# Development of an Inertial Measurement-Based Assessment of Disease Severity in Chronic Fatigue Syndrome

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***Abstract*—While myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is relatively new and poorly understood, a recent upsurge in research has identified the disease's core symptoms, including post-exertional malaise and orthostatic intolerance. The FDA has yet to approve any treatments for ME/CFS, partially due to a lack of validated efficacy endpoints.**

**The central focus of this research is to develop ME/CFS efficacy endpoints using a non-invasive, inertial measurement-based approach. Accessible endpoints will provide a way to properly evaluate potential treatments for ME/CFS. Using a Kalman filter, inertial measurement unit (IMU) data can be converted to optimized leg angle estimates. These angle estimates can then be converted to personalized daily measurements of upright activity, referred to as uptime.**

**In a six-day, case-control study conducted by the Bateman Horne Center, uptime was measured for 15 subjects (five controls, five moderate-level ME/CFS, and five severe-level ME/CFS). Analysis of these uptime scores indicated that each group spends different proportions of their days upright and active. This result shows that uptime can accurately determine disease severity and is, therefore, a reliable endpoint for evaluating ME/CFS treatment efficacy.**

## NOMENCLATURE

| | |
|---|---|
| $\phi$ | Roll, angle relative to a global x-axis |
| $\theta$ | Pitch, angle relative to a global z-axis |
| $\psi$ | Yaw, angle relative to a global y-axis |
| $a_x$ | Acceleration along the x-axis |
| $a_y$ | Acceleration along the y-axis |
| $a_z$ | Acceleration along the z-axis |
| $p$ | Body fixed rotation rate about the x-axis |
| $q$ | Body fixed rotation rate about the y-axis |
| $r$ | Body fixed rotation rate about the z-axis |
| $\theta_c$ | Critical angle, measured from vertical |

## I. INTRODUCTION

More than two million Americans suffer from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with an annual cost of $24 billion [1][2]. While our understanding of the etiology of ME/CFS is currently incomplete, studies have shown that the disease commonly occurs following viral infection and other acutely stressful events, impacting women more frequently than men at a rate of 6:1 [3]. A recent upsurge in ME/CFS research has led to an understanding of the disease's core symptoms: (1) fatigue as a response to physical exertion, (2) post-exertional malaise (PEM), (3) unrefreshing sleep, (4) cognitive impairment, and (5) orthostatic intolerance (OI) [4]. While the scientific community's understanding of ME/CFS is continuously improving, no cure has been discovered. Patients often suffer from ME/CFS for years, and sometimes even until death [5].

PEM causes individuals with ME/CFS to become disproportionately fatigued following mental or physical exertion. It is regarded as the distinctive symptom of ME/CFS [6]. As a result of PEM, individuals with ME/CFS can have difficulty performing mundane tasks such as routine cleaning, grocery shopping, and even showering.

OI refers to the onset of symptoms that occur when standing upright; these symptoms can be alleviated by reclining. While the exact cause of OI remains unknown, Dr. van Campen's research suggests that significantly lower blood volume is common among adults with ME/CFS who experience OI [7]. Sub-normal blood volume is likely the cause of the circulation-related issues many ME/CFS patients endure, such as dizziness, headaches, weakness, and nausea. These are the most common symptoms of OI, all of which occur as a result of prolonged upright posture.

The FDA has yet to approve any treatments—physical or pharmaceutical—for ME/CFS. To some extent, this lack of FDA-approved treatments is due to a lack of validated efficacy endpoints [4]. Efficacy endpoints are used in clinical trials to reliably monitor the improvement of subjects as a result of a

prescribed treatment. In recent years, researchers have developed some ME/CFS efficacy endpoints using blood tests [8] and other invasive methods [9]. The central focus of this research is to develop efficacy endpoints using a completely non-invasive, inertial measurement-based approach. More accessible efficacy endpoints will provide a way to properly evaluate potential treatments for ME/CFS, especially if these endpoints correspond to the disease's core symptoms.

Researchers at the Bateman Horne Center (BHC) in Salt Lake City, Utah recently discovered an endpoint that shows promise as a reliable assessment of functional impairment among patients with ME/CFS. In studies conducted by the BHC, subjects were asked to fill out questionnaires, identifying how much time they spent upright during the previous 24 hours. The BHC refers to this measurement of uprightness as hours of upright activity (HUA).

Due to its strong correlation with PEM, HUA is a simple way to gauge disease severity among individuals with ME/CFS (transcript in progress). While HUA is a valuable efficacy endpoint, its deficiencies are significant. The primary weakness of HUA is the inaccuracy of its current data collection method—questionnaire [10]; it is unreasonable to expect patients to accurately recall the amount of time they spent in an upright position the previous day. Another weakness of HUA is the low resolution offered by the measurement. "Hours" of upright activity is just that, a measurement recorded as whole integers in units of hours. Due to the inaccuracy and low resolution of data collected from HUA questionnaires, the only way to obtain a measurement of upright activity with a higher level of precision involves significant alterations to the current measurement process.

To address HUA's shortcomings, an improved method for evaluating upright activity is proposed. Using an inertial measurement unit (IMU), it is possible to continuously and accurately measure upright activity, thus providing an effective method to assess disease severity among individuals with ME/CFS. By continuously measuring the uprightness of the lower legs, we can obtain a measurement referred to as uptime. The advantages of this approach are two-fold. The first advantage is that healthcare providers will no longer need to rely upon the accuracy of a patient's memory to approximate upright activity. The second advantage comes from increasing the resolution of the measurement from hours—HUA—to seconds— uptime.

The goal of our research is to validate an improved method to assess upright activity. To formally evaluate uptime as an efficacy endpoint for ME/CFS disease severity, this research evaluates the results of a study wherein a healthy control group and an experimental group of ME/CFS patients were outfitted with Shimmers—a commercially available IMU—for six consecutive days. During these six days, the Shimmers continuously measured uptime. Statistical tests and other comparisons were used to evaluate the correlation between data collected by the Shimmer and uptime.

Our research simplifies symptom severity evaluation among patients with ME/CFS. As a result, assessing the long-term efficacy of treatments for patients with ME/CFS will significantly improve the evaluation of disease severity in terms of both ease and accuracy. These changes will enable the development of effective treatments, thus providing a path to recovery for individuals struggling with ME/CFS.

## II. Materials and Methods

The chief objective of this research is to evaluate uptime to prove its value as an efficacy endpoint for ME/CFS. We accomplished this goal in three steps: (1) establish a method to measure lower leg angle using an IMU, (2) verify the accuracy of these IMU-based angle measurements, and (3) perform a case-control study comparing uptime between different ME/CFS and non-ME/CFS groups.

### *A. Uptime Calculation – IMU Sensor Fusion*

Calculating uptime is a two-step process. First, we measure lower leg angle by filtering IMU data. Second, we evaluate this measured angle to determine if the leg is upright. Distinguishing leg uprightness is crucial because it relates to the HUA questionnaire, which quantifies daily time spent in upright postures (see Fig. 1).

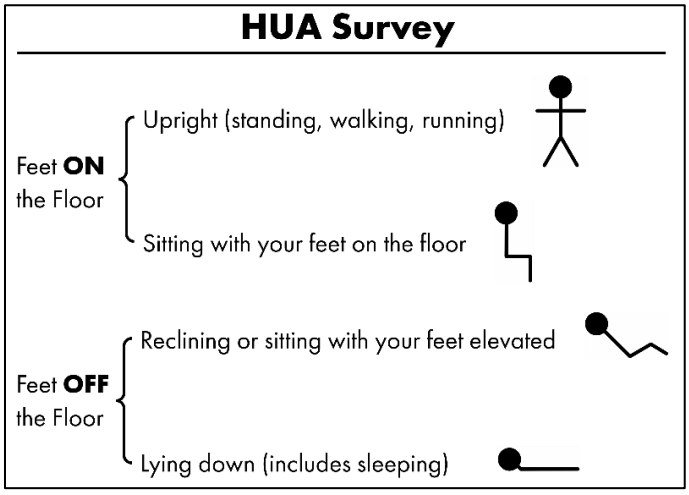


Fig. 1. HUA survey—HUA-based estimates of uptime are calculated by summing the time spent with feet on the floor.

To replace the HUA questionnaire, we chose to calculate uptime using an IMU placed on each lower leg. Lower leg angles allow us to accurately assess whether the feet are on the floor (lower legs vertical) or off the floor (lower legs reclined/horizontal) while maximizing user comfort.

The Shimmer, a commercially available IMU, was selected for use in this research due to its small and lightweight design, data logging capacity, ample battery life, and previous use in related work [11][12]. Using an internal SD card, the Shimmer can simultaneously record accelerometer, gyroscope, and

magnetometer data for extended periods. Accurate angle estimations can be obtained using only the accelerometer and gyroscope.

Combining data from multiple sensors, otherwise known as sensor fusion, has been extensively reviewed in the literature [13]. Sensor fusion reduces measurement uncertainty by merging data from multiple sensors. Our sensor fusion method of choice, the Kalman filter, was used to merge the Shimmer's raw accelerometer and gyroscope data to determine lower leg angle, measured from vertical.

Estimates of lower leg angle can be derived from both the accelerometer and the gyroscope. Equations 1 and 2 show estimates of roll ($\phi$) and pitch ($\theta$) calculated from accelerometer data ($a_x$, $a_y$, and $a_z$) using trigonometry.

$$\phi_{Acc} = \tan^{-1}\left(\frac{a_y}{a_x^2 + a_z^2}\right) \quad (1)$$

$$\theta_{Acc} = \tan^{-1}\left(\frac{-a_x}{a_y^2 + a_z^2}\right) \quad (2)$$

Equation 3 shows how lower leg angle rates were estimated by transforming raw gyroscope data ($p$, $q$, and $r$) into global frame Euler angle rates, which were subsequently integrated to form angle estimates.

$$\begin{pmatrix} \dot{\phi}_G \\ \dot{\theta}_G \\ \dot{\psi}_G \end{pmatrix} = \begin{pmatrix} 1 & \sin(\phi)\tan(\theta) & \cos(\phi)\tan(\theta) \\ 0 & \cos(\phi) & -\sin(\phi) \\ 0 & \sin(\phi)/\cos(\theta) & \cos(\phi)/\cos(\theta) \end{pmatrix} \begin{pmatrix} p \\ q \\ r \end{pmatrix} \quad (3)$$

Both angle estimates were optimally combined using a Kalman filter to minimize measurement noise and bias error.

A custom MATLAB function calculated uptime by comparing the Kalman filter's optimized lower leg angle estimates to a critical angle. The role of the critical angle is to mark the difference between a lower leg that is upright and one that is not upright (see Fig. 2).

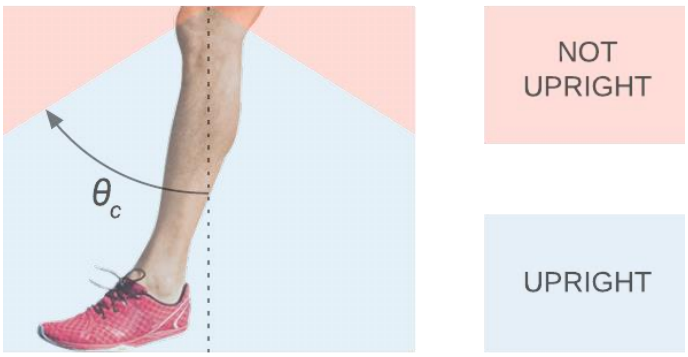


Fig. 2. The angle of each lower leg is compared to the critical angle ($\theta_c$) to determine uprightness.

For our research, the critical angle was set equal to 39 degrees from vertical. After determining each leg's "uprightness," our MATLAB function calculated uptime as a percentage of the day spent with the lower legs in an upright position.

### *B. IMU-Based Uptime Accuracy Confirmation*

To confirm the accuracy of the filtered lower leg angles, we performed a small study using a nine-camera VICON motion capture system as a 100% accurate reference for comparison. The Shimmer's low-noise accelerometer was set to an output range of ± 2 g, and the gyroscope was set to an output range of ± 500 deg/sec.

The VICON and Shimmer systems were then simultaneously used to measure lower leg angles while three subjects followed a series of postures, holding each for approximately five seconds (Fig. 3).

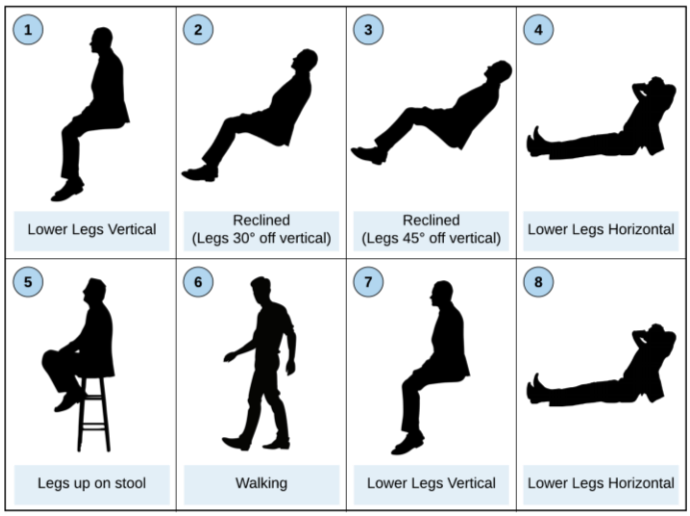


Fig. 3. Sequence of postures imitated by subjects during accuracy confirmation study.

This sequence of postures was explicitly developed to push the limits of the Shimmer's motion capture abilities and encompass the full range of lower leg angles that would be seen in a week-long study, from vertical to horizontal.

Both the VICON and Shimmer systems collected data at a sample rate of 30 Hz. When comparing VICON angles to Shimmer angles, root mean squared error (RMSE) calculations showed that the two measurements differed by an average of 0.53 degrees for all three subjects. RMSE was 0.80 degrees for subject 1, 0.13 for subject 2, and 0.66 for subject 3. Most error occurred during the walking sequence from 30 to 40 seconds (Fig. 4).

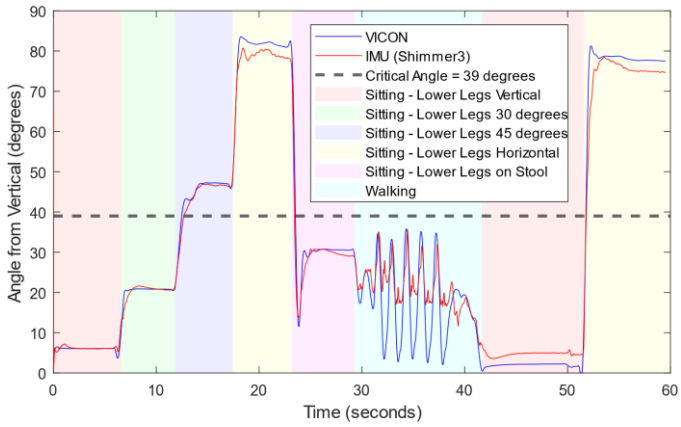


Fig. 4. Comparison of angle data from VICON and Shimmers for one subject.

Uptime was calculated twice for each subject—once using VICON angles and once using Shimmer angles. When reviewing uptime scores for all three subjects, we found that the Shimmer had an average error of 1.88% when compared to the VICON system (Table 1).

TABLE 1. UPTIME DATA FOR BOTH THE VICON SYSTEM AND THE SHIMMER

| System | Uptime (%) | | |
|---|---|---|---|
| | Subject 1 | Subject 2 | Subject 3 |
| VICON | 29.61 | 31.47 | 24.79 |
| Shimmer | 29.74 | 30.67 | 25.45 |
| Error | *2.54%* | *0.42%* | *2.67%* |

This small amount of error was deemed negligible for our application. Subject-to-subject differences in measurement accuracy were also acceptably low.

### C. Case-Control Study Design

For the planned case-control study, a total of 15 subjects were outfitted with a Shimmer on each ankle. Each subject wore both devices for six days—starting on a Monday and ending on a Saturday. The 15 subjects were divided into three groups based on disease level: (1) five subjects without ME/CFS (the controls), (2) five subjects with moderate-level ME/CFS, and (3) five subjects with severe-level ME/CFS. Due to limited Shimmer availability, data collection was staggered so that one or two subjects participated each week.

The six-day data collection period was broken into two phases. Phase one began on a Monday (when the subject traveled to the BHC to be outfitted with the Shimmers) and ended 72 hours later—the following Thursday. Phase two began on Thursday (where phase one ended) lasting another 72 hours before ending on Sunday.

The data collected during phase one was meant to be a baseline against which the data from phase two would be compared; at the beginning of phase two, each subject performed the NASA 10-minute Lean Test—meant to cause the onset of PEM for subjects with ME/CFS, but have no effect on the control group. Subjects were instructed to go about their lives in a normal manner during the study.

## III. RESULTS AND DISCUSSION

### A. Uptime Differences Between Disease Groups

Due to differences in activity levels brought on by the presence and severity of ME/CFS, we expected the control group to have the highest uptime and the severe ME/CFS group to have the lowest uptime, with the moderate ME/CFS group's uptime somewhere in the middle. Group trends for weekly average uptime scores supported this expectation.

Controls generally had average weekly uptimes above 30%. Subjects with moderate ME/CFS generally had uptimes between 20 – 30%. Subjects with severe ME/CFS averaged daily uptime scores below 20%. The non-overlapping group confidence intervals (shown by the vertical colored lines in Fig. 5) are evidence indicating that uptime differs by disease level.

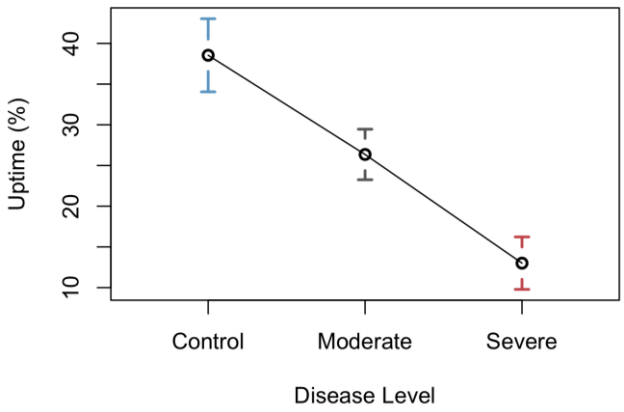


Fig. 5. Mean plot of uptime separated by disease level.

The results of an ANOVA test further substantiated these group uptime differences, confirming that uptime differs significantly between the groups (Table 2).

TABLE 2. RESULTS OF A MULTIPLE-FACTOR ANOVA

| Factor | Degrees of Freedom | Sum of Squares | Mean Sum of Squares | F value | P-value |
|---|---|---|---|---|---|
| Disease Level | 2 | 8570 | 4285 | 61.535 | 1.9e-15*** |
| Day | 5 | 505 | 101 | 1.450 | 0.219 |
| Subject | 12 | 2284 | 190 | 2.733 | 0.005** |
| Residuals | 64 | 4317 | 70 | - | - |

* Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '

The null hypothesis of this ANOVA test is that the mean uptime is the same for all groups. A p-value of 1.9e-15 shows that there is insufficient evidence to support the null hypothesis (at the significance level $\alpha = 0.05$). As a result, we accept that the alternative is true, indicating that there is a difference between the mean group uptimes.

To further expand upon the result of this ANOVA, we used Tukey's HSD (honestly significant difference) test. Up to this point, we have only shown that mean group uptimes are not *all* equal. Tukey's HSD test identified which specific group differences exist. For all pairs of means, the calculated p-values are far less than $\alpha = 0.05$, meaning that each group's mean uptime is different from all other groups (Table 3).

TABLE 3. TUKEY'S HSD TEST COMPARING UPTIME BY DISEASE GROUP

| Disease Level | Difference | Lower | Upper | P-value (adjusted) |
|---|---|---|---|---|
| Moderate-Control | -12.19 | -18.17 | -6.20 | 2.13e-05*** |
| Severe-Control | -25.54 | -31.82 | -19.25 | 0.00e+00*** |
| Severe-Moderate | -13.35 | -19.64 | -7.06 | 9.80e-06*** |

* Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '

With the combined results of the mean plot, ANOVA test, and Tukey's HSD test, we can confidently state that uptime differs for all disease levels. Using the uptime scores collected from all 15 subjects, we can define the uptimes expected for each group. Controls (non-ME/CFS individuals) are expected to have weekly uptime scores above 30%. Patients with moderate ME/CFS are expected to have weekly uptime scores between 20% and 30%. Patients with severe ME/CFS are expected to have weekly uptime scores below 20% (Fig. 6).

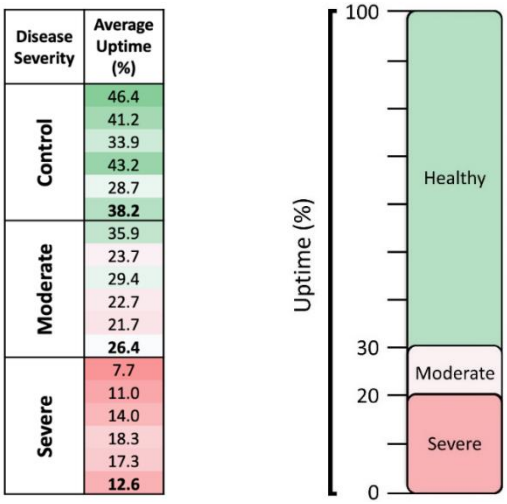


Fig. 6. Subject weekly average uptime scores (left) and corresponding scale of expected uptime scores for each disease group (right).

These conclusions align with the observations of the BHC and their understanding of ME/CFS. Symptoms of this disease—such as post-exertional malaise (PEM) and orthostatic intolerance (OI)—limit a patient's ability to remain upright. As disease severity increases, so do these physical limitations. Therefore, we can objectively conclude that uptime corresponds to the presence and severity of ME/CFS.

### *B. Uptime Before vs. After NASA Lean Test*

Next, we looked for uptime differences before and after the NASA Lean Test. The NASA 10-minute Lean Test requires subjects to stand straight upright and lean against a wall, with only the shoulder blades contacting the wall, and heels six inches from the wall [14]. This test was expected to induce Post-Exertional Malaise (PEM) in subjects with ME/CFS, thereby decreasing subsequent uptime scores.

In this comparison, a baseline uptime score was calculated by averaging the three days before the NASA Lean Test: Monday, Tuesday, and Wednesday. This baseline was used for comparison when reviewing uptime scores for the proceeding days: Thursday, Friday, and Saturday. Therefore, the variable "Number of Days after Lean Test" has the following levels:

- Baseline *(average uptime for Monday, Tuesday, and Wednesday)*
- 1 Day after Lean Test *(Thursday's uptime)*
- 2 Days after Lean Test *(Friday's uptime)*
- 3 Days after Lean Test *(Saturday's uptime)*

Despite our expectations, uptime averages for each group, shown in Fig. 7, do not decrease following the Lean Test. Instead, mean uptimes for ME/CFS groups spike one day after the test.

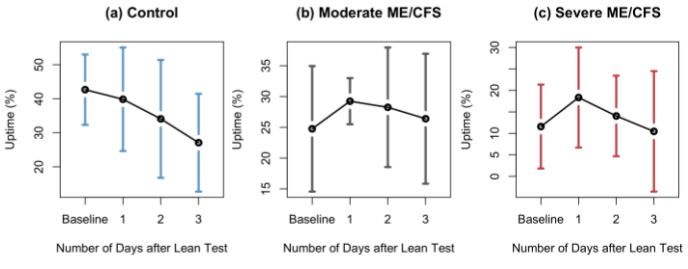


Fig. 7. Group mean plots for uptime.

Interestingly, the control group alone decreases after the Lean Test; however, this change is due to weekend relaxation rather than the effects of the NASA Lean Test. Furthermore, the ME/CFS groups' uptime spikes could have been a direct result of participating in the NASA Lean Test. A 5-10% increase in uptime equals roughly 1-2 hours of upright activity. This increase could easily be the amount of time required to drive to the BHC, take the Lean Test, and drive home.

Because the confidence intervals in Fig. 7 overlap so heavily, we don't expect to find any significant difference in mean uptimes before and after the NASA Lean Test. This suspicion is confirmed by the high p-values shown in Table 4, which indicate that there are no significant differences in uptime by day.

TABLE 4. SINGLE-FACTOR ANOVA TABLES FOR EACH DISEASE LEVEL

| | Factor | Degrees of Freedom | Sum of Squares | Mean Sum of Squares | F value | P-value |
|---|---|---|---|---|---|---|
| CONTROL | Days After Lean Test | 3 | 630 | 210.0 | 1.658 | 0.218 |
| | Residuals | 15 | 1900 | 126.6 | - | - |
| MODERATE | Days After Lean Test | 3 | 58.8 | 19.59 | 0.431 | 0.734 |
| | Residuals | 15 | 682.0 | 45.47 | - | - |
| SEVERE | Days After Lean Test | 3 | 167.4 | 55.80 | 0.905 | 0.465 |
| | Residuals | 15 | 801.5 | 61.65 | - | - |

** Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '*

With the results of Table 4, we find ourselves forced to reject the consensus that activity decreases after the NASA Lean Test. This finding can be explained in a few different ways. For one thing, our experimental design was not without flaws. On the first day of each trial, the subject traveled to and from the BHC to be equipped with the Shimmers. Due to the extreme sensitivity of ME/CFS patients, this travel alone could have unintentionally induced PEM. With patients experiencing PEM throughout the entirety of the study (rather than just during days 4 through 6), we would expect to see constant uptime scores. Future studies should consider home-visits to reduce this effect.

The floor effect could be an alternative explanation for these unexpected results; uptime can only go so low. Baseline uptimes for the ME/CFS groups could already be at minimum allowable levels. Further uptime reductions could mean a significant decrease in lifestyle. (The quality of life for an individual with ME/CFS is already very low). Some subjects in the moderate ME/CFS group have part-time jobs; taking a few days off to recover from PEM may not be an option. For the severe ME/CFS group, it simply may not be possible to lower uptime from their average four hours per day.

Lastly, constant ME/CFS uptime scores could be a result of self-medication. Except for the morning of the Lean Test, ME/CFS subjects were permitted to take their prescribed medication throughout the study. Subjects may have medicated more heavily following the NASA Lean Test to mitigate the effects of PEM, thus unintentionally flattening uptime.

Whatever the reason, it is indisputable that the NASA Lean Test had no statistically significant effect on uptime. A better experiment design would track each subject for a more extended period before and especially after the NASA Lean Test, thus establishing more accurate baseline uptime scores for each subject. However, limitations in funding and time prohibited these design improvements. Further investigation but may provide deeper insight into the causes and effects of PEM.

### *C. Comparison of HUA and Uptime*

Finally, we turn to an evaluation of HUA as a proxy for IMU-based uptime scores. Until this study, the only tool researchers at the BHC had to evaluate daily upright activity was HUA—a questionnaire that crudely captures the amount of time an individual spends with the feet on the floor each day. Historically, HUA was reported in units of hours; however, we have converted HUA to a percentage of the day to accommodate its comparison to IMU-based uptime measurements.

During our case-control study, subjects filled out daily HUA questionnaires. The results of these surveys show that subjects generally tend to overestimate uptime (Fig. 8).

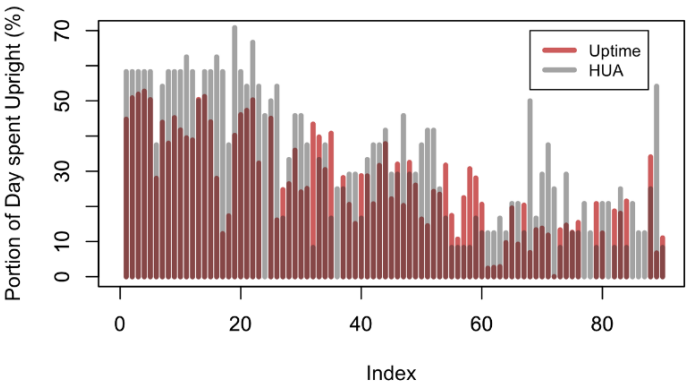


Fig. 8. HUA and uptime compared for the study's combined ninety days of data. Control subject data are included as indices 1-30, moderate ME/CFS data are included as indices 31-60, and severe ME/CFS data are included as indices 61-90. An index where uptime is not shown indicates a lack of Shimmer data.

Indeed, a correlation plot—broken up by disease level—shows that HUA and uptime are not correlated for both ME/CFS groups (Fig. 9).

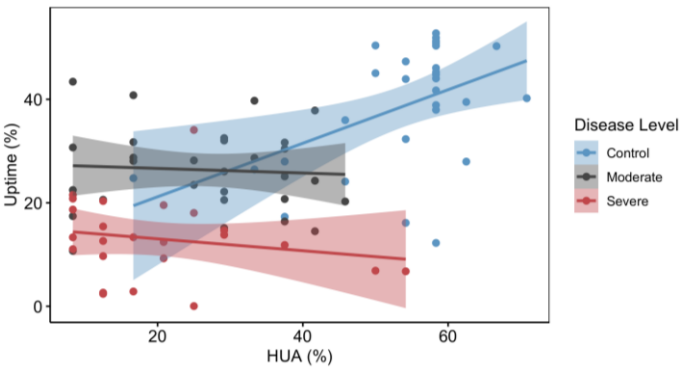


Fig. 9. Correlation plots between uptime and HUA, separated by disease level.

Both ME/CFS groups reported a wide range of HUA scores, while uptime remained relatively invariant. This non-correlation is illustrated by the horizontal grey and red lines in Fig. 9. Conversely, the control group estimated uptime with some level of accuracy. We see a positive, linear correlation between uptime and HUA for this group shown by the blue line in Fig. 9. However, a multitude of blue outliers suggests the weakness of this correlation.

A paired t-test comparing all HUA and uptime scores yielded a p-value of 2.72e-05, confirming that the two measurement types produce significantly different scores. The corresponding 95% confidence interval for the true mean difference is (4.17, 10.91). This interval indicates that we are 95% confident that the average difference between HUA and uptime is between 4.17 and 10.91%.

## IV. Conclusion

This research proves the value of uptime as an objective replacement for HUA. Analysis of collected uptime data indicates that disease groups spend different proportions of the day upright and active. Healthy individuals are expected to have weekly uptime scores above 30%, subjects with moderate ME/CFS are expected to have weekly uptime scores between 20% and 30%, and subjects with severe ME/CFS are expected to have weekly uptime scores below 20%.

Another objective of our study was to evaluate the effects of PEM brought on by the NASA Lean Test. Our results showed no change in uptime after the NASA Lean Test. Although this contradicts our expectations, we have confirmed that this test is humane; patients with ME/CFS do what they can to avoid stress-causing exertion, but we have seen that this test does not cause a drastic decrease in uptime—indicating that they aren't significantly hurt by the test. Future studies should incorporate home-visits to reduce the stress caused by participation, thereby ensuring that PEM is only induced by researchers during the Lean Test.

Accurate uptime measurements will become invaluable for healthcare providers in assisting ME/CFS patients. Furthermore, uptime provides a method for pharmaceutical companies and independent researchers to prove the efficacy of their treatments—a critical step towards receiving FDA-approval. The BHC's data shows that patients with severe ME/CFS are limited to a bed or reclining chair for all but five hours each day; increasing this number would be life-changing.

## Acknowledgements

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