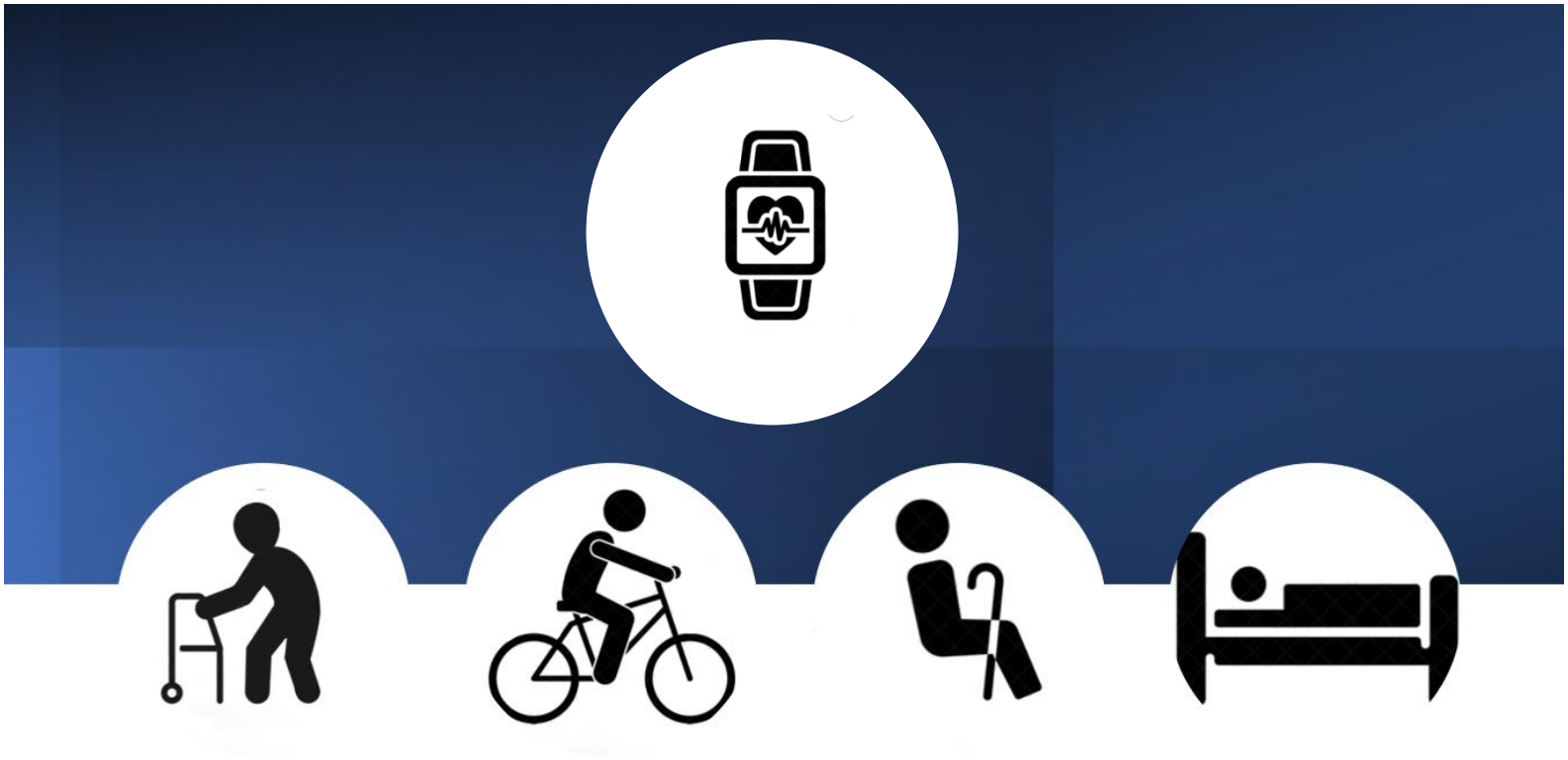
HOMEBASED MONITORING OF PATIENTS AT RISK FOR FUNCTIONAL DECLINE USING AN ACCELEROMETER

E.R.M.Heemskerk



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Eveline Heemskerk

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Supervisor(s):

Dr. M. Stijntjes
Dr. S.K. Schiemanck
Dr. Ir. J.H. de Groot

Thesis committee members:

Dr. C.J.M. van der Ham	Leiden University	Chair
Dr. M. Stijntjes,	TU Delft, LUMC	Technical supervisor
Dr. S.K. Schiemanck	LUMC	Medical supervisor
Dr. Ir. J.H. de Groot	LUMC	Technical supervisor

Universiteit Leiden

TU Delft Delft University of Technology

Erasmus Universiteit Rotterdam

Preface

From the beginning of my bachelor's program, clinical technology, I was interested in rehabilitation medicine, especially in gait analysis and (biomedical) orthoses and prostheses. A ten-week internship, during my master Technical Medicine, at the Rehabilitation Medicine department at the LUMC confirmed my passion and interest in this work field. It may not be obvious, but the rehabilitation medicine field is an excellent fit for technical physicians. It includes many projects and interventions where the connection between medical, technical, and research aspects are made.

My graduation project offered me the experience to develop my program, writing, and research skills. I enjoyed collaborating with researchers, the company McRoberts, and the medical staff from different departments and hospitals. The collaboration and the many (online) meetings highlighted the added value of a technical physician, and I hope to find this multidisciplinary collaboration in my further work. I want to thank Marjon Stijntjes and Jurriaan de Groot for their feedback and support throughout the project and for sharing their knowledge. In addition, I also want to thank Jordi Evers from Mc Roberts for the collaboration and supervision during my feasibility study. Our collaboration gave me more insight from the manufacturer's view, which is valuable for successfully developing and implementing a new product. Furthermore, I want to thank Monica van Eijk for her input, feedback, and the opportunity to use the database of the HIP-CARE study.

Besides the research, I worked many days in the clinic. The experiences in the hospital, patient contact, and being a part of the medical staff was of great value, which I will never forget. I want to thank everyone in the department for their enthusiasm and interest in guiding me in the clinic and teaching me as much as possible. Thanks to Marian and Marjolijn, who guided and supervised me on a daily basis, and to Paul Dekker for the input and feedback on my project. Lastly, a special thanks to Sven Schiemanck for being my medical supervisor. I have been pushed out of my comfort zone, which was hard sometimes. However, I would not have missed a moment of it. It were exciting and educational months.

Eveline Heemskerk
Haarlem, July 2021

Abstract

Introduction

Timely personalized treatment of functional decline depends on early ambulant identification of persons at risk. Regularity of daily body acceleration, quantified by sample entropy (SampEn), is associated with fall risk and is a potential proxy for functional (biopsychosocial) resilience.

Objective

This cross-sectional study associates SampEn of daily life accelerometry with physical (short physical performance battery, SPPB [0 12]) and cognitive functioning (cognitive impairment test, 6 CIT [0-28]).

Method

Data was provided from the HIPCARE cohort of 51 community-dwelling adults [81 (75 – 89)] after femur fracture. The SPPB, CIT, and 7 days accelerometry were recorded at three months follow-up after hip surgery. The mean SampEn for different activities was compared between patients with low (<4), moderate (4-9), and high (>9) SPPB and between low (<8) and high (>7) CIT with a significance of $p \leq 0.05$.

Results

Moderate SPPB scores had more regularity (lower SampEn) in complete daily life acceleration signals and during stair-walking than the high SPPB group. In addition, the cognitive impaired group (i.e., high CIT) had more regularity (lower SampEn) than the healthy group during cycling and sitting activities.

Discussion and conclusions

More regular accelerations indicate the development of limited physical performance and deterioration of cognitive functions. The findings advocate that acceleration entropy in daily life activities is a promising proxy for physical and mental (biopsychological) functions. A large-scale longitudinal study is needed to examine the potential added value of daily acceleration for the early detection of biopsychosocial functioning.

Content

List of abbreviations

ADL	Activities of daily life
BPS	Biopsychosocial
AP	Anterior posterior
ApEn	Approximate entropy
CIT	Cognitive impairment test
CM	Centimeters
dB	Decibels
g	Gravity
Hz	Hertz
ICF	International classification of functioning, disability, and health
IQR	Interquartile range
KG	Kilograms
m	The embedded dimension
m/s^2	Meters per seconds^2
ML	Mediolateral
MSE	Multi-Scale Entropy
N	Number of data points
r	Tolerance
SampEn	Sample entropy
SD	Standard deviation
SPPB	Short physical performance battery
V	Vertical

List of symbols

μ	Mean
σ	Standard deviation
Δ	Delta; change in
∑	Summation
≠	Is not equal to
=	Is equal to
||	Distance between
X	Vector
Log	The logarithm

Introduction

Functional decline is described as a loss of independence in self-care activities or deterioration in self-care skills (i.e., movement and performance of activities of daily life (ADL)) [1]. Individuals with functional decline are more prone to adverse events in comparison with healthy individuals [2]. In combination with a decline in functioning, these adverse events can lead to reduced quality of life, frailty, and hospitalization [3]. Subsequently, individuals with functional decline have a high need for medical attention, leading to increased healthcare costs and increasing demands on the healthcare system [4]. Chronic conditions and related multi- or comorbidities have become increasingly prevalent globally. (Acute) exacerbations of chronic multimorbid conditions may cause deterioration in health, leading to more functional decline [2,3]. Hence, the functional status should be a priority in managing patients with multimorbidity [3]. The current healthcare system uses a linear approach, where symptoms lead to a diagnosis and treatment [5,6]. This approach does not highlight the functional status of the patient. Therefore, the linear approach is not appropriate to detect functional decline.

A shift towards a holistic and ambulatory approach is required for early detection of functional decline [5]. Early detection of patients at risk for functional decline can lead to early personalized care to avert functional decline. Therewith, early detection minimizes the risk for further deterioration of the patient's functional status, for example, by less accidents of falling, fractures, hospitalization, or institutionalization, and more years of independence at home. The biopsychosocial model (BPS) can assess the individual's functional status in a holistic approach. The BPS defines biological, physical, and social factors that play a role in functional decline [7]. However, the current assessments to measure BPS functioning in ambulant settings have some limitations [8]. Commonly used assessments are subjective measurements that require clinical interpretation and therefore introducing inter-rater variability [9]. Additionally, patient-reported outcome measures (PROMs) like diaries, questionnaires, and interviews are sensitive for socially desirable answers or bias due to cognitive impairment such as memory loss [10].

In the healthcare sector, accelerometers are upcoming to assess functioning. Literature supports the possibility to assess both physical and mental functioning using an accelerometer [11,12]. The sensor offers a quantitative alternative and minimizes the risk of self-reported input [13]. Accelerometers are commonly used to monitor characteristics that represent physical activity, such as gait speed, variation, and amount of physical activity [10, 14]. Besides the correlation between gait speed and physical activity, gait speed and cognitive functioning are also associated [15]. However, the used features obtained from accelerometers still have some limitations concerning generalizability, validity, and adaptability [16]. For example, the widely used characteristic gait speed methodologies and descriptions vary in each study. This variation makes it difficult to compare the results [17]. Besides, existing normative values or thresholds to differentiate between healthy and diseases often lack sensitivity [11,18]. Another major challenge is to process large files created by the acceleration sensor and to extract relevant information. Because of these issues, there is a need to develop a high-performance method to analyze raw acceleration signals, enabling caregivers to assess BPS functioning.

Entropy is an upcoming method to analyze raw acceleration signals [19]. Sample entropy (SampEn) is a measure of the regularity of a time series. Previous studies demonstrated that SampEn of daily life trunk accelerometry could discriminate between fallers and non-fallers [20]. In this study, fallers had less regularity in acceleration than healthy individuals. Functional decline is often associated with falls and the fear of falling [21]. Based on previous studies, SampEn of daily life trunk acceleration might be a sensitive biomarker for changes in biopsychosocial functioning since daily activities not only depend on physical components but also cognitive and behavioral components [10,22]. However, there are still inconsistencies between studies on how SampEn should be used and interpreted [19].

Objective

This study aimed to examine the association between sample entropy of daily life trunk accelerometry signals and clinimetrics that assess biopsychosocial functioning. The short physical performance battery and the cognitive impairment test were used as clinimetrics, representing biopsychosocial functioning. The secondary aim was to analyze the influence of different filter settings on the entropy outcome.

Outline

For the analyses of the association between sample entropy and BPS functioning, a proper inspection concerning the use of sample entropy is required. First, background knowledge obtained from the literature is outlined in the next chapter. This knowledge was necessary to answer the research questions, especially to select the correct settings for calculating the sample entropy. Each chapter starts with a short introduction concerning the relevance and the content. Thereafter, the method for the analysis is described, and the results, discussion, and conclusion are given. Additionally, supplementary files are added in the appendices.

Background

Biopsychosocial model

The following chapter will shortly describe the concept of the biopsychosocial model and its use in the healthcare system. The knowledge is necessary to underpin the importance of the study's primary aim and the healthcare system's needs.

Concept

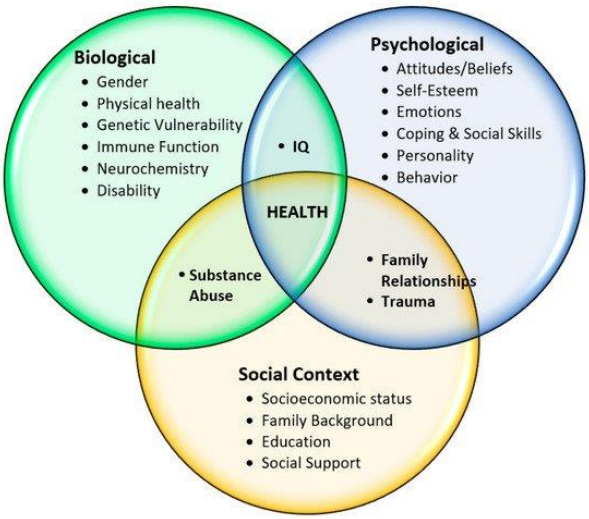

Figure 1 The biopsychosocial model. The model consists of a biological, social, and psychological component. Together this forms the health status of an individual [25].

In 1977 George Engel concluded that the biomedical approach, which focuses only on biological factors, did not consider the social, psychological, and behavioral dimensions of illness [23,24]. To overcome the incompleteness of the biomedical model, Engel introduced the biopsychosocial (BPS) model. This model represents a dynamic, interactional, and holistic view of human health [26]. The BPS model reflects the interaction between biological, social, and psychological aspects. Therefore, the model not only captures changes in health biologically but also on how thoughts, feelings, and the society around the patient influence the perception and determination of health. Essential to keep in mind is the interaction between the components of health. This interaction is a dynamic process, which means that the influences on health are not fixed but interact with each other over time [5]. Figure 1 shows an example of the BPS model and the content of the different components of health. In general, the biological component captures the physical elements of the body. The psychological component includes cognition, emotional status, motivation, attitudes, and the behavioral system. The social component describes the socioeconomic characteristics, environmental, and physical influences. [5,25]. Concluding, the model highlights the role and importance of personal, environmental, and contextual factors in an individual's life.

The current state of the BPS approach and issues that withhold implementation

The World Health Organization describes health as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmary [26]. Functional assessments based on the BPS model can give a broad and complete inside into an individual's health status. Therefore, it leads to specific care without loss of focus on medical problems [4]. The BPS model is increasingly becoming implemented in the healthcare system. Nevertheless, the urge is high to speed up the implementation process. [27,28,29]. Currently, there is little acknowledgment that illness and health-related problems are multi-factorial. Often, there is a categorization of health and non-health issues. However, this categorization is not always appropriate [25,26,30].

Some issues are withholding the implementation and daily use of the BPS approach [24]. Some say the model only gives a general description of the individual, which is inefficient, time-consuming, and not applicable for individual patients on a daily basis [5]. A comprehensive evaluation can be even more time-consuming [31]. Another problem is the applicability of the theory. The BPS approach is vaguely defined and not operationalized in behavioral terms for the patient [32]. Several authors describe the BPS just as a theory for the mind-body connection. The main issue is the fact that predictions concerning functioning and health are hard to make and test. There is no specified method to measure the BPS status of the individual patient [5,33]. Some assessments capture a part of the BPS functioning; however, there are no guidelines or recommendations on which measure is best to use [8]. All the disadvantages concerning the BPS model lead to one central question: how to efficiently quantify essential BPS data of an individual patient at a given point in time. A repeatable and valid method that consistently identifies relevant BPS information to define functioning is needed.

Accelerometers

Information concerning the measurement of daily life accelerometry is needed to examine the association between BPS functioning and accelerometry entropy. First, there is a description concerning the movement assessments currently used in the healthcare system and their (dis)advantages, including the limitations and issues that withhold the implementation of daily life accelerometer. The chapter ends with a short description of the mechanics behind the accelerometer sensor.

Daily life movement analysis

The performance of humans' daily life movement is dependent on the physical and cognitive components of functioning and environmental factors. Therefore, characteristics of daily life movement could be a biomarker for physical and cognitive functioning [34]. Gait analysis is the most commonly performed movement assessment. Gait analysis aims to observe, record, analyze and interpret motion patterns [36, 35] using biomechanical measurements of gait. Gait may be the most commonly analyzed activity, while gait is only one part of daily life movement. Focusing on only one aspect of daily movement may be insufficient to understand behavior and functional status. Examining both active and sedentary tasks provide a more complete inside into daily life movement [37].

Status of accelerometers

Movement analysis can be performed in different ways, as shown in figure 2. It can be done through self-reporting, observation by trained clinicians, with the use of motion capture systems and with (wearable) motion sensors [34,35,38]. These methods help to understand movement, improve performance, diagnose disorders, and evaluate treatment and interventions. Besides, associations between physical activity and (development) of medical conditions or even mortality have been proven based on these methods to analyze movement [39]. Nevertheless, some limitations arise performing movement assessments. A disadvantage of (visual) observation and motion capture systems is the need for laboratory measurements, which is expensive, and patients are only assessed infrequently under controlled situations [34,35,36]. In this way, the analysis does not reflect the regular daily activity pattern. Additionally, visual gait analysis depends on the experience of the observer [36].

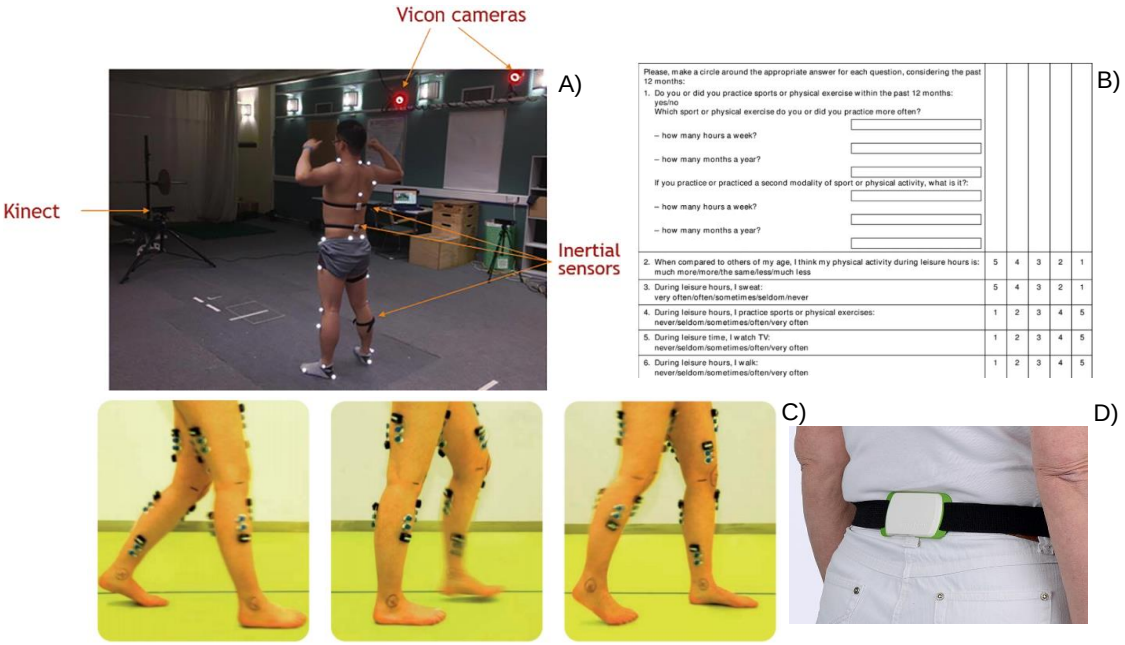

Figure 2 Different methods used for analysis of movement. A) Motion capture systems using inertial sensors that are recorded with cameras and a Kinect system [40], B) questionnaire, C) EMG sensors and visual observation [41], D) Accelerometers [42]

Accelerometers are upcoming in the current healthcare system. They are used to monitor and control diseases, but also for prevention and individualized therapeutic applications [43]
These sensors eliminate the need for individual self-report and, therefore, reduce bias caused by individual recall [13]. Additionally, a wearable sensor is under free-living conditions [44] instead of in laboratory measurements. Measurements during free-living conditions do not only detect gait but all activities during the day, like sedentary tasks and sleep, are measured. Besides, the sensors have low costs, low power consumption and are suitable to use in the daily environment due to the small size and weight of the sensors [42, 34]. However, daily life measurements result in collecting long-term multi-direction data recordings [43,45]. These recordings become large quickly and are sometimes clinically uninterpretable. It is challenging to process such large files and to extract relevant information. Although many algorithms are available to evaluate acceleration signals, there is still no standard method for doing so [13]. Previous research demonstrates the applicability of different algorithms. Nevertheless, there is still an amount of data that remains unprocessed. The unused data may contain relevant information for improving the current healthcare system [43].
There is a need to develop a high-performance method that can process and obtain all relevant information from raw acceleration signals, enabling caregivers to follow rehabilitation progress.

A tri-axial seismic acceleration sensor

Accelerometers measure the acceleration of the body [46]. Acceleration is the rate of change in velocity with respect to time [47]. A vector quantifies how fast the velocity is changing. Equation 1 shows the formula to calculate the acceleration.

A triaxial seismic accelerometer measures the rate of change in velocity in three directions: vertical (V), mediolateral (ML), and anterior posterior (AP). The V direction is the acceleration linear to the body's craniocaudal axis (figure 3). The ML direction is the acceleration linear to the left-right axis, and the AP direction is the acceleration linear to the anteroposterior axis (also dorsoventral). Medial means towards the midline of the body, and lateral is away from the midline. Anterior is on the stomach side and posterior on the backside.
A positive acceleration in V direction represents a movement towards cranial (upwards), in ML direction towards medial, and in AP direction, the movement is towards anterior (forward).

Equation 1 Formula for calculation the acceleration. The outcome approaches the acceleration based on the change in velocity over time [47].

$$a = \frac{\Delta a}{\Delta t} = \frac{(v_j - v_i)}{(t_j - t_i)}$$

Abbreviations: a=acceleration, t=time,v=velocity, Δ =change

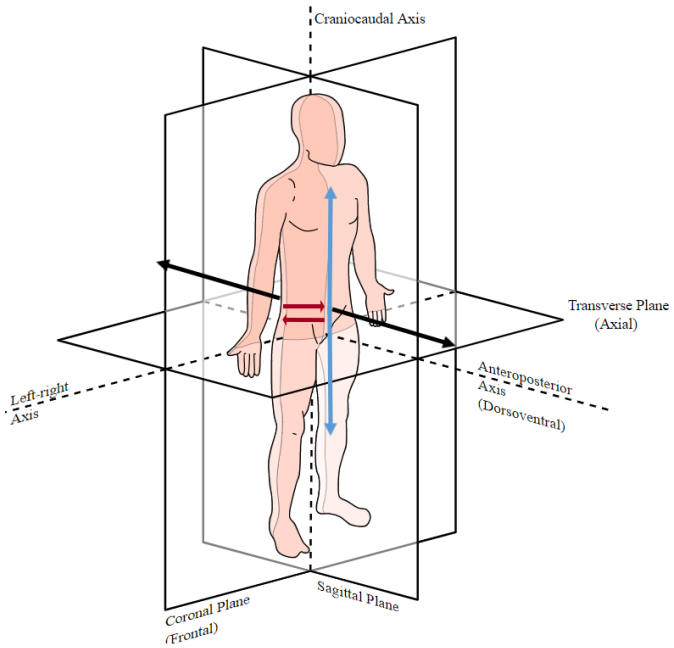

Figure 3 The human body with the anatomical planes and axis, including the three directions of a tri-axial acceleration sensor. Blue arrow: vertical acceleration. Red arrow: medio-lateral acceleration. Black arrow: anterior posterior acceleration [48].

Entropy

Entropy is a promising concept to overcome the limitations of long-term multi-direction data recordings. The next chapter will provide the theory behind entropy, which is needed to perform the analysis and interpret the results correctly. Additionally, the chapter describes the proper use and possibilities of entropy. The first three paragraphs also contain some technical concepts. Finally, the last paragraph discusses previous literature and the clinical relevance of using entropy in the healthcare sector.

Single scale entropy

Single-scale entropy quantifies the regularity of a time series. Regularity evaluates the appearance of (repetitive) patterns in a time series or signal [19]. In 1991 Pincus introduced approximate entropy (ApEn) as a mathematical tool for biological time series. An example of a biological time series is the output of an electrocardiogram that measures the heart's signals [50]. The ApEn value represents the amount of new information in the next state of the time series [49]. A value of 0 represents a system with no new information, and higher values indicate a higher amount of new information in the next state of the time series [50].

Thus, single-scale entropy represents the regularity of the time series. Where 0 indicates a total regular signal, like a sinusoid (figure 4A). The more irregular signal, the higher the entropy value. Noise (i.e., random signals) has a high entropy value, as shown in figure 4B. A signal representing a (semi)-regular pattern and some noise (figure 4C) will score a moderate entropy value lying between a sinusoid and noise. Signals in biological processes, like daily life movement, are most comparable with the example in figure 4C.

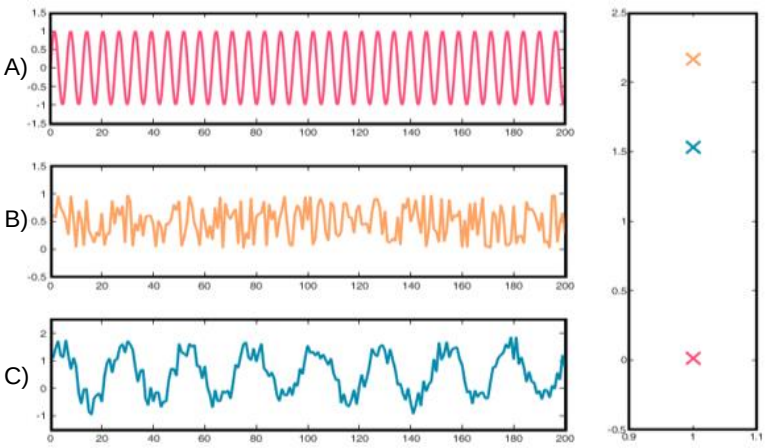

Figure 4 Three different time series with the corresponding entropy value [51]. A) A sinusoid, which represent a total regular signal. This signal has an entropy value of 0. B) Noise, which has a high entropy value C) A sinusoid combined with some noise, this signal has a moderate entropy value in between the values of A and B.

ApEn was the first developed single-scale entropy measure for biological signals. Unfortunately, ApEn is highly dependent on data length, and the algorithm includes self-matches for each vector. Self-matching leads to a lack of relative consistency and creates a bias towards a more probable outcome (a lower entropy value) [52, 53]. Because of these issues, Richman and Moorman introduced Sample entropy as an alternative. SampEn is supposed to eliminate the bias caused by self-matches [53]. The SampEn value is the negative logarithm of the conditional probability that two similar sequences of m points remain similar at the next point (m+1), leading to equation 2 [52]. Appendix A describes an example of the calculation.

Equation 2: Sample entropy. Abbreviations: m = embedding dimensions, r = tolerance radius, N = number of data points, ∑= summation, ≠ = is not equal to, || = distance between, x = vector [52].

$$SampEn\,(m,r,N) = -log\,\frac{\sum_{j=1}^{N-m}\sum_{j=1,j\neq i}^{N-m} matches}{\sum_{j=1}^{N-m}\sum_{j=1,j\neq i}^{N-m} Possibles}$$

$$Matches: number\ of\ times\ that\ d[|x_{m+1}(j) - x_{m+1}(i)|] < r]$$
$$Possibles: number\ of\ times\ that\ d[|x_m(j) - x_m(i)|] < r\ ]$$

Parameters settings

Entropy is a function of three parameters, the embedded dimension (m), the tolerance (r), and the number of samples (N). The embedded dimension (m) is the length of the vectors compared across the entire time series to determine the conditional probabilities (figure 5 A). The tolerance radius (r) is the threshold to determine whether patterns within the time series are similar (Figure 5 B). Lastly, the number of samples (N) is the length of the time series of interest (i.e., the number of data points the signal contains) [50,52].

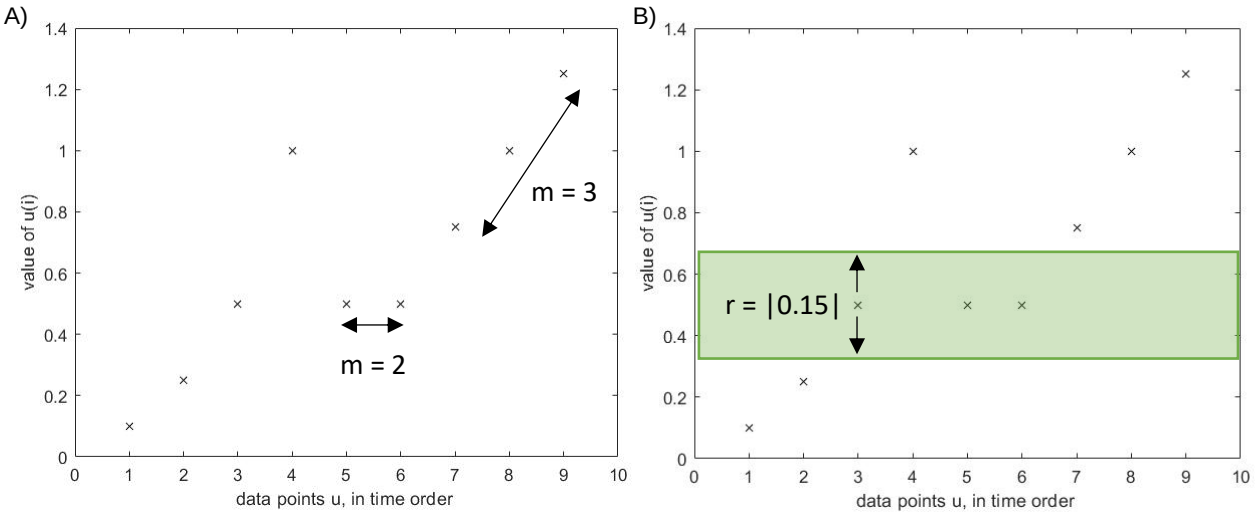

Figure 5 A time series of 9 data points (i.e., N = 9) is shown in the figure. A) the vector created by an embedded dimension of m = 2 and an embedded dimension of m = 3. B) example of the tolerance radius (r = 0.15). r is the maximum distance allowed for two points to be similar. All the points in the green plane have a distance smaller than 0.15 (< r) and thus are similar.
Abbreviations: u = the time series, i = index, A,B = vector , || = distance between, < = smaller than, > = greater than, = = equal to

The user needs to select the parameters for every calculation. However, the parameters should not be selected arbitrarily because improper values can lead to incorrect findings [19]. The embedded dimension (m) depends on the content of the signal and the research question. Most important is to think about the biological meaning. For example, the researcher should wonder if the duration of the vectors has clinical relevance. The parameter r has the highest impact on the results. Too small values will lead to only a few matches, while a high value could lead to too many matches and increase regularity wrongly [19]. Most entropy algorithms multiply the r with the standard deviation of the signal to reduce the influence of the amplitude [52,53].
The time series (N) length depends primarily on the signal of interest and the sampling rate. Theoretically, the outcome of sample entropy is not dependent on the length of N. Earlier research already showed valid results for ≥100 and ≤ 1000 [53]. Before choosing the value for N, one should check if the sampling rate is appropriate for the signal of interest [54]. There is a recommendation to rescale (downsampling) the data to an appropriate rate in case of oversampling. Oversampling leads to redundant data points (i.e., data points with less new information) and will increase regularity, see appendix B for more detailed information. If the data is under-sampled, the time series will not represent the signal of interest and would therefore be inappropriate to calculate the SampEn. When there is an appropriate sample rate, the N could be selected based on the research question.

Multi-Scale Entropy

Multi-Scale Entropy (MSE) is a concept to calculate the entropy of different time scales (from micro to macro). The idea behind MSE is that the complexity of biological systems arises from the interaction of components on multiple scales [19]. The MSE algorithm creates multiple new time series from the original time series (figure 6). The new rescaled time series is comparable to the downscaling. The SampEn of each newly created time series together represents the MSE.

Perform the following steps to calculate the MSE:

1. Derive multiple time series from the original time series by:
   - Divide the original time series into nonoverlapping windows of equal length.
   - Average these windows to create a new value
   - All the new values together represent the new rescaled time series. The rescaled time-series length is equal to the length of the original time series divided by the scale (figure 6 A).
2. Iterate these steps for all scales of interest.
3. Calculate the SampEn of each of the new scaled time series. Use the same input parameters m and r for all scales. An example of the MSE is given in figure 7. [55].

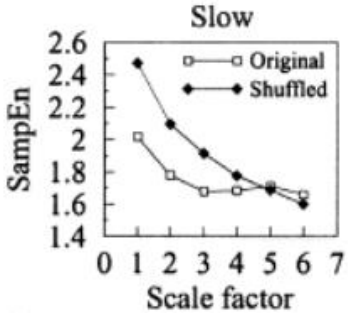

Figure 7 Representation of the MSE. For each scale (1-6) the SampEn is calculated [55].

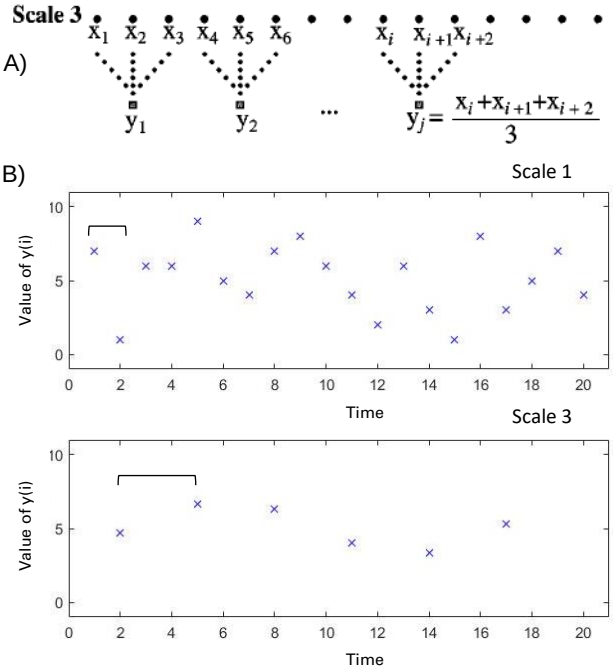

Figure 6 A) Example how to create the new time series for scale 3, by averaging the original time series. B) Two plots showing the data points of the original time series (upper plot) and the rescaled time series of scale 3 (lower plot). The braces represent the difference in time between two different time scales. Abbreviations: y = time series, i = index, j = length time-series / scale.

The entropy of daily movement

In 1998 the entropy was first used to analyze human gait, and entropy of daily movement signals has grown ever since. However, there is still no consensus concerning the expected outcome. Based on the individuality of the datasets and the parameter settings, it is hard to compare the results of different research groups. There is a possibility that it is not even valid to compare findings across papers [19].

Results of earlier performed studies concerning the association between entropy and age are an excellent example of the disagreement of the expected outcome. The results show that an increase in entropy is not specifically correlated with increased or decreased functioning. Older sedentary adults, for example, have a more regular walking pattern (lower entropy) compared to younger healthy adults [56]. On the other hand, older adults have a less regular (higher entropy) joint angle range of motion than younger healthy adults [57]. Another study noticed a U-shaped pattern in MSE outcome concerning entropy vs. age for all the time scales. They saw a decrease from childhood to early adulthood and an increase from early adult to middle-aged and older adults. Although, this was a statistically non-significant difference [58].

Research indicates that the entropy of movement analyses depends on multiple factors. When people were forced to walk at another speed than comfortable, the entropy changed. Walking slower or faster than preferred decreased the regularity (lower entropy) [59]. A decrease in regularity also occurred as one walked on a surface with less stiffness than a walking ground with high stiffness [60]. These factors can cause a higher entropy in healthy individuals, as they have a higher chance of performing activities outside the comfort zone than older sedentary elderly.
Furthermore, increasing task demands decreases the regularity of walking patterns in adults [19]. The latter means that the entropy is not only dependent on physical functioning but also on cognitive functioning. In addition, MSE analysis of postural instability can identify the elderly prone to falling [61]. In this way, early treatment can be offered to prevent falls. Finally, MSE can detect the small adjustment transitions from unbalanced to balanced [63]. All these findings together suggest entropy may detect changes in BPS functioning.

Filtering

There is not yet enough research done concerning the influence of filters on the entropy outcome. Filtering may remove fluctuations that are of biological importance. However, others implicated that filtering is warranted [19]. In general, it is essential to pay careful attention to the filtration process in movement analyses. Inappropriate filtering may produce bias or inaccurate results [13]. Therefore, this chapter will shortly describe the most common filters. The information is helpful to understand the question of our secondary aim. However, the information is not necessary to understand the main aim.

Content of signal

Different accelerometers have different sample frequencies and therefore contain different information. The sensor measures a signal of interest and usually contains some amount of noise. External vibrations, objects bouncing against the sensors, soft tissue under the accelerometers, and displacement of the sensor due to lose attachment, resulting in mechanical resonance, primarily causes noise [64]. Filters remove redundant information or noise from the raw signal [65]. Choosing the right filter depends on the content of the signal (i.e., frequency and amplitude) and the research question [19]. The frequency range of the human body's acceleration depends on the placement of the sensor. However, voluntary muscular work does not exceed a frequency of 15 Hertz (Hz); higher results do not directly result from voluntary muscle contraction [36,64]. The frequency range also depends on the performed activity. For instance, the frequency peak of tremors ranges within 4-10 Hz [67], and the postural balance control (involuntary muscle activity) ranges between 25 and 40 Hz [68]. Though, the most common frequencies of daily life range between 0.3 – 3.5 Hz [14].

Different filters

There are different types of filters. Commonly used are high-pass, low-pass, or band-pass filters (figure 8) [65]. A low-pass filter attenuates signals with frequencies higher than a prespecified cut-off frequency (figure 8A). All signals beneath the cut-off are passed through the filter. Most filters are not ideal, which means they have a transition band. As a result, the frequencies in the transition band are increasingly attenuated. A high-pass filter is the opposite of a low-pass filter (figure 8B). It passes the signal above the cut-off frequency and attenuates the signals beneath. A band-pass filter is the combination of a high and low-pass filter. Instead of one cut-off frequency, there are two (figure 8C). The filter passes all the signals within the two specified cut-off frequency range. Figure 9 shows a sinus with a low frequency, a high frequency, and the combined signal. Most articles performing gait analyses use a low-pass cut-off frequency of 20 Hz. This limit is set based on the range of voluntary muscle work. The low-pass filter passes through muscle activity with high and low frequencies. These studies are interested in the gait signal (i.e., pattern with a low frequency); however, the signal may contain a tremor with a high frequency (8-12 Hz). The combination of high and low-frequency activities is comparable with figure 9C. Combining different activities could be a problem for the calculation of the SampEn. Therefore, the cut-off frequencies should be considered carefully.

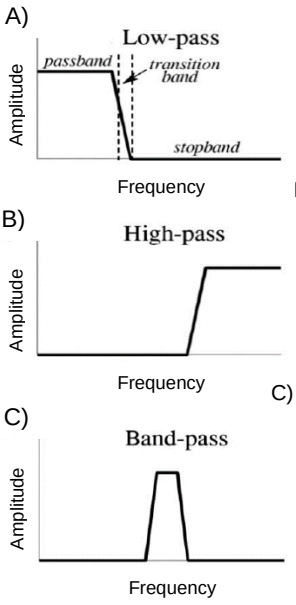

Figure 8 Three types of filters[65]. A)low pass, filter, B) high-pass filter, C) Band-pass filter

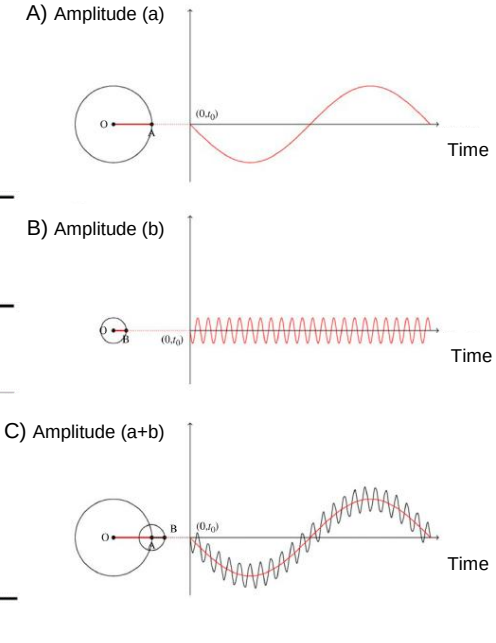

Figure 9 Two signals with different frequency [69]. A) sinus with low freqeuncy, B)sinus with high frequency, C) combined signal.

Methods and Materials

Participants

Data was provided from the HIPCARE cohort of 61 community-dwelling adults after femur fracture. People were eligible for the study if they were aged 70 years and older with a unilateral proximal femur fracture, admitted to HMC Bronovo hospital. Additionally, the patients need to be eligible for (geriatric) rehabilitation needed after hip surgery.

Assessments

Patient characteristics

Patient characteristics were collected during visits at the laboratory. Multiple questionnaires were conducted during baseline and follow-up (at 12 months). Global cognitive functioning was assessed with the 6-item cognitive impairment test (6-CIT) test and physiological functioning with the short physical performance battery (SPPB). In addition, physical activity was measured with a wearable motion sensor.

SPPB

The SPPB is an assessment that measures physical performance based on multiple aspects. It gives insight into walking speed, balance, and muscle strength. The assessment is a commonly used assessment for community-dwelling elderly to assess movement and as an indicator for health status. The SPPB assesses three different tests: a walking speed test, a balance test, and the repeated chair test. The sub-score from each test is 0,1,2 or 4 points, resulting in a maximum score of 12 points. The higher the score, the better the physiological performance of the patient (table 1) [70].

Table 1 Score system of the SPPB [70]

Score	Risk zone	Actions	Group
> 9	Not in the risk zone, healthy functioning	No actions needed	Healthy physical functioning
4-9	Increased risk to (new) disabilities	Indicated for treatment to improve functional status	Risk group
< 4	Already limited in functioning	Indicated for treatment to stop functional decline	Limited physical functioning

6-CIT test

The 6-CIT is a brief cognitive screening instrument used in primary care settings, which takes approximately 3 minutes and covers a couple of cognitive domains. It consists of 6 questions, where a total score of 28 points is the maximum. A score of 0-7 points indicates normal cognitive functioning, 8 or 9 points indicates cognitive impairment, and between 10-28 points, there is a significant cognitive impairment (table 2) [71].

Table 2 Score system of the 6-CIT [71]

Score	Risk zone
0 – 7	Normal functioning
8 – 9	Indicate cognitive impairment
10 – 28	Significant cognitive impairment

Movement assessment

Participants were asked to wear an ambulatory physical activity monitoring system for seven days. The measurement took place three months after hip surgery. The movement assessment was performed using the MoveMonitor (McRoberts B.V. The Hague, The Netherlands, see figure 10). The MoveMonitor is a back-worn sensor composed of a triaxial seismic accelerometer. The sensor is worn on the back of the trunk at belt height using an elastic band (figure 10 C). The triaxial accelerometer measures the rate of change in velocity in the directions: vertical (V), medio-lateral (ML), and anterior posterior (AP). The sensors had a sampling frequency of approximately 100 Hz and a range of 8g (i.e., 78,5 m/s^2). A secure flash memory card of 1 Gigabyte can save up to two weeks of continuous data acquisition [72].

The MoveMonitor has a pattern recognition algorithm that classifies several types of activity based on accelerometry. It can differentiate the activities: (stair)walking, standing, sitting, shuffling, cycling, and lying. It also calculates movement parameters such as duration, intensity, and frequency [72].

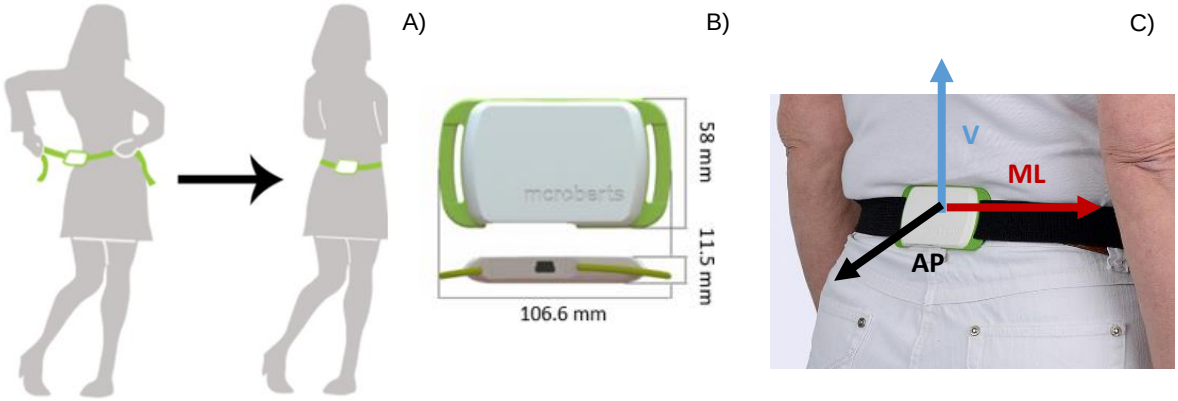

Figure 10 Movemonitor [72]. A) Placement of the sensor with the elastic band on the waist, B) the Movemonitor sensor with the corresponding dimensions, C) The sensor with the corresponding measurement directions.
Abbreviations: mm = millimeter, V = vertical, ML = mediolateral, AP = anterior posterior.

Preprocessing of the data

We decided to use two different filters to separate the high-frequency activities from the low-frequency activities. For an overview of all the preprocessing steps, see figure 11.
The Movemonitor measurements resulted in a file of raw acceleration signals for each patient. Each file consists of the signals in three directions (V, ML, and AP), the time, and the sample frequency. The first and last days were removed so that only full days were included in the analyses. For each file with raw acceleration signals, there is a corresponding file with the activity classification. In this way, the signal is into different activities (figure 12), which results in many short episodes of different activities between 0 – 60 seconds. See appendix D for a visualization of the distribution of episode lengths for each activity. The analysis is performed per activity and for the whole unclassified signal to obtain the SampEn (i.e., regularity) from the different daily life activities.

There is no consensus yet concerning the proper filter settings for calculating the entropy of daily activity [13,19]. Choosing the right filter depends on the content of the signal and the research question. To calculate the entropy, we aimed to separate the high-frequency accelerations from the low-frequency accelerations. A cut-off frequency of 6 Hz is chosen, based on the content of the signal (see appendix E for more information), and to separate the voluntary muscle control from the involuntary muscle control.

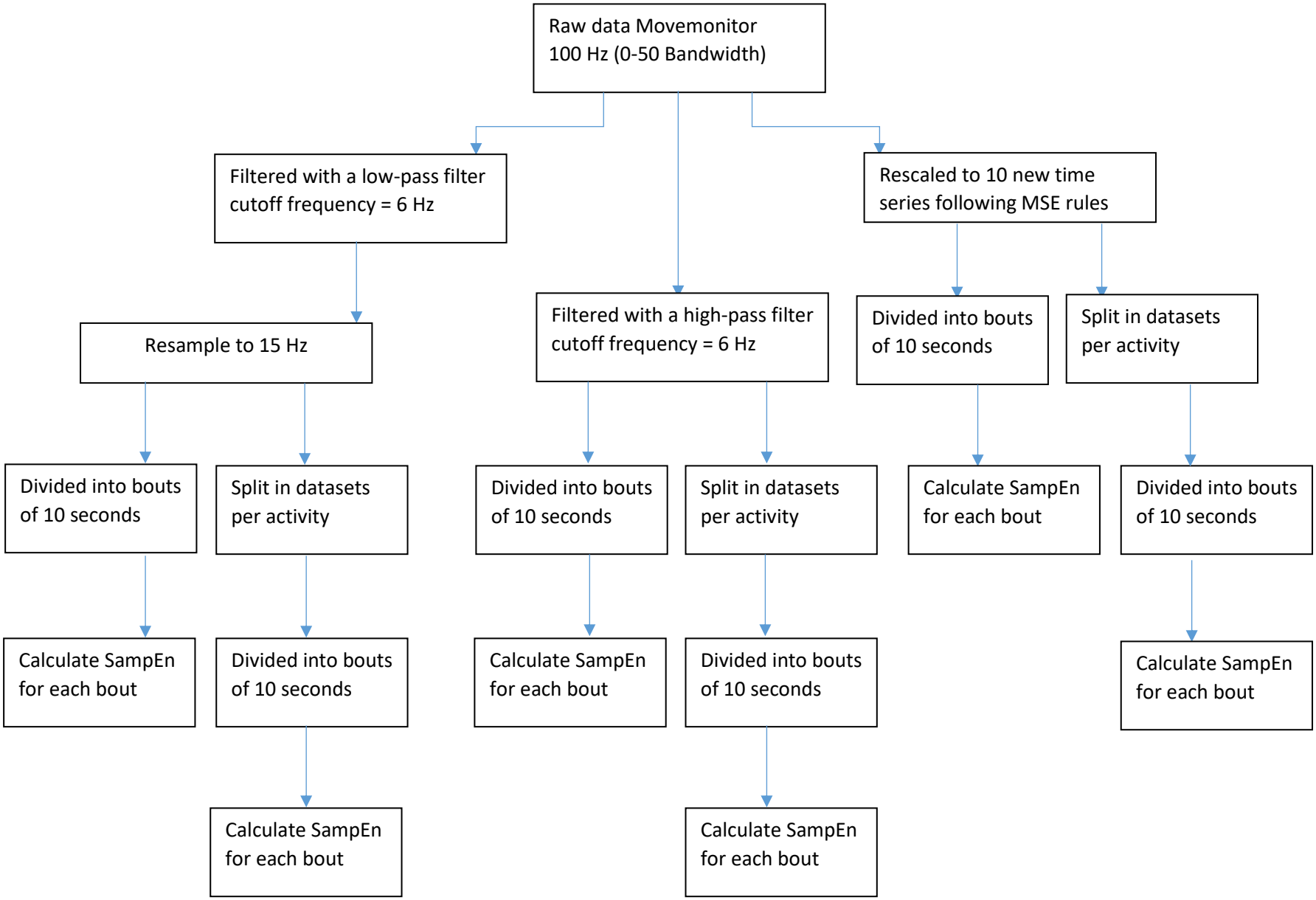

Figure 11 Overview of the steps to prepare the data. From raw data to calculation of the sample entropy. Hz = Hertz. SampEn = Sample entropy

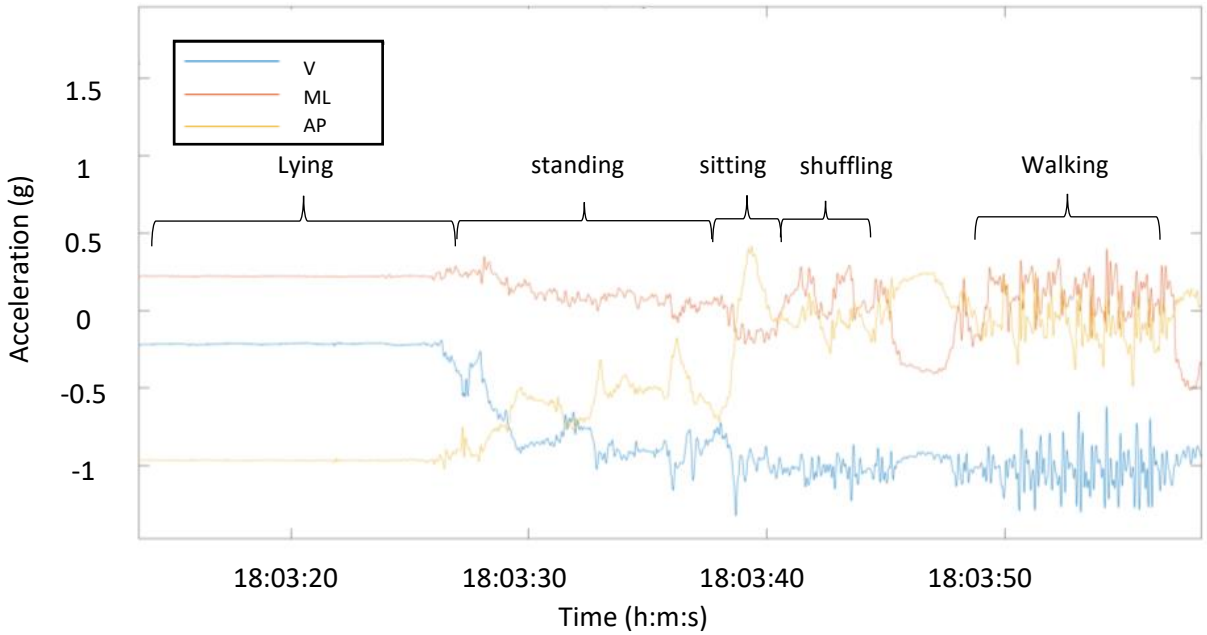

Figure 12 The raw signal in three directions of 40 seconds of functioning. The signal describes five different activities: lying, standing, sitting, shuffling, and walking. Abbreviations: v = vertical, ml = mediolateral, ap = anterior posterior, g = gravity (9.8 meter/seconds^2), h = hours, m = minutes, s= seconds.

A low-pass filter of 6 Hz was applied to capture the most relevant acceleration signals representing functional motions by voluntary muscle contraction. According to the Nyquist theorem, the sample frequency must be at least two times the highest frequency of the input signal [62]. Therefore, the data was resampled to 15 Hertz. Secondly, a high-pass filter of 6 Hertz was applied to obtain the high-frequency accelerations, mainly caused by involuntary muscle contraction. Compared with the raw signal, the low-pass filter has smoothed the signals (figure 13 B).
Additionally, the amplitude of the acceleration becomes smaller after the application of a low-pass filter. After applying the high-pass filter, the signal has a high intensity with lower amplitudes (figure 13 C). Besides the two filters, the signal was also rescaled based on the multi-scale theorem described in the background. No other filter was applied since the MSE acts like a filter because rescaling to a larger scale can be compared to low-pass filtering. The MSE resulted in ten rescaled time series with the range 1 to 19 in steps of 2, as shown in table 3.

Data analyses, Sample Entropy

The main aim of our study is to examine the association between accelerometry entropy and two different clinimetrics (SPPB and CIT). SampEn is used as the outcome measure for the single scale entropy values. SampEn was chosen above ApEn because previous literature has shown less bias in SampEn. Additionally, we calculated the MSE to investigate the entropy of different time scales.

Acquired data from the activity sensor is analyzed using MATLAB R2020A software package.
The SampEn is calculated with the use of a MATLAB toolbox called Sample Entropy. The SampEn algorithm computes the entropy according to the Richman and Moorman recommendations [51]. The MSE was also calculated with the use of a MATLAB package [73]

There are three input parameters needed to calculate the entropy.

- N: The number of data points wherefrom the entropy will be calculated.
- m: (the embedded dimension): The length of the segments compared with the rest of the dataset.
- r (Tolerance): Threshold for the allowed distance between segment and data points.

Parameters m, r, and N must be prespecified to compute the SampEn. In this research, the embedded dimension was 2. This value was chosen based on the theory described in the background. The embedded dimension is set to a minimum because the signal was already downsampled to remove redundant information

N was defined using the time bouts of 10 seconds and the sampling frequency of the measurement. A length of 10 seconds results in a range of N values. It leads to approximately 1000 data points for the high-pass signal and the low-pass signal to approximately 150 data points. This range is already proven to be valid [53]. The exact amount of data points differs for each calculation because of the variation in sample frequency. The tolerance was 0.3 based on earlier performed calculations of the SampEn with comparable data and a selection of data from this study [74]. Thus, the SampEn was calculated for each of the 10-second bouts. Finally, we took the median of all the bouts over the week to represent the gait regularity.

Table 3 Rescaled time series and the corresponding characteristics

Rescaled time series	Sample frequency of the signal	Data points / 10 seconds (N)	Time between data points (m)
Scale 1 (original)	100 Hz	1000	0.01 s
Scale 3	33 Hz	333	0.03 s
Scale 5	20 Hz	200	0.05 s
Scale 7	14 Hz	143	0.07 s
Scale 9	11 Hz	111	0.09 s
Scale 11	9 Hz	91	0.11 s
Scale 13	8 Hz	77	0.13 s
Scale 15	7 Hz	67	0.15 s
Scale 17	6 Hz	59	0.17 s
Scale 19	5 Hz	53	0.19 s

Abbreviations: N = length of the time series, m = embedded dimension

Table 3 Presenting the sample frequency, length of the time series for the SampEn calculation, and the duration of the embedded dimension (m) for all the MSE rescaled time series. For the calculation of the MSE, the N ranges from 1000 data points to 53 data points. The embed dimension is set to 2 (m = 2) for every calculation. The vector created by m will represent different lengths of time for each scale, shown in table 3 by the time between data points.

Statistics

Statistical analyses were performed in R studio and SPSS [75,76]. Descriptive characteristics were compared between the three groups (for both SPPB and CIT), using the t-test (for age, weight, height, BMI, and time spending the activity) and the Kruskal-Wallis test (for gender and FESI). The distribution of time spend for each activity differed between patients. The total time spent was divided into bouts of 10 seconds, leading to a different amount of 10-second bouts for each patient. The number of activities and bouts determined the number of calculations performed, affecting the SampEn outcome. Therefore, the time spending per activity was also compared between groups.

Pearson's correlation was used to investigate the correlation between entropy values and the SPPB or CIT score. The statistics were done for the entropy in V, ML, and AP directions. The correlation coefficient (r) indicates whether one variable increases as the other increases. The outcome ranges from -1 to 1, where 1 indicates a perfect positive linear correlation, -1 a perfect negative linear correlation, and 0 represents no correlation. Furthermore, a score between 0.1 and 0.3 is classified as small, 0.3 and 0.5 as moderate, and higher than 0.5 is a large correlation [77].
The SampEn of each scale from the MSE was compared between groups (for SPPB and CIT) using the t-test. In addition, the SampEn of each rescaled time series was plotted as a function of scale for visual insight.

The limit for the statistically significant difference was set to a p-value of 0.05. However, there were multiple tests performed in the research. Therefore, the Bonferroni method was used to counteract the problem of multiple comparisons. The SampEn value was calculated for the 7 different activities and the unclassified signal, which led to the following calculation: 0.05 / (7+1) = 0.006. Therefore, a p-value lower than 0.006 was considered as a statistically significant difference.

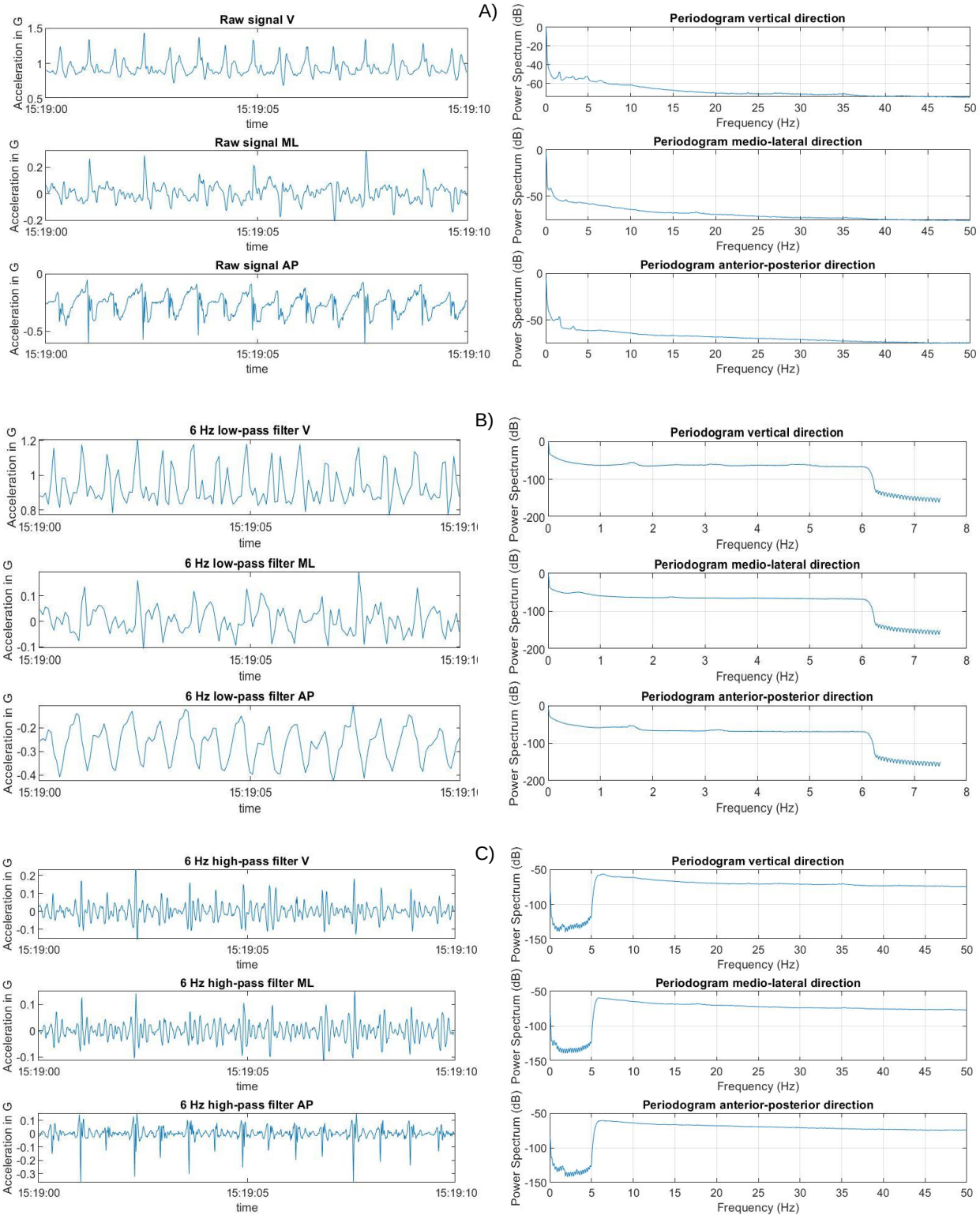

Figure 13 The left side of the figure represents 10 seconds signal during walking. The signal is given in the three different directions from the A) raw signal, B) signal after low-pass filtering, C) signal after high-pass filtering. On the right side, the corresponding periodogram is given.
Abbreviations g= gravity (9.8 meter/seconds^2), v = vertical, ml =mediolateral, ap =anterior-posterior, dB = decibels, Hz = Hertz

Results

Patient characteristics

In the HIP-care study, a total of 61 patients obtained the Movemonitor for a week. Among these patients, 10 were not included. Reasons for the exclusion were incomplete measurements (n = 8, 13%) and missing classification files (n =2, 3%). As a result, 51 (84%) patients were included in this study (figure 14).

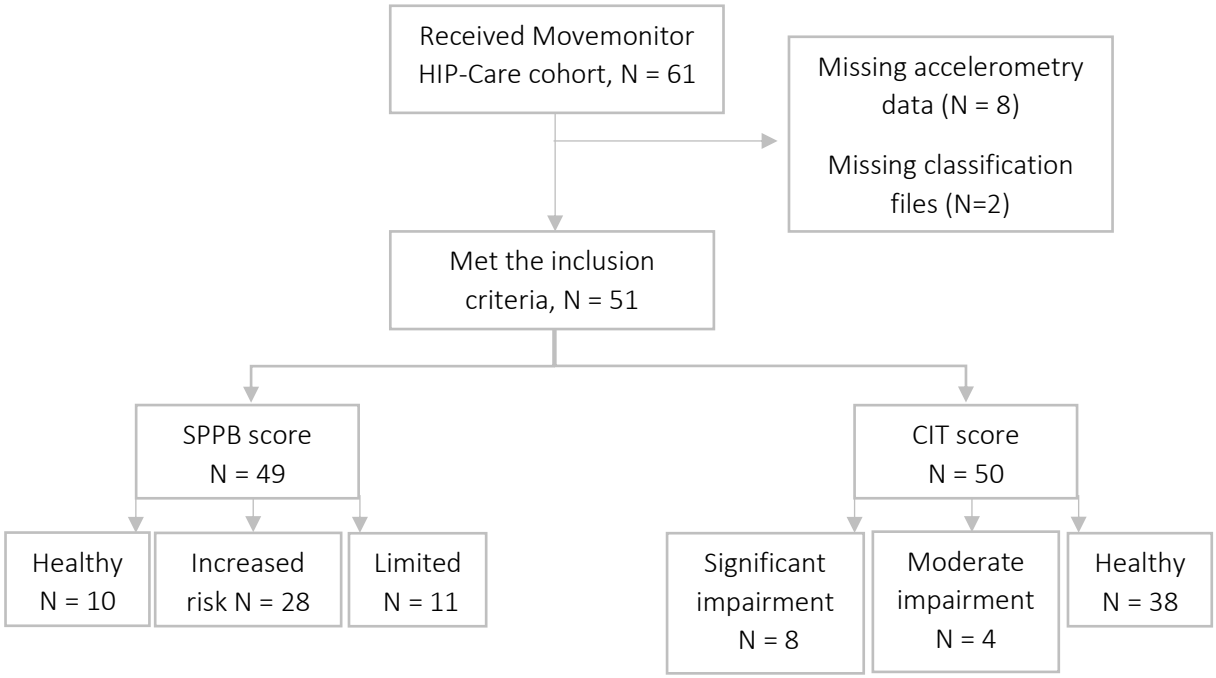

Figure 14 Flowchart patient inclusion.
Abbreviations: N = number of patients, SPPB = short physical performance battery, CIT = cognitive impairment test.

In table 4, a summary of the patient characteristics is shown. The population consisted of 36 women (71 %). The median (interquartile range) age was 81 (75 – 89) years with a mean (standard deviation) BMI of 24 (3.0). Not all patients wore the sensor the whole day. The amount of time the sensor was not worn and the time spend for each activity is also noted in table 3. Every patient performed the activities walking, shuffling, standing, sitting, and lying. A total of 36 (71.6%) patients walked the stairs, and 38 (75%) patients cycled during the week.

Besides the patient characteristics for the total sample, the characteristics are given for the subgroups. Following the SPPB score, ten patients were classified as healthy functioning (29 %), 28 patients have an increased risk of development of disability (55 %), and 11 patients were already limited in functioning (22%). For the CIT score, 38 patients were classified as healthy cognitive functioning (75%), four patients had a moderate cognitive impairment (7.8 %), and eight patients scored significant cognitive impairment (16%). Due to the small groups of significant and moderate cognitive impairment, we decided to merge these two groups to perform stratification based on the CIT score. There were no differences between the subgroups of the CIT and SPPB concerning patient characteristics.

Table 4 Descriptive characteristics of the total sample and for the subgroups for the SPPB and 6-CIT test

Descriptive characteristics	Total sample	SPPB healthy functioning	SPPB increased risk disability	SPPB limited functioning	CIT healthy functioning	CIT moderate cognitive impairment	CIT significant cognitive impairment
Number of participants	51	10 (19.6%)	28 (54.9%)	11 (21.6%)	38 (74.5 %)	4 (7.8%)	8 (15.7%)
Number of females (n, %)	36 (70.6 %)	6 (16.7 %)	20 (55.6 %)	9 (25 %)	29 (80.1 %)	3 (8,3%)	4 (11.1 %)
Age (years)	81 (75 – 89)	77 (74.3 – 82.3)	81 (75 – 89)	87 (78.8 – 91)	80 (75 – 87)	76.5 (63.5 – 85)	89 (79.5 – 91)
Body height (Cm; mean (SD))	166.1 (8.3)	169.3 (6.2)	165 (6.2)	165.8 (6.2)	165.4 (6.2)	170.5 (6.2)	167.9 (6.2)
Body weight (Kg; mean (SD))	66.9 (11.5)	71.5 (9.9)	63.8 (12.3)	69.9 (9.6)	65.9 (11.4)	68.5 (17.9)	72.1 (8.6)
BMI (Kg / m^2, mean (SD))	24.1 (3.0)	24.9 (2.8)	23.2 (2.6)	25.5 (3.5)	24.0 (2.9)	23.2 (3.9)	25.6 (3.3)
Time spent cycling (hours/week) [1]	0.1 (0 – 0.3)	0.2 (0 – 0.3)	0.1 (0 – 0.4)	0 (0 – 0.1)	0.1 (0 – 0.3)	0.1 (0.1 – 0.3)	0.2 (0.1 – 1.1)
Time spent stair walking (hours/week) [2]	0 (0 – 0.1)	0.1 (0 – 0.5)	0 (0 – 0.1)	0 (0 – 0)	0 (0 – 0.1)	0 (0 – 0.2)	0 (0 – 0)
Time spent walking (hours/week)	1.8 (0.7 – 3.5)	6.0 (2.0 – 10.7)	2.0 (0.8 – 3.4)	0.7 (0.3 – 1.0)	1.9 (0.8 – 3.6)	2.4 (0.8 – 5.3)	1.7 (0.7 – 3.2)
Time spent shuffling (hours/week)	1.3 (0.7 – 2.5)	1.5 (0.9 – 2.3)	2.1 (1.1 – 2.9)	0.9 (0.5 – 1.2)	1.3 (0.8 – 2.5)	2.9 (1.7 – 3.0)	1.2 (0.8 – 1.6)
time spent standing (hours/week)	12.1 (6.0 – 17.4)	13.1 (6.2 – 17.9)	14.2 (8.1 – 18.3)	5.7 (4.5 – 14.2)	11.1 (5.0 – 18.0)	11.8 (7.3 – 20.7)	13.1 (8.6 – 14.9)
time spent sitting (hours/week)	59.4 (34.6 – 72.8)	58.9 (37.5 – 72.1)	59.8 (35.1 – 69.3)	56.4 (23.9 – 75.8)	63.4 (36.9 – 75.0)	60.9 (37.0 – 66.7)	34.8 (22.9 – 55.9)
time spent lying (hours/week)	27.1 (8.9 – 70.7)	16.1 (7.4 – 24.0)	29.0 (9.4 – 73.7)	46.5 (20.9 – 74.8)	29.0 (9.1 – 70.2)	42.5 (7.1 – 75.1)	24.0 (10.2 – 44.5)
not worn (hours/week) [3]	65.5 (3.7 – 78.8)	66.9 (58.5 – 98.7)	65.5 (2.0 – 76.5)	70.1 (6.4 – 91.8)	64.2 (2.4 – 76.2)	68.8 (34.5 – 75.7)	88.5 (69.4 – 92.0)

Note: Values represent the median (IQR) unless noted otherwise.
Abbreviations: CM= centimeters, KG= kilograms, M= meters, IQR= interquartile range, SD= standard deviation. BMI calculated with the function= $BMI = weight/length^2$
SPPB= Short physical performance battery, CIT= cognitive impairment test
[1]: 38 patients have cycled, [2]: 36 patients walked the stairs, [3]: 51 patients did not wear the sensor for some amount of time

Entropy calculations

High-pass and Low-pass filtered signals

Table 5 presents the correlation between the SampEn and the SPPB score for the high-pass and low-pass filtered signals. The corresponding scatterplots are shown in appendix F. For the high-pass filtered signal, there is a large correlation between the SPPB and the SampEn in V and ML directions for stair walking. The correlation indicates that a lower SampEn value measured during stair walking is associated with a higher SPPB value, which means that more regularity correlates with fewer limitations in physical functioning. In addition, during sitting, a lower entropy in V direction (for both high- and low-pass signals) indicates more cognitive impairment.
Lastly, there is a high correlation between the SPPB and the SampEn in the V direction walking signals for the low pass filtered signal, meaning a lower entropy correlates with healthy physical functioning. The other activities had no correlations between SampEn and SPPB or CIT score.

Table 5 Correlation between the sample entropy and the SPPB and CIT scores for the high-pass filter signals

Activity	clinimetric	Sample Entropy Vertical ρ (p)		Mediolateral ρ (p)		Anterior posterior ρ (p)	
		High-pass	Low-pass	High-pass	Low-pass	High-pass	Low-pass
Cycling[1]	**CIT**	0.03 (0.87)	0.13 (0.46)	0.05 (0.77)	-0.02 (0.91)	0.11 (0.54)	0.20 (0.24)
	SPPB	-0.10 (0.54)	-0.03 (0.87)	0.03 (0.84)	0 (1)	-0.08 (0.64)	-0.04 (0.80)
Stair - Walking[2]	**CIT**	-0.09 (0.69)	0.27 (0.22)	-0.13 (0.58)	0.09 (0.78)	-0.21 (0.35)	0.06 (0.82)
	SPPB	**-0.60 (0.003)**	-0.11 (0.64)	**-0.58 (0.005)**	0.11 (0.62)	-0.43 (0.04)	0.23 (0.31)
Walking	**CIT**	0 (0.82)	0.02 (0.94)	0.05 (0.76)	0.21 (0.28)	0.06 (0.67)	0.04 (0.83)
	SPPB	-0.24 (0.11)	**-0.69 (0.00)**	-0.27 (0.06)	0.02 (0.91)	-0.43 (0.04)	-0.16 (0.42)
shuffling	**CIT**	-0.21 (0.17)	-0.03 (0.85)	-0.21 (0.17)	-0.17 (0.26)	-0.17 (0.26)	-0.06 (0.69)
	SPPB	-0.17 (0.27)	-0.03 (0.84)	-0.03 (0.87)	-0.25 (0.11)	-0.08 (0.61)	0.02 (0.91)
standing	**CIT**	-0.20 (0.17)	-0.24 (0.10)	-0.28 (0.06)	-0.12 (0.40)	-0.05 (0.73)	0.10 (0.51)
	SPPB	-0.05 (0.72)	-0.01 (0.95)	-0.12 (0.40)	-0.27 (0.06)	0.02 (0.91)	-0.11 (0.47)
Sitting	**CIT**	**-0.39 (0.006)**	**-0.39 (0.005)**	**-**0.33 (0.023)	-0.31 (0.03)	-0.33 (0.022)	-0.17 (0.24)
	SPPB	-0.06 (0.69)	-0.06 (0.70)	-0.06 (0.67)	-0.03 (0.85)	-0.13 (0.38)	-0.04 (0.81)
Lying	**CIT**	-0.28 (0.05)	-0.18 (0.23)	-0.23 (0.11)	-0.16 (0.27)	-0.28 (0.05)	-0.04 (0.81)
	SPPB	-0.11 (0.44)	-0.11 (0.44)	-0.12 (0.40)	-0.18 (0.23)	-0.16 (0.29)	-0.11 (0.44)
Unclassified	**CIT**	-0.21 (0.16)	-0.18 (0.23)	-0.15 (0.29)	0.03 (0.82)	-0.15 (0.31)	0.07 (0.66)
	SPPB	-0.20 (0.18)	0.12 (0.41)	-0.03 (0.86)	0.22 (0.14)	-0.11 (0.44)	0.15 (0.31)

Note: Bold values represent a statistically significant correlation after Bonferroni correction (p <0.006).
Abbreviations: CIT = cognitive impairment test; SPPB = short physical performance battery; ρ = Pearson's correlation coefficient, p = p-value, [1]: 38 patients have cycled, [2]: 36 patients walked the stairs

Multi-scale Entropy

The MSE profile, presenting the SampEn from the unclassified signal for each group of the SPPB, is visualized in figure 15. Visual inspection shows higher SampEn for healthy individuals on all the scales. However, except for scale 5, there were no statistically significant differences between healthy and limited functioning and non between the healthy and the risk group. The SampEn value from scale 5 (in ML direction) indicated that the group of patients that scored healthy functioning (μ =1.50, σ =0.09) have less regularity in their daily life movement than patients who were at risk for limited functioning or disabilities (μ =1.37, σ =0.18). The SampEn calculated from the unclassified signal showed no between healthy cognitive individuals and the patients with cognitive impairment (see Appendix H for detailed information).

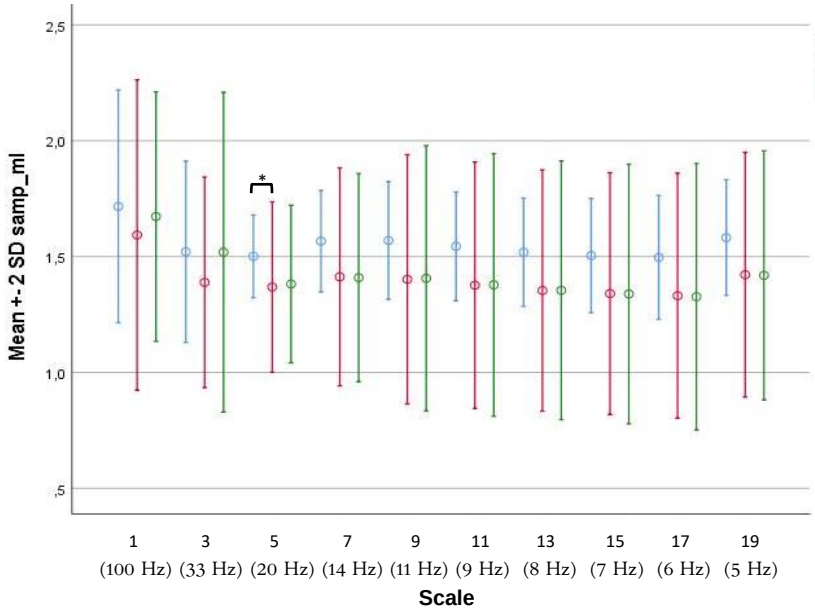

Figure 15 Multi-Scale Entropy profile *(μ +/- σ) representing the SampEn group means for the SPPB score for each time scale. The means are calculated from the unclassified signal (i.e., interval), in ML direction. The entropy is derived for the healthy subgroup (blue), the risk group (red) and the limited group (green). Abbreviations: SampEn = sample entropy, SPPB = short physical performance battery, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction. *p = 0.005*

In figure 16, the visualization of the MSE is shown for the activities walking and stair walking. For stair walking (figure 16 A), the mean SampEn for the healthy functioning group was higher than the risk group of the SPPB for all the time scales, except scale 1. There were differences in the AP direction and ML direction (See appendix G). These findings indicate that healthy individuals have less regularity in acceleration signals during stair walking than the risk group. During walking (Figure 16 B), the mean entropy for the at-risk group and limited patients was higher than the group mean for healthy individuals, which means that healthy individuals have more regularity in their acceleration during walking. Additionally, for the signals during lying and sitting (ML direction), more regularity in acceleration on one scale was associated with cognitive decline, see appendix H for more detailed information. The other activities showed no different group means for both SPPB and CIT scores, indicating no difference in regularity during these activities (i.e., cycling, standing, and shuffling) based on cognitive and physical functioning. The MSE profiles of all activities (of all acceleration directions) are presented in appendix G & appendix H.

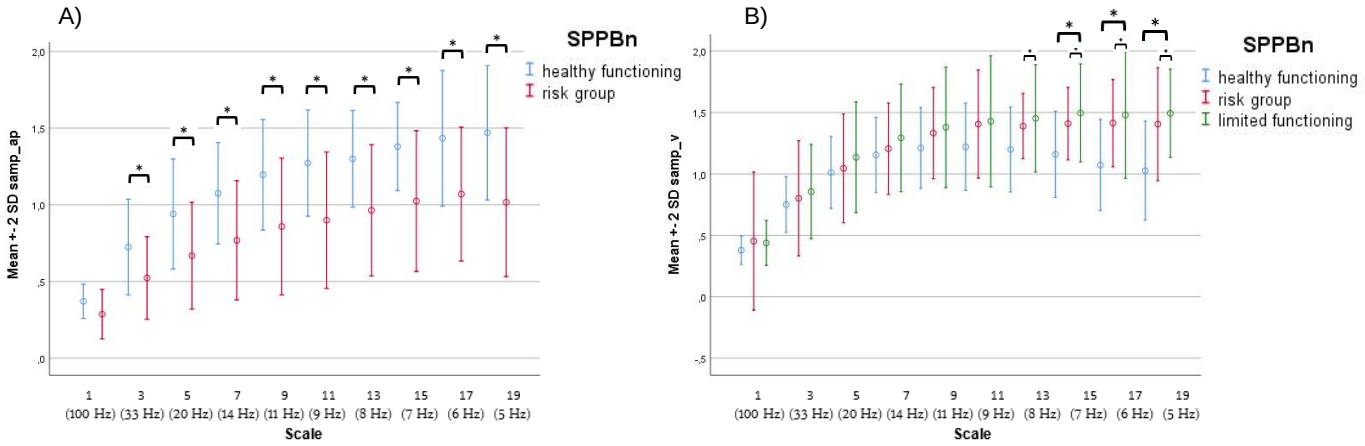

Figure 16 Multi-Scale Entropy *outcomes (μ +/- σ) represents the SampEn group means for the SPPB score. The means are calculated from the signals during A) stair walking (vertical direction), B) walking (anterior-posterior direction). Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*

Discussion

Take home message

This study aimed to examine the association between sample entropy of daily life trunk accelerometry signals and clinimetrics that assess biopsychosocial functioning. The results show that patients with moderate SPPB scores had more regularity (lower SampEn) in their complete daily life acceleration signal and during stair-walking than the high SPPB group. This indicates that patients at risk for developing limited physical performance have more regularity in their daily life movement than healthy physical functioning patients. In addition, the cognitive impaired group (i.e., high CIT) had more regularity (lower SampEn) than the healthy group during cycling and sitting activities. However, the difference was only seen on one time scale. The SampEn of healthy cognitive individuals was not different from the cognitive impaired group during other activities. Nevertheless, the findings suggest daily life acceleration entropy is a promising measure to identify and signal functional decline.
The secondary aim was to analyze the influence of different filter settings on the entropy outcome. There were no SampEn differences in the low and high-frequency domains concerning the correlation between the clinimetrics and the SampEn. However, the MSE showed opposite associations between SampEn and clinimetrics compared to the high- and low-pass filter. The contrary results advocate for an influence of the filter setting on the outcome of the SampEn. These findings underline the importance of the prespecified settings and the possibility that research with different filter/parameter settings cannot be compared with each other.

Comparison with previous literature

Our study is the first to our knowledge that calculated the regularity of all activities captured in daily life movement and associated the corresponding SampEn with physical and cognitive functioning. Thus, the study distinguishes itself from earlier performed research since the SampEn was calculated for daily life movement instead of merely walking activity. Additionally, different filter settings were applied to investigate the influence of prespecified settings

There were contrary findings in the MSE calculation between the SampEn during walking compared to the other activities. The activity walking showed less regularity in patients at risk for limited physical functioning and already limited patients than healthy individuals. The literature also describes this association. For example, higher fall risk is associated with less regularity in acceleration signals while walking [19,20]. So, looking at pure walking activities, the existing literature and our result indicate that healthy individuals' acceleration shows more regularity than physically impaired individuals. Thus, there are differences between the healthy population and the individuals at risk or already limited during walking. However, the SampEN of the other activities was only different between the healthy population and the individuals at risk for physical limitation. The other activities showed no differences between healthy and physically limited individuals. This could indicate a nonlinear correlation between the regularity of acceleration signals and the physical functional status of individuals. On the lower scale of the MSE, the comparison between the three groups of the SPPB resulted in a U-shape-like image (figure 15, scale 1-3). Although, there was no significant difference. Bisi and colleagues described the same U-shape difference between the MSE curve associated with age [58]. The U-shape-like results suggest linear correlation or regression analysis may not be appropriate to analyze the SampEn.

The use of entropy in medical research has grown over the last few years. Still, there are a lot of unsolved problems concerning the use of entropy measures [78,79]. For example, there is little knowledge concerning the selection of appropriate parameter settings [78]. In addition, the literature did not extensively describe the influence of filters on the entropy outcome [19]. Our results corroborate these challenges. The results from the high and low-pass filtered signals were comparable. However, the multi-scale method resulted in contrary findings. These contrary results highlight the significant influence of the chosen method and parameter settings to calculate the entropy. In this study, the kind of filter was not of influence on the outcome of the SampEn value. However, there is a difference between the MSE, which is the calculation of the unfiltered signal.

Therefore, we detected the influence of filtering on the entropy outcome. Unfortunately, based on our results, we cannot define if the filter removes fluctuations of biological or if it removes noise, which influences the entropy outcome. Further research should investigate the contribution of filters on the entropy outcome.

Interpretation in terms of mechanisms

The main findings show a higher SampEn (i.e., less regularity) for healthy physical functioning than physical deterioration. There is still an ongoing discussion about what causes a higher entropy in acceleration signals. Higher entropy in healthy individuals, compared to low entropy in physically limited patients, may be explained by the performed activities. Generally, physical deterioration is associated with sedentary behavior, and healthy individuals are more likely to have more variation in daily life activity. The SampEn measures the regularity of the acceleration. A logical explanation for less regularity is a considerable variation of activities. Performing activities in the woods, for example, leads to higher SampEn values because the ground is less stiff [60], and there are more external disturbances. Increased task demands are also known to be associated with higher entropy values [17]. Sedentary behavior can lead to fewer dual tasks during the day, which may lead to more regularity.

Besides, physically healthy individuals are more likely to perform daily activities at higher speeds than less healthy individuals. Slow movement causes more samples per performed activity, meaning more redundant data is included in the SampEn calculation. The redundant data points cause low entropy values. Thus, speed difference may be one of the elements explaining the difference between physically healthy and limited individuals. We tried to remove redundant data points using different filters. However, the same settings are used for healthy and limited individuals. Thus, the used filter settings did probably not remove redundant data points caused by speeds differences. The same theorems might explain the association between cognitive impairment and more regularity. Individuals who are cognitively impaired have less movement speed [80] and are likely to perform fewer high-intensity activities and fewer dual tasks.

Contrary results were noticed for the SampEn values of the gait signals. There was an association between higher SampEn values and physical limitations. These findings defy the arguments we just described. The control of the neuromuscular system could explain the decrease of regularity [81]. Neurophysiological deterioration leads to less control of the neuromuscular system and possibly leads to less control in muscle selection during gait. We think that less control could be an explanator of an increase in SampEn. Variation in daily life movement and highly complex activities or more dual tasks are likely to result in less regularity in healthy individuals. However, less stability (i.e., limited functioning) could lead to less regularity during gait. Nevertheless, it may be too early to make these conclusions. Further research should investigate the pathophysiological mechanism behind SampEn changes.

Strengths and weaknesses

One of the strengths of our research is the chosen study population. The research question is focused on community-dwelling older individuals and functional decline. Patients after hip fracture are at high risk for (further) functional decline. The included population consists of healthy physical individuals, persons at risk for decline, and already limited patients. Therefore, it was possible to investigate the possibility of using the SampEn as a biomarker for at-risk patients. We noticed differences between the healthy individuals and the individuals at risk for decline and not between healthy and limited individuals. So based on our study population, the SampEn is a possible indicator for the at-risk population.

Contrary to most studies, our study's measurement is based on daily life trunk acceleration signals. So, the results are representing the everyday life of the individual. This assessment offers the opportunity to measure the functional status of a person ambulatory in a non-time-consuming manner. Therefore, this assessment is accessible to implement in daily practice. Additionally, the algorithm used to analyze the daily life activities separately is already validated in different research settings [14].

Some limitations should be considered. First, the patient population was less representative for cognitive impairment. The moderate cognitive impaired group only consisted of 4 patients and the significant impairment group of 8. Therefore, the two subgroups were merged, leading to a group of 12 patients that showed cognitive impairment. Due to this merge, it was not possible to associated patients at risk (i.e., moderate cognitive decline) for a decline in mental functioning. Secondly, there were lower than specified sample sizes of 45 per group, leading to potentially underpowered conclusions'. Therefore, there is a possibility that larger group sizes lead to more entropy differences between groups.

Lastly, the calculation of SampEn excluded all the activity periods less than 10 seconds. This method led to the exclusion of most activity periods during (stair)walking, shuffling, and standing. The periods of these activities generally took less than 10 seconds. The accuracy of the classification algorithm could be a part of this. The sensitivity of the Mc Roberts classification algorithm is 93.5 %, and the specificity is 71.8 % [14]. A sensitivity of 93.5% may have led to wrongly classified signals. For example, very short periods (< 1 second) of standing and shuffling interrupt the walking episodes. Whether this should have been considered as walking is debatable [82]. We decided to exclude these data to avoid misleading results. Despite the limitations, we believe the potential errors are not the explanation of our findings.

Clinical relevance

Signals obtained from daily-life acceleration may help to improve the identification and treatment of functional decline. The SampEn difference between healthy and limited physical patients indicates the possibility to detect individuals at risk for physical functioning. Therefore, acceleration entropy is a possible biomarker for the early detection of functional decline. If the measurement is successful, implementation could lead to early personalized care to minimize the individual's functional status deterioration. Less deterioration of the functional status will lead to less accidents and less hospitalization, leading to decreased demand on the healthcare system and less healthcare costs. Additionally, SampEn is a high-performance algorithm that analyses raw acceleration signals without being time-consuming for both patient and caregiver. Additionally, the SampEn is a user-friendly method that enables caregivers to follow their patients' functional status or rehabilitation progress.

Further research is necessary before the acceleration entropy is eligible for implementation into the healthcare system. First, our study only included patients after hip surgery. The patient characteristics (i.e., hip fracture and the mean age of the population) imply the population is already (at risk) for limited functioning. Comparison with healthy and younger individuals is desirable to validate the possibility of detecting at-risk patients. The inclusion of healthy individuals is also necessary to investigate normative entropy values. However, it is unknown if there is a possibility of setting these limits due to the limited possibilities to compare different studies and the unknown mechanism behind the changes in regularity. It may not be possible to set normative entropy values. Nevertheless, we aim to use entropy to detect changes in the functional status of an individual. Longitudinal data are needed to measure the sensitivity and possibility of detecting intra-individual decline of functioning.
It is recommended to describe the used parameter and filter settings carefully to make sure further research can be compared with each other. We compared only two different filter settings, and there was no difference between them. However, we saw the difference between the SampEn outcome of the filtered signals compared to the unfiltered signal. Further research is needed to investigate the contribution of filters on the entropy outcome. It should be defined if the removement of biologically significant fluctuation or the movement of noise causes these differences in SampEn outcome,

Conclusion

More regular accelerations indicate the development of limited physical performance and deterioration of cognitive functions. The findings advocate that acceleration entropy in daily life activities is a promising proxy for physical and mental (biopsychological) functions. A large-scale longitudinal study is needed to examine the potential added value of daily acceleration for the early detection of biopsychosocial functioning.

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Appendices

Appendix A: Example Calculation of the Sample Entropy

In figure 17, a time series with N = 21 is shown. The following steps describe how to calculate the SampEn.

1. For the calculation of the SampEn value, some must select a window size for the vectors. In this case, the window will be 2 (m = 2). The same applies to the selection of the radius tolerance. In this case we select 0.15 (r = 0.15)
2. The signal is "divided" into vectors with length m. Each vector will be compared with all the other vectors within the time series, except for itself. Thus x(1) with x(2), x(3),...,x(N). and so forth.
   Two vectors are considered possible (i.e., similar) if the comparison between elements is within the tolerance window r. This step is repeated for length m+1 to check for a match.
   a. Comparison from vector x(1) with x(2)
      The first vector is x(1) = [u(1) u(2)] = [-0.5, -0.4]
      The second vector is x(2) = [u(2) u(3)] = [-0.4, -0.3]
      Are these vectors a possible? => $d[|x_m(j) - x_m(i)|] < r$]
      => |[u(1) – u(2)]| = |[-0.5 – 0.4]| = |0.1| < 0.15 => Thus it is possible
      => |[u(2) – u(3)]| = |[-0.4 – 0.3]| = |0.1| < 0.15 => Thus it is possible
      Are these vectors a match => $d[|x_{m+1}(j) - x_{m+1}(i)|] < r$]
      => |[u(1) – u(2)]| = |[-0.5 – - 0.4]| = |0.1| < 0.15 => Thus it is possible
      => |[u(2) – u(3)]| = |[-0.4 – -0.3]| = |0.1| < 0.15 => Thus it is possible
      => |[u(3) – u(4)]| = |[-0.3 – -0.2]| = |0.1| < 0.15 => Thus it is Match

   b. Comparison from vector x(9) with x(12)
      The first vector is x(9) = [u(9) u(10)] = [0.3, 0.4]
      The second vector is x(12) = [u(12) u(13)] = [0.4, 0.3]
      Are these vectors a possible? => $d[|x_m(j) - x_m(i)|] < r$]
      => |[u(9) – u(12)]| = |[0.3 – 0.4]| = |-0.1| < 0.15 => Thus it is possible
      => |[u(10) – u(13)]| = |[0.4 – 0.3]| = |0.1| < 0.15 => Thus it is possible
      Are these vectors a match => $d[|x_{m+1}(j) - x_{m+1}(i)|] < r$]
      => |[u(9) – u(12)]| = |[0.3 – 0.4]| = |-0.1| < 0.15 => Thus it is possible
      => |[u(10) – u(13)]| = |[0.4 – 0.3]| = |0.1| < 0.15 => Thus it is possible
      => |[u(11) – u(14)]| = |[0.5 – 0.2]| = |0.3| > 0.15 => Thus it is no Match
3. The total amount of matches and possibles are filled into the equation from paragraph 3.2.1 and the entropy is calculated.

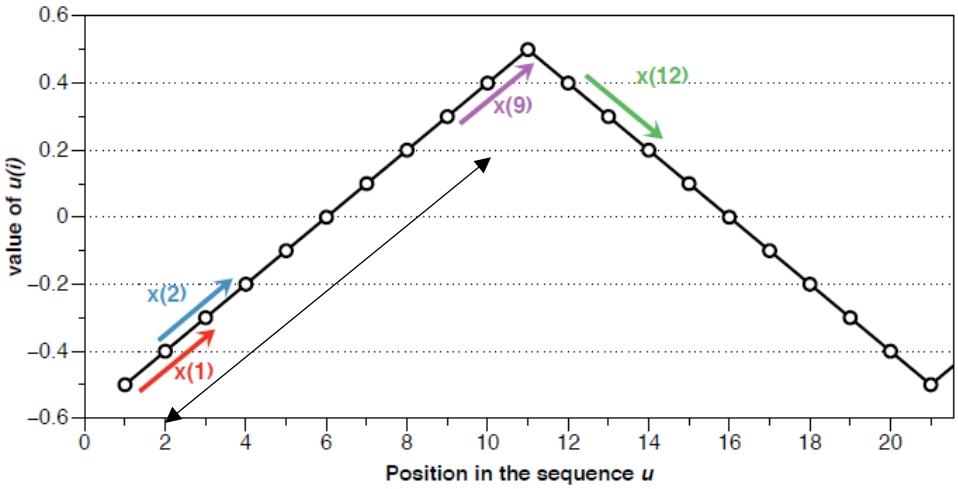
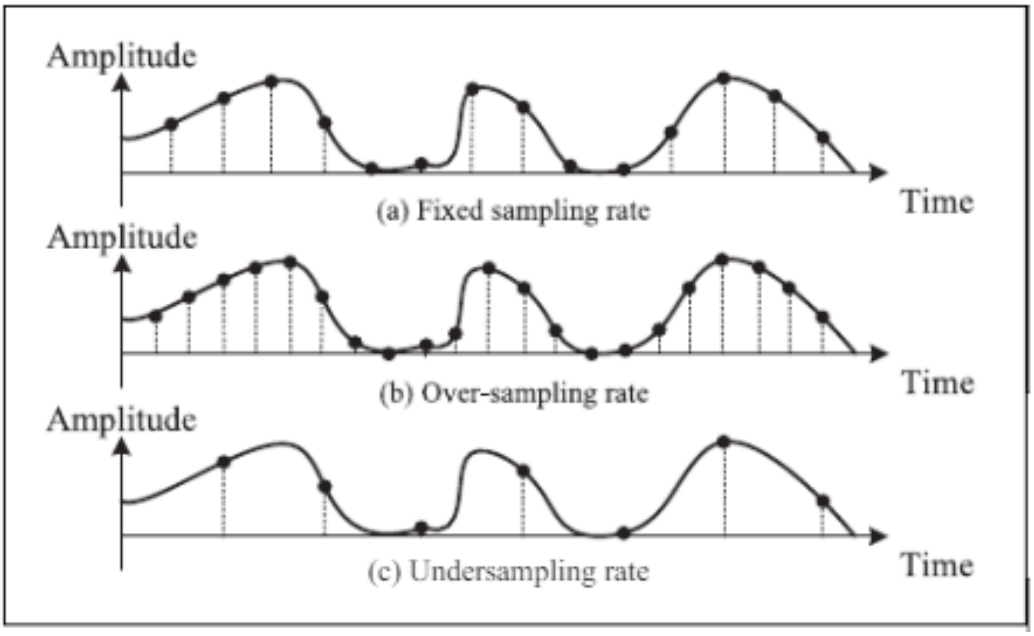


Figure 17 Example of a time series [46]. Abbreviations: u = the timeseries, x = vector

Appendix B: Sampling rate time series

Figure 18 presents a signal (black line) with some data points (dots). These data points are measured using a fixed sampling rate. These data points are eligible to recreate a matching line when the signal is unknown. A higher sample frequency (figure B) will add more unnecessary data points to represent the signal. A lower sample frequency will lead to fewer data points (figure C). With these few data points, it is almost impossible to recreate the original signal [bron afbeelding]. Thus, when oversampling occurs, there will be redundant data points. The redundant data points will lower the entropy value (i.e., less new information) [17]. Therefore, there is a recommendation to rescale (downsampling) the data to an appropriate rate in case of oversampling. If the data is under-sampled, the time series will not represent the signal of interest and would therefore be inappropriate to calculate the SampEn. When there is an appropriate sample rate, the N could be selected based on the research question.



18 Signal with corresponding data points, measured by:
A) Fixed and appropriate sampling rate, B) Higher sample frequency, causing oversampling, C) To low sample frequency, causing under sampling [Spatiotemporal correlation–based adaptive sampling algorithm for clustered wireless sensor networks]

Appendix C: Preparation of the data

As mentioned in the methods, the MoveMonitor has a pattern recognition algorithm that classifies several types of activity based on linear acceleration. It can differentiate the activities: walking, stair-walking, standing, sitting, shuffling, cycling, and lying. It also calculates movement parameters such as duration, intensity, and frequency.
Patterns of transitions between activities are used to differentiate between upward and downward actions. Upward transitions are detected at the beginning of a standing phase and downward transitions at the beginning of a sitting or lying phase (figure 19).
The algorithm uses angle calculation based on sensor tilt to determine whether the activity is lying (angle <30) or sitting.
Gait period detection is based on an intensity threshold. The periods are scanned using frequency and already validated step detection methods [ ]. The number of steps, intensity, and direction of the motion defines if the patient is walking or shuffling

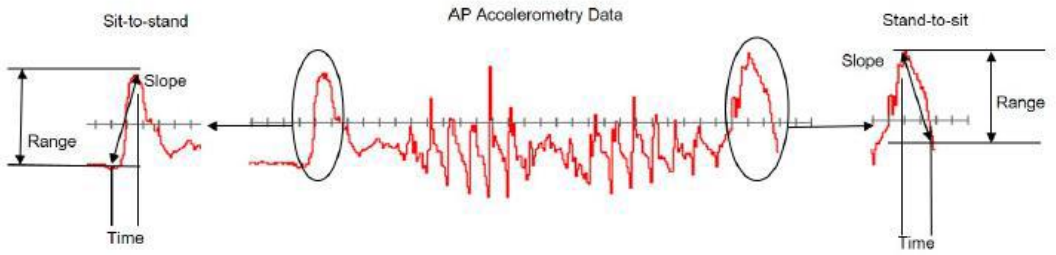


Figure 19 Pattern recognition of transitions

With the use of this classification, the raw signal is divided into different activities. The classification of activities is available in a separate file for each patient. For this analysis, the entropy is calculated from periods of 10 seconds. First, the activities < 10 seconds are removed from the file. Next, all the episodes are sorted per activity. The activity episodes were divided into bouts of 10 seconds. For each of these bouts, the entropy was calculated (figure 20). This distribution was done so that the input for the entropy calculations is the same size.

	1 Activity	2 Duration
1	'sitting'	16.0450
2	'walking'	17.5300
3	'walking'	20.2300
4	'sitting'	39.7700
5	'sitting'	60.0000
6	'sitting'	60.0000
7	'sitting'	36.0300
8	'walking'	17.2650
9	'standing'	1.9450
10	'sitting'	4.7600
11	'sitting'	60.0000
12	'sitting'	16.6500
13	'standing'	0.6550
14	'walking'	42.6950
15	'walking'	58.3800
16	'standing'	1.2400
17	'walking'	0.3800
18	'walking'	12.9900
19	'sitting'	1.0950

	1 Activity	2 Duration
1	'sitting'	16.0450
2	'walking'	17.5300
3	'walking'	20.2300
4	'sitting'	39.7700
5	'sitting'	60.0000
6	'sitting'	60.0000
7	'sitting'	36.0300
8	'walking'	17.2650
9	'sitting'	60.0000
10	'sitting'	16.6500
11	'walking'	42.6950
12	'walking'	58.3800
13	'walking'	12.9900

	1 Activity	2 Duration	
1	'walking'	17.5300	10 seconds
2	'walking'	20.2300	2x 10 seconds
3	'walking'	17.2650	10 seconds
4	'walking'	42.6950	4x 10 seconds
5	'walking'	58.3800	5x 10 seconds
6	'walking'	12.9900	10 seconds

Figure 20 Distribution of the activity classification. First, activities less than 10 seconds are filtered out. Secondly, the activity periods are divided into separate files for each activity. Finally, the activity periods are divided into bouts of 10 seconds.

Appendix D: distribution of episodes duration per activity

The classification files list all the activities performed by the patient during the week, resulting in short periods representing one activity, from 0-60 seconds. The length of all these periods for all the included patients is shown in figure 21. Most sitting and lying, and cycling episodes lasted 60 seconds. The majority of the (stair)walking, standing, and shuffling episodes took less than 15 seconds.

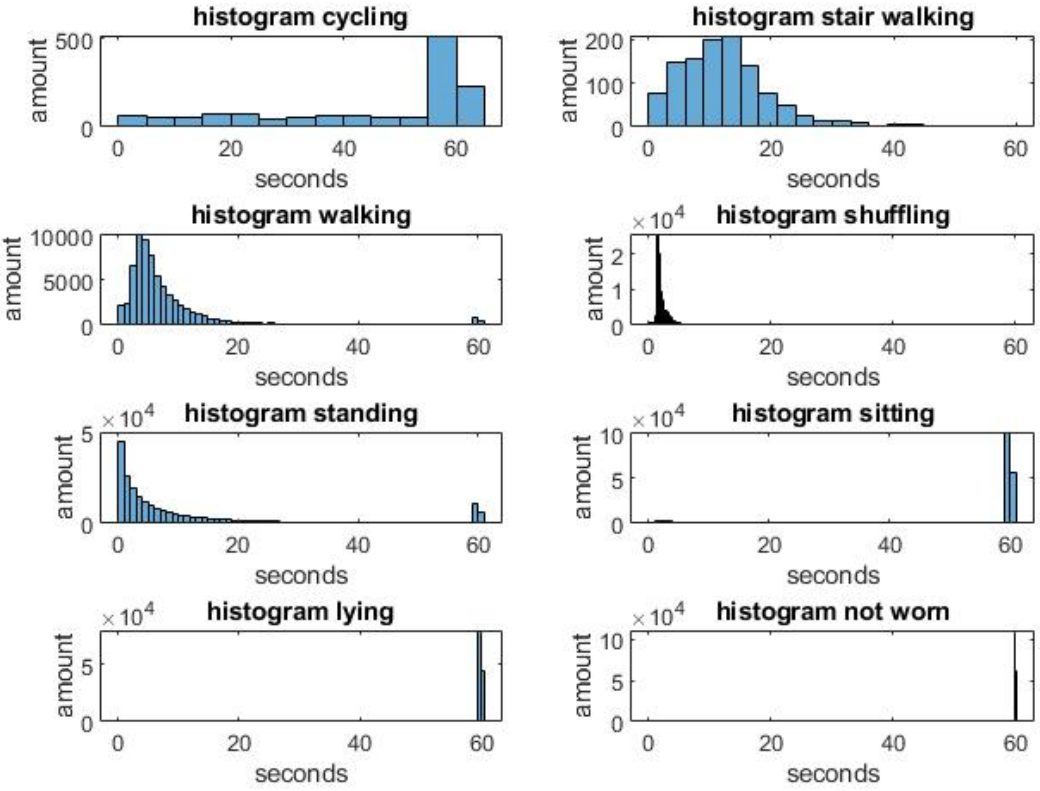


Figure 21 Histograms of all the episodes duration per activity

Appendix E: Visualization of the raw acceleration signal

The content of the raw signal is decisive for the selection of the parameter settings of the SampEn calculation and the selection of the most appropriate filter. An example of the week measurement of one patient is given in figure 22. The corresponding periodograms is shown in figure 23. The periodogram showed that most signals were in the low-frequency spectrum, and there is a downwards trend towards higher frequencies. For the V direction, the last frequency peak is at approximately 6 Hz. Beyond 6 Hz, there is a downwards trend in the occurrence of the frequencies. The highest observed frequency is 50 Hz, because of a low-pass filter of 50 hertz.

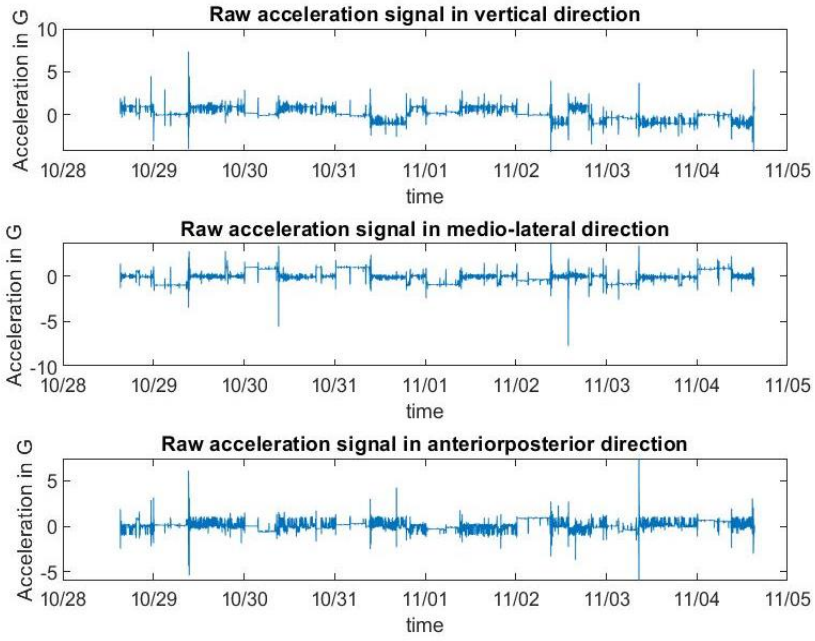


Figure 22 Example of the whole measurement. The raw acceleration signals are shown for the three different directions. The x-axis represents the time (days), and the y-axis gives the amount of acceleration (g). G: gravity (9.8 meter/seconds²)

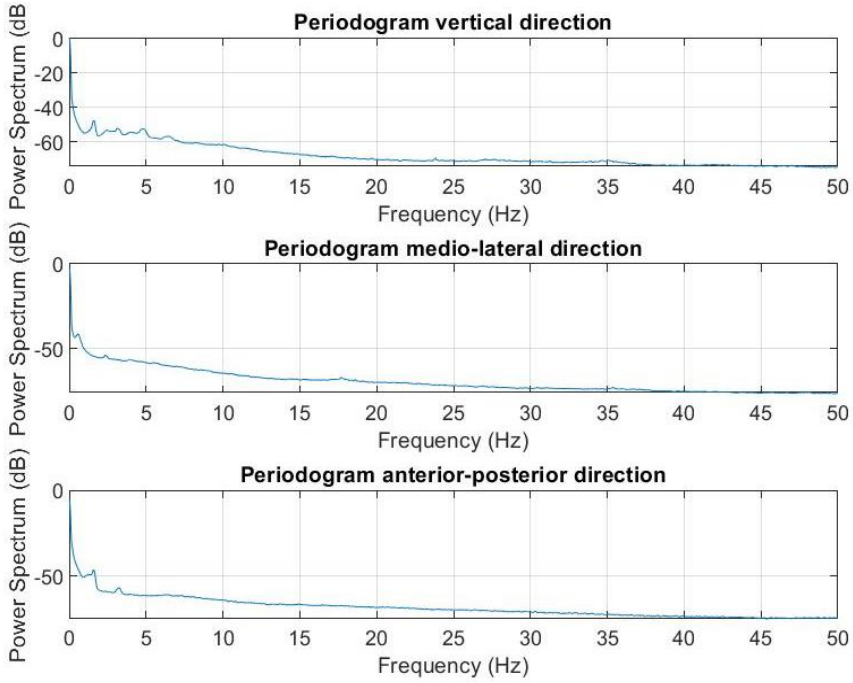


Figure 23 Example of the periodogram. The figure represents the distribution of the measured frequencies during the whole week. dB: decibels, Hz: Hertz

Appendix F: Scatterplots sample entropy vs. clinimetrics, High-pass filter

This appendix shows the relation between the sample entropy values and the SPPB or CIT score, using scatterplots. The scatterplots were made for all the different activities and the unclassified signal. The y-axis describes the SampEn (from the signal in V, ML, and AP direction) derived from the high-pass filtered signals, and the x-axis represents the SPPB or CIT score.

Scatterplot signals during walking: SampEn vs SPPB / CIT

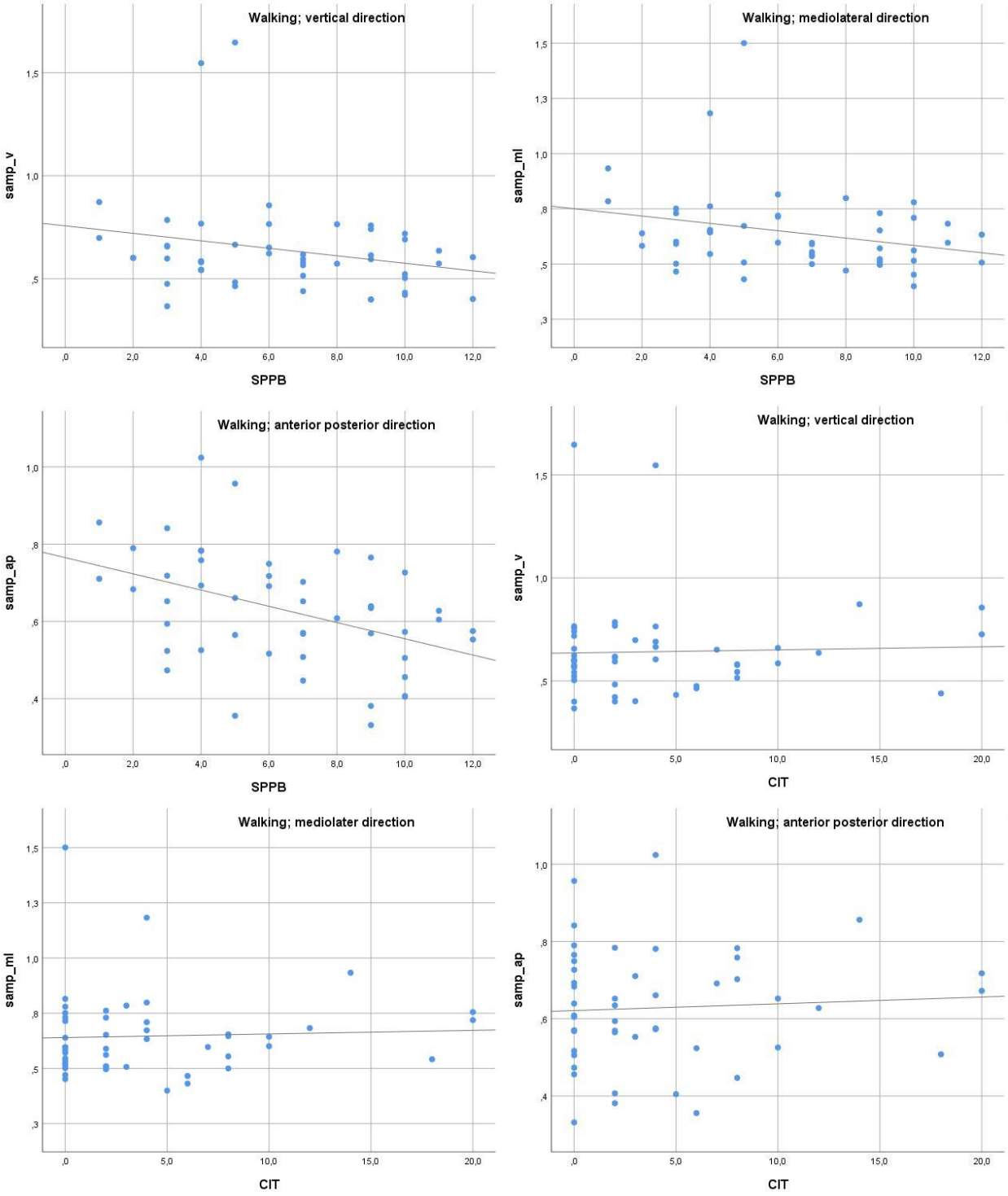


Figure 24 Scatterplot of sample entropy of the highpass signals during walking against clinimetrics, with the corresponding regression line fitted through the data points. A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score

Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during cycling: SampEn vs SPPB / CIT

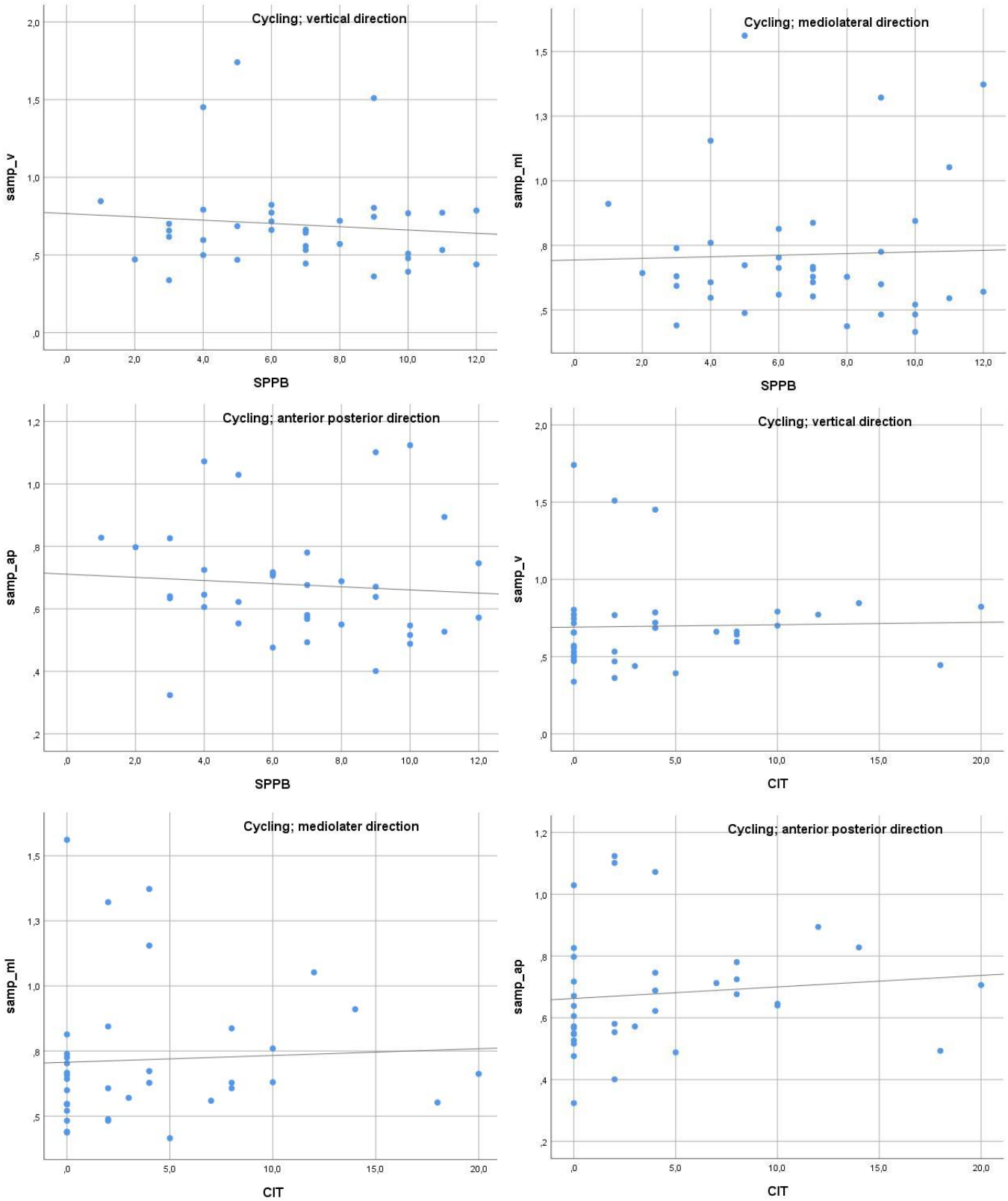


Figure 25 Scatterplot of sample entropy of the highpass signals during cycling against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during stair walking: SampEn vs SPPB / CIT

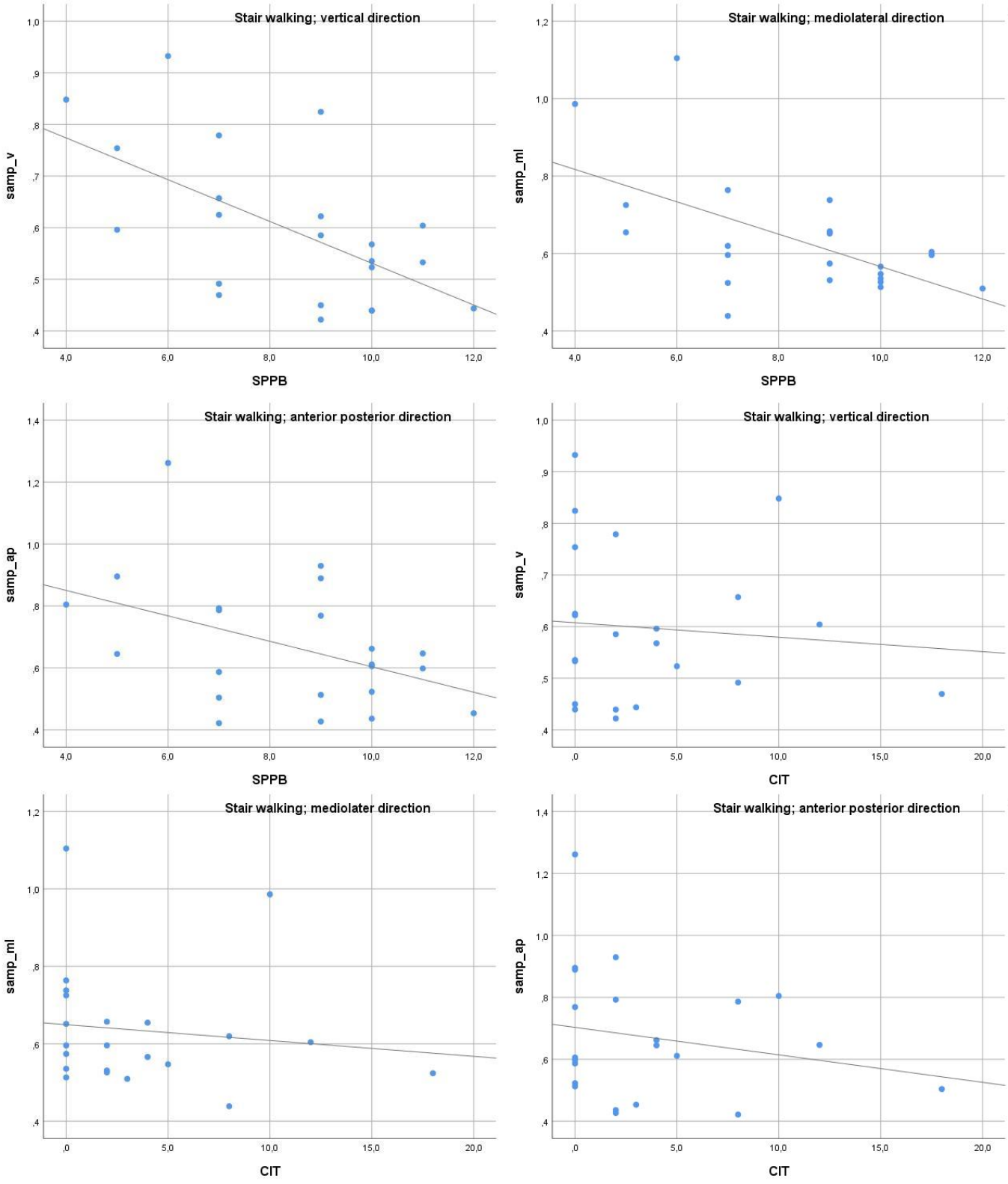


Figure 26 Scatterplot of sample entropy of the highpass signals during stair walking against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during shuffling: SampEn vs SPPB / CIT

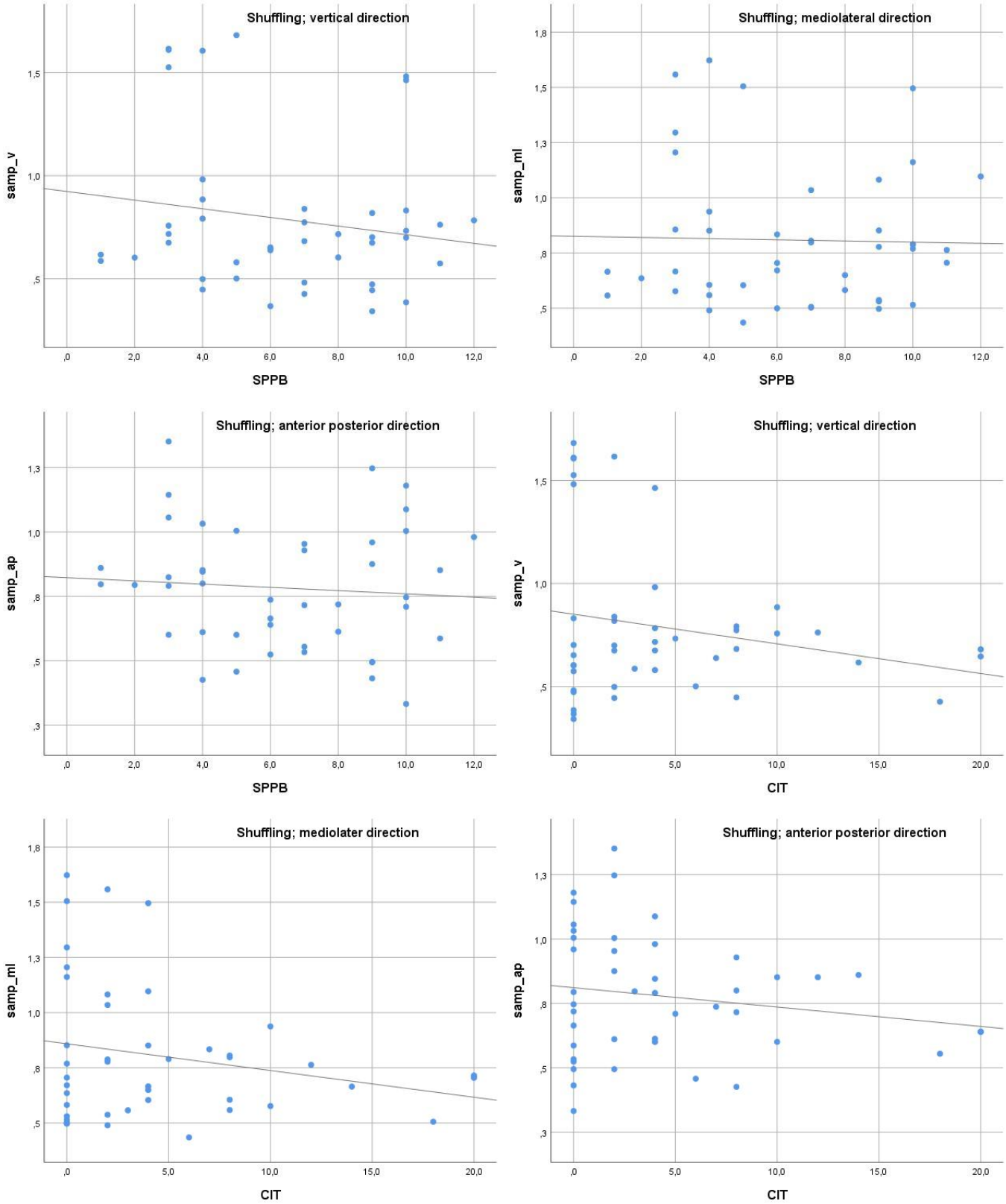


Figure 27 Scatterplot of sample entropy of the highpass signals during shuffling against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during standing: SampEn vs SPPB / CIT

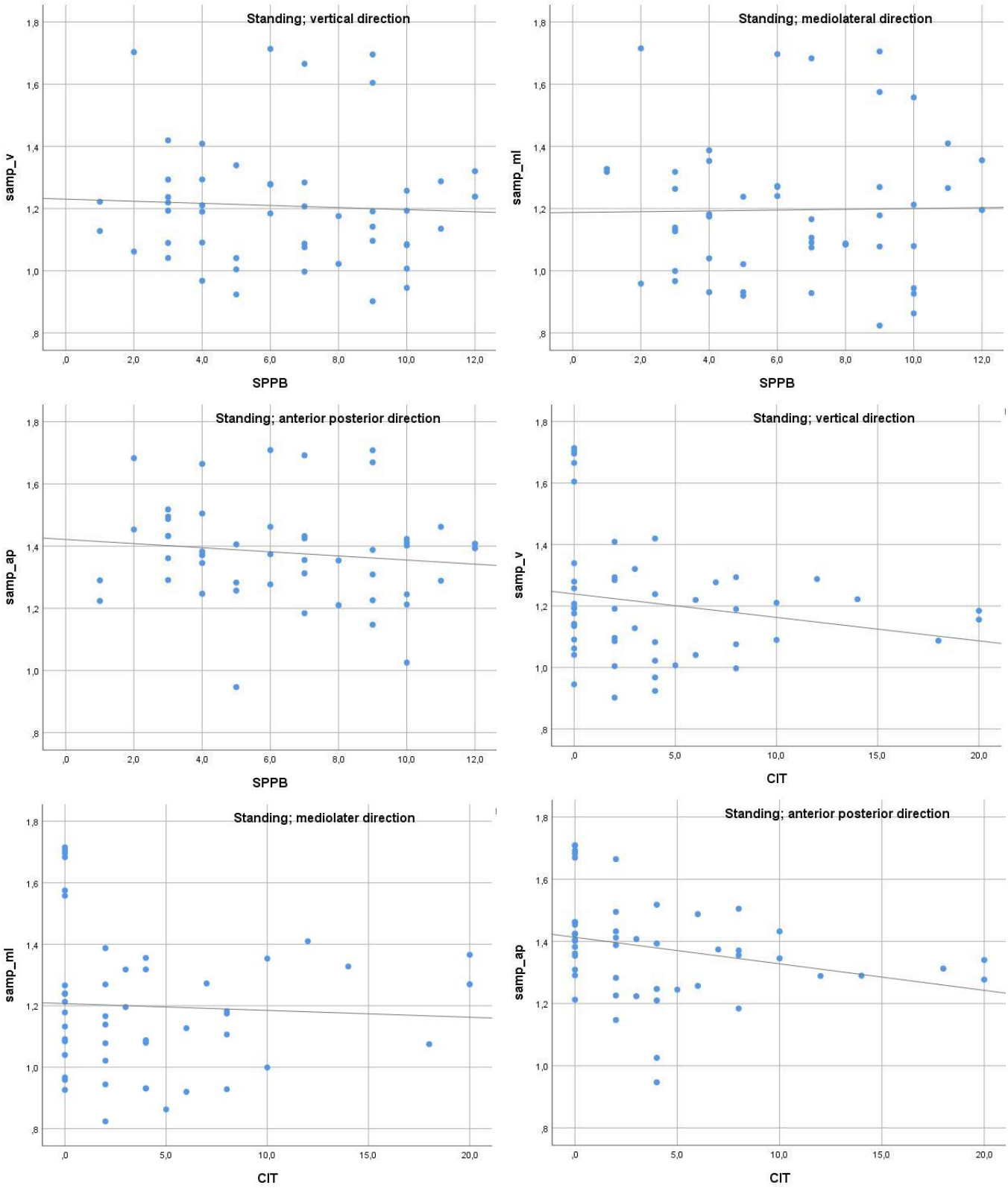


Figure 28 Scatterplot of sample entropy of the highpass signals during standing against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during sitting: SampEn vs SPPB / CIT

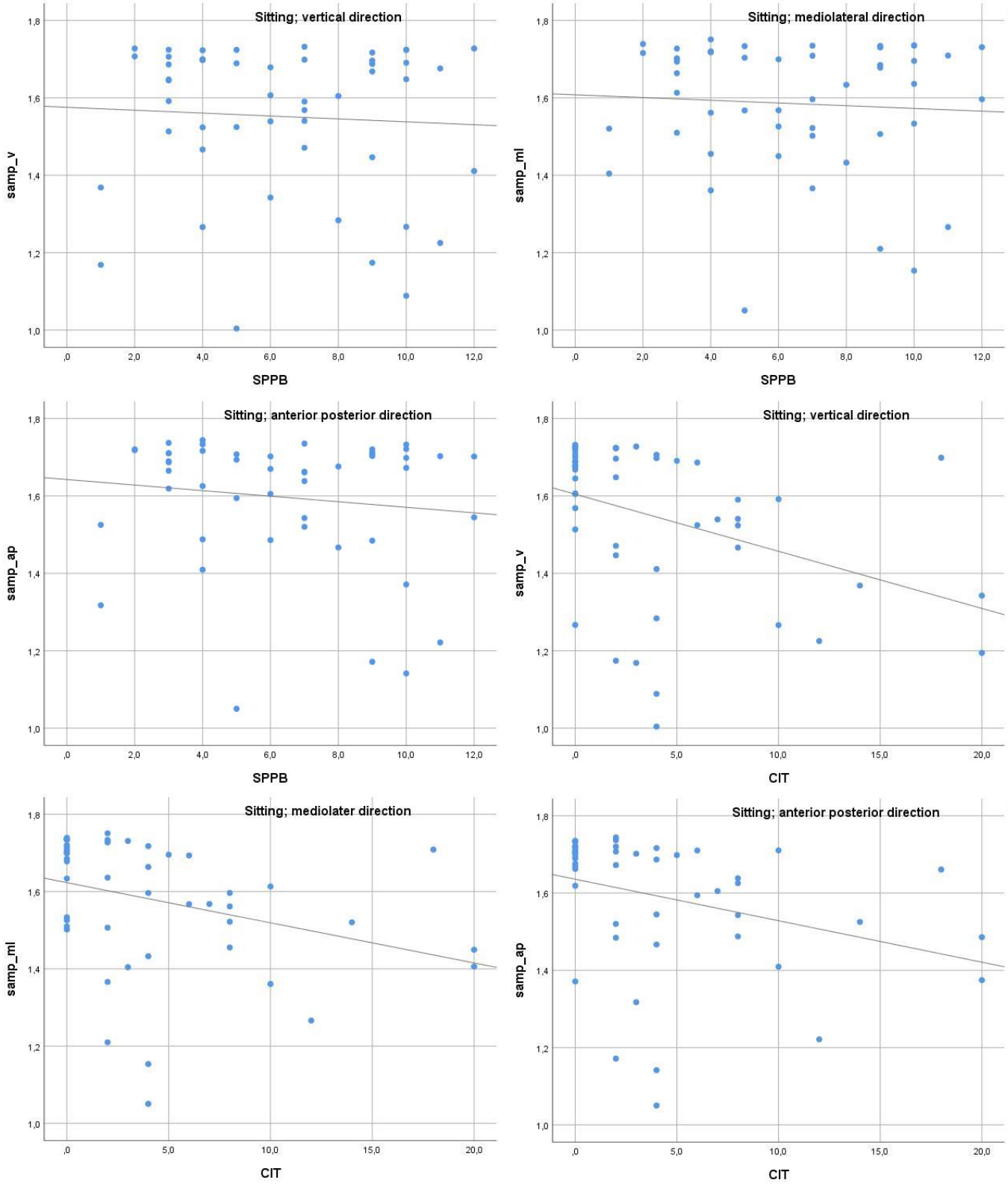


Figure 29 Scatterplot of sample entropy of the highpass signals during sitting against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals during lying: SampEn vs SPPB / CIT

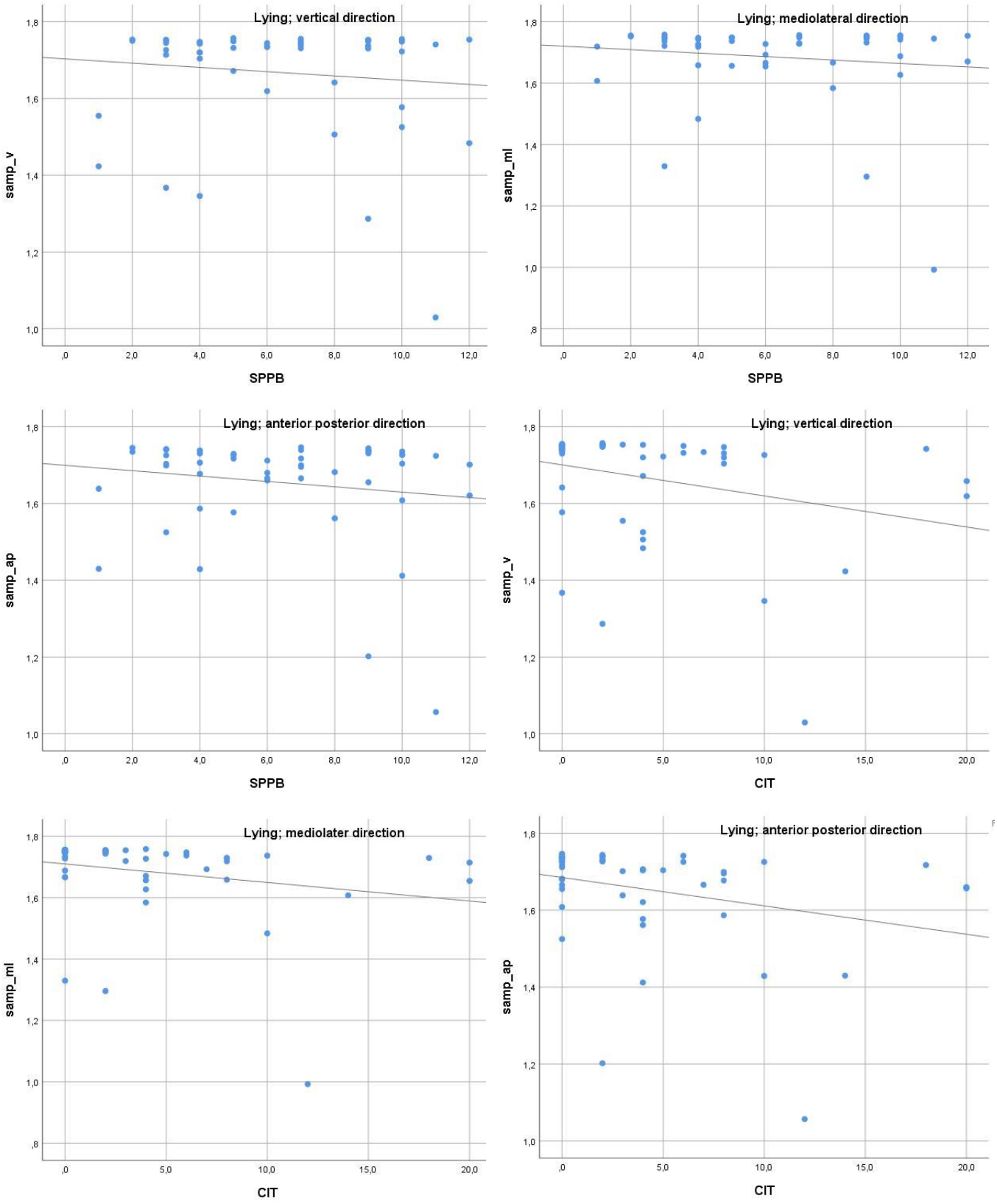


Figure 30 Scatterplot of sample entropy of the highpass signals during lying against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Scatterplot signals unclassified signal: SampEn vs SPPB / CIT

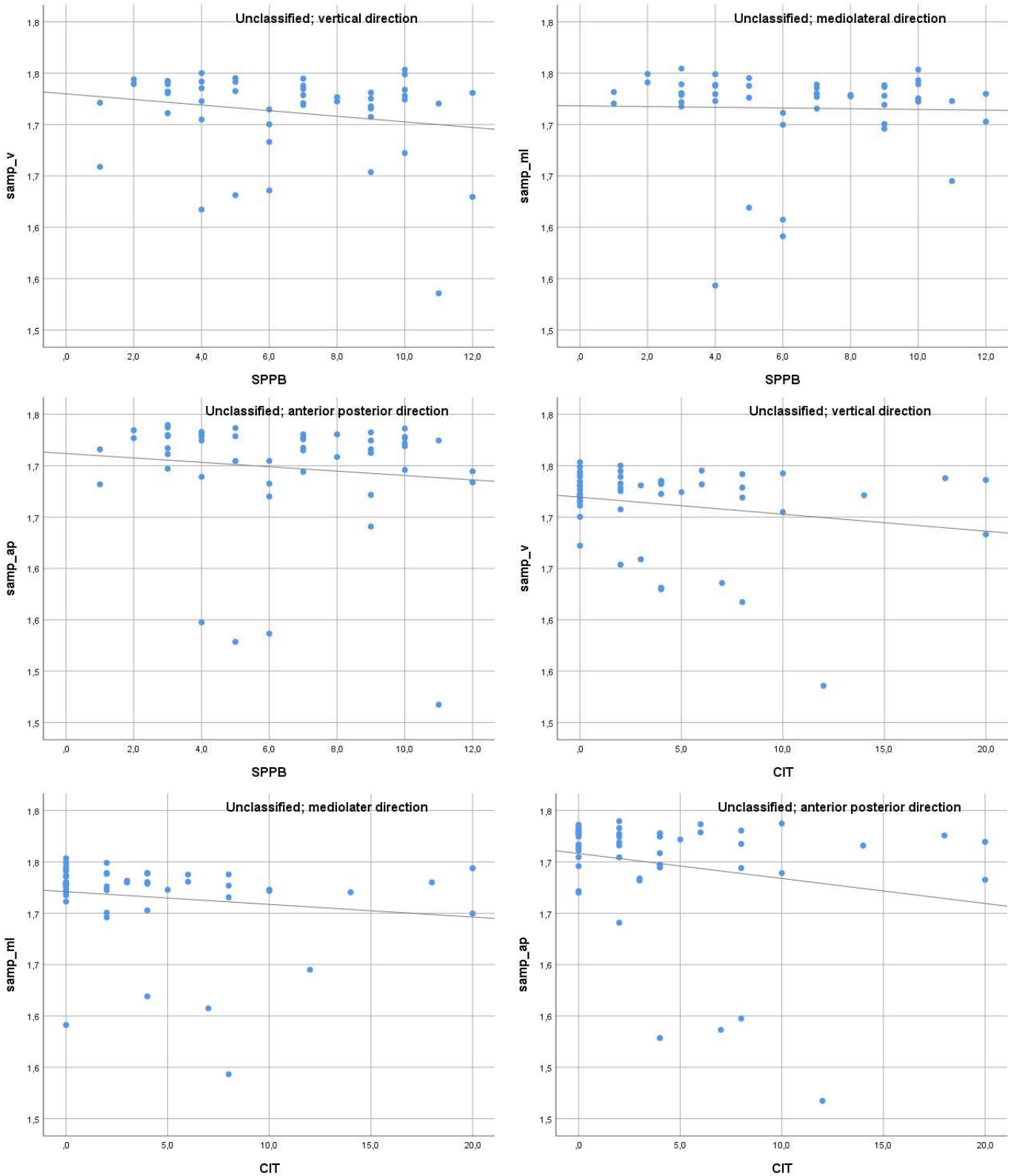


Figure 30 Scatterplot of sample entropy of the highpass signals from the unclassified signal against clinimetrics, with the corresponding regression line fitted through the data points.
A) Sample entropy of acceleration in vertical direction against the SPPB score, B) Sample entropy of acceleration in mediolateral direction against the SPPB score, C) Sample entropy of acceleration in anterior posterior direction against the SPPB score, D) Sample entropy of acceleration in vertical direction against the CIT score, E) Sample entropy of acceleration in mediolateral direction against the CIT score, F) Sample entropy of acceleration in anterior posterior direction against the CIT score
Abbreviations: samp_v = sample entropy in vertical direction, samp_ml = sample entropy in mediolateral direction, samp_ap = sample entropy in anterior posterior direction, CIT = cognitive impairment scale, SPPB = short physical performance battery

Appendix G: Visualization of the Multi-Scale Entropy, stratified by SPPB score

MSE plots: Mean SampEn, SPPB groups, cycling

For each activity, the SampEn value is calculated on different timescales. The calculations are done using the Multi-Scale Entropy approach, resulting in SampEn group means for each scale. The groups were stratified by the SPPB score, as described in the method. The appendix visualizes the MSE profiles for each activity in the directions: V, ML, and AP.

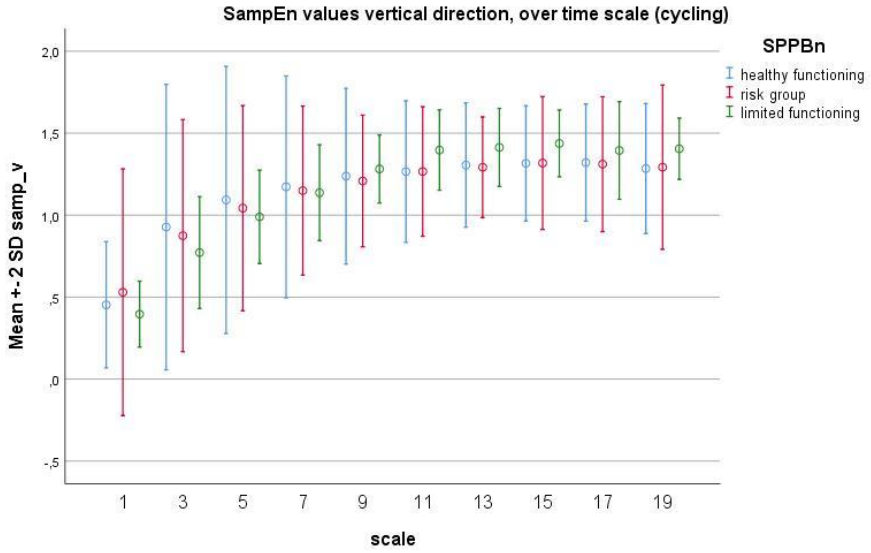
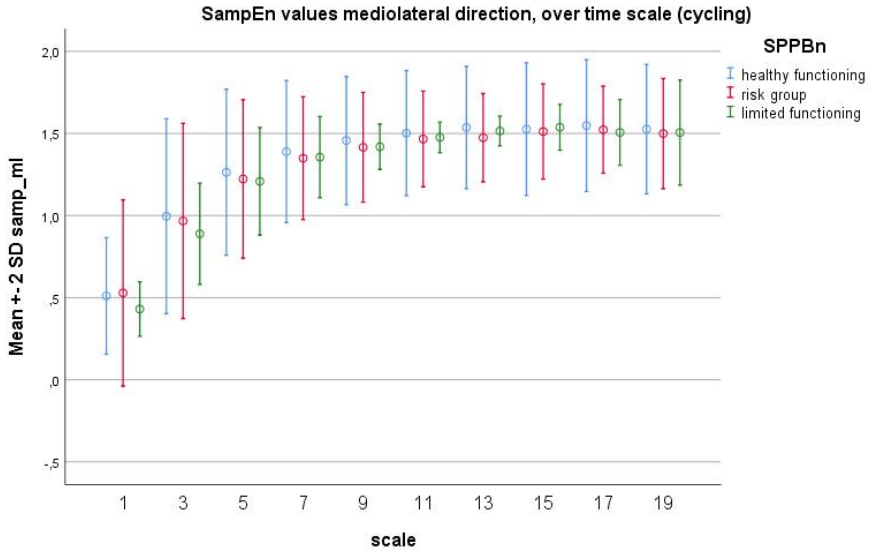
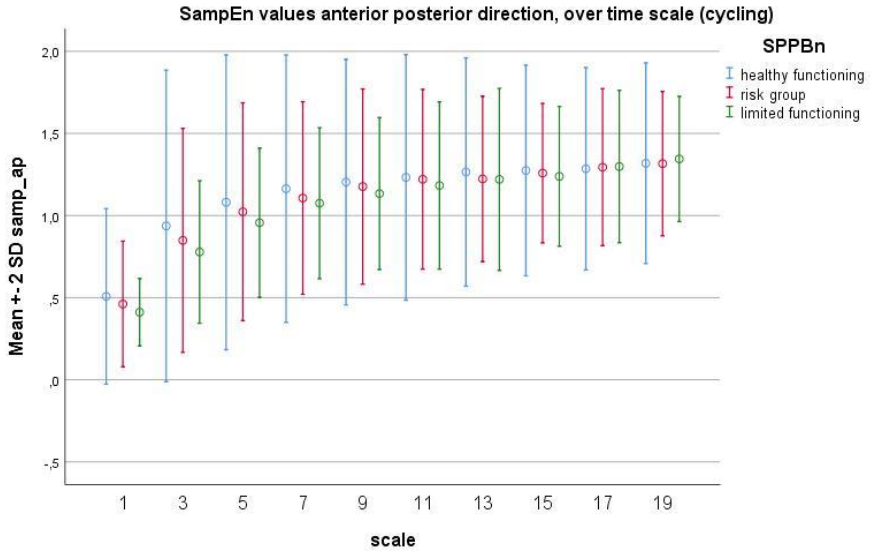


Figure 31 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, Stair walking

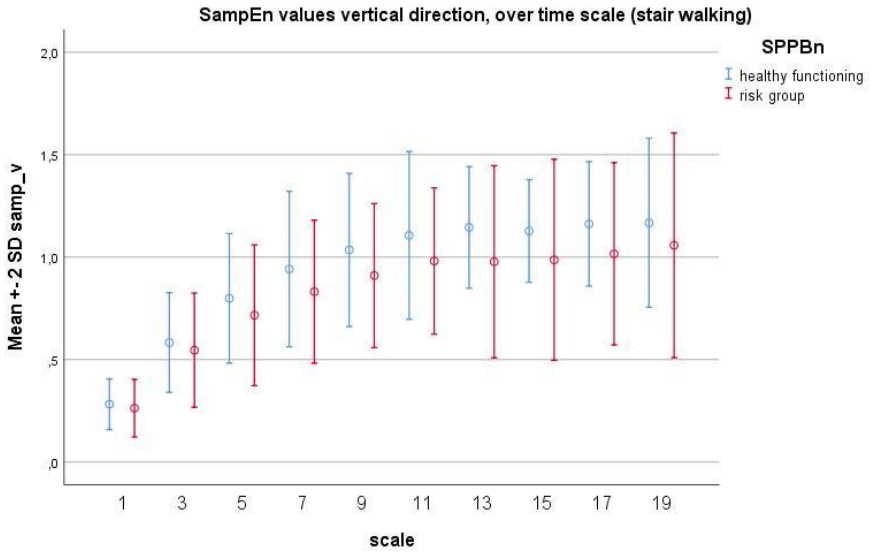
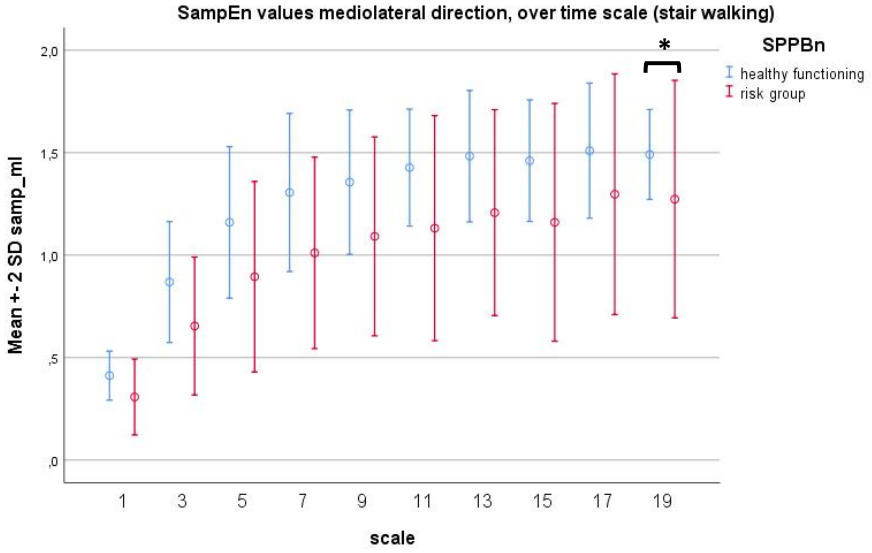
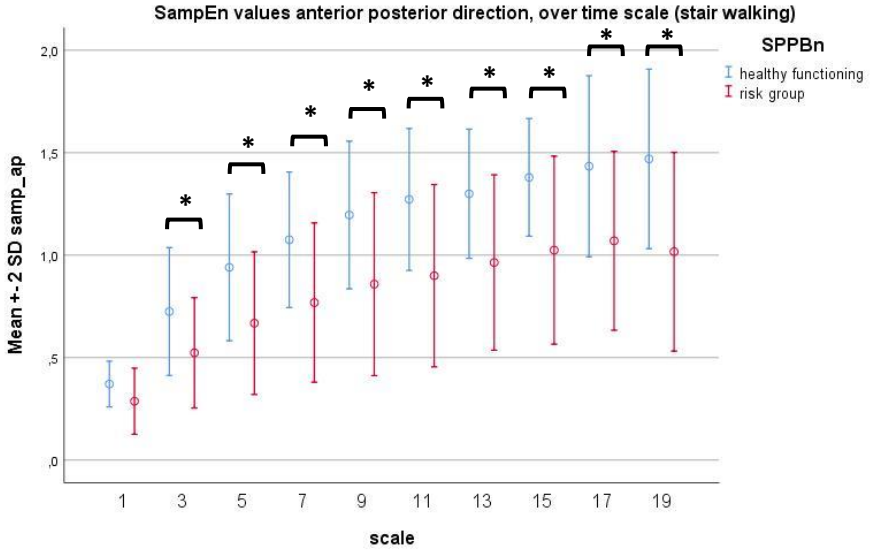


Figure 32 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, Walking

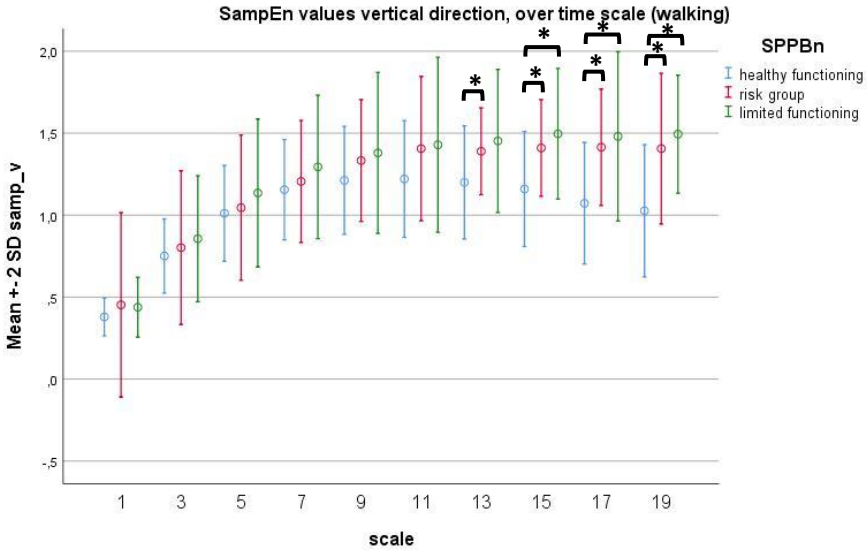
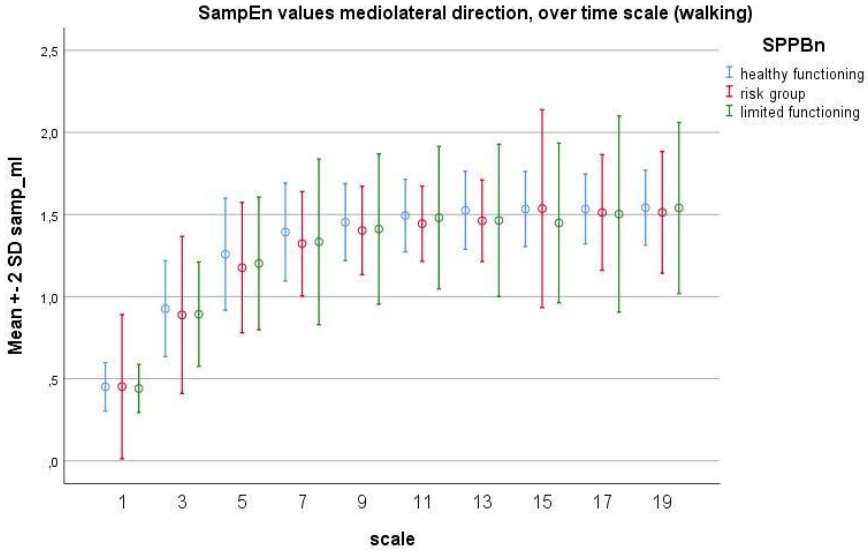
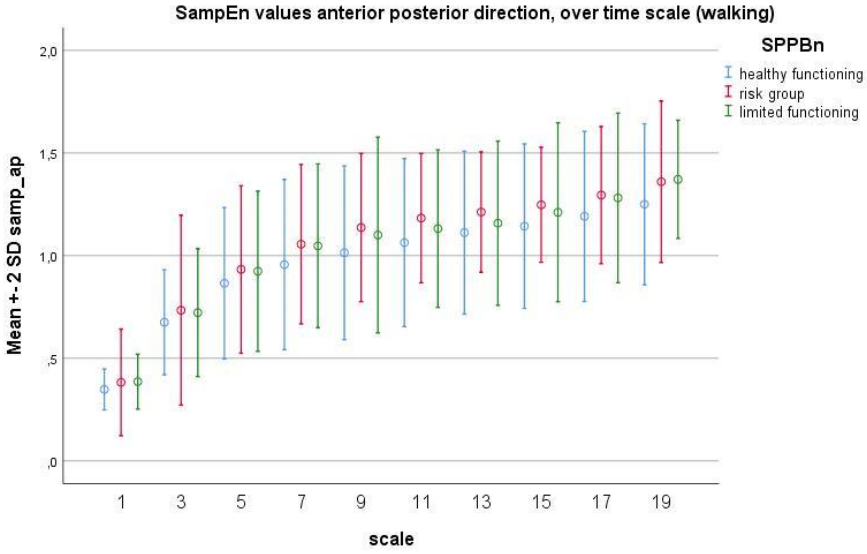


Figure 33 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, Shuffling

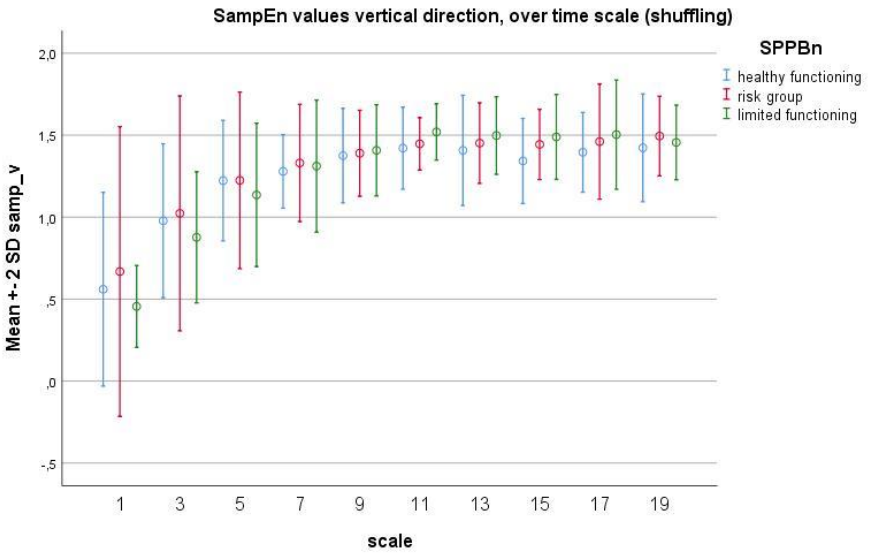
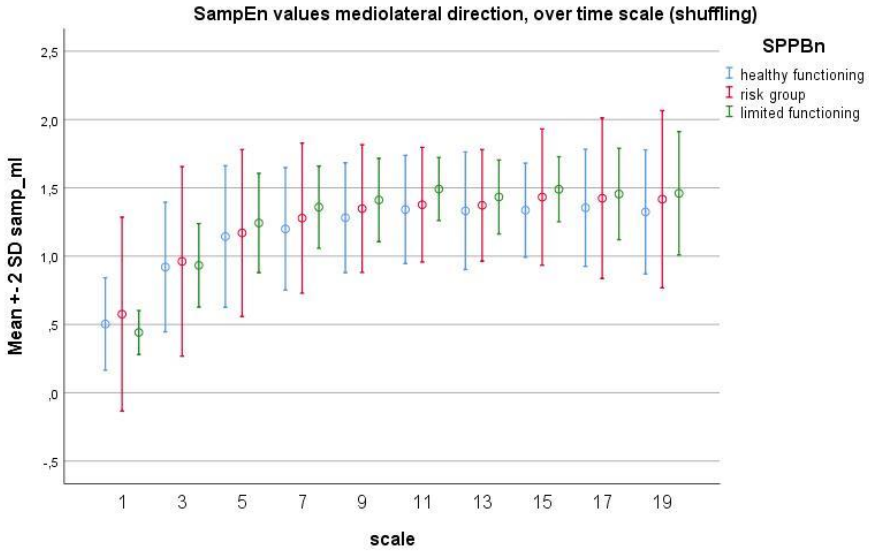
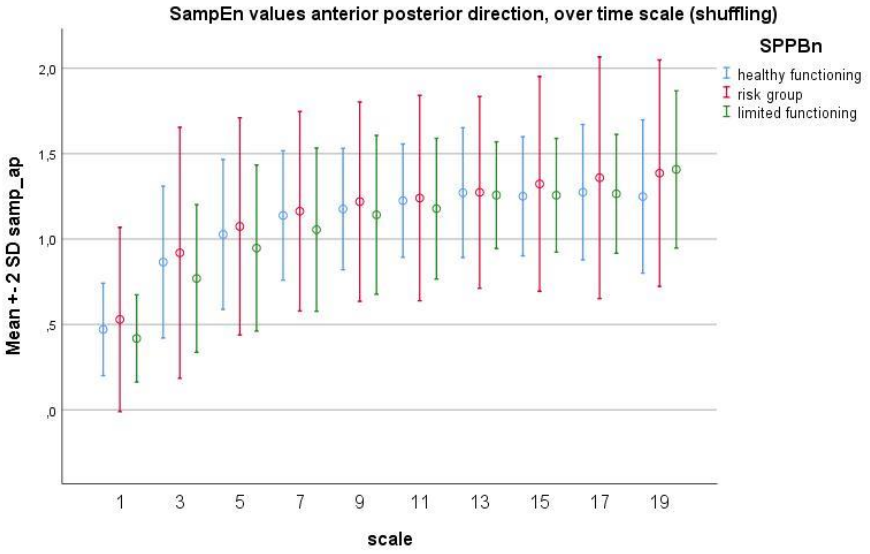


Figure 34 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, standing

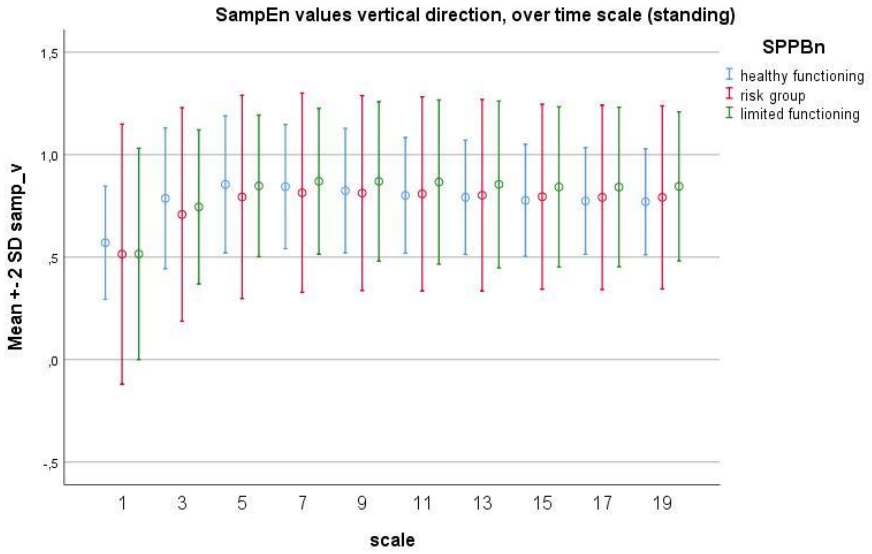
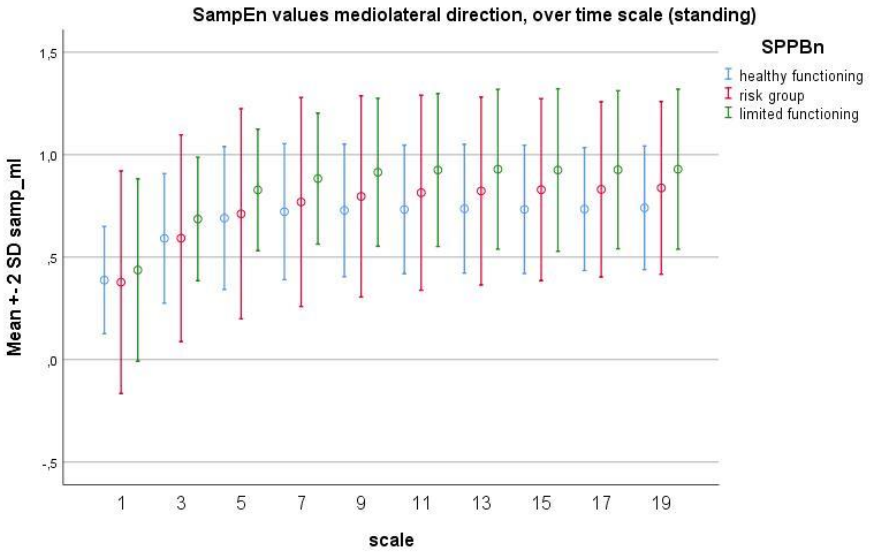
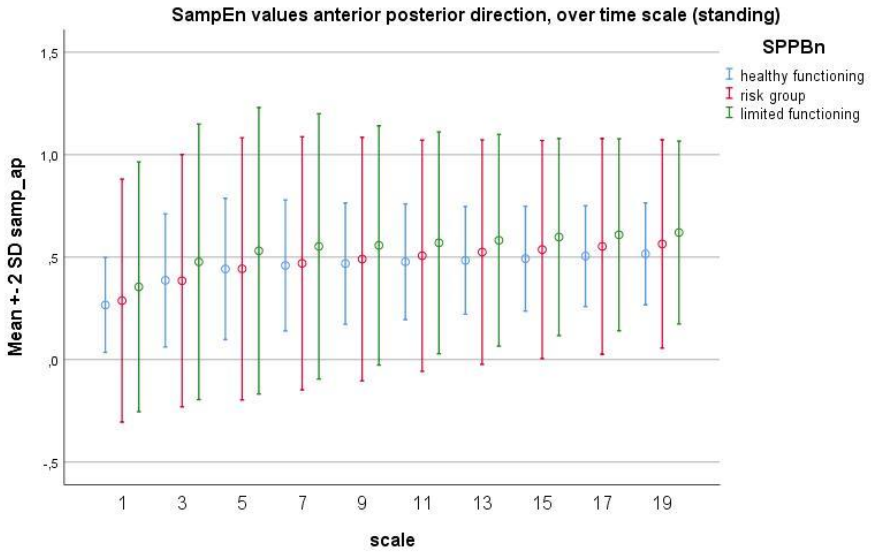


Figure 35 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, sitting

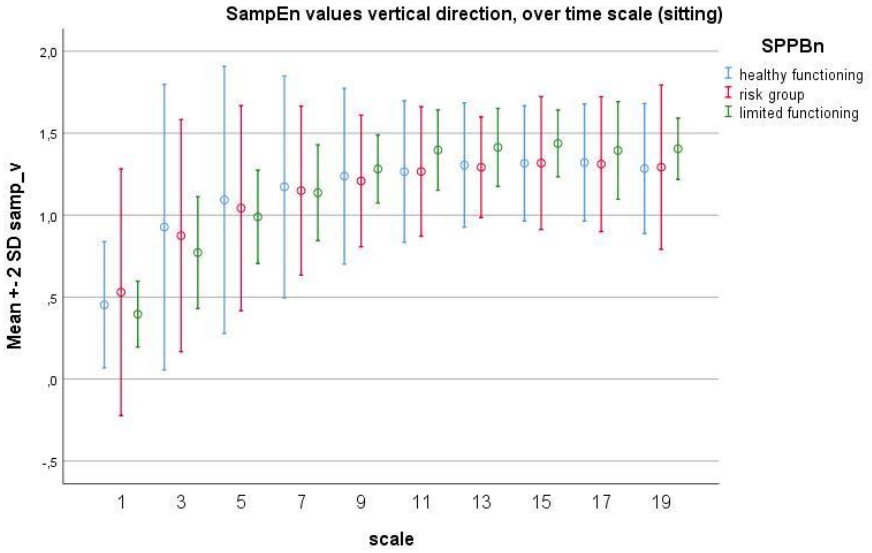
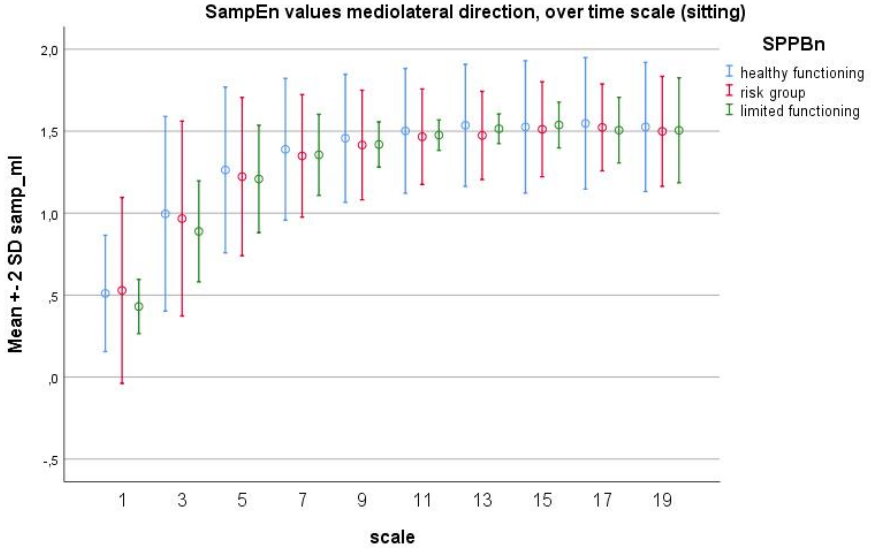
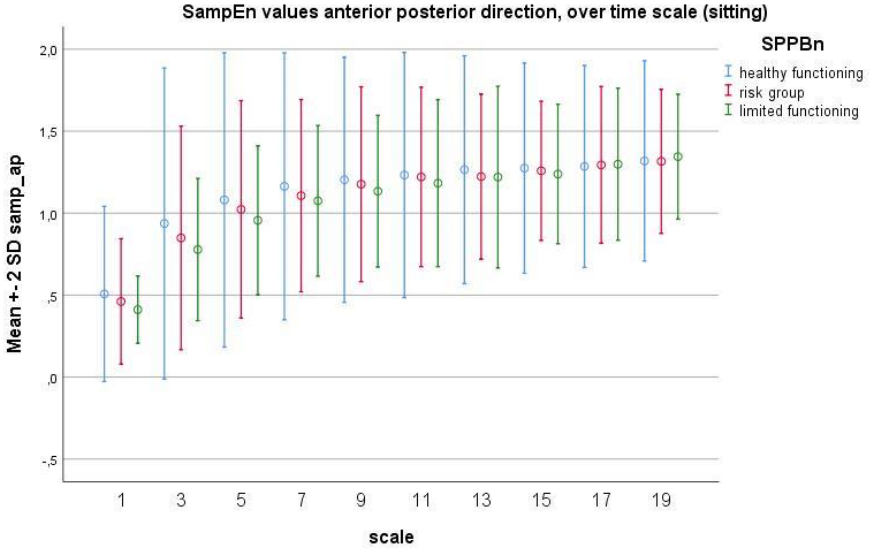


Figure 36 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





MSE plots: Mean SampEn, SPPB groups, Lying

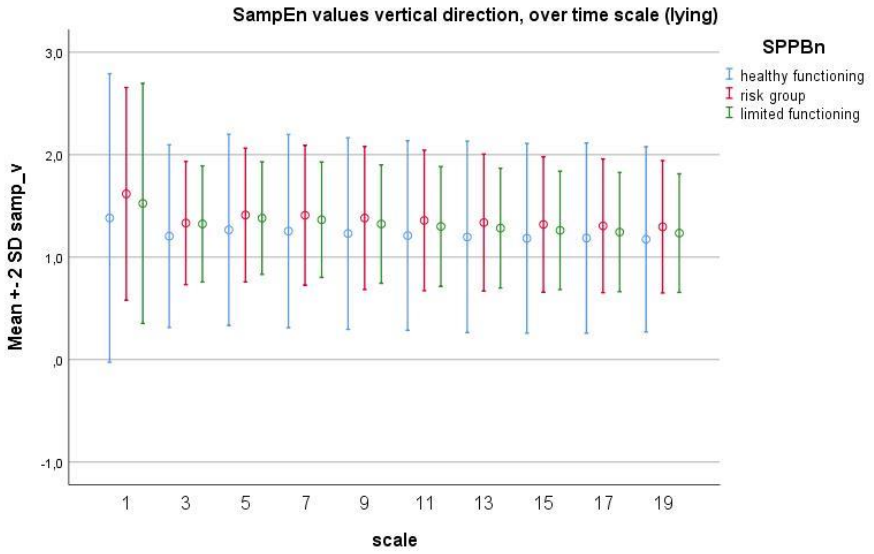
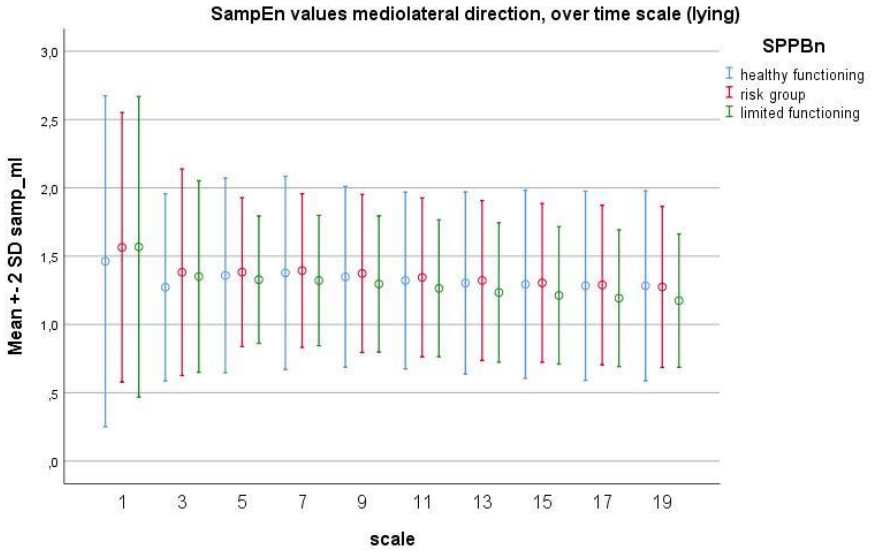
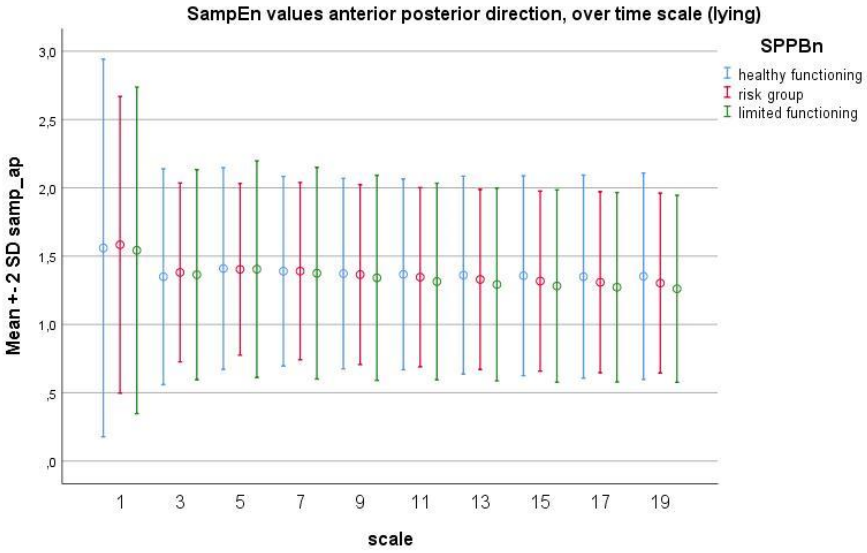


Figure 37 SampEn *outcomes (μ +/- σ) represents the groups means for the SPPB score, in the directions: vertical, mediolateral and anterior posterior. Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation. SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction*





Appendix H: Visualization of the Multi-Scale Entropy, stratified by CIT score

MSE plots: Mean SampEn, CIT groups, cycling

For each activity, the SampEn value is calculated on different timescales. The calculations are done using the Multi-Scale Entropy approach, resulting in SampEn group means for each scale. The groups were stratified by the CIT score, as described in the method. The appendix visualizes the MSE profiles for each activity in the directions: V, ML, and AP.

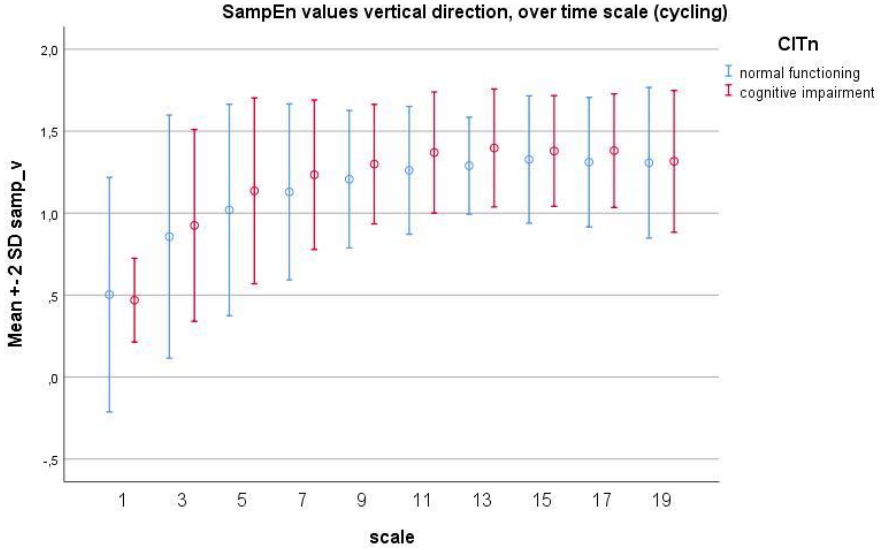
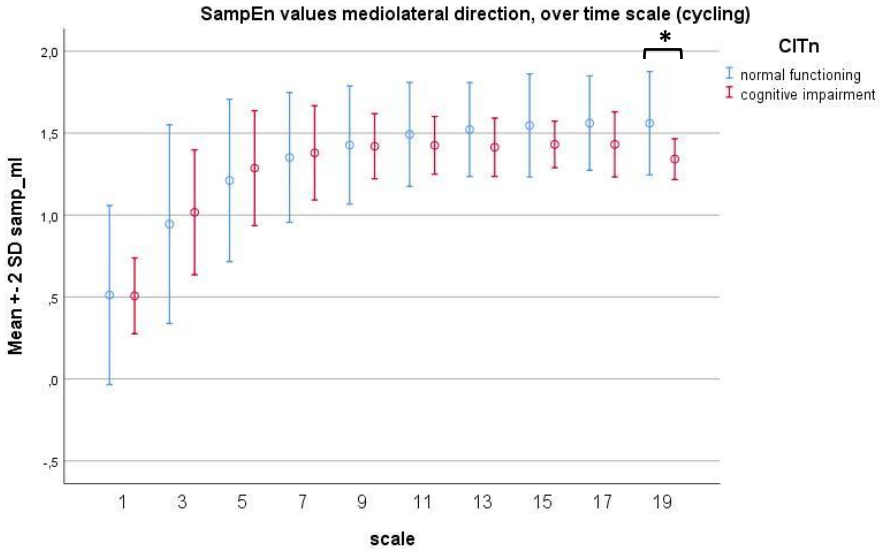
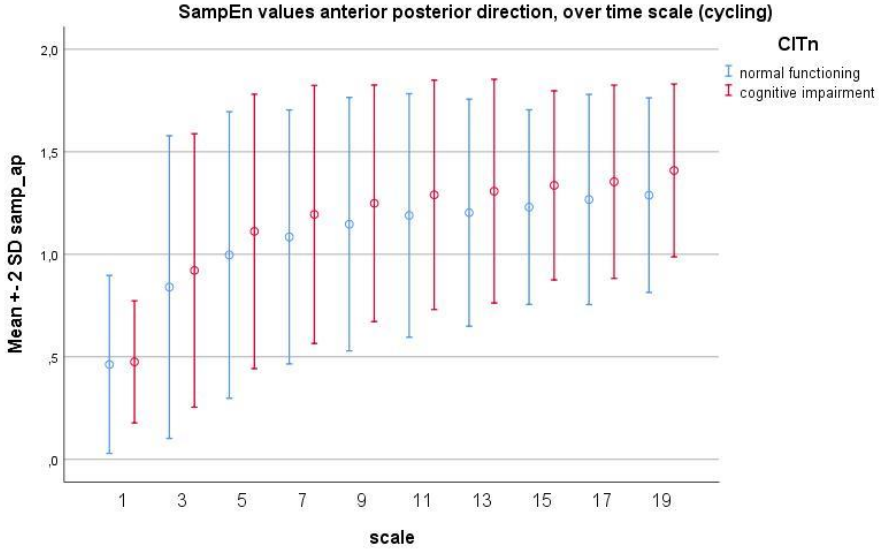


Figure 38 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction,
samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, Stair walking

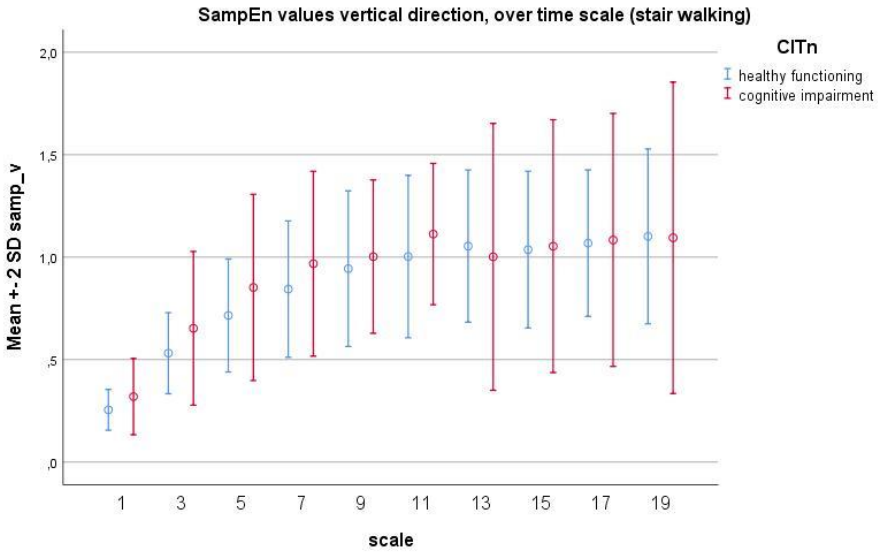
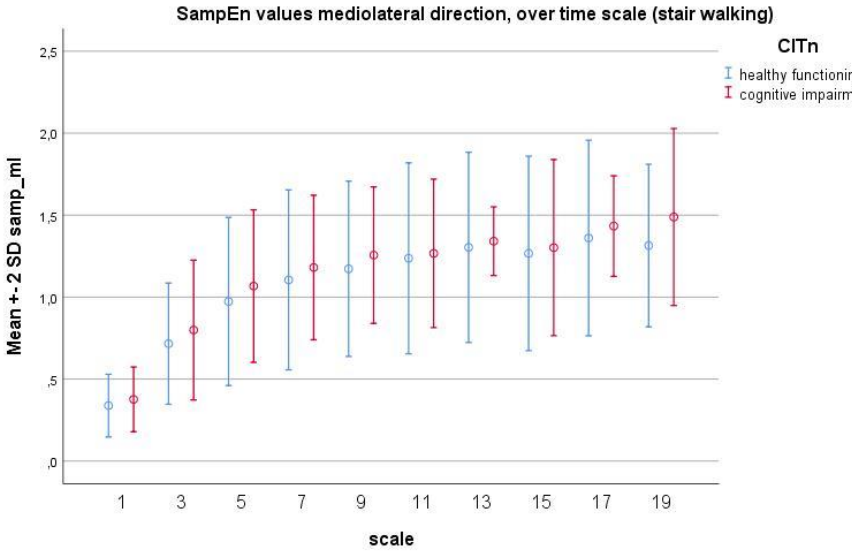
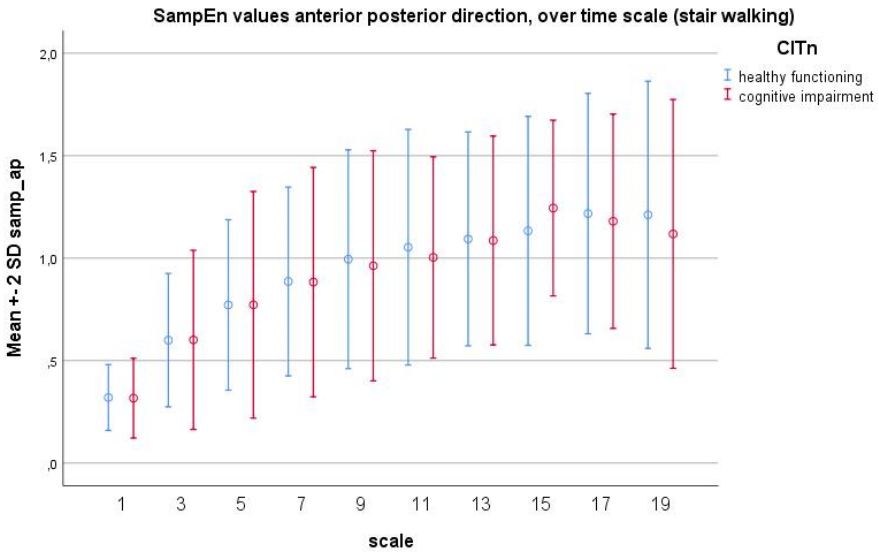


Figure 39 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, Walking

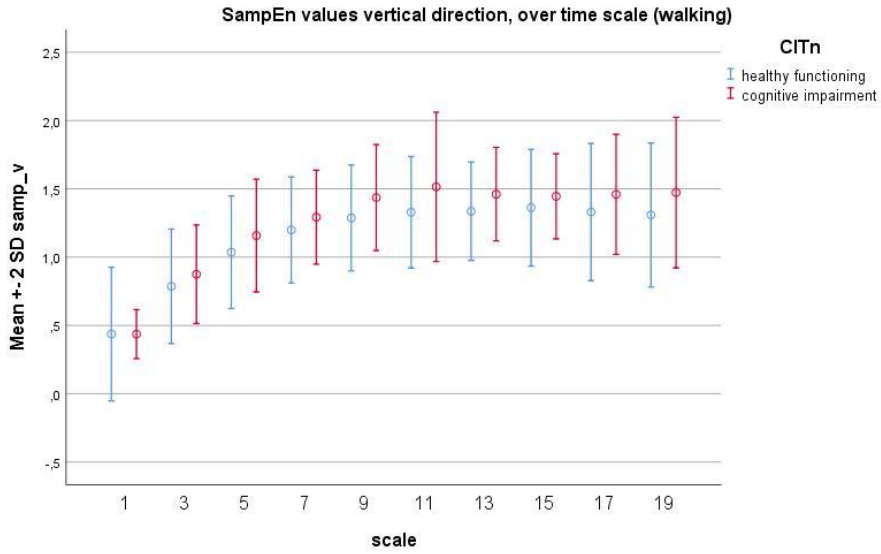
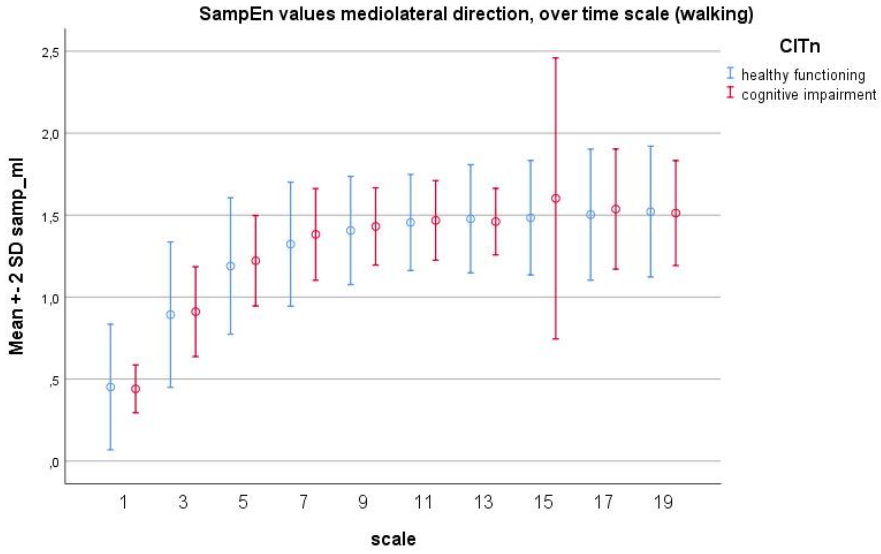
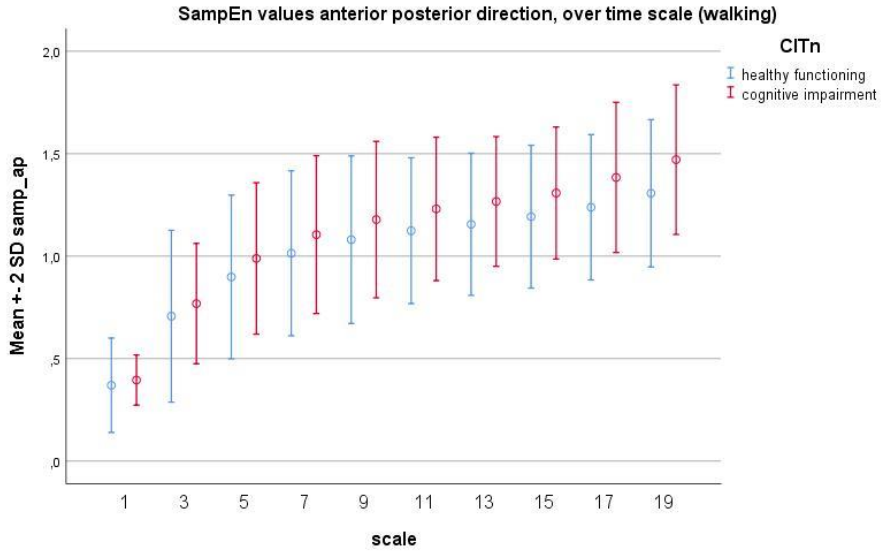


Figure 40 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, Shuffling

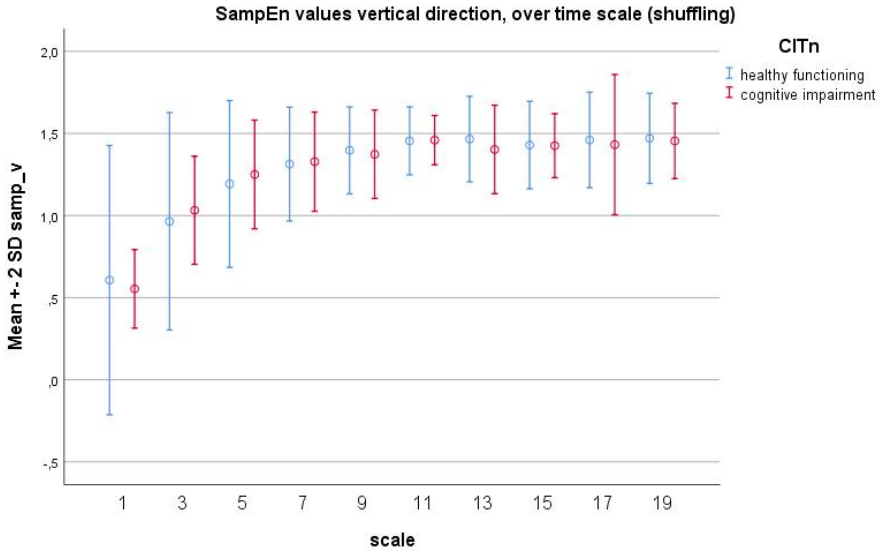
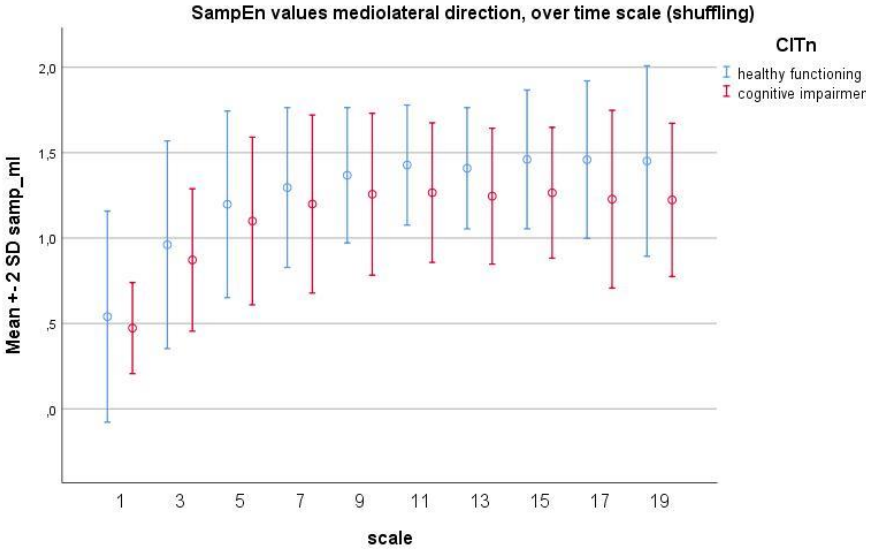
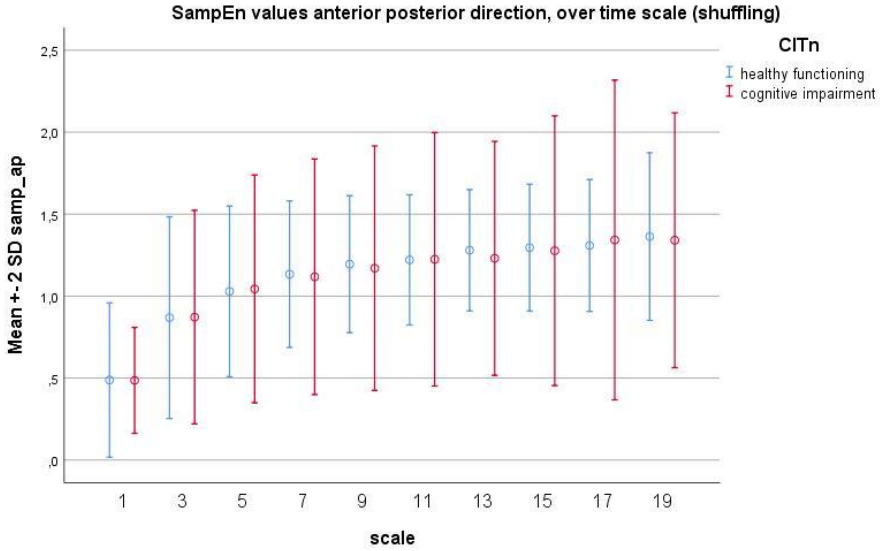


Figure 41 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, standing

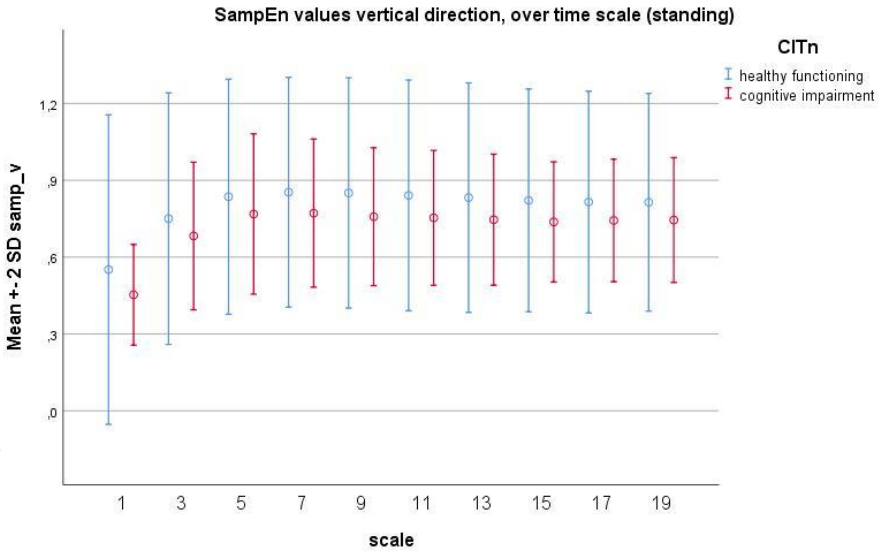
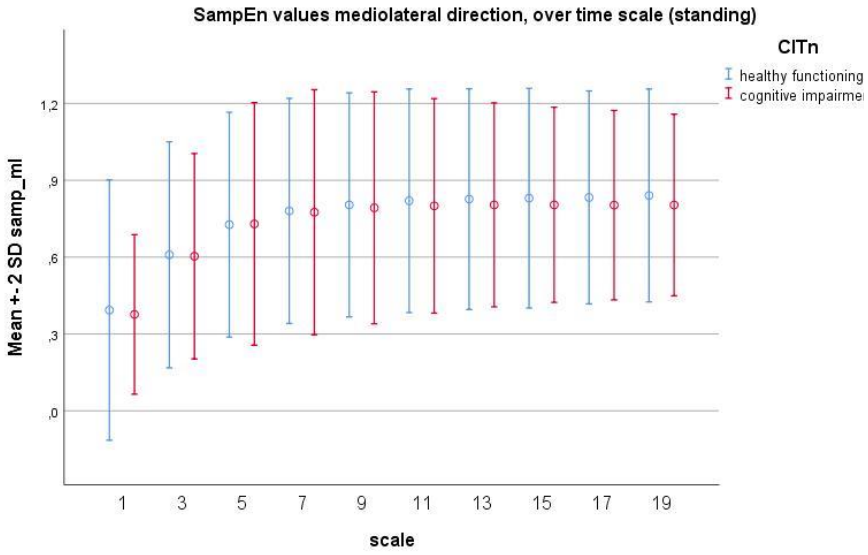
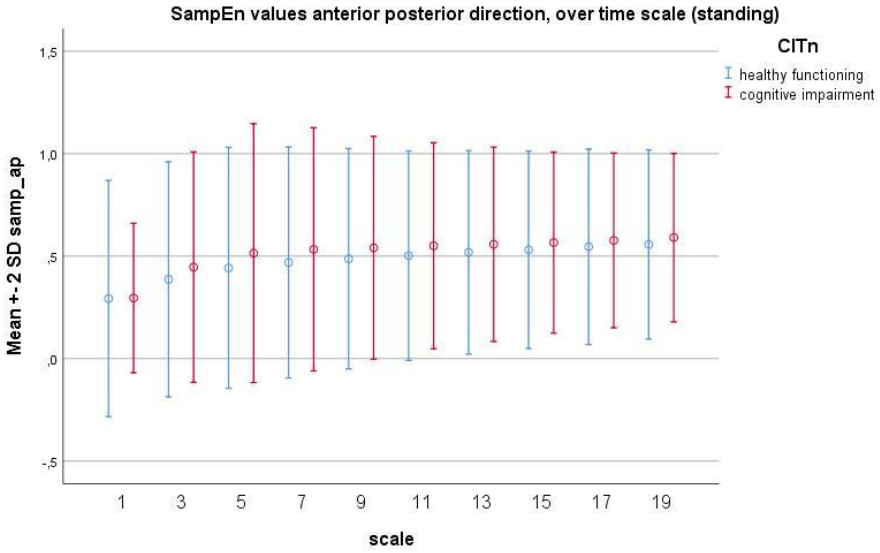


Figure 42 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, sitting

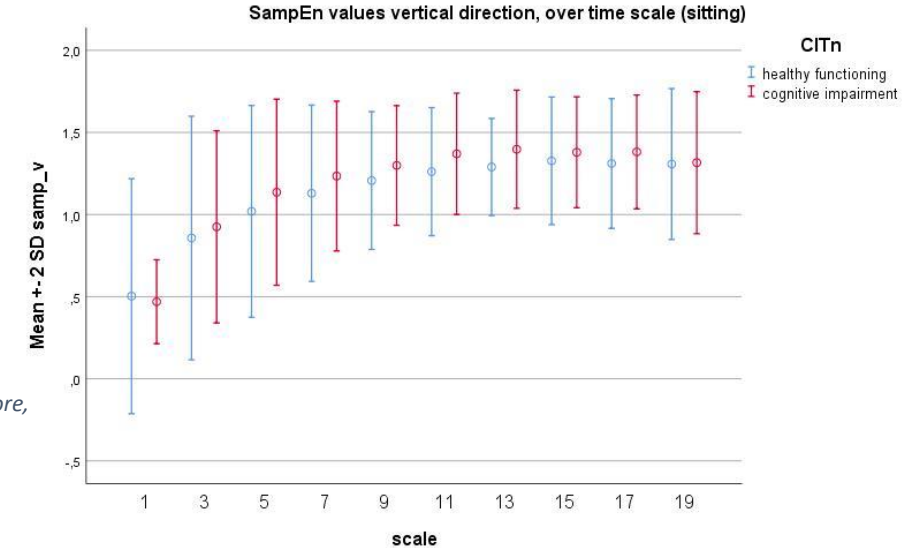
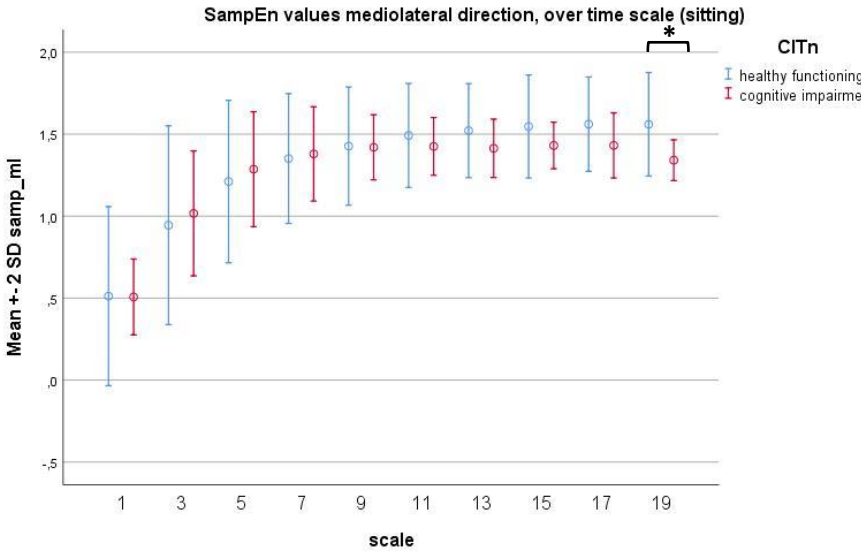
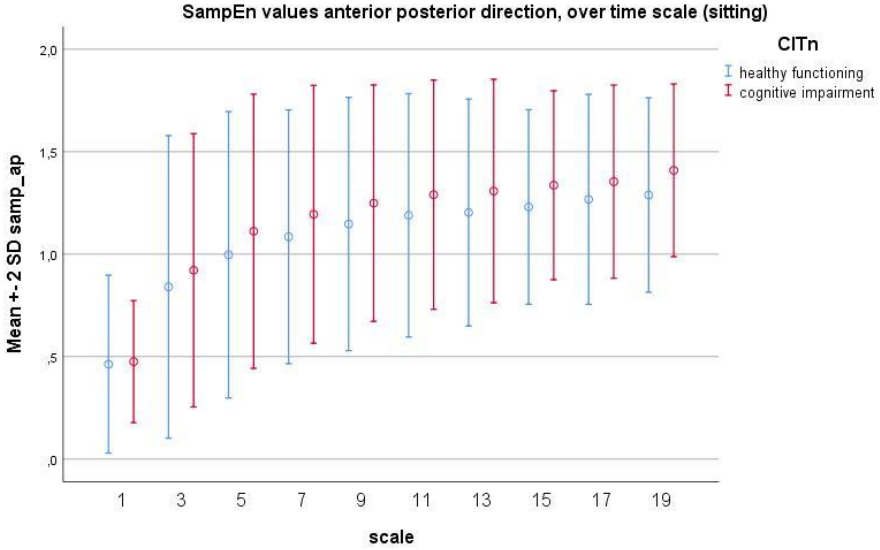


Figure 43 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction





MSE plots: Mean SampEn, CIT groups, Lying

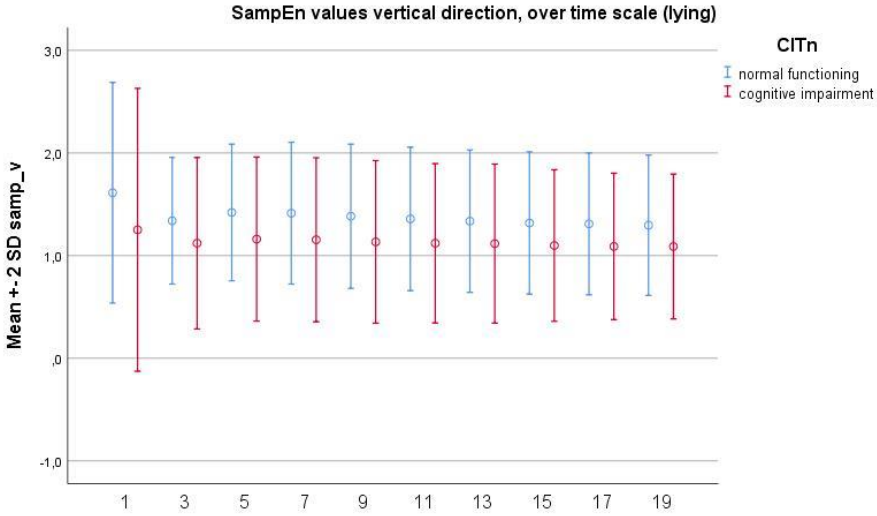


Figure 44 SampEn *outcomes (μ +/- σ) represents the groups means for the CIT score, in the directions: vertical, mediolateral and anterior posterior.*
Abbreviations: SampEn = sample entropy, μ = mean, σ = standard deviation.
SD = standard deviation, samp_ml = sample entropy in mediolateral direction, samp_v = sample entropy in vertical direction