Depression is associated with discoordination between heart rate variability and physical acceleration in older women

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Abstract

Depression associates closely with autonomic nervous system and physical activity, however, there have been no studies on the relationship between depression and the coordination of heart rate variability (HRV) and physical acceleration (PA). Ninety-five adult women were divided into non-older and older groups. The non-older group comprised 50 adulte women (below 60 years), and the older group comprised 45 women (above 60 years). HRV and PA data were simultaneously obtained every minute for 24 h during the free-moving day by using the ActiveTracer accelerometer. The ratios of low frequency/high frequency and high frequency were used as HRV indices, indicating sympathetic and parasympathetic nervous activities, respectively. Lag time was determined as the time difference indicated by the maximum absolute cross-correlation coefficients obtained from the analysis between the HRV components and the PA. We defined %Lag0 as the % frequency of the lag = 0 min between HRV and PA in 1 h. The General Health Questionnaire 28 (GHQ28) was used to evaluate the effects of psychological distress, including depression. In the hour before the night's sleep, %Lag0 was significantly lower in older women with depression (GHQ28 subscale D) than in older women without depression ($p < 0.05$). However, no significant difference between %Lag0 and depression status was observed in the hour after waking in older women. The results suggest that impairments in coordination between HRV and PA are associated with depression in older women, particularly in the hour before a night's sleep on free-moving days.

Introduction

Depression is one of the most widespread mental illnesses globally and is associated with an increased risk of morbidity and suicide (Figueiredo et al., 2017). Depression is associated with physical and cognitive decline, reduced social life, and greater self-neglect, thereby increasing mortality (Almeida & Pfaff, 2005; Felipe et al. 2016). In addition, the prevalence of depressive symptoms in patients aged >60 years may reach 40% (Jacomo et al., 2020).

Nevertheless, psychological distress is also widely used as an indicator of the mental health of the public. Psychological distress implies the undifferentiated combination of symptoms ranging from depression and general anxiety symptoms to personality traits, functional disabilities, and behavioral problems (Jacomo et al., 2020). Reportedly, the incidence of psychological distress in women is approximately twice that in men, although both men and women have an increasing frequency as they get older (American Psychiatric Association, 2014). The General Health Questionnaire 28 (GHQ28) has been often utilized for the evaluation of psychological distress from subscales of somatic symptoms, anxiety and insomnia, social impairments, and severe depression (Goldberg & Hillier, 1979; Iwata & Saito, 1992).

Habitual activity and heart rate variability (HRV) have been reported to differ between men and women (Aoyagi & Shephard, 2013 Koenig & Thayer, 2016). The beneficial effects of physical activity (PA) on health have been widely studied, and PA proved an effective treatment for depression in older patients (Felipe et al., 2016). Plausible mechanisms to explain the association of PA with depression include PA-

induced changes in physiological/neurological and psychological parameters (Loprinzi et al., 2013). PA may prevent depression by increasing the functional activity of monoamines (Craft & Perna, 2004).

HRV is a non-invasive tool for assessing variations in beat-to-beat intervals and autonomic nervous system activity (ANS). Most human studies on the HRV spectrum have examined the power of high-frequency (HF) and low-frequency (LF) ranges (Klieger et al., 1991; Task Force, 1996). Normalized spectral indices, defined as HFnu = HF/(LF + HF), are regarded as markers of the parasympathetic nervous system (Stein et al., 2011). Studies have reported that increases in LF/HF may represent a shift toward sympathetic predominance and reduced vagal activity (Ashare et al., 2012; Malliani & Montano, 2002); thus, it has been used as a measure of sympathovagal balance (Sprangers et al., 1991), although the physiological underpinnings of this metric are controversial (Eckberg, 1997).

Physical acceleration has been utilized to evaluate PA in participants with severe mental illness (Dubbert et al., 2000) and several clinical settings (Bauman et al., 2016). During exercise with an increasing PA, an increase in the heart rate and sympathetic activity and a decrease in vagal discharge are detected (Proper et al., 2002). Moreover, previous studies have shown that immediately after initiating exercise, the heart rate increases due to a withdrawal of parasympathetic nervous activity and increased sympathetic nervous activity (Rowell & O'Leary, 1990). Under healthy conditions, we considered that PA causes an immediate HRV response, whereas in impaired conditions, the response is altered.

Cross-correlation analysis generates 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, 1995). To investigate the association of HRV with a physiological signal, cross-correlation analysis is widely used (Abdullah et al., 2010). Based on a cross-correlation analysis between the time series of HRV and PA, we reported that an increase in the lag time decreases with aging in the daily lives of free-moving adults (Taniguchi et al., 2015). Furthermore, we reported that increased lag was closely associated with depression, although sex dependency remained unclear because of the small number of subjects employed (Taniguchi et al., 2015).

In this study, we hypothesized that, in older women, the lag between HRV and PA was associated with depression and psychological distress and investigated whether this mental stress was associated with the coordination between HRV and PA in daily life. To the best of our knowledge, this study is the first attempt to reveal the relationship between depression and the coordination between HRV and PA in free-moving adult women.

Methods

Participants

A total of 106 volunteers participated in this study. Study participants were adult women whose daily activities were not restricted by disease or injury. Excluded participants included five who drank alcohol on the experimental day, six who had significant arrhythmias, two who were taking beta-blockers, and

three who had excessive electrical noise in the PA devices described below (these numbers overlapped). All participants were screened based on their responses to medical interviews about their previous and present illnesses, physical findings, blood test results, and electrocardiogram (ECG) (Fig. 1). Finally, 95 participants aged 22–85 years were included in this study. Of these, 4 had type II diabetes, 17 had hypertension, 35 had dyslipidemia, 6 had hepatic dysfunction, and 2 had renal dysfunction. However, these comorbidities were mild, and none of the participants had psychological medication and restricted movement.

Protocols

Participants completed the GHQ28 before or on the day of the assessment and were then brought to the laboratory. They arrived at the laboratory at approximately 13:00 and underwent a physical examination and ECG. The participants then wore a portable monitor (Active Tracer AC301; GMS Inc., Tokyo, Japan) to record PA and R-R intervals for 24 h. During monitoring, participants were instructed to continue with their usual lives but to avoid bathing. After the completion of the 24-h monitoring period, each participant returned to the laboratory. Experimental protocols were described in detail in our previous studies (Taniguchi et al., 2015; Taniguchi et al., 2021).

Questionnaires

We used the Japanese version of the GHQ28 to evaluate psychological distress (Nihon Bunka Kagakusya Co., Ltd.). The GHQ28 is a self-report instrument and is frequently used to indicate psychological well-being and the psychological dimensions of the quality of life (Goldberg & Hillier, 1979). The GHQ28 has four subscales: (A) somatic symptoms, (B) anxiety and insomnia, (C) social impairments, and (D) severe depression (Goldberg & Hillier, 1979). Each of these subscales includes seven items. Items were scored using 2-point scores of 0-0-1-1, and the sum of these scores reportedly indicates the severity of mental or psychological distress (Goldberg & Hillier, 1979). GHQ scores were defined as low (total <8, A and B <2, C and D=0) and high (total ≥8, A and B ≥2, C and D ≥1) (Fukuda, & Kobayashi, 1983).

Physical activity

To measure PA, an ActiveTracer equipped with a triaxial accelerometer (72 g in weight) was used (Iwashita et al., 2003). The body of the accelerometer was positioned on the frontal midline of the waist above the navel to avoid disturbance of sleep or free movement. The resolution of acceleration was 2 mG, and the sensitivity ranged between 0 and 4.0 G. The absolute values of the resultant vectors, which were calculated from the signals of triaxial acceleration, were averaged for every minute. The times at which participants fell asleep and woke up were estimated based on the records kept by the participants and changes in body positions evaluated from the acceleration vectors. It was difficult to accurately identify falling asleep, nocturnal waking, and waking up without an electroencephalogram. However, we confirmed that the results obtained from this method did not significantly alter the %Lag0 index described below (*Definition of %Lag*), even if the accurate time of falling asleep differed by 5 or 10 min. We defined

three periods as follows: evening, from the start of the monitoring to sleep at night; sleep, participants on the bed; and morning, after waking up to the end of the monitoring.

HRV analysis

Analysis of the HRV was performed at 1-min intervals using the MEMCalc System software (Suwa Trust Co., Ltd., Tokyo), which uses a maximal entropy combined with the least square method (Sawada et al., 1997). LF power (0.04–0.15 Hz) and HF power (0.15–0.40 Hz) were analyzed as HRV parameters (Task Force, 1996). In this study, HRV indices were defined as HFnu = HF/(LF + HF) and LF/HF, which have been regarded as markers of the ANS (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HFnu is generally associated with cardiac vagal balance (Klieger et al., 1991). Increased LF/HF may represent a shift toward sympathetic predominance and reduced vagal activity (Ashare et al., 2012).

Definition of %Lag0

Cross-correlation is a mathematical calculation representing the similarity of two signals changing over time, allowing for a defined lag time. Lag was determined as the time difference indicated by the minimum p-value obtained from an analysis of the cross-correlation between the HRV components (HFnu or LF/HF) and the PA. Cross-correlation coefficients were calculated for 10-min time windows over consecutive 60-min periods. In our preliminary cross-correlation analysis, we confirmed that similar results were obtained regardless of whether we used a time window of 10 or 20 min for evaluating the lag between HRV and PA (data not shown).

In previous cross-correlation studies, HRV components were extracted every 5 min (Takanishi et al., 2010). In this study, we employed 1-min data collection intervals to obtain more precise information. Active and passive changes in fundamentally different cardiovascular effects for approximately 20 s are involved in the central command, muscle receptors, high-pressure receptors, and low-pressure receptors (Kim et al., 2018). Moreover, in a head-up tilt test, a gradual change in hemodynamic parameters is observed, with plateau levels reached at 20–30 s (Sprangers et al., 1991). Therefore, lag=0 was defined when the HRV in response to PA was within -30 to 30 s. The coordination between HRV and PA is synchronized when the lag=0. If the response requires >30 s or <-30 s, the lag was determined as lag≠0 and judged that HRV and PA was not coordinated. Thus, the lag between PA and HRV would express the coordination levels. Furthermore, %Lag0 was defined as the percent ratio of lag=0 min in 1 h and an index of coordination between HRV and PA. Thus, low levels of %Lag0 would indicate impairment of coordination between PA and HRV.

Participants in Each Group

A previous report showed that older adults (aged >60 years) in Japan were better protected from distress following a disaster than did younger adults (Kato et al., 1996). Depression was also different between those groups (Kato et al., 1996). Therefore, in this study, the participants were divided into non-older and older age groups based on a cut-off of 60 years.

In this study, 95 participants were divided into four groups: non-older with low distress (age <60 years and GHQ total score <8, n=37, I), non-older with high distress (age <60 years and GHQ total score ≥8, n=13, II), older with low distress (age ≥60 years and GHQ total score <8, n=26, III), and older with high distress (age ≥60 years and GHQ total score ≥8, n=19, IV).

Statistical Analyses

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

Results

As shown in Table 1, no significant differences were observed in basic characteristics (age, body mass index, and sleeping hours), PA, and HRV (LF/HF and HFnu) in every period, except for PA in the evening, between the high- and low-distress groups of the same age group. In the older group, PA in the evening was significantly lower in the high-distress group (IV) than in the low-distress group (III). Among older participants, the high-distress group (IV) had significantly higher frequencies of nocturnal awakening than the low-distress group (III). As shown in Table 1, scores in the GHQ A–D subscales were significantly higher in the high-distress groups (II) than in the non-older low-distress groups (I). Similarly, in older participants, the scores in the GHQ A–D subscales were significantly higher in the high-distress groups (IV) than in the low-distress groups (III).

To understand %Lag0 better, two representative case studies are shown in Figs. 2 and 3. In this study, %Lag0 was defined as the % ratio of lag=0 case numbers over the total number of 10-min time windows over consecutive 60-min periods. In a participant without depression, the lag between the time series of PA and LF/HF is illustrated in Fig 2 as an example. This case indicated that the time series between them were synchronized, because their correlation coefficient indicated maximal correlation at lag=0 min. If this synchronization continues for 1 h, %Lag0=100%, as defined in Methods.

As another example case with depression, the time series with a lag=2 min of PA and LF/HF are shown in Fig. 3. Both time series indicate that PA preceded any change in LF/HF. In this case, %Lag0 would be 0% if this lag continues for 1 h, and PA and LF/HF because their correlation coefficient was maximal at lag=2 min, and LF/HF response to PA would not be considerably coordinated. Detailed explanations were described in our previous paper (Abdullah et al., 2010).

Relationships between age and %Lag0 1 h before and after sleep are shown in Table 2. The %Lag0 between HRV parameters and PA was significantly lower in the older group than in the non-older group 1 h before and after sleep. Both groups had a higher %Lag0 1 h before sleep than 1 h after waking up, but the differences were not significant.

Fig. 4 illustrates %Lag0 between the time series of HRV and PA 1 h before sleep (left panel) and after sleep (right panel). Each panel indicates the comparisons of %Lag0 between the time series of PA and HFnu or LF/HF in participants with low or high distress components (GHQ total, A–D) among the non-older (left) and older groups (right).

At 1 h before sleep (left panel of Fig. 4), the older group with high GHQ total and GHQ A–D scores had significantly lower %Lag0 than the non-older group. Remarkably, the older group with high GHQ D scores (severe depression) showed significantly lower %Lag0 between the time series of PA and both of HFnu and LF/HF than the older group having low GHQ D scores 1 h before sleep. Nonetheless, in the non-older group, no significant differences were found in %Lag0 between those with lower and higher GHQ total and A–D scores.

At 1 h after waking up (right panel of Fig. 4), the older group with high GHQ A–D scores had significantly lower %Lag0 than the non-older group, except in %Lag0 of PA and HFnu in GHQ B and C subscales. However, no significant difference was observed between the older groups with high GHQ D scores (severe depression) and older groups with low GHQ D score, in both HFnu and LF/HF.

Discussion

In adult women, we confirmed that %Lag0 is reduced with aging. It was significantly lower in older participants before and after sleep than in non-older participants, as reported in our previous study (Taniguchi et al., 2015). Furthermore, older women with depression had significantly lower %Lag0 1 h before sleep. These results indicate that depression is closely associated with impairments in the coordination between HRV and PA before sleep in older women, suggesting that %Lag0 between the time series of PA and HRV (both HFnu and LF/HF) could be an indicator for the detection of depression in older women.

In this study, we defined lag=0 as the time difference within -30 to 30 s indicated by the minimum p-value obtained from an analysis of the cross-correlation between the HRV components (HFnu or LF/HF) and PA. Active and passive changes in fundamentally different cardiovascular effects for approximately 20 s (within 30 s) involve the central command, muscle receptors, and high- and low-pressure receptors (Kim et al., 2018). Therefore, the definition of lag was based on our hypothesis that PA causes an immediate HRV response under healthy conditions. Therefore, in this study, we determined lag=0 (-30 to 30 s) as an indicator of the coordination between HRV and PA. However, very few studies have used this definition.

Psychological stress can be accurately evaluated using the total GHQ28 score (Goodwin et al., 2013). These findings appear to support our present results in older and non-older individuals with depressive tendencies based on their GHQ28 D subscale scores and lower %Lag0 between HRV and PA; however, the decrease was not significant in non-older individuals. These results indicate that depression is closely associated with the discoordination between HRV and PA in older women alone, particularly 1 h before sleep. To the best of our knowledge, this study is the first to focus on the association of depression with coordination between HRV and PA in adult women.

The hypothalamic-pituitary-adrenal axis plays a significant role in controlling neuroendocrine stress responses (Jankord & Herman, 2008). In vivo, human imaging studies reported that hypothalamic-pituitary-adrenal axis responses to several different stressful stimuli are gated through various brain regions (Holsen et al., 2012; Tobet et al., 2013). All activities in the body initiated from the telencephalon, including those controlled by neuronal programs in the hypothalamus and mesencephalon, co-opt the lower brain stem centers (Janig, 2006). PA is considered linked with the ANS (Mueller, 2007). Moreover, depression is associated with decreases in the total power of HRV, and medications used in the treatment also affect HRV (Burst et al., 1992). Additionally, the ANS and hypothalamic-pituitary-adrenal axis are highly coordinated and interconnected (Rotenberg & McGrath, 2016). We considered that the lag between PA and HRV was affected not only by direct interaction between the ANS and PA but also by the higher central nervous system, including mental or psychological conditions. Therefore, impairments in the coordination between the HRV and PA may be affected by depression and derived from compromised links among their systems.

Patients with depression have been reported to have sleep disorders (Franzen & Buysse, 2008). Participants with sleep difficulties are three- to fourfold more likely to be depressed, and those with depression have low sleep efficiency (Almeida & Pfaff, 2005). In this study, no significant difference in %Lag0 was detected between participants with or without incidents of nocturnal awakening on the experimental day or irregular sleep cycles, based on the questionnaires (data for reviewers). In the groups with depression, a close relationship was observed between HRV and depression before and during sleep, reflecting the coordination between HRV and PA. Impairments in the coordination between PA and the HRV before sleep, especially 1 h before sleep, may be associated with reduced sleep efficiency and quality.

The menopausal years in Japanese women reportedly begin approximately at age 52 (Gold et al., 2000). We divided participants into the non-older (age $\leq$59 years) and older groups (age $\geq$60 years). Therefore, the older group may have comprised postmenopausal women alone. By contrast, some of the participants in the non-older group may also have been postmenopausal, as they were in their late 40s and early 50s. Estrogen has been reported to reduce cardiomyocyte contractile function and sympathovagal nervous activity, whereas androgen enhances these (Gold et al., 2000). Estrogen acts on the central nervous system to reduce sympathovagal activity (Joyner et al., 2015). In postmenopausal women, sympathovagal nervous activity is elevated due to changes in the hormonal balance (Magri et al., 2006). Further, menopause or the menstruation cycle could also affect depression (Payne et al., 2007).

Limitations

The analytical method used in this study to evaluate the coordination between the HRV and PA has limitations. First, it remains unclear why the %Lag0 decreases significantly in older people with depression. In this study, we could not establish why menopause affected the %Lag0 in non-older and older women. Second, this study did not control for the comorbidity score or physical condition of participants. All participants had no or mild diseases. However, we considered that various kinds of metabolic and/or neuromuscular diseases could be involved in the discoordination, especially in older women who were postmenopausal. As the number of participants was limited, the effects of diseases on %Lag0 also remained unclear. Taking the above limitations into consideration, further controlled studies with large numbers are required in the future.

Conclusion

By using the “%Lag0” index, which was determined by the time-series correlation analysis between HRV and PA, this study suggests that impairments in the coordination between HRV and PA are closely associated with depression in older women, particularly 1 h before sleep on free-moving days. This index may detect depression using a non-invasive and quantitative analysis obtained from PA and HRV monitors in clinical or even home settings.

Declarations

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Conflicts of interest/Competing interests: Not applicable

***Availability of data and material*:** The datasets generated during and/or analysed during the current study are not publicly available due to etical reason but are available from the corresponding author on reasonable request.

Ethics approval: This study was approved by the Ethics Committee at the National Cerebral and Cardiovascular Research Center (M18-19-2, M26-158), Chubu University (280031), Kyoto University

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Consent to participate: All participants provided written informed consent before participation in this study.

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Tables

Table 1. Comparisons of the demographic, questionnaire, and extracted parameters between General Health Questionnaire 28 (GHQ) total scores

Group		I	II	III	IV
Age (years)		<60	<60	≥60	≥60
GHQ total score		score <8	score ≥8	score <8	score ≥8
N		37	13	26	19
Age (years)		42.8±1.9	42.2±3.6	69.8±1.1	71.4±1.4
Body mass index		21.6±0.4	23.2±0.8	23.1±0.7	22.4±0.6
Sleeping hours		6.8±0.2	7.1±0.5	7.2±0.3	7.5±0.3
Frequency of nocturnal awakening		0.46±0.12	0.54±0.22	0.73±0.15	1.41±0.22*
GHQ A: somatic symptoms		1.2±0.2	4.1±0.4#	1.4±0.3	3.3±0.5*
GHQ B: anxiety & insomnia		1.5±0.2	4.5±0.5#	1.4±0.3	5.4±0.4*
GHQ C: social impairment		0.2±0.1	2.2±0.6#	1.1±0.1	2.6±0.4*
GHQ D: severe depression		0.1±0.0	1.8±0.6#	0.0±0.0	2.7±0.6*
PA (mG)	evening	37.3±1.9	44.0±5.4	44.6±2.2	33.8±2.7*
	morning	49.8±3.1	51.3±5.2	54.8±4.8	44.9±3.3
HFnu	evening	0.26±0.01	0.27±0.02	0.28±0.02	0.32±0.02
	sleep	0.46±0.02	0.45±0.04	0.40±0.03	0.41±0.03
	morning	0.24±0.01	0.26±0.02	0.29±0.02	0.31±0.02
LF/HF	evening	6.06±0.44	5.40±0.75	4.97±0.41	4.43±0.44
	sleep	2.61±0.23	2.66±0.47	3.56±0.42	3.48±0.44
	morning	7.01±0.51	5.74±0.68	4.79±0.43	4.57±0.41

# $p<0.05$ I vs. II, * $p<0.05$ III vs. IV; evening, from the start of the monitoring to sleep at night; morning, after waking up to the end of the monitoring; night time, subjects in bed; PA, physical activity; HFnu, HF/(LF + HF); LF/HF, low/high frequency

Table 2. Age dependencies of %Lag0 1 h before and after sleep among non-older and older participants

		Non-older	Older
1 h before sleep (evening)	%lag0 between PA and HFnu	58.2±5.8	30.7±5.1**
	%lag0 between PA and LF/HF	43.3±4.9	18.3±3.9**
1 h after sleep (morning)	%lag0 between PA and HFnu	52.4±5.4	24.5±4.8**
	%lag0 between PA and LF/HF	31.1±4.5	11.0±3.1*

*p<0.05, **p<0.01, non-older vs. older; PA, physical activity; LF/HF, low/high frequency

Figures

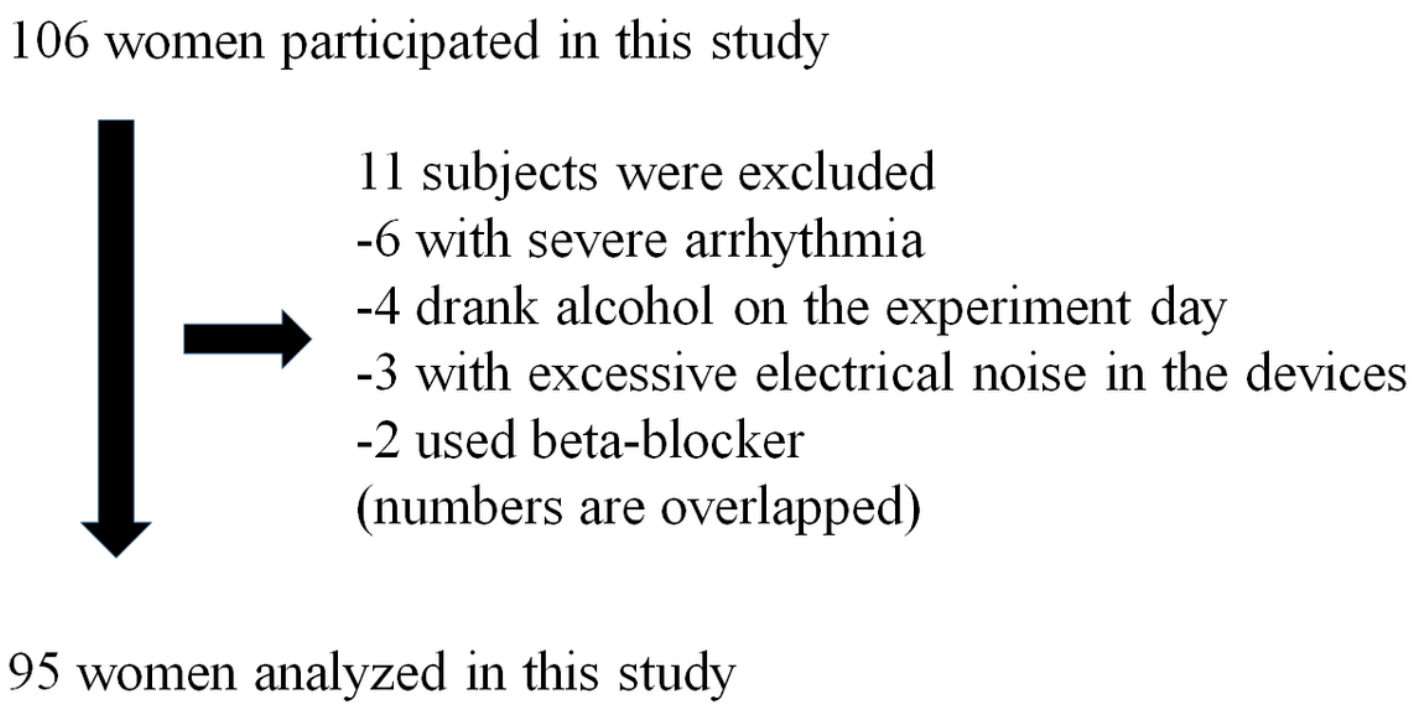

Figure 1

Study population for the evaluation of the coordination between heart rate variability (HRV) and physical activity (PA)

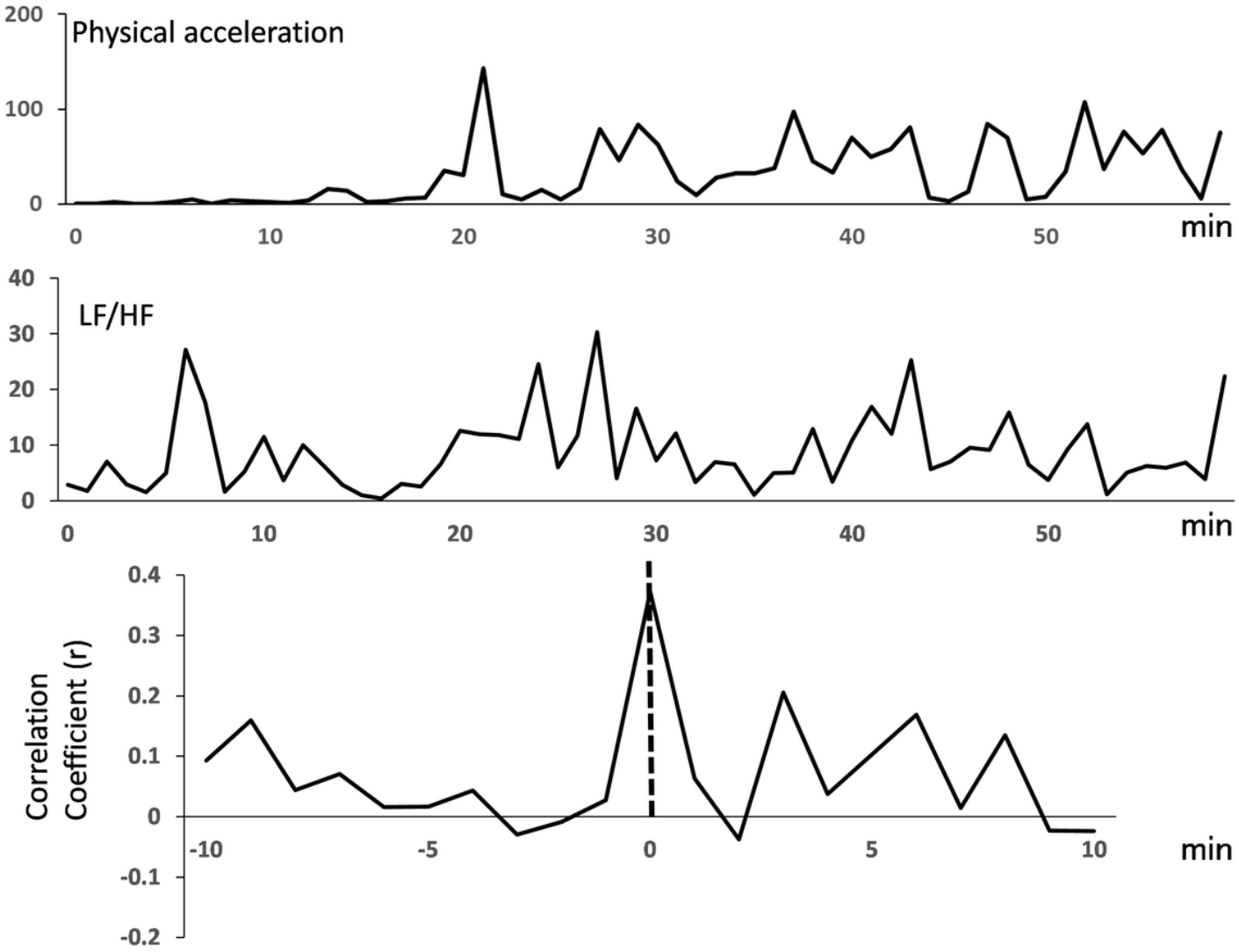

Figure 2

Case example with lag=0 of PA and LF/HF PA, physical acceleration; LF/HF, low/high frequency

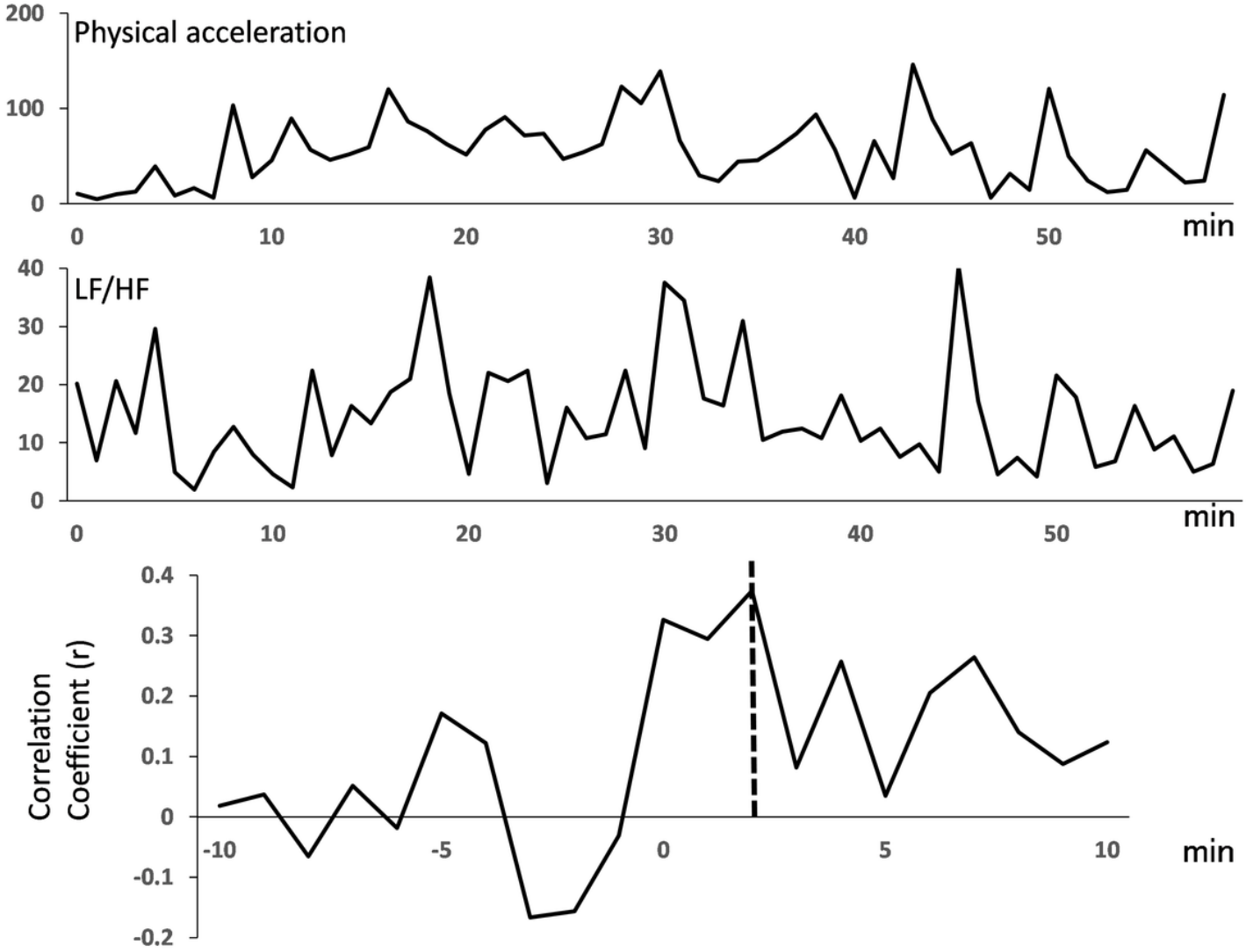

Figure 3

Case example with lag=2 min of PA and LF/HF PA, physical acceleration; LF/HF, low/high frequency

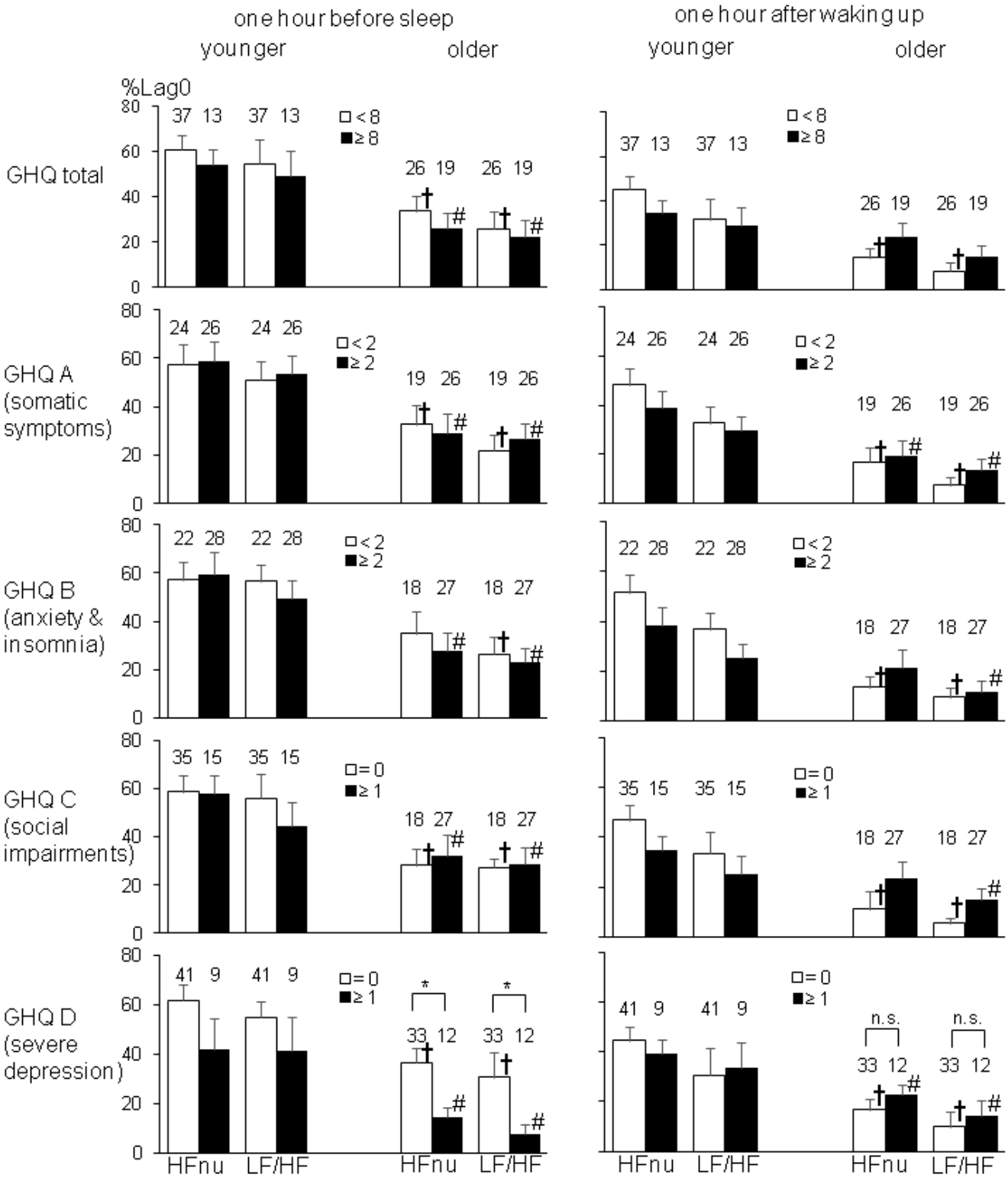

Figure 4

Relationships between %Lag0 and GHQ scores in the non-older and older groups Values above error bars show the number of participants. † p<0.05, non-older vs. older participants with low score of GHQ; # p<0.05, non-older vs. older participants with high GHQ scores; * p<0.05, older participants with low GHQ D score vs. older participants with high GHQ D scores. Error bars represent standard error. Open bar: low

GHQ scores (total <8, A and B <2, C and D=0). Closed bar: high GHQ scores (total ≥8, A and B ≥2, C and D ≥1). HFnu, HF/(LF + HF); LF/HF, low/high frequency; GHQ, General Health Questionnaire

Supplementary Files

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

- QuestionnireinEnglishGHQ28.pdf
- QuestionnaireinJapaneseGHQ28.pdf
- supplementaldata.pdf