# Fatigability is among the factors of discoordination between heart rate variability and physical acceleration during free-moving days in non-older women

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# Abstract

Fatigability is related to several diseases as well as the autonomic nervous system. We investigated whether fatigability is associated with the coordination between the physical acceleration (PA) and heart rate variability (HRV) in women. Overall, 95 adult women were divided into non-old (n=50; age: 22–59 years) and old group (n=45; age: ≥ 60 years). HRV and PA data were simultaneously obtained every minute for 24 h. We defined %lag0 as the percent ratio of lag=0 min between HRV and PA in 1 h. Cornell Medical Index was used to determine the degrees of physical and psychological symptoms. In the non-older group in the hour before sleep, the participants with high fatigability scores had significantly lower %lag0 than those with low fatigability %lag0 ($p<0.05$). Additionally, those with higher fatigability combined with exhaustion in the morning had significantly lower %lag0 than those without exhaustion in the hour before sleep ($p<0.05$) but not in the hour after waking up. These results suggest that fatigability in non-older women was associated with the discoordination between HRV and PA in the hour before sleep. Additionally, exhaustion in the morning may be related to the discoordination of HRV and PA the previous night.


# Introduction

Fatigue is one of the major symptoms in general conditions irrespective of health or illness. A large survey reported that half of the general population suffers from fatigue (Pawlikowska et al, 1994). There are some differences between fatigue and fatigability; therefore, assessment of fatigability can be used to better characterize fatigue (Murphy et al, 2016). Fatigability has been defined as the degree of fatigue experienced while performing a defined activity, which normalized fatigue to activity level (Eldadah 2010). Therefore, understanding fatigability is vital in evaluating the impact of fatigue on physical activities and vice versa (Kim et al, 2018). Furthermore, it has been reported that the fatigue experienced in the morning may be distinct from that in the evening; however, both are closely related to each other (Dhruva et al, 2013).

Cornell Medical Index (CMI)—a questionnaire devised for collecting a large amount of pertinent medical and psychiatric data with minimum expenditure of resources—includes a section on fatigability (Brodman et al, 1949). We used this questionnaire in this study as it has been widely used in clinical practice as a screening procedure to evaluate neurotic tendencies (Sawada et al, 2014). Furthermore, we employed the term “fatigability” based on its usage in CMI.

The fatigability in older people is different from that in younger ones (Santansato et al, 2015). There are age-related differences in the neurovascular and neuromuscular systems between the two; therefore, older people exhibit different rates of fatigability than young adults during a fatigable task. However, the mechanisms underlying the age-related differences in fatigability are not fully understood (Yoon et al, 2015).

Habitual physical activity and Heart Rate Variability (HRV) have been reported to differ significantly between men and women (Aoyagi and Shephard 2013, Koenig and Thayer, 2016). Broadly speaking, non-older women are less fatigable than non-older men during isometric fatiguing contractions (Hunter 2014); therefore, fatigability also depends on the sex of the individual. Moreover, non-older women with environmental factors, such as changes in hormones, could lead to alterations in their homeostasis. Furthermore, work-related fatigue among non-older women is complicated by the added work associated with housekeeping (Kivimäki et al, 2002). Thus, evaluation of women's fatigability appears to require more objective analysis.

So far, several kinds of possible biomarkers and indexes for quantitative evaluation of fatigue have been reported (Japanese Society of Fatigue Science, Watanabe et al, 2008); e.g., fatigue-related oxidative stress, inflammatory markers and auonomic nerve balance (Fukuda et al, 2016, Tanaka et al, 2011, Tanaka et al, 2015). Among them, autonomic nerve balance obtained from ECG appears to be practically convenient.

HRV is a non-invasive tool to assess the variations in the beat-to-beat interval. It is used to assess cardiac autonomic functions and is related to the outcomes following cardiac events and stress (Task Force, 1996; Klieger et al., 1992). Most human studies on the HRV spectrum have examined the low-frequency (LF: 0.04–0.15 Hz) and high-frequency (HF: 0.15–0.40 Hz) spectral power bands (Task Force, 1996). A study has previously demonstrated that patients with chronic fatigue syndrome had significantly lower average daily physical acceleration (PA) (Sisto et al, 1998).

Cross-correlation analysis gives a series of correlation coefficients between two-time series by overlaying and temporally shifting the two series over a range of successive time lags (Chatfield, 1975). Cross-correlation analysis is widely used to investigate the association in a physiological signal (Abdullah et al., 2010, Drinnan et al, 2001). Based on a cross-correlation analysis between the time series of HRV and PA, the coordination is defined as the time lag, and previously we found that the lag in older participants was significantly higher than that in the non-older participants (Taniguchi et al, 2015). Therefore, we considered that the coordination between HRV and PA in daily lives is affected not only by aging but also by mental or physical stress. We hypothesized that fatigability affects the coordination between HRV and PA, i.e., fatigability induces a mismatch between HRV and PA, increasing the lag between them.

Previous studies have shown that immediately after the initiation of exercise, heart rate increases due to a withdrawal of parasympathetic nervous activity and an increase in sympathetic nervous activity (Rowell and O'Leary 1990). Under healthy conditions, PA causes the HRV response immediately, whereas in the impaired conditions, the response would be altered. Therefore, the lag may indicate the coordination between PA and neuro-cardiovascular systems including the autonomic nervous system. Based on a cross-correlation analysis between the time series of HRV and PA, we previously reported that lag increases with aging in the daily lives of free-moving adults (Taniguchi et al, 2015).

In the present study, we propose a new index, %Lag0, which may indicate the coordination between physical activity and the autonomic nervous system. %Lag0 was defined as the percentage of the lag = 0 min between HRV and physical acceleration every one hour. Thereby, we attempted to investigate whether or not this method could be used to detect fatigability in adult women during free movement.

# Materials And Methods

## Participants

Overall, 106 adult women (age: 20–85 years) volunteered to participate in this study. Based on medical interviews, physical examinations, laboratory blood investigations, and electrocardiogram (ECG), we excluded five participants who had consumed alcohol on the day of the experiment, six participants with severe arrhythmias, two participants who were on beta-blockers, and three participants with excessive electrical noise in the devices described below (Figure 1). Arrhythmias were identified using a 12-lead ECG. Finally, we examined 95 participants with the the stated comorbidities. Of these, four had type II diabetes, 17 had hypertension, 35 had dyslipidemia, six had hepatic dysfunction, and two had renal dysfunction. However, these comorbidities were mild, and none of the subjects had restricted movements.

## Protocols

The participants completed the questionnaire before or on the day of the assessments. They arrived at the laboratory at approximately 13:00 and underwent venous blood sampling and ECG. They wore a portable monitor (Active Tracer AC301; GMS Inc., Tokyo, Japan) that recorded PA and R-R intervals over 24 h. During monitoring, the participants were instructed to continue their normal activities and avoid bathing. After the completion of the 24-h monitoring, they returned to the laboratory. The experimental protocols have been described in detail previously (Taniguchi et al, 2015, Taniguchi et al, 2020)

## Questionnaires

We used the Japanese version of CMI (J-CMI) (Sankyobo Co. LTD., Kyoto, Japan), which was created by Kanehisa and Fukamachi (1972), to assess the physical and psychological symptoms (Brodman et al, 1949 Pendleton et al, 2004, Kanehira et al, 2001). J-CMI for women comprises 213 questions in 18 sections. Fatigability included the following seven questions: “Q1. Do you often get spells of complete exhaustion or fatigue?”; “Q2. Does working tire you out completely?”; “Q3. Do you usually get up tired and exhausted in the morning?”; “Q4. Does every little effort wear you out?”; “Q5. Are you constantly too tired and exhausted even to eat?”; “Q6. Do you suffer from severe nervous exhaustion?”; and “Q7. Does nervous exhaustion run in your family?”. Each question invited “yes” or “no” as answers and was scored as one or zero, respectively. A yes response indicated that the individual has recently or previously experienced the symptoms (Brodman et al, 1949).

## Physical acceleration (PA)

The body of the Active Tracer (GMS Inc., Japan) equipped with a triaxial accelerometer (72 g) (Iwashita et al, 2003) was positioned on the frontal midline of the waist above the navel to avoid free movement of the device. The resolution of acceleration was 2 mG, and the sensitivity ranged between 0 and 4.0 G. The absolute values of the resultant vector, which were calculated from the signals of triaxial acceleration, were averaged every 1 min.

## Analysis

Spectral analysis of HRV was performed at 1-min intervals using maximal entropy combined with the least square method (MemCalc System; Suwa Trust Co., Ltd., Tokyo, Japan) and, subsequently, separated into the HF and LF ranges for power analysis (Task Force, 1996). These indices were defined as LFnu = LF/(LF+HF) and HFnu = HF/(LF+HF). They are regarded as the markers of the sympathetic and parasympathetic nervous systems, respectively (Xhyheri et al, 2012). We estimated the times at which the participants fell asleep and woke up based on the changes in the body positions evaluated by the monitor.

## Definition of %Lag0

Lag was determined as the time difference indicated by the maximum correlation coefficient obtained from the cross-correlation analysis between HRV and PA. Cross-correlation coefficients were calculated for 10-min moving time windows over consecutive 60-min periods. We defined impairments of coordination between HRV and PA as a lag time of 1 min or longer. The lag analysis has been discussed in detail in our previous study (Taniguchi et al, 2015). Subsequently, we defined %Lag0 as the percentage of lag = 0 min in 1 h, and it is an index of coordination between HRV and PA. Low levels of %Lag0 indicated discoordination between PA and HRV.

## Statistical analysis

Data are expressed as mean ± standard error of the mean. Statistical analysis was appropriately performed by Mann–Whitney U-test using Excel and SPSS. All $p < 0.05$ were considered statistically significant.

### Ethics

This study was approved by the Ethics Committee at the National Cerebral and Cardiovascular Research Center, Chubu University, and Kyoto University. All participants provided written informed consents before participation in this study.

## Results

The participants were divided into the following four groups: group I: non-older with low fatigability (age < 60 years and fatigability score < 3; n = 39); group II: non-older with high fatigability (age < 60 years and fatigability score ≥ 3; n = 11); group III: older with low fatigability (age ≥ 60 years and fatigability score < 3; n = 31); and older with high fatigability (age ≥ 60 years and fatigability score ≥ 3; n = 14). There were no significant differences in age, body mass index, sleeping hours, and PA for one hour (mG/h) both before sleep and after waking between groups I and II. In contrast, the older participants with high fatigability had significantly longer sleep duration and higher PA before sleep compared with those with low fatigability (Table 1).

In this study, %lag0 was defined as the percentage of lag = 0 between PA and HRV case numbers in 1 h. Low levels of %Lag0 indicated discoordination between PA and HRV. In a participant with low fatigability, the lag between the time series of PA and LF/HF is shown in Figure 2. These indicate that the time series between PA and LF/HF were coordinated, and the lag equals zero. If this coordination continues for 1 h, then %Lag0 = 100 as defined in the Methods sections. As another example case with high fatigability, the time series with a lag = 3 min of PA and LF/HF are shown in Figure 3. These indicate that PA preceded in LF/HF. In this case, %Lag0 would be 0 if this lag continues for 1 h, and PA and LF/HF would not be considerably coordinated. Detailed explanations are described in our previous paper (Taniguchi et al,2015).

In the hour before sleeping at night, non-older participants with high fatigability had significantly lower %Lag0 between HFnu or LF/HF and PA than those with low fatigability (left Panel in Figure 4). However, in the older groups, there were no significant differences in %lag0. In the hour after night sleep, there were no significant differences in %lag0 between participants with low fatigability and those with high fatigability, both, in the non-older and older groups (right panel in Figure 4).

Of the 50 non-older participants, the numbers of those who answered “yes” to the aforementioned seven questions were 16, 16, 9, 10, 1, 2 and 4, respectively. Of the 45 older participants, 9, 20, 9, 13, 0, 1 and 3, respectively, answered yes to the same questions. Participients in the non-older group who answered “yes” to Q2 (Does working tire you out completely?) had significantly lower %lag0 between HFnu and PA in the hour before sleep compared to those who answered “no”. However, in the older groups, there were no significant differences in %lag0 between PA and both HFnu and LF/HF. Additionally, those in the non-older group who answered “yes” for Q3 (Do you usually get up tired and exhausted in the morning?) had significantly lower %lag0 between HFnu or LF/HF and PA compared to those who answered “no”, whereas there were no significant differences in %lag0 HFnu and LF/HF before sleep both as to Q1 and 4 , and

Q1, Q2, Q3, and Q4 after waking up (Table 2 and 3). Statistical analyses were not performed for the relationships between %lag0 and the answers to Q5, Q6, or Q7, because the numbers were too small.

# Discussion

The major finding of this study was that the participants in the non-older group with high fatigability scores had significantly lower %lag0 compared with those with low fatigability in the hour before sleep; however, the difference was not significant in the hour after waking up. Additionally, participants in the non-older group with higher fatigability and exhaustion in the morning had significantly lower %lag0 than those without exhaustion in the hour before sleep but not in the hour after wake-up.

In non-older participants, no significant differences were observed in terms of basic characteristics between the high and low fatigability groups. In the older group, however, the high fatigability group had significantly longer sleeping hours and lower PA in the evening than the low fatigability group. The sleeping hours at night also involved nocturnal awakening.

A previous study reported that improved sleep may lead to low fatigability in older people (Christie et al, 2016). Additionally, an experimental study has demonstrated that exercise has a positive effect on sleep in older adults with sleep complications (King et al, 2008). Therefore, we believe that low PA before sleep is linked with low sleep quality and fatigability.

In the non-older group, %lag0 one hour before sleep between HRV (both HFnu and LF/HF) and PA was significantly higher in the low fatigability group than that in the high fatigability group (Figure 4). There were no such significant differences in the older group. It has been reported that fatigue stems not only from training overload or daily activities with inadequate rest but also from various inputs, such as psychological stress (Meeusen et al, 2013). Therefore, daily PA may be related to fatigability, and may affect HRV. As a result, fatigability may be one of the factors that affect the coordination between HRV and PA in non-older people.

Participants who answered “yes” to the question Q3 “Do you usually get up tired and exhausted in the morning?” had significantly lower %lag0 between HFnu and LF/HF and PA in the hour before sleep compared to those who answered “no”, but there was no significant differences in the hour after waking (Table 2 and 3). We considered that %lag0 in the hour before sleep and that in the hour after waking up had different clinical relevance since %lag0 of these two time periods had no significant correlation (data not shown, Appendix 1). Futheremore, in the hour after waking up, the participants generally performed a higher level of daily activities than they did in the hour before sleep (Table 1). Various social events happen in the daytime period for most people, during which %Lag0 varied markedly depending on the participants (data not shown, Appendix 4). Taking the above considerations together, our present results suggested that one hour before night sleep appeared to involve less social activities and the most significant time for analysis of the relationship of fatigability and the coordination between HRV and PA.

In this study, we focused on evaluating the relationship between fatigability and HRV more clearly by using PA. It has been reported that altered autonomic nervous balance has been observed in adults with fatigue (Watanabe et al, 2008, Tanaka et al, 2011). Moreover, previous studies have shown that mental fatigability and altered HRV are both related to selective regions of the prefrontal cortex, which serves as a functional circuit (Leavitt and DeLuca 2010). Additionally, another study showed that the medial orbitofrontal cortex is associated with fatigability in chronic fatigue syndrome (Tanaka et al, 2006). Therefore, we considered that fatigability may affect selective regions of the brain and/or neuro-muscular system, and in turn this affects the coordination between HRV and PA.

Our newly developed %Lag0 index may be available in various kinds of clinical settings at least in non-older women during free-moving. Further studies are required to clarify the detailed physiological mechanism of discordination betweeen HRV and PA.

The analytical method employed in this study to evaluate fatigability and the coordination between the autonomic nervous system and physical activity has limitations. This study did not include controls with matched comorbidities or physical conditions. Further controlled studies involving subjects with various metabolic and/or neuro-muscular diseases that are associated with discoordination, are required.

# Conclusions

The coordination between HRV and PA was diminished due to fatigability in non-older women in the hour before sleep. Additionally, %lag0 can be estimated using a non-invasive and simple method. This index could prove useful in public health or sports science disciplines to formulate measures to avoid fatigability.

# Declarations

### Acknowledgments

### Research ethics and patient consent

This study was approved by the Ethics Committee at the National Cerebral and Cardiovascular Research Center (M18-19-2, M26-158), Chubu University (280031), and Kyoto University (R1758). All participants provided written informed consent before participation in this study. All participants provided written and explicit consent for their anonymized data to be used in publications.

### Conflict of interests

The Authors declare that there is no conflict of interest.


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### Author contributions

KT performed all parts of the method and wrote all of the manuscript. AShimouchi performed experimental plan and methodological procedures, rewrote all parts of the manuscript. NJ performed several parts of the experiment and gave advice for presentation. ASeiyama gave an idea of analysis and rewrote the original manuscript. All authors have read and approved the manuscript


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# Tables

Table 1. Comparisons of the basic characteristics of age, body mass index, sleeping hours, PA, HFnu, and LF/HF between fatigability scores.

| Group | | I | II | III | IV |
|---|---|---|---|---|---|
| Fatigability score | | < 3 | ≥ 3 | < 3 | ≥ 3 |
| Age (years) | | < 60 | < 60 | ≥ 60 | ≥ 60 |
| Fatigability | | < 3 | ≥ 3 | < 3 | ≥ 3 |
| n | | 39 | 11 | 31 | 14 |
| Age | | 41.9±1.9 | 44.9±3.8 | 70.4±1.0 | 70.7±1.6 |
| Body mass index | | 21.9±0.5 | 22.4±0.7 | 22.3±0.5 | 23.9±1.0 |
| Sleeping hours(h) | | 6.9±0.2 | 6.6±0.6 | 7.2±0.2 | 8.0±0.3* |
| Frequency of nocturnal awakening | | 0.4±0.1 | 0.8±0.3 | 1.0±0.1 | 1.2±0.3 |
| PA(mG/h) | before sleep | 37.9±2.2 | 42.9±4.7 | 43.8±2.0 | 33.2±3.4* |
| | after waking | 51.3±3.1 | 46.3±4.4 | 54.8±4.0 | 42.7±4.7 |

* $p < 0.05$ III vs. IV

PA, physical acceleration; HF, high frequency; LF, low frequency; HFnu=HF/(LF+HF).

Table 2. %Lag0 before sleep in response to the questionnaire items.

| Questionnaires | %Lag0 | Non-older | | Older | |
|---|---|---|---|---|---|
| | | No | Yes | No | Yes |
| Q1Do you often get spells of complete exhaustion or fatigue? | HFnu and PA | 62.8±6.8 | 48.3±10.9 | 31.6±7.2 | 29.4±7.2 |
| | LF/HF and PA | 54.9±6.4 | 47.0±10.4 | 23.8±6.7 | 27.6±6.5 |
| Q2: Does working tire you out completely? | HFnu and PA | 66.9±6.6 | 39.8±10.2* | 33.5±7.6 | 27.1±6.6 |
| | LF/HF and PA | 55.3±6.5 | 46.1±6.5 | 27.0±6.8 | 19.1±5.8 |
| Q3: Do you usually get up tired and exhausted in the morning? | HFnu and PA | 66.3±6.0 | 21.5±10.7** | 29.2±5.6 | 36.7±12.4 |
| | LF/HF and PA | 60.3±5.7 | 16.3±8.1** | 23.8±5.5 | 27.6±9.4 |
| Q4: Does every little effort wear you out? | HFnu and PA | 60.7±6.3 | 48.3±14.7 | 34.1±9.5 | 22.2±7.0 |
| | LF/HF and PA | 55.5±6.0 | 39.7±12.9 | 24.9±8.4 | 23.6±8.6 |

*: p <0.05, **: p<0.01, non-older *vs.* older

Table 3. %Lag0 after waking up in response to the questionnaire items.

| Questionnaires | %Lag0 | Non-older | | Older | |
|---|---|---|---|---|---|
| | | No | Yes | No | Yes |
| Q1:Do you often get spells of complete exhaustion or fatigue? | HFnu and PA | 44.5±5.5 | 40.7±10.2 | 14.4±4.2 | 33.9±7.7 |
| | LF/HF and PA | 31.6±5.2 | 29.9±8.7 | 9.0±3.6 | 27.6±6.5 |
| Q2: Does working tire you out completely? | HFnu and PA | 44.6±5.8 | 40.5±9.4 | 13.7±3.9 | 24.2±7.2 |
| | LF/HF and PA | 30.3±5.4 | 32.5±8.3 | 9.1±3.9 | 13.5±5.0 |
| Q3: Do you usually get up tired and exhausted in the morning? | HFnu and PA | 45.8±5.3 | 31.9±13.1 | 14.4±3.6 | 33.9±12.6 |
| | LF/HF and PA | 31.1±4.9 | 30.9±10.5 | 9.0±3.9 | 19.0±9.4 |
| Q4: Does every little effort wear you out? | HFnu and PA | 45.7±5.3 | 33.7±12.9 | 25.9±6.7 | 16.8±7.3 |
| | LF/HF and PA | 31.0±4.9 | 31.3±11.0 | 13.6±6.9 | 10.0±4.7 |

# Figures

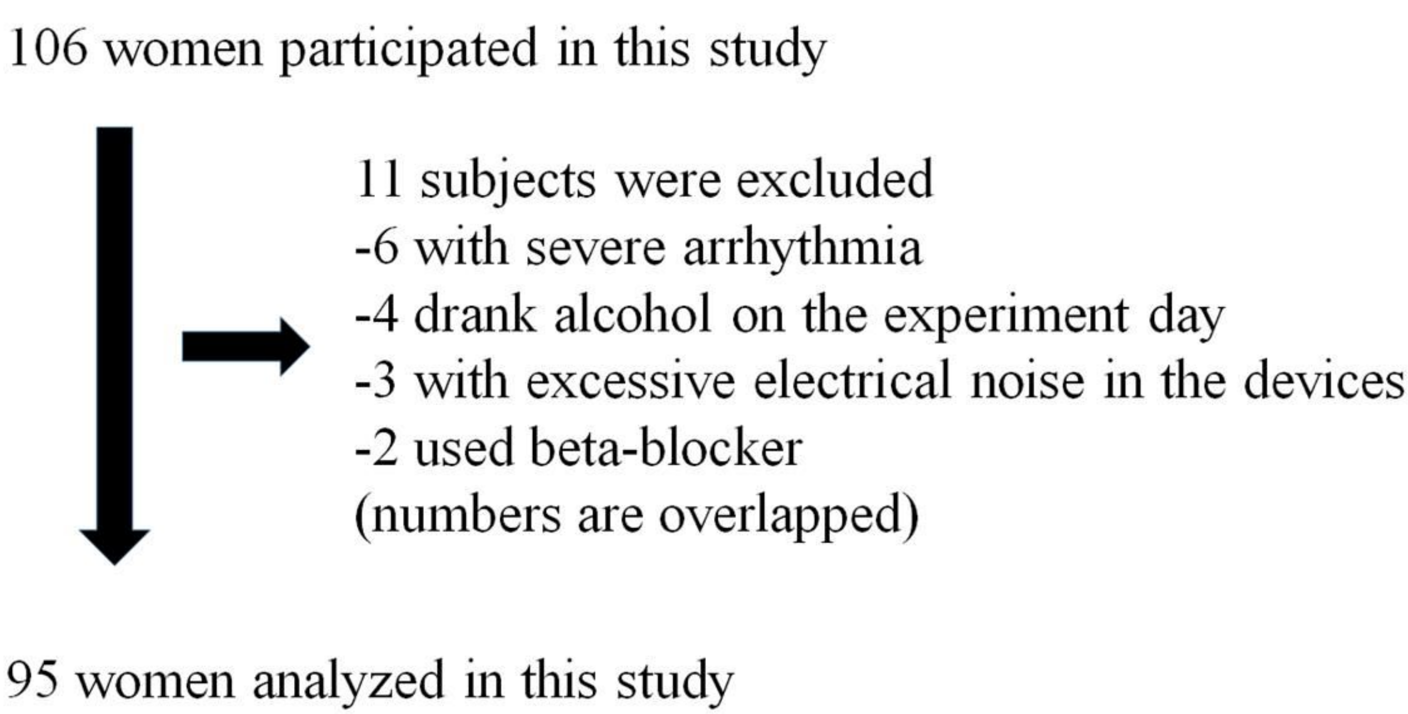
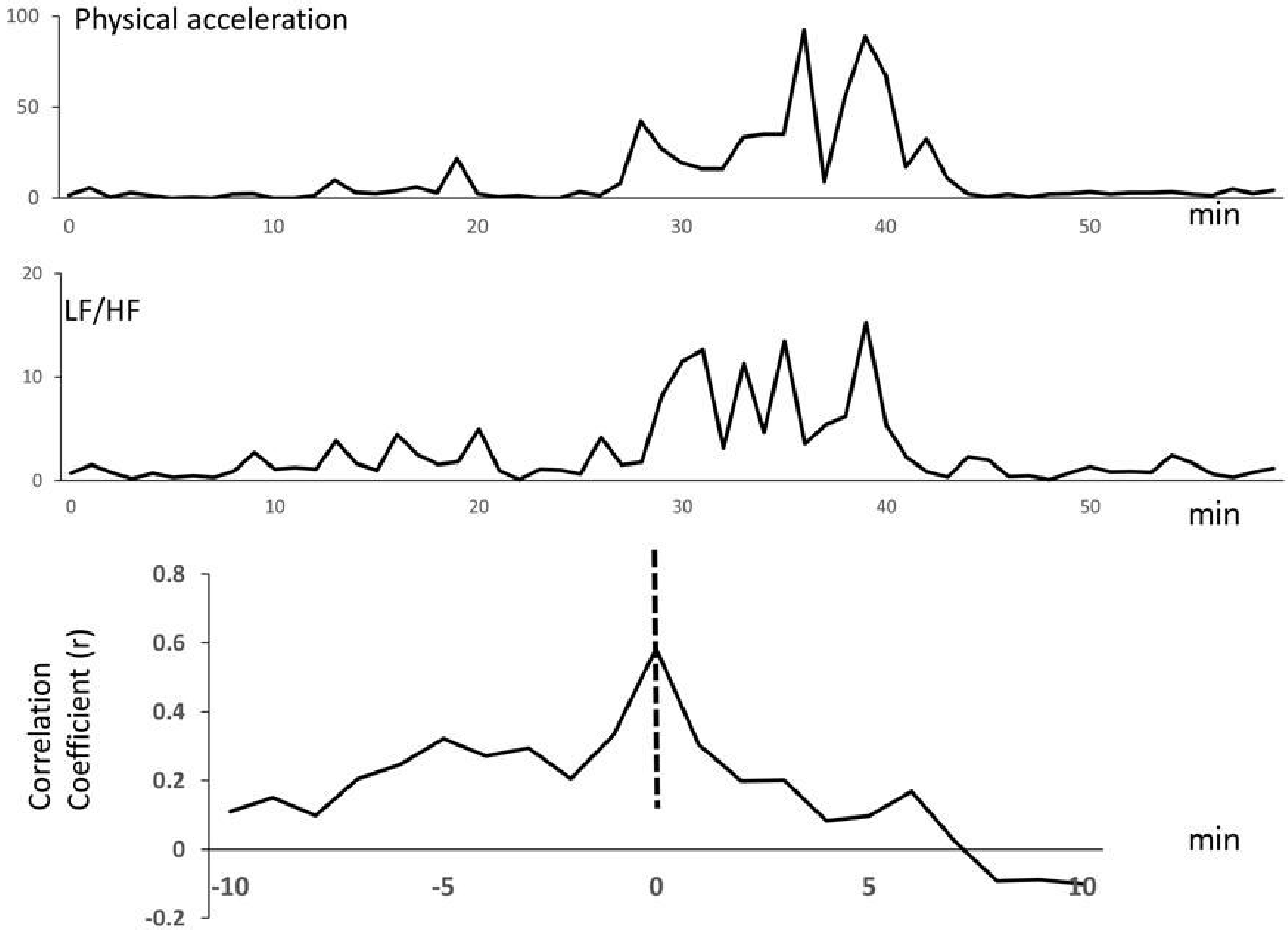


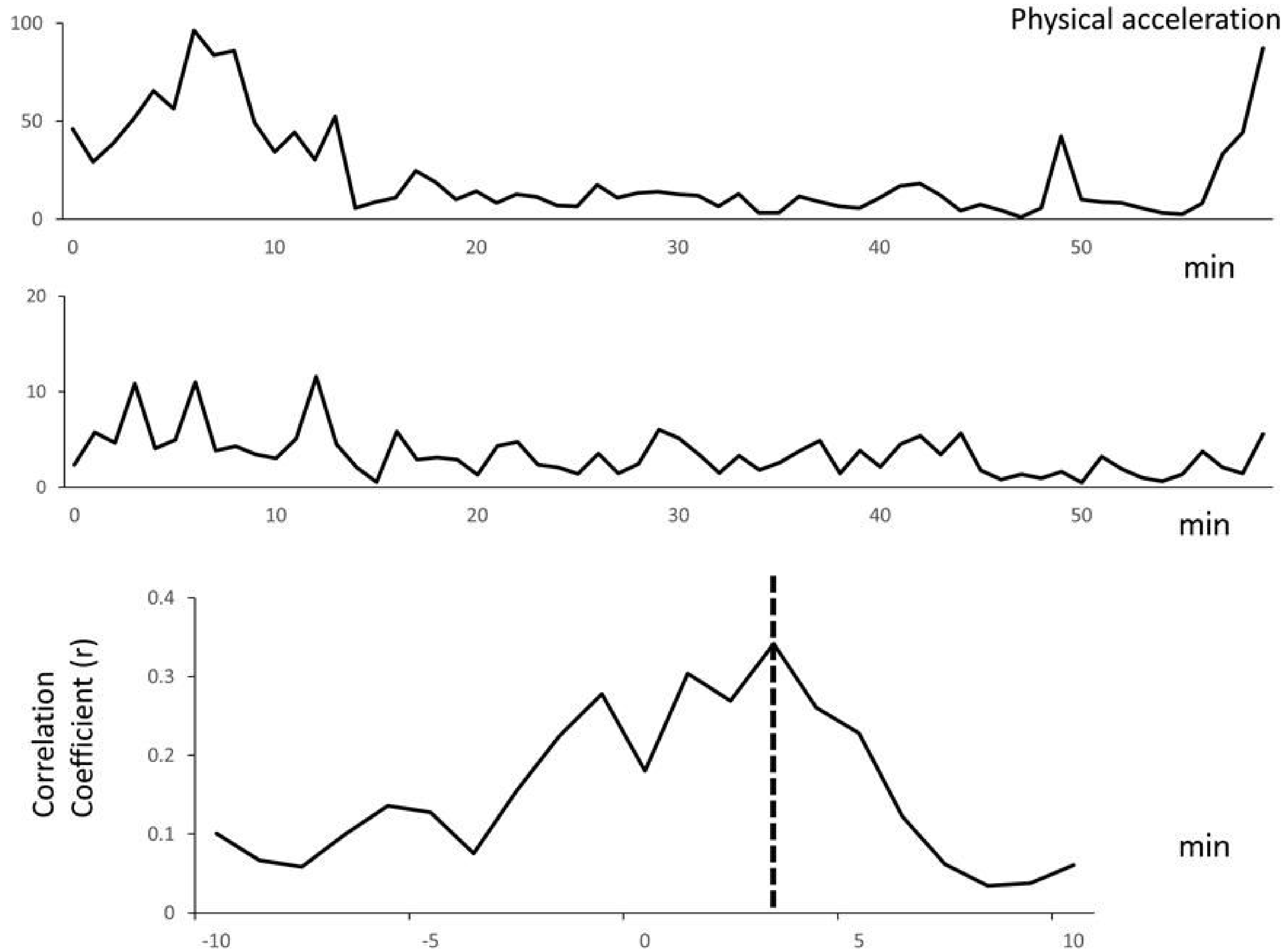

Figure 1

The study population for the evaluation of coordination between heart rate variability (HRV) and physical acceleration (PA).




## Figure 2

Lag = 0 in PA and LF/HF before night sleep.




## Figure 3

Lag = 3 min of PA and LF/HF before night sleep

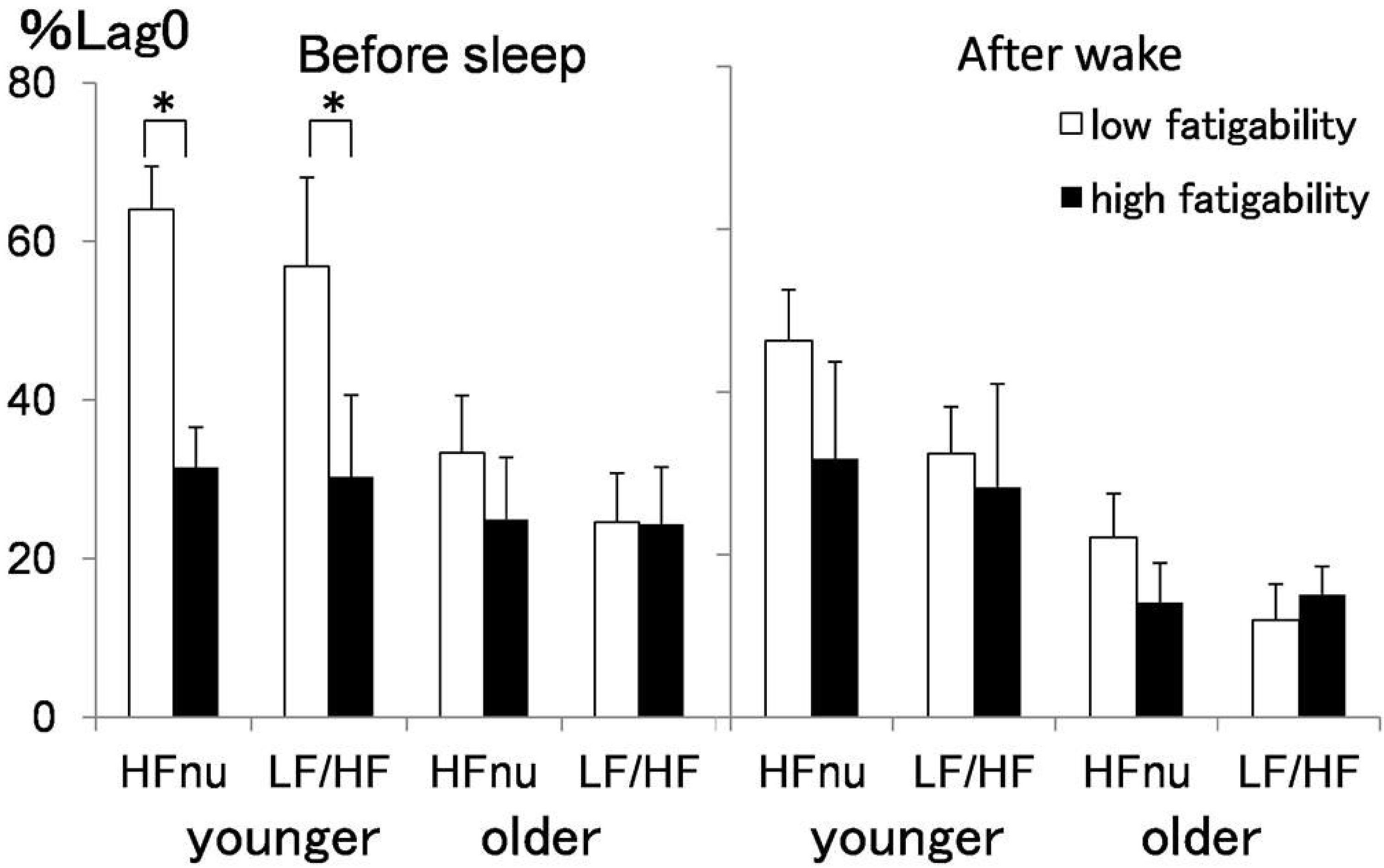



**Figure 4**

The relationship between %lag0 and fatigability during 1 h before and after night sleep in the non-older and older groups. * $p < 0.05$ low fatigability vs. high fatigability

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- QuestionnaireinEnglishCMI.pdf
- QuestionnaireinJapaneseCMI.pdf
- supplementaldata.pdf