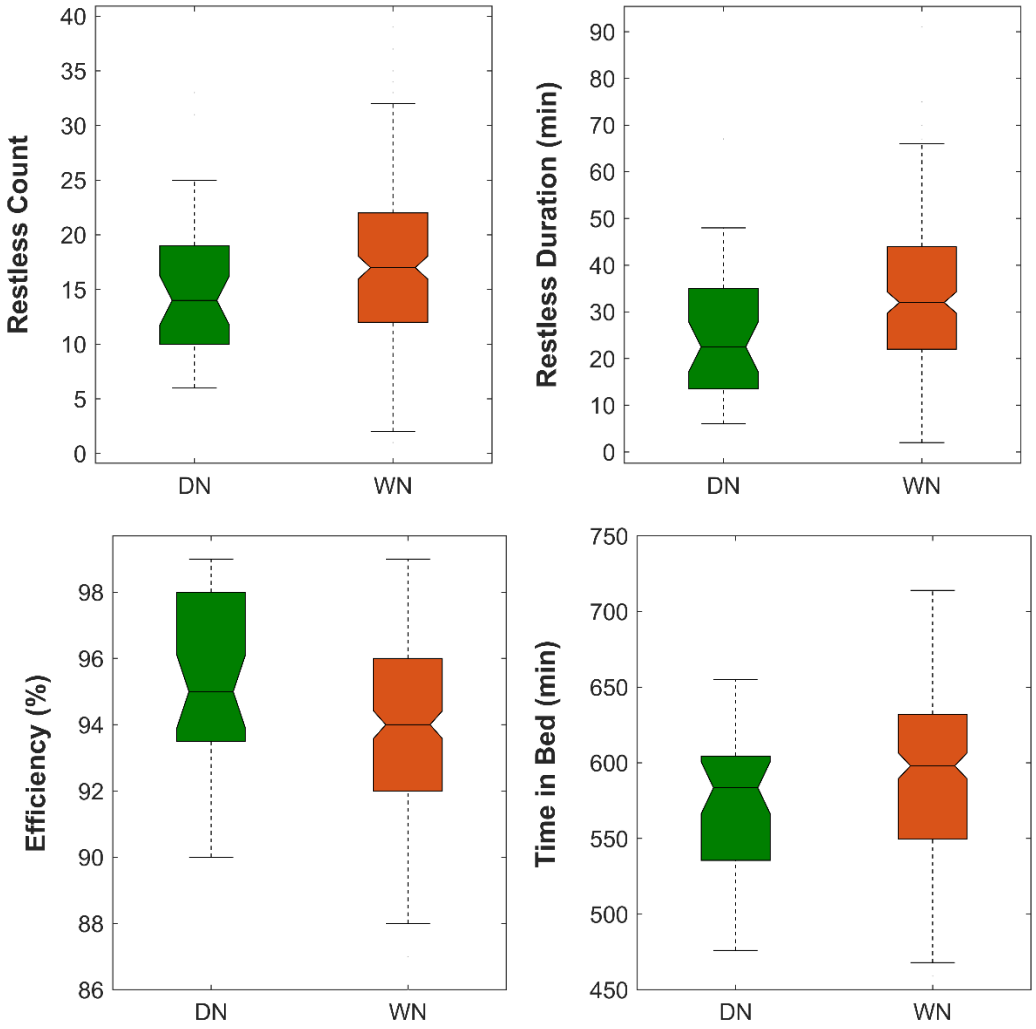
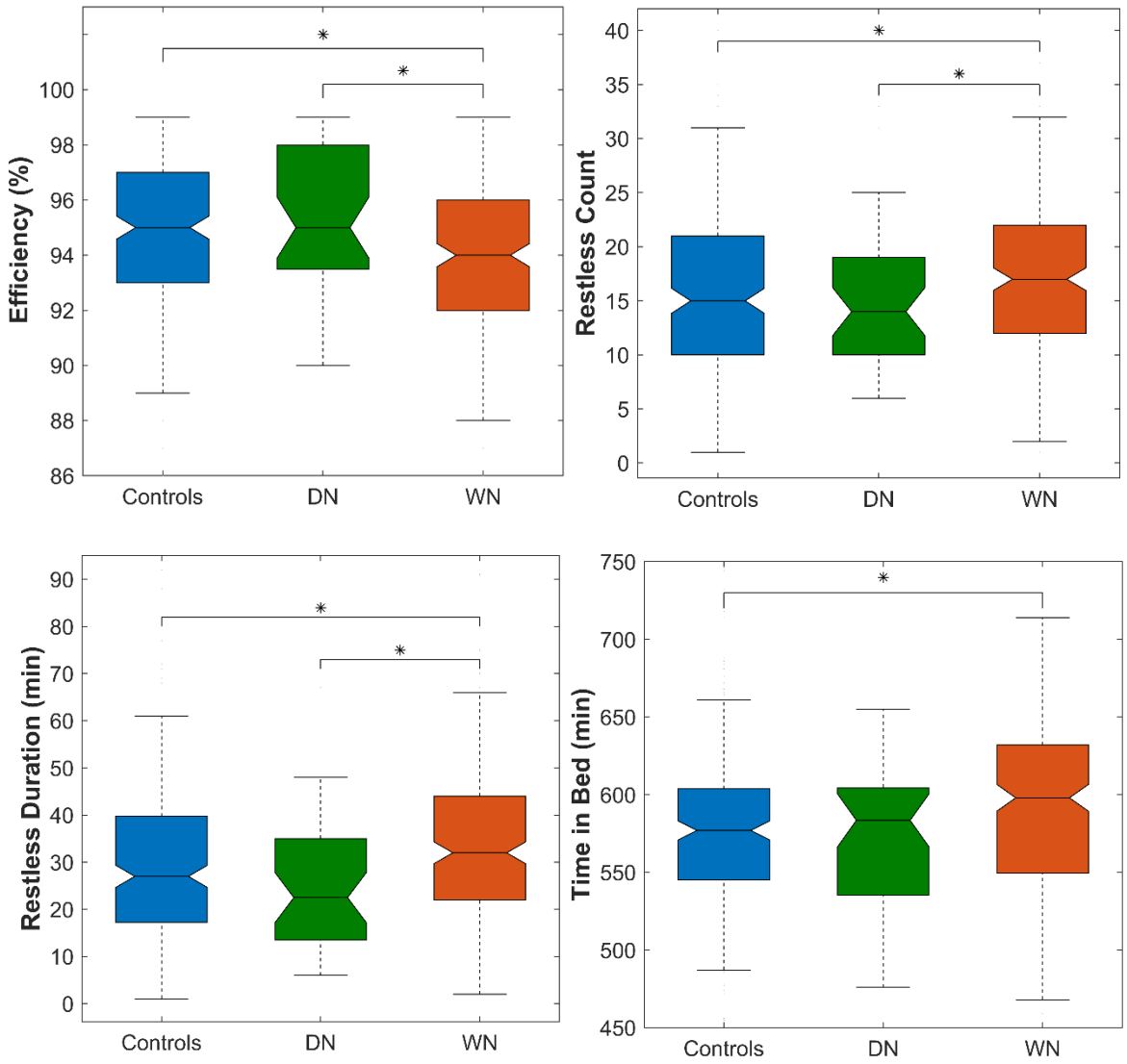

Restless Count
40
35
30
25
20
15
10
5
0
DN
WN
Restless Duration (min)
90
80
70
60
50
40
30
20
10
0
DN
WN
Efficiency (%)
98
96
94
92
90
88
86
DN
WN
Time in Bed (min)
750
700
650
600
550
500
450
DN
WN

Figure 3


Efficiency (%)
100
98
96
94
92
90
88
86
Controls
DN
WN
*
*
Restless Count
40
35
30
25
20
15
10
5
0
Controls
DN
WN
*
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Restless Duration (min)
90
80
70
60
50
40
30
20
10
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Controls
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Time in Bed (min)
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Controls
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Figure 4

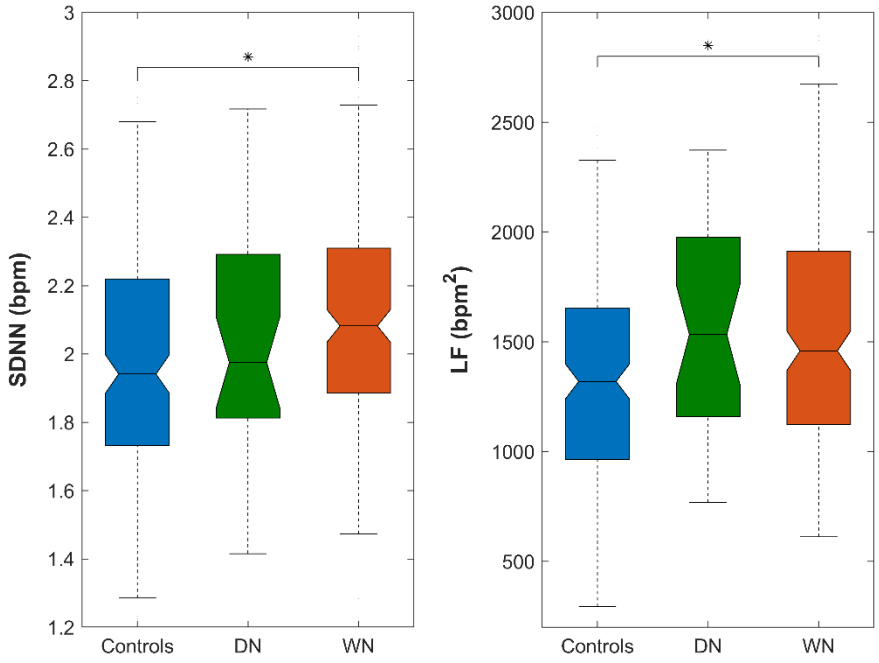
SDNN (bpm)
3
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
*
Controls
DN
WN
LF (bpm^2)
3000
2500
2000
1500
1000
500
*
Controls
DN
WN

Figure 5