ASSOCIATION OF HEART RATE AND BLOOD PRESSURE VARIABILITY WITH PSYCHOLOGICAL STATE AND PHYSICAL PERFORMANCE IN ELDERLY

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FACULTY OF ENGINEERING
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ASSOCIATION OF HEART RATE AND BLOOD PRESSURE VARIABILITY WITH PSYCHOLOGICAL STATE AND PHYSICAL PERFORMANCE IN ELDERLY

## ABSTRACT

The issue of falls among older individuals is one of the most common public health problems which has become a global concern. In Malaysia, the prevalence of falls was 14% among community-dwelling older adults aged 60 years and above in the past year. Previous studies have established the associations between both autonomic function indicators; heart rate variability (HRV) and blood pressure variability (BPV) with fall recurrence, as well as physical inactivity and psychological disorders as risk factors for falls, however, the influence of these fall risk factors on autonomic dysfunction among older fallers has not been adequately investigated. Therefore, this thesis aims to: 1) identify the differences between elderly fallers and non-fallers in terms of psychological function, physical activity, physical performance and autonomic nervous system, 2) investigate HRV or BPV indices that are most closely correlated to physical activity or psychological disorder in elderly adults, 3) identify physical activity, physical performance or psychological disorder measures that best predict autonomic function indices.

This was a cross-sectional study with 92 adult participants aged ≥60 years recruited from a tertiary hospital. Of those, forty-five older individuals who had at least one fall incident in the past two months were labelled as the fall cohort, while forty-seven older individuals with no history of fall in the past two months were labelled as the non-fallers cohort. Continuous non-invasive blood pressure and heart rate was monitored over 5 minutes of supine rest and 3 minutes of standing upright. Subsequently, time domain

and frequency domain analysis was performed on the continuous blood pressure signal to derive autonomic function indices (i.e., HRV and BPV).

Findings based on comparison between fallers and non-fallers showed that fallers were significantly older, requiring longer time to complete Time-Up and Go test, having weaker hand grip strength and lower physical activity scale (PASE), as well as reduced functional dependency (Lawton IADL). The HRV and BPV results from this study indicated potential deterioration in the autonomic function in older fallers, as compared to non-fallers.

Lawton Instrumental Activities of Daily Living (IADL) Scale and Physical Activity Scale for the Elderly (PASE) that indicate physical dependency and daily lifestyle of an individual were found to be the best independent predictors for autonomic function, as measured by the HRV and BPV indices. On the other hand, the stress and depression scores in the DASS-21 questionnaire best predict autonomic function (as measured by the HRV and BPV indices) during supine and standing, respectively. By knowing the association between these modifiable risk factors and autonomic function, early identification of patients at risk of recurrent falls and cardiovascular diseases can be performed to allow timely intervention.

**Keywords:** fall, heart rate variability, blood pressure variability, psychological disorder, physical performance

PERKAITAN DI ANTARA FLUKTUASI DEGUPAN JANTUNG DAN TEKANAN DARAH DENGAN KEADAAN PSIKOLOGI DAN PRESTASI FIZIKAL DI DALAM KALANGAN WARGA EMAS

## ABSTRAK

Isu jatuh di dalam kalangan warga emas merupakan salah satu masalah kesihatan awam yang paling biasa sehingga menjadi kebimbangan global. Di Malaysia, kekerapan jatuh adalah 14% di kalangan komuniti warga emas berumur lingkungan 60 tahun dan ke atas pada tahun lalu. Kajian terdahulu telah mewujudkan perkaitan di antara dua jenis indikator fungsi autonomi iaitu; fluktuasi degupan jantung (HRV) dan fluktuasi tekanan darah (BPV) dengan jatuh yang berulang, serta ketidakaktifan fizikal dan gangguan psikologi sebagai faktor risiko untuk jatuh. Walaubagaimanapun, pengaruh faktor risiko kejatuhan terhadap kegagalan autonomi di kalangan warga emas masih belum dikaji dengan secukupnya. Oleh itu, kajian ini bertujuan untuk: 1) mengenal pasti perbezaan di antara warga emas yang jatuh dan tidak jatuh dari segi fungsi psikologi, aktiviti fizikal, prestasi fizikal dan sistem saraf autonomi, 2) menilai HRV atau BPV yang berkait rapat dengan aktiviti fizikal atau gangguan psikologi dalam kalangan warga emas, 3) mengenal pasti jenis aktiviti fizikal, prestasi fizikal dan gangguan psikologi yang terbaik untuk meramal fungsi autonomi.

Kajian ini merupakan suatu kajian keratan rentas yang terdiri daripada 92 warga emas berumur 60 tahun ke atas, direkrut daripada hospital berdekatan. Daripada jumlah itu, empat puluh lima individu warga emas mengalami sekurang-kurangnya satu insiden jatuh dalam tempoh dua bulan yang lalu, dilabelkan sebagai kohort jatuh, manakala, empat puluh tujuh individu warga emas tidak mempunyai sejarah insiden jatuh dalam tempoh dua bulan yang lalu, dilabel sebagai kohort normal (tidak jatuh). Tekanan darah serta degupan jantung berterusan dan tidak invasif telah dipantau selama lima minit secara

baring dan tiga minit secara berdiri tegak. Seterusnya, analisis domain masa dan domain frekuensi dihasillkan daripada isyarat tekanan darah yang berterusan untuk memperoleh indeks fungsi autonomi (iaitu, HRV dan BPV).

Penemuan berdasarkan perbandingan di antara kohort jatuh dan normal (tidak jatuh) mendapati bahawa kumpulan warga emas yang pernah jatuh adalah lebih tua, memerlukan masa yang lama untuk menyelesaikan ujian *Time-Up and Go*, mempunyai kekuatan cengkaman tangan yang lebih lemah, skala aktiviti fizikal (PASE) yang juga rendah serta kebergantungan fungsi fizikal (Lawton IADL) yang semakin berkurangan. Keputusan HRV dan BPV daripada kajian ini juga menunjukkan potensi kemerosotan dalam fungsi autonomi dalam kalangan warga emas yang jatuh berbanding warga emas yang normal dan tidak jatuh.

Skala *Lawton Instrumental Activities of Daily Living (IADL)* dan Skala Aktiviti Fizikal untuk warga emas (PASE) yang kedua-duanya menunjukkan kebergantungan fizikal dan gaya hidup harian seseorang individu didapati sebagai peramal bebas terbaik untuk fungi autonomi, diukur oleh indeks HRV dan BPV semasa baring dan berdiri tegak. Sebaliknya, skor tekanan *(stress)* dan kemurungan *(depression)* soal selidik (DASS-21) diramalkan sebagai salah satu kayu ukur terbaik untuk fungsi autonomi (seperti yang diukur oleh indeks HRV dan BPV) semasa baring dan berdiri tegak. Dengan mengetahui perkaitan di antara faktor risiko yang boleh diubah suai ini, pengecaman awal pesakit yang berisiko untuk jatuh yang berulang dan penyakit kardiovaskular boleh dikenal pasti dengan kadar segera, membolehkan rawatan yang sewajarnya dilakukan pada masa yang tepat.

**Kata Kunci:** jatuh, fluktuasi degupan jantung, fluktuasi tekanan darah, ganguan psikologi, prestasi fizikal

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## LISTS OF SYMBOLS AND ABBREVIATIONS

| | | |
|---|---|---|
| % | : | percentage |
| ABPM | : | Ambulatory Blood Pressure Monitoring |
| ABPV | : | Ambulatory Blood Pressure Variability |
| AHA | : | American Heart Association |
| ANS | : | Autonomic Nervous System |
| ARV | : | Average Real Variability |
| BP | : | Blood Pressure |
| BPV | : | Blood Pressure Variability |
| CASP-12 | : | 12-items Control, Autonomy, Self-realization and Pleasure |
| CDC | : | Centers of Disease Control and Prevention |
| cm | : | centimeters |
| CV | : | Coefficient Variation |
| CVD | : | Cardiovascular Disease |
| DASS-21 | : | 12-items Depression, Anxiety and Stress Scale |
| DBP | : | Diastolic Blood Pressure |
| DBPV | : | Diastolic Blood Pressure Variability |
| ECG | : | Electrocardiographic |
| EMG | : | Electromyography |

| | | |
|---|---|---|
| FES-1 | : | Short Falls Efficacy Scale International |
| FFT | : | Fast Fourier Transform |
| HF | : | High Frequency |
| HPA | : | Hypothalamic pituitary-adrenal |
| HR | : | Heart rate |
| hrs/hr | : | hours |
| HRV | : | Heart Rate Variability |
| Hz | : | Hertz |
| KAP | : | Keele Assessment of Participation |
| Kg | : | Kilogram |
| kHz | : | kilo Hertz |
| Lawton IADL | : | Lawton's Instrumental Activities of Daily Life |
| LF | : | Low Frequency |
| LF : HF | : | Ratio of Law Frequency and High Frequency |
| LiAF | : | Life After Falls |
| LSNS | : | Lubben Social Network Scale |
| m | : | meters |
| nu | : | normalized unit |
| OH | : | Orthostatic Hypotension |
| PASE | : | Physical Activity Scale for the Elderly |
| PD | : | Panic Disorder |

| | | |
|---|---|---|
| QoL | : | Quality of Life |
| RMSRV | : | Root Mean Square of Real Variability |
| RSD | : | Residual Standard Deviation |
| SA | : | Spectral Analysis |
| SBP | : | Systolic Blood Pressure |
| SBPV | : | Systolic Blood Pressure Variability |
| SD | : | Standard Deviation |
| SDNN | : | Standard Deviation of NN intervals |
| TFM | : | Task Force Monitor |
| TP | : | Total Power |
| TUG | : | Time-up-and-Go |
| VCAT | : | Visual Cognitive Assessment Test |
| VIM | : | Variation Independent of Mean |
| VLF | : | Very Low Frequency |
| $X^0$ | : | degree |

# LIST OF APPENDICES

# CHAPTER 1: INTRODUCTION

## 1.1 General Introduction

Falls among older adults is a major public health concern due to an increase in the risk of death or serious injuries arising from the fall incidents (World Health Organization, 2018). In fact, in 2018, one out of four older people (28%) in United States aged 65 years and above had reported falling each year, which is equivalent to 36 million falls annually. In those who fell, approximately 20% to 30% of them may suffer moderate to severe injuries, such as broken bone, hip fracture, or head injuries (Centers for Disease Control and Prevention, 2018).

In Malaysia, incidence of falls among community-dwelling older adults (60 years and above) was 14% (Sahril et al., 2020), whereas 32.8% population of institutionalized elderly had reported having one or more falls in the past 1 year, with another 13.3% having moderate to high risk of falls (Kioh & Rashid, 2018). Older adults who experience falls and sustain an injury are more likely to be moved into long-term care facilities or healthcare facilities, which eventually impede their daily activities (Yeong et al., 2016). Besides, falls may also result in immobility and increase their dependency towards others due to fall-related injuries (Pirrie et al., 2020).

Over the past decade, the occurrence of falls in elderly has been linked to disorder within the autonomic function (Bhangu et al., 2017). According to Richter & Wright (2013), autonomic nervous system is comprised of two main branches (sympathetic and parasympathetic nervous system) and was defined as a complex of cells that maintains bodily homeostasis and coordinates bodily responses involuntarily. Recent published studies have implemented heart rate variability (HRV) and blood pressure variability (BPV) measures to observe the activity of the autonomic function in an individual. This was supported by a study where Goh et al. (2017) observed a reduction in continuous

BPV while standing in individuals with a history of falls. In addition, Furthermore, impaired autonomic function with increased sympathetic activity and decreased parasympathetic activity (as indicated by HRV) has been found to be independent predictors of recurrent falls (Chambi et al., 2020).

Furthermore, the occurrence of falls in older adults is associated with psychological factors. Fallers may avoid physical activity because of fear of recurrent fall (Hull et al., 2013; Hellström et al., 2009), with negatives effects on their cognitive and mental wellbeing (Hellström et al., 2009; Van Haastregt et al., 2008). Previous studies have reported that fear of falling causes a significant increase in anxiety and/or depression among older fallers in the United States (Hellström et al., 2009) and Europe (Stegenga et al., 2012). Bidirectional relationship between mental state and physical inactivity have also been observed among the African-American population, where depressive symptoms were more common among those with mobility limitation (Thorpe et al., 2011).

Physical inactivity and psychological disorders are both associated with changes in the autonomic function. Exercise training (Levy et al., 1998) and physical activity (Reland et al., 2003; Melo et al., 2005) improved parasympathetic and overall autonomic tone in older adults, regardless of age (Soares-Miranda et al., 2014; Tonello et al., 2014; Veijalainen et al., 2019). Furthermore, sedentarism and physical inactivity resulted in lower HRV (De Meersman, 1993), indicating impaired autonomic cardiac modulation (Zaffalon Júnior et al., 2018). In addition to physical inactivity, a direct correlation has been reported between autonomic function and psychiatric illness, such as major depressive disorder, panic disorder, and anxiety (Perna et al., 2020; Jung et al., 2019; Carr et al., 2018; Martinez et al., 2010). Impairment in autonomic function, as reflected by both HRV and BPV measures, has also been linked to an increase in cardiovascular diseases among psychiatric patients (Robson & Gray, 2007; Miller et al., 2006; De Hert et al., 2011).

While previous studies have established associations between HRV and BPV with fall recurrence, as well as physical inactivity and psychological disorders as risk factors for falls, the influence of physical performance and psychological status on autonomic dysfunction among older fallers has not been adequately investigated. Identification of measures of physical performance and psychological status can be used as pre-screening tools which could help identify patients with an increased risk of autonomic dysfunction and therefore useful for early intervention. Furthermore, this could aid in the diagnosis of autonomic dysfunction severity and reduce the risk of future falls and cardiovascular diseases.

## 1.2 Research Questions

The research questions of this study are:

i. What are the differences between elderly fallers and non-fallers in terms of psychological function, physical performance and autonomic nervous system?
ii. Are there any associations between psychological function, and physical performance with autonomic nervous system?
iii. Which physical performance or psychological disorder measures best predict autonomic function indices?

## 1.3 Research Objectives

The objectives of this study are:

i. To identify the differences between elderly fallers and non-fallers in terms of psychological function, physical performance and autonomic nervous system.
ii. To investigate HRV or BPV indices that are most closely correlated to physical performance or psychological disorder in elderly adults.
iii. To identify physical performance or psychological disorder measures that best predict autonomic function indices.

### 1.4 Thesis layout

This thesis consists of six chapters. The arrangement of the chapters is as follows:

**Chapter 1** provides a general background on the topic of interest, which includes general introduction, research questions and specific research objectives.

**Chapter 2** contains the literature review section, which starts with the statistics and a clear definition of falls. This is followed by a detailed description of the non-invasive indicators of the autonomic nervous system, i.e., heart rate variability (HRV) and blood pressure variability (BPV), presented in both time- and frequency-domains. Next, the risk factors for falls and the risk assessment tools are described.

**Chapter 3** features a detailed explanation on the methodology used in this project. The sections presented in this chapter are study design and recruitment, data collection, data processing, data analysis and statistical analysis.

**Chapter 4** reports the results of this study. Differences between fallers and non-fallers with respect to their baseline demographics and HRV and BPV indices during supine and standing are presented. In addition, relationship between psychological disorder, physical performance and HRV/BPV indices, as well as the independent predictors for HRV and BPV indices, used as non-invasive indicators for autonomic function in this study, are presented.

**Chapter 5** consists of the discussion section. Differences between fallers and non-fallers with regards to their baseline demographic and autonomic function indices are discussed. The relationship between HRV/BPV indices and psychological disorder as well as physical performance is discussed. Finally, discussions on the independent predictor analysis results are presented.

**Chapter 6** describes the summary of findings, conclusions, study limitations, and recommendations for future work.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Statistics of Fallers

Falls in older individuals is a major public health concern globally and is the main cause of injury or death in older adults. According to Melzer, Benjuya, & Kaplanski in 2004, 30% of people over 65 years old and 50% of people over 80 years old experience at least one fall each year. Furthermore, the Centers for Disease Control and Prevention (CDC) in 2020 reported that 88 older adults died every day and more than 8 million falls required medical attention or reduced mobility as the fall itself threatened their health and independence. Apart from the increase in mortality rates (World Health Organization, 2021; Rubenstein, 2006; Dunn et al., 1992; Tan et al., 2016), the consequences of falls also include morbidity (Rubenstein, 2006; Dunn et al., 1992; James et al., 2019; Masud & Morris, 2001), fractures (Ambrose et al., 2015; Santy-Tomlinson et al., 2018; Gomez et al., 2019), reduced mobility and physical functioning (Vellas et al., 1997; Azidah et al., 2012; Low & Balaraman, 2017; Tan et al., 2016).

Generally, a study by the CDC on statistics of older fallers shows that falls can vary according to gender, age as well as race or ethnicity and it was reported that falls are more likely to happen among older females aged 85 years old and most probably among American Indians and Alaskan Natives (refer Figure 2.1). Besides that, a review article on falls prevalence and risk assessment tools showed that the percentage of the prevalence of falls also varies according to the countries as well (Shaharudin et al., 2018). These findings were supported by other studies which showed that the prevalence of falls among adults aged 65 years old and above generally residing in Malaysia was between 15% to 34% (Rizawati & Mas, 2008; Singh et al., 2015), while specifically in urban-living Kuala Lumpur was 23.5%, whereas 31% was recorded in China, 20% in Japan and 34% was found in Chile (Gardner et al., 2000).

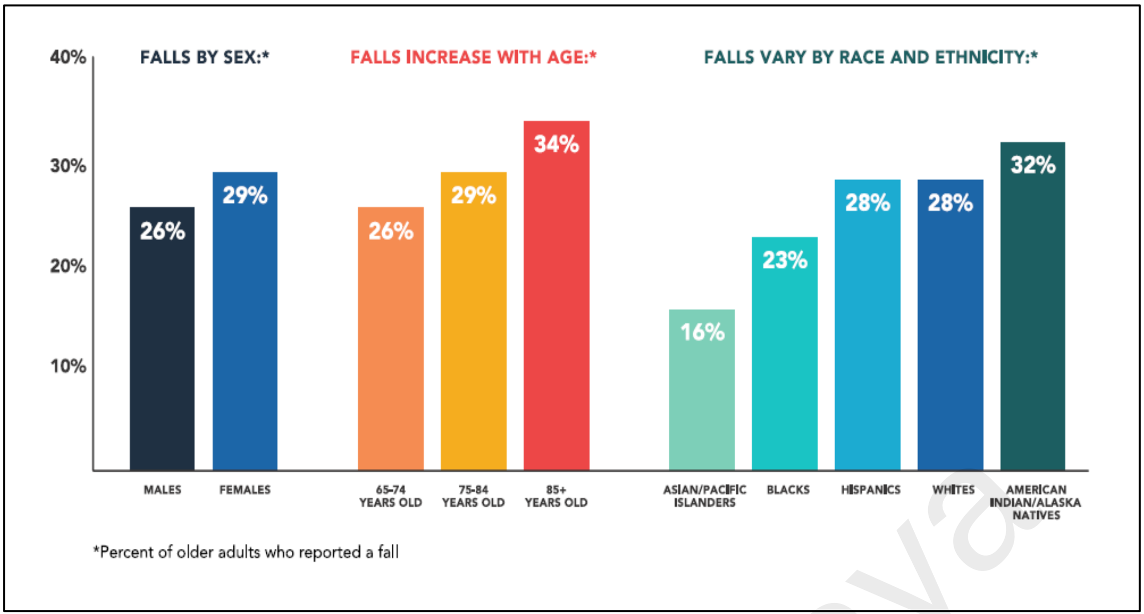



**Figure 2.1: Percentage of older fallers according to sex, age, race, and ethnicity (Centers for Disease Control and Prevention, 2020)**

## 2.2 Definition of Falls

Two systematic review studies on the definitions and methods of measuring falls in 2006 had revealed that there were no clear or explicit definitions of falls used as a designated gold standard (Hauer et al., 2006; Zecevic et al., 2006). This statement was further supported by another systematic review on randomised controlled trials (RCT) studies in 2012, where a variety of definitions had been spotted among other published studies, and the limited standardisation in defining falls hampered the comparability of study results (Schwenk et al., 2012). There are a lot of factors that can cause someone to trip and fall, including an uneven surface, slippery conditions, a weakened body, and dizziness, all of which can result in injuries, fractures, and other health issues (Scott et al., 2010). As a result of various factors that can cause falls, the term "fall" itself has come to define different things to different people.

In order to allow comparability between research findings and to avoid any inconsistency or confusion, the Kellogg's International Working Group on the Prevention of Falls in the Elderly had come up with the first official definition of a fall in 1987. The group defined a fall as “unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure”. Since then, many studies have adapted the definition, especially studies related to identifying factors that impaired the gait and balance controls of an individual (Tinetti et al., 1988; Hauer et al., 2006; Azidah et al., 2012). However, some of the definitions are not comprehensive enough as they do not take into account the causes of falls. This is because, falls are multifactorial, therefore, broader definitions that include cardiovascular and neurological fall risk factors such as dizziness, syncope, orthostatic hypotension and cardiac arrest are needed. This statement was further supported by the Prevention of Falls Network Europe Consensus groups (Lamb et al., 2005).

Hence, a simplified version of falls can be observed in 2008, where a global report on falls prevention by the World Health Organization (WHO) had defined a fall as “Inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or bed” (World Health Organization, 2008). As a result, we have used the WHO global report's widely accepted definition of falls in defining our sample population and the exclusion and inclusion criteria for elderly fallers in this study.

## 2.3 Common Risk Factors for Falls

In epidemiology studies, a risk factor can be defined as a determinant that is associated with an increased risk of disease or infection and is frequently used as a predictor when conducting clinical trials. Furthermore, having a complete understanding of the potential risk factors will assist medical researchers and practitioners in better diagnosing and preventing certain diseases and infections (Offord & Kraemer, 2000).

Therefore, a better understanding on the potential fall risk factor will be a great help in reducing the statistics of falls among the elderly, indirectly preventing any recurrent falls.

Several studies published on falls have shown that a major fall risk factor is commonly associated with the host's sociodemographic and medical health conditions. Apart from that, a study by Boelens et al. (2013) further differentiated risk factors into two categories: intrinsic and extrinsic (Kronfol, 2015). Intrinsic risk factor is related to the host body as exemplified in age, gender, genes as well as lower socioeconomic status (Stewart Williams et al., 2015), whilst extrinsic risk factor is related to environmental (location, slippery floor, stairs, improper footwear and clothing). On the other hand, behavioural (fear of falling and physical inactivity) and medical fall risk factors are also common among the elderly which includes poor cognitive functioning, arthritis, poorer physical function and any comorbidity associated with ageing such as chronic diseases and vision changes (Kronfol, 2015; Susilowati et al., 2020; Dyer et al., 1998).

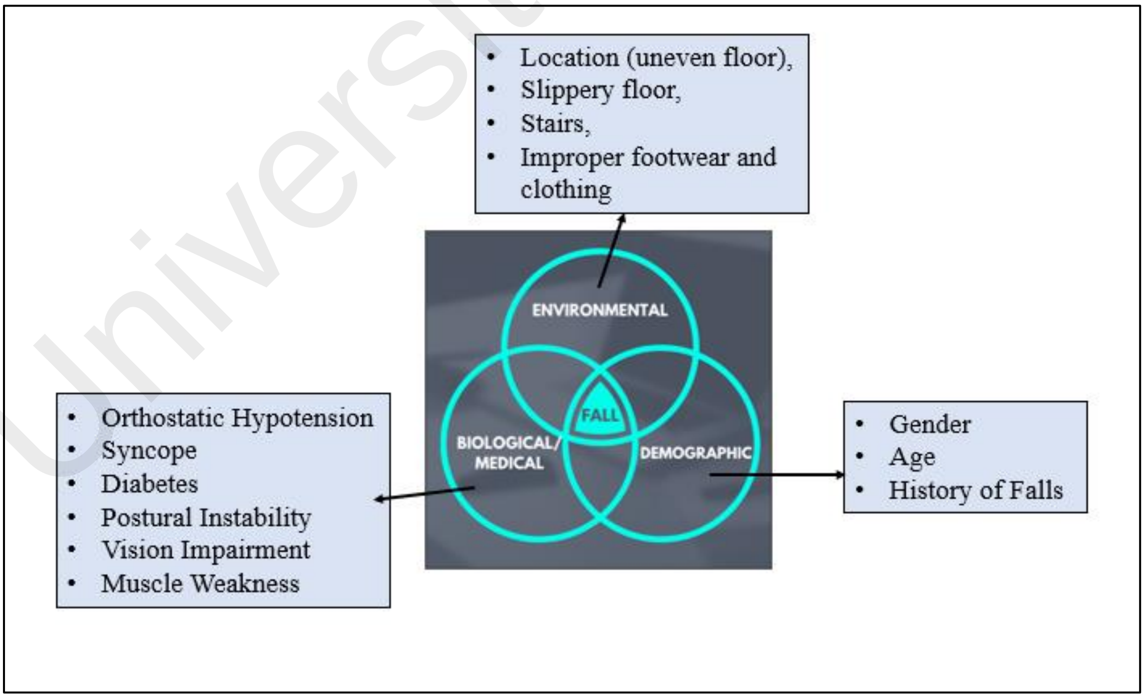



**Figure 2.2: Interaction between common fall risk factors (Rajagopalan et al., 2017)**

## 2.4 Autonomic Function as a Risk Factor for Falls

Autonomic function or commonly known as autonomic nervous system (ANS) is an important body regulator to maintain the homeostasis of the body. The ANS is a part of the peripheral nervous system that regulates involuntary processes such as blood pressure, heart rate, respiration as well as digestion without conscious effort (Benito-Gomez et al., 2019). Furthermore, autonomic function has been divided into two important branches which are the sympathetic and parasympathetic nervous systems. The sympathetic nervous system can be understood as a function that occurs when the subjects underwent "fight or flight" situations or in other words, a dangerous or stressful condition. Sympathetic reactions that can occur are increase in heart rate or blood pressure, pupil dilation and secretion of epinephrine and norepinephrine hormones. As opposed to the sympathetic nervous system, parasympathetic reaction will be activated when a person is in the rest and digest situation. Parasympathetic reactions include pupil constriction, reduced heart rate, lowering of blood pressure and digestion (Benito-Gomez et al., 2019; Richter & Wright, 2013; McCorry, 2007). However, both sympathetic and parasympathethic reactions will work together to maintain the homeostasis of the body, hence, a good autonomic nervous sytem can be reflected by the mechanism of these two important branches of autonomic function. According to McCorry (2007), generally, a good autonomic response can be observed with a higher parasympathetic activity during rest and higher sympathetic activity during tilt or sudden changes of the position. In other words, heightening of the sympathetic system only occurs when the subjects underwent "fight or flight" situations, while the parasympathetic system is predominant during resting and quiet conditions.

Moreover, apart from commonly published fall risk factors, autonomic dysfunction is often linked to falls and is more prevalent among the elderly as compared to younger people, but this association remains unclear (Mellingsaeter, 2015). However, several studies have proved that people with diseases related to autonomic failure are more prone to falls events or chances of recurrent falls. This can be explained where several studies had observed that falling is commonly associated with Parkinson disease, a disease related to the failure of the autonomic function in controlling body functions such as movement, gait and balance (Wood et al., 2002). In other words, decrease in gait function impedes the ability of the person in maintaining the equilibrium of the body and to stabilise the body's centre of mass over its base of support (Horak, 2009), indirectly leading to a fall event. This is further supported by a recent review by LeWitt et al. (2020) on recognition and management of risk factors for falls in the elderly with Parkinson disease (PD) where they stated that this disease is a chronic neurodegenerative disorder that increases gait impairment as well as limiting their mobility, indirectly doubling the risk of falls and increasing the percentage of falls up to 70% annually and 13% weekly (Wood et al., 2002; Playfer, 2001; Robinson et al., 2005).

Besides that, due to the consequences of the diseases related to autonomic function, other symptoms may exist such as dizziness or fainting upon changing the position from supine (lying) to standing or clinically known as orthostatic hypotension (OH). Several definitions arise in explaining the nature of orthostatic hypotension where OH was defined as a decrease in >20mmHg of systolic blood pressure (SBP) and >10mmHg of diastolic blood pressure (DBP) within the three minutes of standing (Izzati et al., 2020; Lanier et al., 2011). The reduction in both blood pressure was compared to the blood pressure during sitting or supine position (Lanier et al., 2011). This unfortunate situation is due to the inability of the autonomic function to maintain the physiological responses of blood pressure upon a postural change. Hence, a person with symptoms of orthostatic hypotension is more tend to fall.

### 2.4.1 Non-invasive Assessment of Autonomic Nervous System using Autonomic Function Tests

In order to accurately identify the fall risk factors, many risk assessments tools have been established to evaluate the risk of falls. In detecting autonomic dysfunction, several methods have been used as exemplified in the Valsalva maneuver test and tilt table assessment. The Valsalva maneuver test is where a forced expiratory effort against a closed airway is used to measure the continuous blood pressure and heart rate (Pstras et al., 2016). In other words, this test can be performed by closing one's mouth and pinching one's nose shut while pressing out as if blowing out a balloon. This test involves a complex reflex arc that includes sympathetic and parasympathetic pathways to the heart, sympathetic pathways to the vascular tree, and baroreceptors to the chest and lungs.

Alternatively, concerning orthostatic hypotension symptoms, the diagnosis can be made by using a postural challenge test known as head-up-tilt table testing. Literature suggests that the orthostatic challenge test has widely been used to observe the ability of the brain to maintain the amount of blood perfusion when in an upright position (Goswami et al., 2017). This method has been implemented by several studies where the patients are required to be in supine rest for at least 10 minutes and active stand for at least 3 minutes or passive standing/tilt at an angle of at least 60 degrees to 80 degrees (Goh et al., 2017; Lanier et al., 2011), with appropriately sized finger cuff attached on the middle and index fingers.

During tilt procedure, the most common tilting angle protocol that has been used was $70^0$ (Benditt et al., 1996), however, some studies performed passive tilt table with an angle elevated to $45^0$ (Fitzpatrick et al., 1991), $60^0$ (Schutzman et al., 1994; Fitzpatrick et al., 1991; Martinez et al., 2010) and $90^0$ angle head up tilt (Piccirillo et al., 1997). The difference in the angle of tilt may bring different results and may result in false negative tests. According to Fitzpatrick et al. (1991) in their study on syncope, 75% of positive responses was seen in the patients that had undergone $60^{o}$ tilt, meanwhile only 30% of the vasovagal syncope rate could be observed in the patients that had undergone $45^{0}$ tilt. On the other hand, due to no ‘gold standard’ protocol on tilt table testing, some studies have proven that the steeper the angle of tilt, the less specific the results that were obtained. Davies et al. (1976) tested on a tilt angle of $85^{0}$ and found only 35% of vasovagal response rate in healthy controls.

In addition, this test is more preferable as it is convenient, non-invasive and accurate as compared to other more invasive techniques (Zygmunt & Stanczyk, 2010). As advancement of technology has allowed for the detection of beat-to-beat blood pressure (BP) and heart rate (HR) in conjunction with tilt-table procedure, this study implemented non-invasive techniques rather than haemodynamic invasive techniques (e.g. transesophageal echocardiography (TEE), artery cannulation, pulmonary artery catheterization) to monitor the changes of blood pressure and heart rate upon active standing, indirectly detecting any symptoms related to orthostatic hypotension.

### 2.4.2 Non-invasive Indicators of the Autonomic Nervous System

Advancement in medical technology in detecting continuous blood pressure and heart rate using non-invasive techniques in turn has enabled the calculation of beat-to-beat blood pressure variability (BPV) and heart rate variability (HRV). Over the past decade, the incidence of falls, especially in older adults, has been hypothesised to be closely associated with an impairment in their autonomic function. Recent research which utilised heart rate variability (HRV) and blood pressure variability (BPV) measures as indicators of autonomic function has further strengthened this hypothesis. Goh et al. (2017) observed that a reduction in beat-to-beat BPV while standing was independently associated with increased risk of falls, whereas impaired autonomic function with higher sympathetic activity and reduced parasympathetic activity (as indicated by HRV) has become a predictor for recurrent falls, independent of orthostatic phenomena (Chambi et al., 2020).

#### 2.4.2.1 Heart Rate Variability (HRV)

Heart rate or heart pulse is the number of heartbeats per minute, whilst heart rate variability (HRV) or also known as RR variability is the variation in the time interval between heartbeats (Shaffer & Ginsberg, 2017). It is measured by the calculation of fluctuation or variations in the continuous interval. Heart rate variability results from the continuous changes in the sympathetic and parasympathetic reaction and the best method that can be used to detect continuous heart rate is through electrocardiographic (ECG) signals (ChuDuc et al., 2013; Hämmerle et al., 2020).

Members of the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) stated that HRV was one of the most promising markers in detecting failure in autonomic function and it was recommended to be used as a tool in clinical and research study, especially for cardiologists. A review on HRV and its application stated that fluctuation in heart rate was crucial in determining and treating several diseases, specifically cardiovascular system diseases, stroke, Alzheimer, renal failure and many more (ChuDuc et al., 2013). This was supported by other similar studies where HRV as a useful non-invasive technique could also be used as a strong independent predictor model of any cardiovascular event such as myocardial infarction (MI) and mortality associated with cardiovascular diseases (Hämmerle et al., 2020).

#### 2.4.2.2 Blood Pressure Variability (BPV)

Blood pressure is variable and not constant. It will change according to the individual's neurohumoral, environmental and autonomic stimuli (Höcht, 2013). A study by Floras (2013) stated that each beat-to-beat blood pressure varies in response to their psychological and physical activity, as well as sleep pattern. Hence, a fluctuation of blood pressure is known as blood pressure variability (BPV).

Currently, blood pressure variability has been classified into three types which are short-term, long-term as well as ultrashort-term. Although these three categories of BPV measurement have been used to indicate autonomic nervous system, their results are substantially different. The observed findings could be explained by the difference in the duration of time taken for the measurement of these three types of BPV. Before the continuous non-invasive blood pressure and heart rate measurement were widely implemented, ambulatory blood pressure monitoring (ABPM) was widely used as a tool in detecting autonomic failure (Lodhi et al., 2019). Blood pressure fluctuations help to gain deeper insights on parasympathetic and sympathetic branches of ANS, thus indirectly helping to determine the autonomic failure in healthy and diseased subjects (Omboni et al., 1996).

Short-term BPV includes the oscillation of blood pressure within 24 hours (Höcht, 2013). In short-term BPV, the 24-h ABPM procedure is used to access blood pressure fluctuations during daytime and nighttime (Brien et al., 2013), as well as nocturnal BP dipping and morning BP surge (Chadachan et al., 2018). As compared to short-term BPV, ultra-short term is a beat-to-beat variation (every second) and mainly reflects the influences of the behavioural, central neural and humoral factors (Höcht, 2013; Parati & Rizzoni, 2005; Parati et al., 2018).

Besides that, long-term BPV also used ABPM as part of the measurement. However, long-term BPV required repeated BP measurements in detection of long-term BP changes in days, week, months, seasons and even years (Rothwell et al., 2010; Parati et al., 2013). Since the interval of the long-term BP assessment was huge, they have less prognostic value as compared to 24-hour short-term BPV (Tully et al., 2017). Apart from the difference in the duration of assessment, another contributing factor of the insignificance of long-term BPV could be due to the limitations of the methodology (e.g. improper BP-measurement methods, improper handling of ABPM devices, and lack of physician visits or treatments over a longer period of time) (Chenniappan, 2015; Parati et al., 2013). Therefore, the prognostic significance of long-term BPV over short-term BPV remains unclear with factors such as BP treatment and changes in methods of measurement over time likely to confound the overall finding. This can be further explained by Goldstein et al. (2003) who reported that BPV decreased after 5 years of follow-up phase in 162 healthy adults aged 55 to 79 years old. On the other hand, a recent study by McDonald et al. (2016) showed that ambulatory blood pressure variability (ABPV) increased over 10 years of follow-up in community-dwelling older people aged 65 years and above. This may indicate that autonomic nervous system activity has been deteriorated as someone ages.

#### 2.4.2.3 Time-domain and Frequency-domain Indices for Heart Rate Variability and Blood Pressure Variability

Time domain and frequency domain analysis can be used to access ANS activity. Increase in ABPV is also related to arterial stiffness, cardiovascular events, mortality, and morbidity as exemplified in myocardial infarction (MI), coronary artery disease and stroke (Alici et al., 2013; Martinez et al., 2010). Increase in BPV provides a prognostic understanding on cardiovascular outcomes in patients with and without hypertension (Otsuka et al., 2004; Kasim et al., 2019). Lowering of BPV and heightening of HRV could help in preventing arterial stiffness which subsequently minimises the risk of cardiovascular disease (Parati et al., 2018).

Regarding time domain indices, several studies on short-term BPV (Alici et al., 2014; Carels et al., 2000; Otsuka et al., 2004), long-term BPV (Tully & Tzourio, 2017; Tully et al., 2017) and ultrashort-term BPV (Bystritsky & Shapiro, 1992; Davydov et al., 2007; Martinez et al., 2010; Piccirillo et al., 1997; Virtanen et al., 2003; Vasudev et al., 2011; Yeragani et al., 2004) are using standard deviation (SD) of mean BP from 24-h AMBP to analyse the autonomic response of the participants. A recent study by Lodhi et al. (2019) had observed the usefulness of the BPV and HRV indices (e.g. standard deviation (SD), coefficient variation (CV), average real variability (ARV), variation independent of mean (VIM) and residual standard deviation (RSD)) from ABPM in determining the autonomic failure. This finding shows that SD-daytime is the best diagnostic index as it is strongly associated with autonomic failure before and after adjusted to multivariate models such as age, history of Parkinson disease, smoking, history of cardiovascular disease (CVD) and blood pressure medication. In contrast, a study on postural changes on fallers and non-fallers in older people aged 65 years and above illustrated that SD value can be easily influenced by a large amount of noise present with the non-invasive continuous measurement. This limits the suitability of SD for the ultrashort-term BPV calculation due to measurement errors that may be present (Goh et al., 2016).

According to Omboni et al. (1996) in their study on autonomic disorders, spectral analysis (SA) or frequency domain analysis of BP and HR fluctuations was introduced to gain more understanding about the cardiovascular (CV) regulatory mechanisms. Spectral analysis of BPV and HRV are preferable especially in ultrashort-term analysis. As mentioned by Goh et al. (2017), SD of time domain indices may not yield much findings when it comes to analysing the ultrashort-term BPV and HRV due to the large amount of noise that may be present during the continuous blood pressure and heart rate measurements. Continuous BP and HR may vary according to each continuous heartbeat especially when the patients are lying down, sitting or standing. Fast Fourier transform (FFT) method in spectral analysis can help to differentiate and separate the noise and interferences from the desired continuous signals (Haberl et al., 1988). As a result, frequency domain analysis can be more accurate than time domain analysis, without any loss of sensitivity (Haberl et al., 1988). Recently, three frequency ranges have been used for the interpretation of cardiovascular autonomic activity: very-low frequency (VLF, HRV: 0.003-0.04Hz, BPV: 0.016-0.04Hz), low frequency (LF, HRV: 0.04-0.15Hz, BPV: 0.07-0.14Hz) and high frequency (HF, HRV: 0.15-0.4Hz, BPV: 0.14-0.35Hz) (Chambi et al., 2020; Goh et al., 2017). VLF is related to renin-angiotensin system, HF component gives a measure on parasympathetic activity, while LF measures the indicators of sympathetic activity (Piccirillo et al., 1997; Akselrod et al., 1981; Martinez et al., 2010). Therefore, the ratio of LF and HF (LF:HF) reflects the symphatovagal balance between both sympathetic and parasympathetic activity (Martinez et al., 2010; Pagani et al., 1986).

## 2.5 Physical Activity and Performance as Risk Factors for Falls

Gait impairment is often stated as one of the fall risk factors. Other prior evidence reported that fear-related activity avoidance and an increase in the feelings of anxiety and symptoms of depression may exist among elderly (Van Haastregt, Zijlstra, Van Rossum, Van Eijk, & Kempen, 2008; Hellström, Vahlberg, Urell, & Emtner, 2009; Rask et al., 2015). A possible explanation is fallers may develop fears of recurrent falls that further impede their physical activity, reduce mobility level (Vellas et al., 1997; Akosile et al., 2014; Duray & Genç, 2017; Bell, 2008), reduce muscular strength, flexibility, gait and fitness, and ultimately worsen their physical performance and increase their future falling risks (Furtado et al., 2015; Gouveia et al., 2013). Furthermore, fall-related injuries have resulted in the inability to socialise, and increased dependency towards family members to maintain mobility. Several assessments representing physical activity and performance have been widely implemented by researchers and health care provider to determine the physical activity level of an individual. The examples of the assessment are time-up-and-go (TUG), functional reach, hand grip strength and 6-minute walking test.

### 2.5.1 Relationship between Physical Activity, Physical Performance and Autonomic Function

Although studies on fall and physical impairment are well known, bidirectional relationship between physical inactivity and lower cardiac autonomic modulation is also crucial to prevent any diseases related to falls (Espinoza-salinas et al., 2021; Nascimento et al., 2019; Tebar et al., 2020). Several studies reported that sedentary behaviour resulting from poorer physical activity can lead to a reduction in HRV, a cardiac autonomic modulation. As cardiac autonomic modulation reflects the activity of sympathetic and parasympathetic for the heart, there is enhancement of cardiac autonomic modulation following a higher physical activity (Moraes-Silva et al., 2013; Tebar et al., 2020; Nascimento et al., 2019). According to Tornberg et al. (2019), increasing physical activity among adults is associated with a consistent increase in cardiorespiratory physical fitness, allowing the cardiovascular system to adapt properly. This action leads to lower heart rate and resting heart rate while increasing left ventricle filling, venous return, and stroke volume, which is strongly associated with parasympathetic action of the heart (Kazeminia et al., 2020).

Hence, in this study, some of the assessment tools were used (e.g. questionnaire) to determine the physical inactivity among the elderly using self-reported physical activity. This functional assessment is focuses on the individual's baseline capabilities, allowing for early detection of changes that may indicate the need for rehabilitation or a medical work-up (Gallo & Paveza, 2006; Graf, 2006). In addition, reduction in overall physical independence has been linked to diminished health outcomes as well as cognitive performance in an individual. According to a study by Hoshi et al. (2012), comparing the one-time physical performance and self-reported questionnaire, the self-reported questionnaire had a predictive validity and can predict decline in physical function.

## 2.6 Psychological Function as a Risk Factor for Falls

Psychological status can be understood as a state of mental condition which includes depression, anxiety, fear, suicide attempt and stress. However, mental health can be defined as a state of well-being in which individuals recognise their own strengths and abilities, are able to cope with everyday stresses, work productively, and contribute to their communities (World Health Organization, 2003). The number of people that are admitted to private and public hospitals due to clinically diagnosed mental disorders is increasing annually. These mental health problems can affect society, but the risk is higher and more challenging among the poor, homeless, unemployed and neglected elderly (World Health Organization, 2003). In Landau's New Straits Times article (2018), Tan Sri Lee Lam Thye, the Patron of the Malaysian Psychiatric Association (MPA) had reported that 29% of adolescents in the country are suffering from depression and anxiety disorder as compared to only 12% in 2011 as indicated by the National Health and Morbidity Survey 2017 on mental health in Malaysia.

Several studies have showed the relationship between falls and increased psychological disorders. Due to the fear of recurrent falls, fallers have shown signs of physical activity avoidance (Hull et al., 2013; Hellström et al., 2009), which subsequently worsen their cognitive function and affects their mental health (Hellström et al., 2009; Van Haastregt et al., 2008). Previously published studies had reported a significant increase in the level of anxiety and/or depression level among older populations in the United States (Hellström et al., 2009) and European adults (Stegenga et al., 2012) who experienced falls. Furthermore, in order to accurately identify psychological disorders or mental states that are the risk factors for falls, the commonly used validate 21-item Depression, Anxiety, Stress (DASS-21) questionnaire has been implemented in most of the fall studies. The questionnaire contains three 3-subscales to measure depression score, anxiety score and stress score. Early detection of the mental state by using this self-reported questionnaire may help the physician or researcher in identifying the best treatment, indirectly reducing the cases involving mental disorders among the population (González-Rivera et al., 2020; Duc Tran et al., 2013; Rao et al., 2019).

### 2.6.1 Relationship between Psychological Function and Autonomic Function

Participants with psychological disorders, such as depression, major depressive disorder, panic disorder (PD), anxiety, generalized anxiety disorder and hostility, may have deregulated autonomic nervous system (ANS). The relation between these disorders and ANS have been observed in some studies (Yeragani et al., 2004; Virtanen et al., 2003; Piccirillo et al., 1997; Tully & Tzourio, 2017; Otsuka et al., 2004; Carel et al., 2000; Martinez et al., 2010; Piccirillo et al., 1997). A study by Alici et al. (2013) on circadian (24-h) BP variation showed that PD patients had significantly higher non-dipper BP pattern, with less than 10% nighttime BP reduction as compared to control subjects. Similarly, another study on emotional reactivity and blood pressure showed that participants with high emotional reactivity in response to stress stimuli (Melamed, 1987), anxiety (Ifeagwazi et al., 2017) and panic attacks (Davies et al., 1999) tend to have elevated blood pressure and heart rate. The association between psychological disorders and elevated blood pressure/heart rate may be explained by greater sympathetic activity in those with high emotional responsivity (Veith et al., 1994). BP and HR tend to increase in response to stress stimuli and stressful conditions (Conley & Lehman, 2011).

## 2.7 Summary on Designated Methodology

Impaired autonomic function, as reflected in both sympathetic and parasympathetic activity of the autonomic nervous system, is associated with an increased risk of cardiovascular diseases (DePace et al., 2014). Conventional methods to assess autonomic function include measurement of heart rate and blood pressure changes in response to a series of challenge maneuvers. These methods are relatively crude and lack sensitivity, and therefore not routinely used in practice (Conte et al., 2012). Newer methods of measuring heart rate and blood pressure changes include measurement of heart rate variability (HRV) and blood pressure variability (BPV). These methods require minimal patient cooperation and have a high level of sensitivity.

Based on literature review, HRV is an assessment of beat-to-beat variation in the heart, and is increasingly used because it is simple to measure and is a reliable indicator for autonomic function (Berntson et al., 1997; Oparil et al., 2018). On the other hand, BPV refers to fluctuations in blood pressure that occur within several minutes, over a 24-hour period or a longer period of time (several years) (Parati et al., 2013). While blood pressure fluctuations over a 24-hour period are normally obtained using non-invasive ambulatory blood pressure recorders, continuous, beat-to-beat blood pressure measurements are acquired using the photoplethysmographic (PPG) technique. Long term BPV has been associated with stroke and coronary events in high risks patients (Stevens et al., 2016), while visit-to-visit short term BPV is a prognostic indicator for cardiovascular mortality in patients with hypertension (Parati et al., 2015). Although the association between BPV, HRV and coronary diseases has been widely reported, the mechanisms linking these two are unclear due to the dynamic natures of blood pressure and heart rate, which fluctuate with environmental stimulations and daily life challenges (Parati et al., 2015; Parati et al., 2020). Some modifiable risk factors that may alter BPV and affect cardiovascular health outcomes include subjects' reactivity to emotional stimuli (e.g., mental state, physiological stress) and behavioural factors (e.g., level of physical activity, sleep cycles, postural changes) (Parati et al., 2020). These were further strengthened by previously published studies where they observed a reduction in continuous BPV while standing in individuals with a history of falls while, impaired autonomic function with increased sympathetic activity and decreased parasympathetic activity (as indicated by HRV) has been found to be independent predictors for recurrent falls. Hence, based on the evidence from the other studies, we found that beat-to-beat or ultrashort term BPV/HRV has become the best measurement in observing the emotional stimuli as well as the behavioural factors among the fallers group as compared to short-term and long-term BPV/HRV.

# CHAPTER 3: METHODOLOGY

## 3.1 Study Design and Study Population

This exploratory cross-sectional study was conducted by the Life After Falls (LiAF) group. LiAF is a research team under University of Malaya that is concerned for the elderly who have fallen down. Furthermore, this study aims to investigate post-fall behaviour among older fallers, spread public health awareness and provide accessible medical facilities. This study involved 45 fallers and 47 non-fallers, recruited between October 2019 and April 2021. Falls were defined as "unintentionally coming to rest on the ground, floor or other lower level" (Masud & Morris, 2001).

The inclusion criteria for the fallers participants recruitment were adults; a) aged 60 years and above recruited from an emergency department, primary care clinics and geriatric outpatients as well as referrals from other departments and specialists at the University of Malaya Medical Center, b) who had at least one fall in the past two months, c) who are able to move and are not bedridden (mobile). On the other hand, inclusion criteria for non-fallers group were age matched healthy volunteers with no history of falls recruited from the patients' family members or word of mouth advertising. Participants that are not mobile (with no capability to move, stand or lying down) during hemodynamic blood pressure and heart rate measurement were excluded at the beginning of the assessment. This study protocol was approved by the University of Malaya Research Ethics Committee (MREC ID No: 2019525-7445) prior to commencement of the study. Written informed consent was obtained from all subjects.

## 3.2 Data Collection and Outcome Measure

Baseline characteristics, including age, gender, characteristics of falls, past medical history, medication review and anthropometric measurements (height, weight, waist and hip ratio), as well as continuous blood pressure (BP) and heart rate (HR), were obtained from all subjects on the day of assessment. All study data were collected and managed using the REDCap electronic data capture tools hosted at the University of Malaya (Harris et al., 2019). Refer to Appendix C (e) for an overall of study protocol flow.

### 3.2.1 Basic Anthropometric measurements

Figure 3.1 shows a portable standing stadiometer (SECA ®, Hamburg, Germany) in centimetre (cm) used to measure height. The elderly participants were required to remove their shoes or footwear and stand against the footplate of the height scale.

**Figure 3.1: Portable standing stadiometer used for height measurement**

Weight was measured in kilogram (kg) using a single calibrated weighting scale (SECA 7650 ®, Hamburg, Germany). Shoes or footwear were removed when the measurement took place.

**Figure 3.2: Calibrated weighing scale to measure weight**

Waist and hip measurements were obtained using a measuring tape. The elderly participants were required to stand with their arms at the side and feet positioned close together. Waist circumference was measured at the smallest part of the waist, approximately above the belly button, whilst hip circumference was measured around the largest or widest part of the buttocks (World Health Organization, 2011).


(a) (b)

**Figure 3.3: (a) Measuring tape used to measure waist and hip; (b) The standard position of waist and hip**

### 3.2.2 Physical Performance Assessments

We conducted three types of tests to assess individual's physical performance: timed-up-and-go test, functional reach, and handgrip strength. Questionnaires including the Lawton's Instrumental Activities of Daily Life (IADL) scale and Physical Activity Scale for the Elderly (PASE) were also used.

#### *(a) Time-up-and-go (TUG)*

Timed-up-and-go test evaluates the time taken to rise from the sitting position on a standard arms chair, walk for 3 meters, turn back, and sit down again. The details of TUG have been illustrated by Chan et al. (2017). Longer duration taken by a subject to complete the task indicates a poorer physical performance (Beauchet et al., 2011).

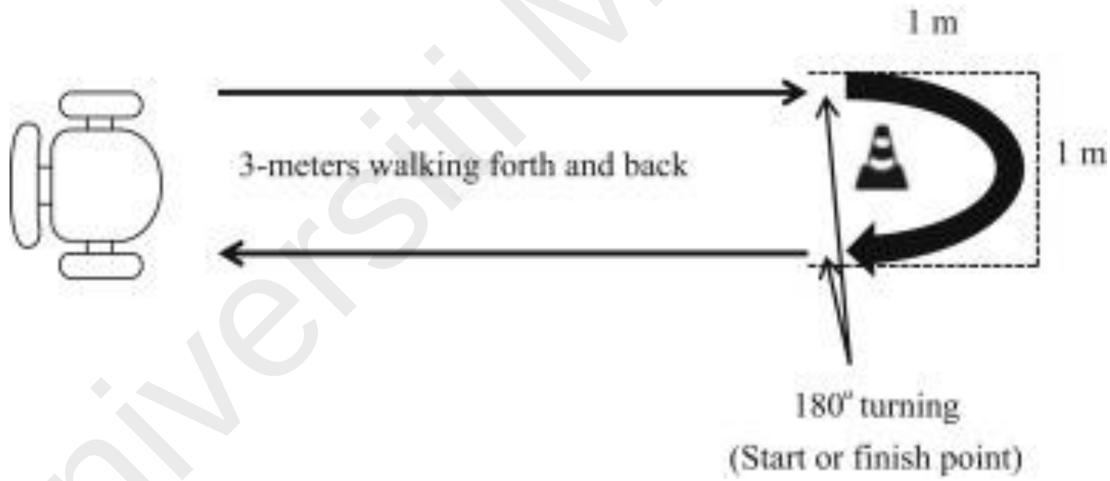



**Figure 3.4: Illustration of time-up-and-go test (Chan et al., 2017)**

#### *(b) Functional Reach*

Functional reach was measured by asking the subjects to stand with feet shoulder-width apart with the right hand outstretched in a maximal forward reach, while maintaining a fixed base of support (point B) (Williams et al., 2017). The distance between the positions of the third distal interphalangeal joint when the subjects were at the upright position and then at maximal forward stretch was calculated in centimeters (cm) as illustrated in Figure 3.5 (Point C – Point B). A longer stretch distance indicates a better balance outcome and this test have been widely used to assess physical function, risk of falling and frailty among elderly (Debra. et al., 1992).

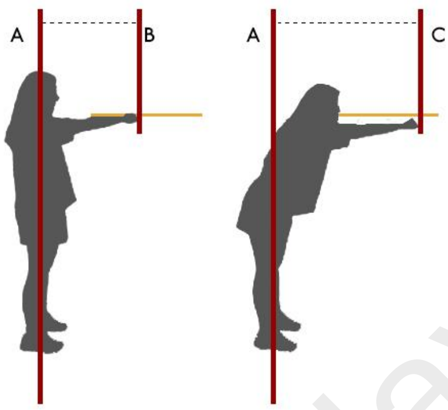



**Figure 3.5: Illustration of functional reach**

***(c) Hand-Grip Strength***

Muscle strength was assessed with handgrip strength test, conducted using the Jamar digital hand grip dynamometer (Sammons Preston, Bolingbrook, IL, USA) (refer Figure 3.6). The average of three measurements obtained for both right and left hand with the elbow flexed at 90°, was calculated in centimeters. The purpose of hand grip strength is for the indicator of overall muscle strength in elderly (Unal et al., 2018).

**Figure 3.6: Jamar digital hand grip dynamometer for measuring hand grip strength**

*(d) Instrumental activities of daily living (IADL)*

Instrumental activities of daily living were assessed using the Lawton's Instrumental Activities of Daily Life (IADL) scale (Graf, 2008). This scale measures functional independence by recording the ability of the participants to perform common daily living activities, which include use of telephone and transportation, shopping, food preparation, doing housework, managing own laundry, managing medication and ability to handle finances. The maximal score of this scale is 8 and a lower score indicates reduced functional independence. Refer to Appendix C (b) for the questionnaire.

*(e) Physical Activity Scale*

Physical Activity Scale for the Elderly (PASE) was used to assess the current level of physical activity and sedentary activities among older adults (Akosile et al., 2021). Test items reflect leisure, domestic life and work. Participants were required to answer the questions on frequency ("none", "seldom", "sometimes" and "often") as well as duration ("less than 1 hour", "1-2 hours", "2-4 hours" and "more than 4 hours" of each activity. Higher scores indicate higher activity levels. Refer to Appendix C (c) for the questionnaire.

### 3.2.3 Cognitive Performance

Cognitive performance was assessed with the Visual Cognitive Assessment test (VCAT), a visual- based cognitive screening tool designed for early diagnosis of dementia (Kandiah et al., 2016). The VCAT is a 30-point test within the domains of memory, executive function, visuospatial function, attention and semantic knowledge. The highest possible score is 30, and the lowest score is 0. A higher score indicates a better cognitive performance. In this study, only the overall score and not the individual domain score is considered.

### 3.2.4 Psychological Questionnaire

#### *(a) 21-item Depression, Anxiety, Stress Scale (DASS-21)*

Depression, anxiety and stress were measured with the 21-item Depression, Anxiety, Stress Scale (DASS-21). Participants were required to self-report the frequency and severity of the negative emotions of depression, anxiety and stress over the previous week. The frequency and severity ratings are based on a 4-point Likert scale, with 0 indicating “did not apply to me at all” and 3 indicating “applied to me very much, or most of the time.” The scores were calculated individually for the three components of depression, anxiety and stress (González-Rivera et al., 2020). Refer to Appendix C (d) for the questionnaire.

#### *(b) Short Falls Efficacy Scale International (FES-1)*

In addition, fear of falling or concern of falling was measured using the Short Falls Efficacy Scale International (FES-1) questionnaire. This questionnaire records the participants’ concern with falling while getting dressed or undressed, taking bath or shower, getting in or out of a chair, going up or down stairs, reaching for something above the head or the ground, walking up or down a slope and going out for social event using a four-point Likert scale. Higher scores indicate a higher concern for falling, with a maximal score of 28 (Tan et al., 2018).

### 3.2.5 Quality of Life (QoL)

Participants’ quality of life (QoL) was measured using the 12-item Control, Autonomy, Self-realization and Pleasure (CASP-12) questionnaire. The questionnaire employed a validated 12-item version scale, made on a 4-Likert scale, with 0 indicating “Never” and 3 indicating “Often”. Higher scores indicate a better QoL in an individual (Nalathamby et al., 2017).

### 3.2.6 Social Participations

The Keele Assessment of Participation (KAP) was used to measure level of participation in various activities including work, education, social activities and activities of daily living for the past four weeks (Wilkie et al., 2005). Responses were recorded using a 4-point Likert scale, with 0 indicating "none of the time" and 1 indicating "all the time, most of the time, some of the time and a little of the time". Higher scores indicate better levels of participation.

### 3.2.7 Social Network

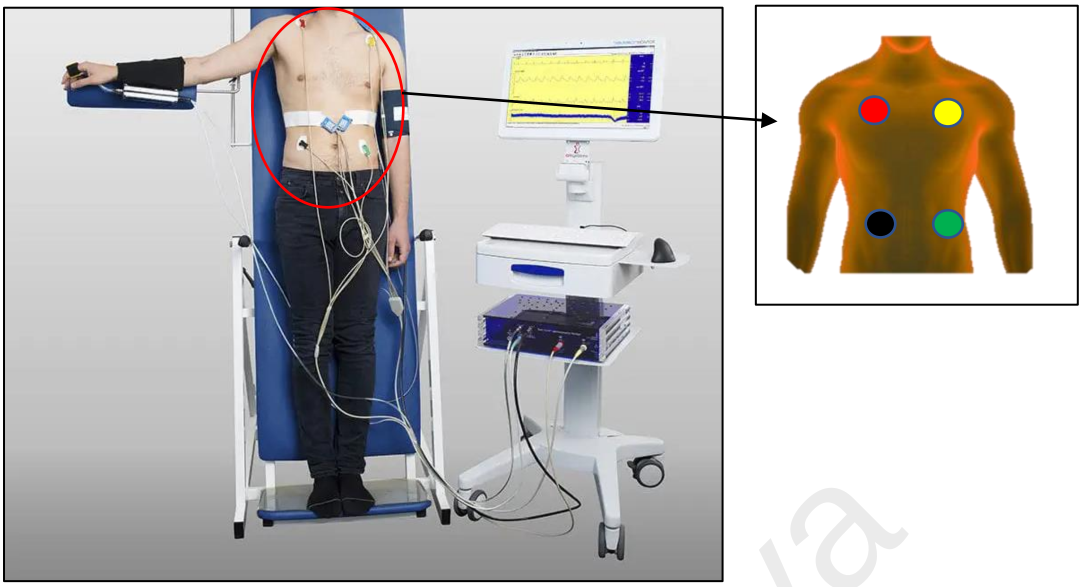
Social network or peer relationship was measured using the Lubben Social Network Scale (LSNS). Perceived social support received from family and friends was assessed by participants answering the 6 items provided: 1) How many relatives do you see or hear from at least once a month, 2) How many relatives do you feel at ease with that you can talk about the private matters, 3) How many relatives do you feel close to such that you could call on them for help, 4) How many of your friends do you see or hear from at least once a month, 5) How many friends do you feel at ease with that you can talk about the private matters, 6) How many friends do you feel close to such that you could call on them for help . A higher score indicates a greater social support (Kuru Alici & Kalanlar, 2021).

## 3.3 Beat-to-Beat Heart Rate and Blood Pressure Assessment

Every participant was required to undergo a supine-to-standing orthostatic test with non-invasive continuous beat-to-beat electrocardiogram (ECG) and blood pressure (BP) monitoring obtained using the vascular unloading technique (Task Force, CNSystem, Austria). R-R intervals were derived based on the electrocardiogram (ECG) signal (sampling rate = 1 kHz), while beat-to-beat blood pressure values were derived from the fingertip photoplethysmographic (PPG) signal (sampling rate = 100 Hz), with the signal processing details described in the following section.

Firstly, the participants were asked to lie supine on a bed. Next, a blood pressure upper arm cuff was placed on their left upper arm with the artery arrow mark (white) positioned directly over the brachial artery. The cuff was checked to ensure that it fitted the arm tightly to avoid any false measurement. Next, an appropriately sized finger cuff (small, medium and large) was selected according to the size of the finger to measure the continuous blood pressure signal. The finger cuff was attached on the middle and index finger of the right hand. For ECG signal monitoring, four electrodes were placed on the chest according to the Einthoven's Triangle (refer Figure 3.7 (b)), with color clips (red, yellow, green, black) clipped on the electrodes.

After completing the set-up (refer Figure 3.7 (a)), the initialization process of the machine was activated. Blood pressure was measured at the brachial artery every 5 minutes when the system is started, followed by calibration of the beat-to-beat finger pressure measurements. All subjects were required to lie supine for at least 10 minutes, before the 3-minute active stand test was continued (Goh et al., 2017). Older participants were refrained from talking and moving to reduce artefact and noise in the signals, unless they experienced any discomfort during the assessment. All recordings were performed at spontaneous breathing rate. The presence of any symptoms of dizziness during standing was recorded.



(a) (b)

**Figure 3.7: (a) Complete Task Force Monitor (TFM) set-up (ECG and continuous blood pressure measurement); (b) Placement of ECG electrodes according to Einthoven's Triangle**

## 3.4 Signal Processing

The continuous heart rate and blood pressure signals recorded from the TFM machine were exported to the MATLAB software and analyzed with designated MATLAB algorithms (Version R2014b, MathWorks Inc., Natick, Massachusetts, United States).

### 3.4.1 Filtering and Removal of Continuous Beat-to-Beat Blood Pressure and ECG Signals

The ECG and finger blood pressure waveforms were pre-processed using custom written algorithms, where filtering, tracing, and denoising were performed to remove any unwanted artefacts. Cardiovascular signals collected from the machine were potentially contaminated with noise or also known as powerline interference. The 50 Hz filter was first applied to remove any electromagnetic power noise detected in the signal (Kher, 2019). Apart from the powerline interference, other artefact such as motion artefacts, electrode motion, baseline wander and EMG noise, were also present in the signal. Therefore, the following inclusion and exclusion criteria were used to ensure high quality signal:

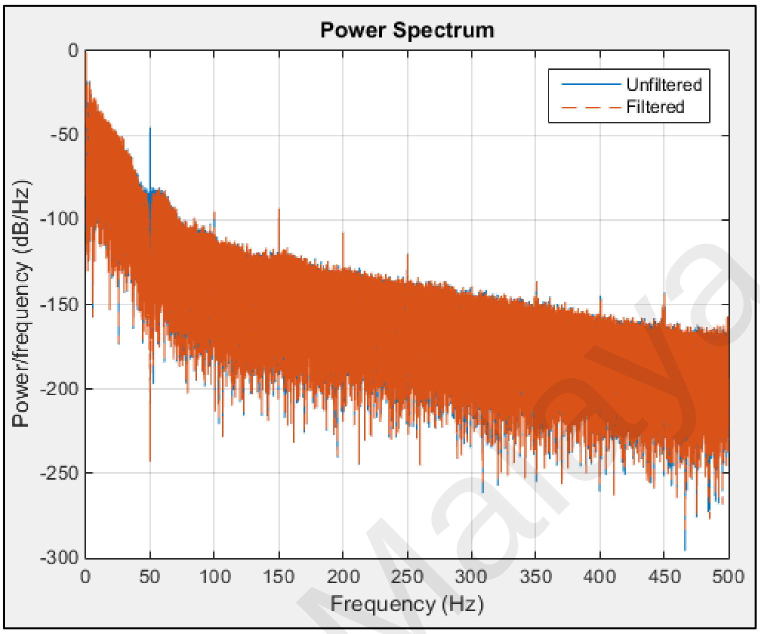



**Figure 3.8: 50Hz Powerline interference filtering**

*Inclusion Criteria*

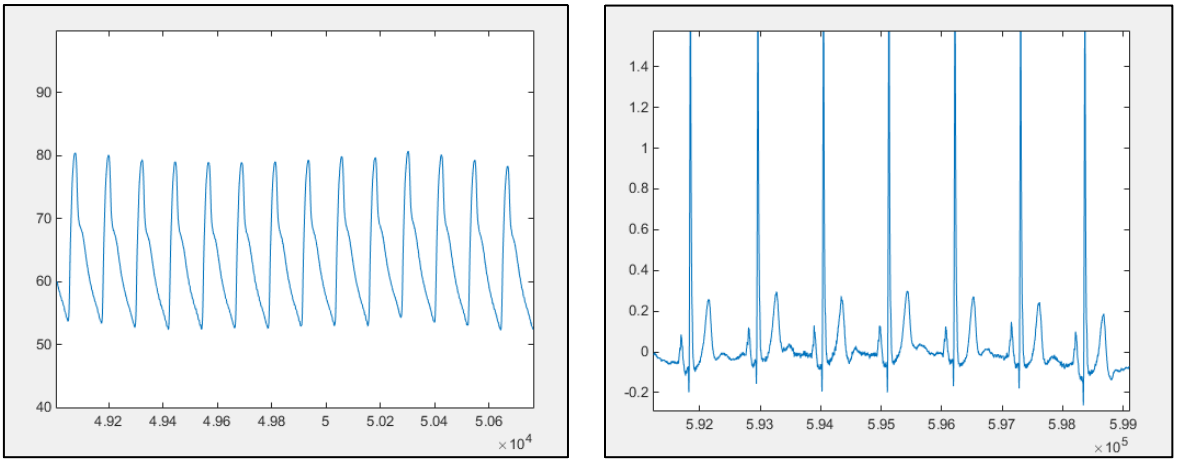
i) All clean and acceptable continuous blood pressure and ECG signals recorded with continuous non-invasive hemodynamic monitoring machine.

*Exclusion Criteria*

i) All continuous blood pressure and ECG signals that were fully contaminated with noise and motion artefacts.

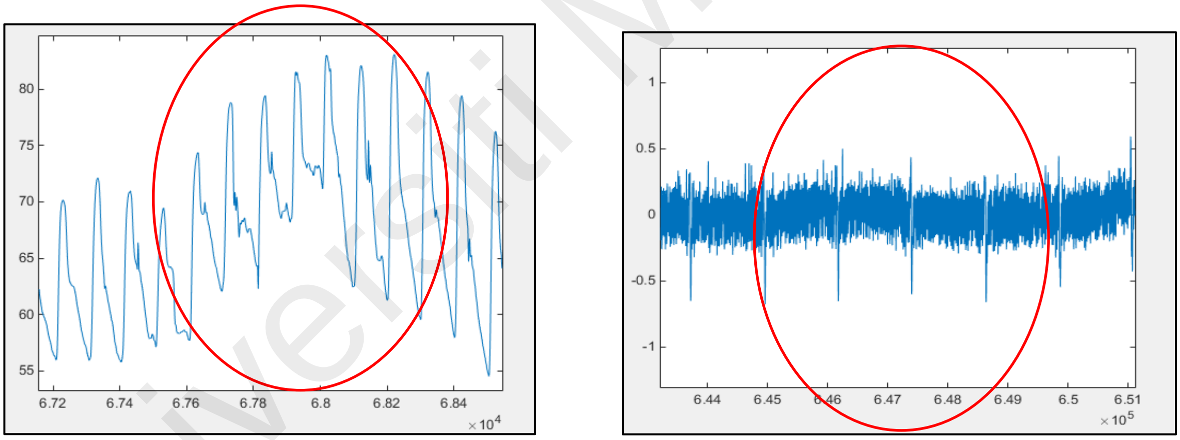
ii) Large differences (>15mmHg) between finger beat-to-beat blood pressure and oscillometric readings (arm cuff) (Lee et al., 2020).

iii) As for ECG signals, discontinuous ECG signals due to detachment of the electrodes or badly contaminated signals, which inhibited the detection of the QRS complex.




(a) (b)

**Figure 3.9: (a) Clean and acceptable continuous blood pressure signals; (b) Clean and acceptable continuous ECG signals**




(a) (b)

**Figure 3.10: (a) Irregular continuous blood pressure signals; (b) Noise and motion artefacts of continuous ECG signals**

Based on the selection criteria above, clean and acceptable continuous blood pressure and ECG signals were selected (refer Figure 3.9). The QRS peaks of the ECG as well as the peaks/troughs of the cyclical blood pressure waveform within every cardiac cycle were then detected using standard derivative or threshold algorithms for the purpose of estimating heart rate and systolic or diastolic blood pressure. Beat-to-beat HR and BP readings were identified and separated into three different segments: supine rest, interval and standing according to the markers from the TFM machine. Blood pressure variability (BPV) and heart rate variability (HRV) were computed with two methods of analysis: time domain analysis and frequency domain analysis (spectral analysis).

Time domain analysis measures dispersion of blood pressure values over a given time window, while frequency domain analysis measures blood pressure fluctuation as a function of frequency. Time-domain indices are divided into two categories: (1) measures of dispersion of average values over a given time window of 10-min supine rest and 3-min standing, which include standard deviation (SD) and coefficient of variation (CV); (2) estimation that accounts for the sequence of measurements over time, which include average real variability (ARV) and root mean square of real variability (RMSRV). On the other hand, frequency-domain indices are obtained through spectral analysis techniques, in which we measured fluctuations in beat-to-beat blood pressure as a function of frequency. Linear detrending technique was first performed, followed by the application of Fast Fourier transform (FFT) algorithms on the extracted beat-to-beat heart rate and systolic/diastolic blood pressure data to obtain the frequency-domain HRV and BPV indices: low-frequency power (LF-HRV: 0.04-0.15Hz, LF-BPV: 0.07-0.14Hz), high-frequency power (HF-HRV: 0.15-0.4Hz, HF-BPV: 0.14-0.35Hz), total power (TP), and ratio of low-frequency power to high-frequency power (LF/HF) (Chambi et al., 2020; Goh et al., 2017). Low-frequency and high-frequency power were presented in normalized unit (nu). The high frequency component measures the parasympathetic activity, while the low frequency component measures the sympathetic activity (Chambi et al., 2020; Goh et al., 2017). The ratio of the low to high frequency components reflects the sympathovagal balance between the sympathetic and the parasympathetic activities (Goh et al., 2017).

**Table 3.1: Indices for time domain and frequency domain of blood pressure and heart rate variability**

| BPV and HRV Indices | Description | Formula |
|---|---|---|
| ***Time Domain Analysis*** | | |
| Coefficient of Variation (CV) | Measure of the dispersion of segments around the mean. | $\left(\frac{SD}{\bar{x} = \frac{\Sigma_{i=1}^{n} x_i}{n}}\right) \times 100$ |
| Standard Deviation (SD) | Standard deviation of entire segments | $\sqrt{\frac{\Sigma_{i=1}^{n}(x_i - \tilde{x})^2}{n-1}}$ |
| Standard Deviation of NN (SDNN) | Standard deviation of NN (R-R) intervals<br>NN= is the same as RR-interval or the time interval between heartbeat (R) peaks | $\sqrt{\frac{1}{N-1}\sum_{i=2}^{N}(RR_i - \overline{RR})^2}$ |
| Average Real Variability (ARV) | Average of absolute differences between adjacent blood pressure values | $\frac{\Sigma_{i=1}^{n}(D_i)}{n}$<br>$D_i = \lvert x_{i+1} - x_i \rvert$ |
| Root Mean Square of Real Variability (RMSRV) | Root Mean Square of the successive difference between adjacent blood pressure values | $\sqrt{\frac{\Sigma_{i=1}^{i=n-1}(Di)^2}{n-1}}$<br>$D_i = \lvert x_{i+1} - x_i \rvert$ |
| ***Frequency Domain Analysis/Spectral Analysis*** | | |
| Total Power (TP) | Sum of VLF, LF and HF power at each segment of the individuals | $VLF + LF + HF$ |
| Ratio of Low-Frequency and High-Frequency (LF/HF) | Ratio of LF and HF power | $\frac{LF\ power}{HF\ power}$ |
| LFNUs | LF normalized unit | LFNUs = [LF power/(TP-VLF power)] x 100 |
| HFNUs | HF normalized unit | HFNUs = [HF power/(TP-VLF power)] x 100 |

## 3.5 Data Analysis

A priori sample size calculations were performed using G*Power statistical software (Faul et al., 2007), and with an effect size of 0.70 at a power of 90%, a minimum of 92 participants were required (Brydges, 2019). In addition, using the general rule of thumbs described by Wilson Van Voorhis and Morgan (2007), no fewer than 50 participants are required for a correlation or regression, and an absolute minimum of 10 participants per predictor variable is required for regression equations with six or more predictor variables. Therefore, with seven predictors used in this study, we need a sample size of at least 70 people. As a result, during data collection, 45 fallers and 47 non-fallers were included.

Statistical analysis was conducted using the SPSS V23 statistical software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous variables, and frequencies with percentages for categorical data. Differences between groups of fallers and non-fallers in their demographic characteristics, autonomic response and psychological disorder was determined using the independent *t*-test for normally distributed continuous variables (this analysis was applied in Table 4.1, Table 4.2 and Table 4.3). For non-normally distributed data, continuous variables were expressed as median with quartile 1 to quartile 3 in parenthesis and the differences between groups were determined using Mann-Whitney U test. Then, correlation between psychological disorder and autonomic response were measured using the Pearson's correlation coefficient. This analysis was applied in Table 4.4, Table 4.5 and Table 4.6. Finally, multivariate linear regression was used to adjust for potential confounding variables and to determine potential predictor models for the autonomic dysfunction. History of falls, DASS-21 score (depression, anxiety and stress score), PASE, TUG and LAWTON were used as potential variables that can predict autonomic function in this study. The assumption of linear regression was checked, and all met for normality, linearity and homoscedasticity. This analysis was applied in Table 4.7, Table 4.8, Table 4.9 and Table 4.10. A *p*-value of <0.05 was considered as statistically significant in this study.

# CHAPTER 4: RESULTS

## 4.1 Recruitment and Group Characteristics

A total of 150 older individuals residing in Selangor and Kuala Lumpur have been identified. However, 58 (38.7%) participants were excluded due to incomplete hemodynamic measurements of blood pressure and heart rate, or artifacts or motion noise detected in the continuous blood pressure and heart rate signals. Hence, continuous blood pressure and heart rate data from a total of 92 participants with acceptable quality were included. Of those, forty-five older individuals (49%) who had at least one fall incident in the past two months were labelled as the fall cohort, while forty-seven older individuals (51%) with no history of fall in the past two months were labelled as the non-fallers cohort.

Table 4.1 shows that fallers group are significantly older (p = 0.024) and have poorer cognitive performance as shown by the Visual Cognitive Assessment Test (p = <0.001). In addition, fallers group required a longer time to complete the time-up-and-go test (p = 0.004), tend to have weaker hand grip strength for both right (p = <0.001) and left hands (p = <0.001). Besides, in terms of physical activity performance, fallers showed a lower physical activity scale (PASE; p = <0.001) and reduced functional independency (LAWTON; p = <0.001) as compared to the non-fallers group. In terms of psychological disorder, the fallers group experienced more fear of falling or concern of falling (FES-1 score) as compared to the non-fallers group (p = 0.016). Furthermore, older fallers who experienced at least one fall had significantly lower quality of life (p = 0.029) and social networking (LSNS; p = 0.025). However, they had higher level of participation in various activities including work, education or social activities as compared to non-fallers (p = 0.001). Significantly higher supine systolic blood pressure (p = 0.014) and heart rate (p = 0.012) were observed among older fallers as compared to non-fallers.

Table 4.2 and Table 4.3 summarize the heart rate variability (HRV) and blood pressure variability (BPV) indices in fallers and non-fallers, respectively, during supine and standing. During supine, comparison between history of falls and autonomic function indicators revealed that the fallers group tends to have higher time domain indices, mainly systolic blood pressure variability (SBPV) ARV ($p = 0.015$) and RMSRV ($p = 0.015$). In terms of frequency domain indices, only TP (total power) index of SBPV were significantly higher in the fallers group ($p = 0.004$). On the other hand, during standing, time domain HRV-SDNN ($p = 0.032$) index and frequency domain SBPV low-frequency normalised unit (LFnu) were significantly lower ($p = 0.012$) in the fallers group as compared to non-fallers. Opposite results were observed in the SBPV and DBPV high frequency normalised unit (HFnu), where fallers demonstrated significantly higher values as compared to non-fallers.

**Table 4.1: Baseline characteristics of participants.**

| | Fall in the past 2 months | | *p*-value |
|---|---|---|---|
| | Yes (N=45) | No (N=47) | |
| **Age, years (mean ± s.d.)** | 73.76 ± 8.62 | 70.11 ± 6.33 | **0.024*** |
| Body mass index, kg/m2, (mean ± s.d.) | 24.38 ± 5.12 | 23.81 ± 4.55 | 0.576 |
| Gender, female, n (%) | 28 (62.2) | 31 (66.0) | 0.713 |
| Ethnicity, n (%) | | | 0.344 |
| Malay | 8 (17.8) | 6 (12.8) | |
| Chinese | 30 (66.7) | 30 (63.8) | |
| Indian | 6 (13.3) | 10 (21.3) | |
| Others | 1 (2.2) | 1 (2.1) | |
| **Education, n (%)** | | | **0.012*** |
| No Formal | 4 (8.9) | 2 (4.3) | |
| Primary | 9 (20.0) | 3 (6.5) | |
| Secondary | 16 (35.6) | 13 (28.3) | |
| Tertiary | 16 (35.6) | 28 (60.9) | |
| Cognitive Performance | | | |
| **VCAT** | 23.84 ± 5.38 | 27.37 ± 2.72 | **<0.001**** |
| Physical Performance (mean ± s.d.) | | | |
| **Time-up-and-go (TUG) test** | 21.94 ± 17.77 | 12.8 ± 10.00 | **0.004*** |
| Functional Reach | 23.93 ± 8.35 | 26.50 ± 7.80 | 0.131 |
| **Hand grip strength (Right)** | 16.58 ± 5.17 | 21.63 ± 7.23 | **<0.001**** |
| **Hand grip strength (Left)** | 14.68 ± 5.75 | 20.33 ± 7.13 | **<0.001**** |
| Psychological Status (mean ± s.d.) | | | |
| DASS-21 Depression | 4.41 ± 6.33 | 2.38 ± 4.01 | 0.070 |
| DASS-21 Stress | 6.18 ± 7.20 | 5.23 ± 5.89 | 0.493 |
| DASS-21 Anxiety | 5.23 ± 5.14 | 3.70 ± 4.09 | 0.120 |
| **FES-1** | 12.98 ± 5.42 | 10.53 ± 3.95 | **0.016*** |
| Social Participants (mean ± s.d.) | | | |
| **KAP** | 4.62 ± 2.91 | 2.83 ± 1.81 | **0.001**** |
| Quality of Life (mean ± s.d.) | | | |

Table 4.1, continued

| | Fall in the past 2 months | | *p*-value |
|---|---|---|---|
| | Yes (N=45) | No (N=47) | |
| **CASP12** | 28.71 ± 5.85 | 31.13 ± 4.47 | **0.029*** |
| Social Network (mean ± s.d.) | | | |
| **LSNS** | 16.78 ± 5.571 | 19.21 ± 4.68 | **0.025*** |
| Physical Activity (mean ± s.d.) | | | |
| **PASE** | 68.29 ± 52.63 | 116.34 ± 55.92 | **<0.001**** |
| **LAWTON** | 5.44 ± 2.80 | 7.43 ± 1.25 | **<0.001**** |
| Baseline Haemodynamic Parameters (mmHg) | | | |
| **Supine SBP** | 118.80 ± 18.49 | 110.22 ± 13.66 | **0.014*** |
| Supine DBP | 75.94 ± 15.29 | 70.76 ± 10.79 | 0.065 |
| **Supine HR** | 71.20 ± 10.61 | 65.68 ± 10.02 | **0.012*** |

*DASS-21* Depression Anxiety Stress Scale 21, *FES-1* Falls Efficacy Scale-1, *KAP* Keele Assessment of Participant, *CASP12* Control, Autonomy, Self-realization, and Pleasure (CASP)-12 scale, *LSNS* Lubben Social Network Scale, *PASE* Physical Activity Scale for the Elderly, *LAWTON* Lawton Instrumental Activities of Daily Living Scale, *VCAT* Visual Cognitive Assessment Test, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HR* Heart Rate

*Independent T-test *p*-value < 0.05

** Independent T-test *p*-value <0.001

**Table 4.2: HRV and BPV indices during supine between fallers and non-fallers**

| | HR | | | SBP | | | DBP | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fallers (N=45) | Non-Fallers (N=47) | *p*-value | Fallers (N=45) | Non-Fallers (N=47) | *p*-value | Fallers (N=45) | Non-Fallers (N=47) | *p*-value |
| *Time Domain* Indices *(mean ± s.d.)* | | | | | | | | | |
| SDNN | 29.32 ± 15.04 | 34.99 ± 17.40 | 0.099 | 4.78 ± 3.12 | 3.94 ± 2.48 | 0.156 | 3.13 ± 1.99 | 2.80 ± 1.49 | 0.363 |
| CV | 0.033 ± 0.014 | 0.733 ± 4.78 | 0.320 | 0.05 ± 0.04 | 0.04 ± 0.03 | 0.131 | 0.055 ± 0.034 | 0.047 ± 0.024 | 0.171 |
| ARV | 18.68 ± 13.06 | 22.15 ± 16.21 | 0.262 | 1.22 ± 0.68 | 0.944 ± 0.32 | **0.015*** | 0.886 ± 0.39 | 0.804 ± 0.321 | 0.280 |
| RMSRV | 24.51 ± 16.77 | 28.99 ± 21.86 | 0.274 | 1.79 ± 1.02 | 1.37 ± 0.46 | **0.015*** | 1.424 ± 0.65 | 1.258 ± 0.478 | 0.166 |
| *Frequency Domain Indices (mean ± s.d.)* | | | | | | | | | |
| LF-nu | 49.99 ± 20.69 | 48.13 ± 17.42 | 0.641 | 67.26 ± 18.02 | 71.88 ± 14.75 | 0.181 | 66.47 ± 17.41 | 70.92 ± 13.52 | 0.173 |
| HF-nu | 50.00 ± 20.69 | 51.86 ± 17.42 | 0.641 | 32.74 ± 18.02 | 28.12 ± 14.75 | 0.181 | 33.53 ± 17.41 | 29.08 ± 13.52 | 0.173 |
| TP | 221686.27 ± 222960 | 337386.59 ± 394362.12 | 0.089 | 4011.17 ± 5016.78 | 1679.15 ± 1169.68 | **0.004**** | 1855.82 ± 2744.60 | 1030.48 ± 655.54 | 0.055 |
| LF/HF | 1.43 ± 1.22 | 1.18 ± 0.85 | 0.283 | 3.16 ± 2.73 | 4.02 ± 4.37 | 0.264 | 3.19 ± 2.93 | 3.53 ± 3.35 | 0.617 |

*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SDNN* standard deviation of NN interval, *CV* coefficient variation, *ARV* average real variability, *RMSRV* root mean square of real variability, *LF-nu* low-frequency normalized unit, *HF-nu* high-frequency normalized unit, *TP* total power, *LF/HF* ratio of LF and HF

*Independent T-test *p*-value < 0.05

**Table 4.3: HRV and BPV indices during standing between fallers and non-faller**

| | HR | | | SBP | | | DBP | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fallers (N=43) | Non-Fallers (N=47) | *p*-value | Fallers (N=43) | Non-Fallers (N=47) | *p*-value | Fallers (N=43) | Non-Fallers (N=47) | *p*-value |
| *Time Domain Indices (mean ± s.d.)* | | | | | | | | | |
| SDNN | 29.53 ± 16.50 | 38.04 ± 20.07 | **0.032*** | 5.73 ± 3.11 | 5.55 ± 2.15 | 0.748 | 3.79 ± 1.85 | 3.82 ± 1.50 | 0.932 |
| CV | 0.037 ± 0.017 | 0.968 ± 6.33 | 0.338 | 0.063 ± 0.036 | 0.058 ± 0.025 | 0.270 | 0.060 ± 0.037 | 0.051 ± 0.021 | 0.162 |
| ARV | 14.73 ± 10.27 | 18.59 ± 15.96 | 0.181 | 1.165 ± 0.539 | 1.135 ± 0.546 | 0.794 | 0.86 ± 0.33 | 0.94 ± 0.42 | 0.336 |
| RMSRV | 21.83 ± 19.58 | 25.24 ± 22.72 | 0.451 | 1.86 ± 0.97 | 1.72 ± 0.94 | 0.482 | 1.37 ± 0.57 | 1.46 ± 0.69 | 0.520 |
| *Frequency Domain Indices (mean ± s.d.)* | | | | | | | | | |
| LF-nu | 52.17 ± 18.90 | 53.91 ± 20.86 | 0.680 | 67.02 ± 20.12 | 76.66 ± 14.77 | **0.012*** | 68.68 ± 18.29 | 76.24 ± 16.48 | 0.043 |
| HF-nu | 47.83 ± 18.90 | 46.09 ± 20.86 | 0.679 | 32.98 ± 20.12 | 23.34 ± 14.77 | **0.012*** | 31.32 ± 18.29 | 23.76 ± 16.48 | **0.042*** |
| TP | 79707.7 ± 104406.7 | 98065.3 ± 112321.9 | 0.425 | 1560.36 ± 1402.50 | 1380.58 ± 1755.23 | 0.591 | 763.05 ± 772.38 | 731.49 ± 559.69 | 0.826 |
| LF/HF | 1.49 ± 1.14 | 1.82 ± 1.67 | 0.279 | 3.95 ± 4.15 | 5.66 ± 5.83 | 0.116 | 4.46 ± 5.14 | 5.81 ± 6.39 | 0.275 |

*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SDNN* standard deviation of NN interval, *CV* coefficient variation, *ARV* average real variability, *RMSRV* root mean square of real variability, *LF-nu* low-frequency normalized unit, *HF-nu* high-frequency normalized unit, *TP* total power, *LF/HF* ratio of LF and HF

*Independent T-test *p*-value < 0.05

## 4.2 Relationship between autonomic nervous system (ANS) and psychological disorder

Table 4.4 summarized the relationship between psychological disorder variables and both time domain and spectral domain indices of autonomic function for both groups of fallers and non-fallers during supine and standing. Overall, among the stress, depression, and anxiety scores extracted from the DASS-21 questionnaire, only stress score showed a correlation with autonomic function index in supine. Significant correlation was observed between stress and SBPV-CV (r = - 0.250, p = 0.017) in supine. On the contrary, none of the spectral domain indices for BPV was observed to correlate with psychological disorder. Similarly, neither time domain indices nor spectral analysis of HRV showed any correlation with psychological disorder in supine. On the other hand, during standing, only HRV showed a correlation with the autonomic function index. Significant correlation was observed between depression and HRV-SDNN (r = -0.251, p = 0.018). On the contrary, none of the spectral domain indices for HRV was observed to correlate with psychological disorder. Similarly, neither time domain indices nor spectral analysis of BPV showed any correlation with psychological disorder during standing.

**Table 4.4: Bivariate correlation between psychological disorder and autonomic function indices according to supine and standing in both group of fallers and non-fallers**

| | **Supine (n=92)** | | | **Standing (n=91)** | | |
|---|---|---|---|---|---|---|
| | DASS-21 Depression | DASS-21 Anxiety | DASS-21 Stress | DASS-21 Depression | DASS-21 Anxiety | DASS-21 Stress |
| Time domain | | | | | | |
| ***HRV*** | | | | | | |
| SDNN | -0.135 | -0.021 | 0.073 | **-0.251*** | -0.147 | 0.080 |
| CV | 0.132 | -0.056 | -0.027 | 0.132 | -0.058 | -0.026 |
| ARV | -0.148 | -0.026 | 0.026 | -0.198 | -0.101 | 0.041 |
| RMSRV | -0.102 | -0.002 | 0.052 | -0.159 | -0.118 | 0.104 |
| ***SBPV*** | | | | | | |
| SDNN | 0.067 | -0.019 | 0.176 | -0.070 | 0.007 | 0.031 |
| CV | 0.066 | -0.038 | **-0.250*** | 0.042 | 0.055 | 0.124 |
| ARV | -0.015 | -0.064 | 0.001 | -0.053 | -0.054 | 0.087 |
| RMSRV | 0.009 | 0.052 | -0.004 | -0.044 | -0.001 | 0.137 |
| ***DBPV*** | | | | | | |
| SDNN | 0.079 | -0.002 | 0.180 | 0.006 | 0.023 | 0.137 |
| CV | 0.043 | -0.068 | 0.176 | 0.062 | 0.045 | 0.147 |
| ARV | -0.002 | 0.029 | 0.053 | -0.054 | -0.038 | 0.088 |
| RMSRV | 0.009 | 0.052 | 0.041 | -0.059 | -0.051 | 0.070 |
| Spectral Analysis | | | | | | |
| ***HRV*** | | | | | | |
| LF-nu | 0.117 | 0.076 | 0.029 | 0.047 | 0.009 | -0.076 |
| HF-nu | -0.117 | -0.076 | -0.029 | -0.047 | -0.009 | 0.076 |
| TP | -0.137 | -0.046 | 0.044 | -0.196 | -0.126 | 0.090 |
| LF/HF | 0.154 | 0.071 | 0.045 | 0.057 | -0.025 | -0.100 |
| ***SBPV*** | | | | | | |
| LF-nu | -0.060 | 0.187 | 0.063 | -0.118 | -0.002 | -0.072 |
| HF-nu | 0.060 | -0.187 | -0.063 | 0.118 | 0.002 | 0.072 |

Table 4.4, continued

| | Supine (n=92) | | | Standing (n=90) | | |
|---|---|---|---|---|---|---|
| | DASS-21 Depression | DASS-21 Anxiety | DASS-21 Stress | DASS-21 Depression | DASS-21 Anxiety | DASS-21 Stress |
| TP | -0.072 | 0.088 | -0.032 | -0.035 | -0.031 | -0.013 |
| LF/HF | -0.120 | 0.116 | 0.005 | -0.118 | 0.092 | -0.022 |
| ***DBPV*** | | | | | | |
| LF-nu | -0.004 | 0.172 | 0.065 | -0.097 | 0.028 | -0.040 |
| HF-nu | 0.004 | -0.172 | -0.065 | 0.097 | -0.028 | 0.040 |
| TP | -0.052 | 0.122 | -0.027 | 0.040 | -0.021 | 0.071 |
| LF/HF | -0.084 | 0.118 | 0.048 | -0.084 | 0.071 | -0.076 |

*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SDNN* standard deviation of NN interval, *CV* coefficient variation, *ARV* average real variability, *RMSRV* root mean square of real variability, *LF-nu* low-frequency normalized unit, *HF-nu* high-frequency normalized unit, *TP* total power, *LF/HF* ratio of LF and HF

* Pearson's correlation significant at *p*-value < 0.05

** Pearson's correlation significant at *p*-value <0.001

## 4.3 Relationship between autonomic nervous system (ANS) and physical performance

Table 4.5 summarized the relationship between physical performance variables and both time domain and spectral domain indices of autonomic function for both groups of fallers and non-fallers during supine. For time domain indices, significant correlation was found between physical dependency measure, i.e., the Lawton IADL, and SBPV as well as DBPV. Specifically, significant correlation was observed for SBPV-SDNN (r = -0.256, p = 0.014), SPBV-CV (r = -0.212, p = 0.034), SBPV-ARV (r = -0.374, p = <0.001), SBPV-RMSRV (r = -0.363, p = <0.001) as well as DBPV-SDNN (r = -0.212, p = 0.042), DBPV-ARV (r = -0.295, p = 0.004) and DBPV-RMSRV (r = -0.300, p = 0.004). On the contrary, none of the time domain indices for HRV were observed to correlate with physical performance.

Moreover, for spectral domain indices, all three autonomic function indicators (HRV, SBPV, DBPV) showed correlation with physical performance. Specifically, for HRV, significant correlation was observed between HRV-LFnu and TUG (r = 0.247, p = 0.018) as well as LAWTON (r = -0.032, p = 0.028). Furthermore, TUG was correlated with HRV-HFnu and HRV-LF/HF (r = -0.247, p = 0.018 and r = 0.397, p = <0.001), respectively. Next, SBPV and DBPV-TP showed significant correlation with LAWTON (r = -0.313, p = 0.002 and r = -0.256, p = 0.014), whilst SBPV and DBPV-LF/HF showed significant correlation with PASE score (r = 0.347, p = 0.001 and r = 0.322, p = 0.002), respectively.

Table 4.6 summarized the relationship between physical performance variables and both time domain and spectral analysis indices of autonomic function among both groups of fallers and non-fallers, during standing. Significant correlation was observed between HRV-SDNN and LAWTON (r = 0.292, p = 0.005), while in terms of BPV, only DBPV showed a correlation with physical performance during standing. Specifically, DBPV-SDNN (r = -0.236, p = 0.025) and DBPV-CV (r = -0.221, p = 0.037) showed a significant correlation with LAWTON, while only DBPV-CV (r = -0.212, p = 0.045) showed a correlation with the PASE score. Furthermore, none of the spectral domain indices for HRV were observed to correlate with physical performance during standing. Significant correlation can be observed between TUG and SBPV-TP (r = 0.297, p = 0.005) as well as DBPV-TP (r = 0.216, p = 0.042). Besides, PASE score was only correlated with DBPV-LF/HF (r =0.342, p = 0.001), whilst LAWTON was correlated with DBPV-TP (r = -0.229, p = 0.030).

**Table 4.5: Bivariate correlation between physical performance and autonomic function indices according to supine condition in both group of fallers and non-fallers**

| | Supine (n=92) | | | | |
|---|---|---|---|---|---|
| | TUG | HGS (Right) | HGS (Left) | PASE | LAWTON |
| Time domain | | | | | |
| ***HRV*** | | | | | |
| SDNN | -0.003 | 0.081 | 0.157 | 0.196 | 0.212 |
| CV | -0.036 | 0.018 | 0.033 | -0.008 | 0.070 |
| ARV | -0.154 | 0.042 | 0.115 | 0.109 | 0.117 |
| RMSRV | -0.109 | 0.043 | 0.121 | 0.109 | 0.071 |
| ***SBPV*** | | | | | |
| SDNN | 0.086 | -0.066 | -0.032 | -0.132 | **-0.256 *** |
| CV | 0.152 | -0.146 | -0.082 | -0.162 | **-0.212 *** |
| ARV | 0.026 | 0.060 | 0.072 | -0.124 | **-0.374 **** |
| RMSRV | 0.050 | 0.026 | 0.026 | -0.175 | **-0.363 **** |
| ***DBPV*** | | | | | |
| SDNN | 0.053 | -0.013 | 0.041 | -0.085 | **-0.212 *** |
| CV | 0.121 | -0.051 | 0.049 | -0.144 | -0.202 |
| ARV | 0.111 | 0.122 | 0.093 | -0.107 | **-0.295 **** |
| RMSRV | 0.110 | 0.031 | 0.013 | -0.128 | **-0.300 **** |
| Spectral Analysis | | | | | |
| ***HRV*** | | | | | |
| LF-nu | **0.247 *** | -0.047 | -0.059 | -0.071 | **-0.032 *** |
| HF-nu | **-0.247 *** | 0.047 | 0.059 | 0.071 | 0.032 |
| TP | -0.107 | 0.107 | 0.147 | 0.167 | 0.172 |
| LF/HF | **0.397 **** | -0.085 | -0.151 | -0.174 | -0.078 |
| ***SBPV*** | | | | | |
| LF-nu | -0.004 | -0.075 | -0.029 | 0.011 | 0.202 |

Table 4.5, continued

| | Supine (n=92) | | | | |
|---|---|---|---|---|---|
| | TUG | HGS (Right) | HGS (Left) | PASE | LAWTON |

| | | | | | |
|---|---|---|---|---|---|
| HF-nu | 0.004 | 0.075 | 0.029 | -0.011 | -0.202 |
| TP | 0.059 | -0.058 | -0.058 | -0.199 | **-0.313 **** |
| LF/HF | -0.101 | 0.041 | 0.072 | **0.347 **** | 0.205 |
| ***DBPV*** | | | | | |
| LF-nu | -0.138 | -0.075 | -0.046 | 0.124 | 0.181 |
| HF-nu | 0.138 | 0.075 | 0.046 | -0.124 | -0.181 |
| TP | 0.030 | -0.037 | -0.072 | -0.107 | **-0.256 *** |
| LF/HF | -0.136 | -0.041 | -0.044 | **0.322 **** | 0.196 |

*TUG* Time-up-and-go, *HGS* Hand Grip Strength, *PASE* Physical Activity Scale for the Elderly, *LAWTON* Lawton Instrumental Activities of Daily Living Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SDNN* standard deviation of NN interval, *CV* coefficient variation, *ARV* average real variability, *RMSRV* root mean square of real variability, *LF-nu* low-frequency normalized unit, *HF-nu* high-frequency normalized unit, *TP* total power, *LF/HF* ratio of LF and HF

* Pearson's correlation significant at *p*-value < 0.05

** Pearson's correlation significant at *p*-value <0.001

**Table 4.6: Bivariate correlation between physical performance and autonomic function indices according to standing condition in both group of fallers and non-fallers**

| | Standing (n=91) | | | | |
|---|---|---|---|---|---|
| | TUG | HGS (Right) | HGS (Left) | PASE | LAWTON |
| Time domain | | | | | |
| ***HRV*** | | | | | |
| SDNN | -0.161 | 0.107 | 0.185 | 0.152 | 0.292 ** |
| CV | -0.035 | 0.017 | 0.032 | -0.009 | 0.068 |
| ARV | -0.155 | 0.006 | 0.055 | 0.019 | 0.090 |
| RMSRV | -0.136 | 0.052 | 0.107 | 0.055 | 0.072 |
| ***SBPV*** | | | | | |
| SDNN | 0.026 | 0.084 | 0.087 | -0.102 | -0.177 |
| CV | 0.038 | -0.068 | -0.044 | -0.186 | -0.200 |
| ARV | 0.114 | 0.091 | 0.054 | -0.032 | -0.177 |
| RMSRV | 0.141 | -0.032 | -0.051 | -0.105 | -0.123 |
| ***DBPV*** | | | | | |
| SDNN | 0.069 | 0.039 | 0.062 | -0.115 | -0.236 * |
| CV | 0.046 | -0.055 | 0.002 | -0.212 * | -0.221 * |
| ARV | 0.052 | 0.179 | 0.147 | -0.034 | -0.156 |
| RMSRV | 0.061 | 0.148 | 0.117 | -0.066 | -0.140 |
| Spectral Analysis | | | | | |
| ***HRV*** | | | | | |
| LF-nu | -0.017 | 0.117 | -0.003 | 0.169 | 0.182 |
| HF-nu | 0.017 | -0.117 | 0.003 | -0.169 | -0.182 |
| TP | -0.135 | 0.028 | 0.078 | 0.110 | 0.163 |
| LF/HF | -0.090 | 0.205 | 0.112 | 0.168 | 0.180 |
| ***SBPV*** | | | | | |
| LF-nu | 0.046 | -0.086 | -0.032 | 0.128 | 0.104 |

Table 4.6, continued

| | Standing (n=91) | | | | |
|---|---|---|---|---|---|
| | TUG | HGS (Right) | HGS (Left) | PASE | LAWTON |

| | | | | | |
|---|---|---|---|---|---|
| HF-nu | -0.046 | 0.086 | 0.032 | -0.128 | -0.104 |
| TP | **0.297 ** ** | -0.120 | -0.079 | -0.036 | -0.173 |
| LF/HF | -0.014 | -0.141 | -0.041 | 0.071 | 0.046 |
| ***DBPV*** | | | | | |
| LF-nu | 0.023 | -0.001 | 0.042 | 0.180 | 0.104 |
| HF-nu | -0.023 | 0.001 | -0.042 | -0.180 | -0.104 |
| TP | **0.216 *** | -0.050 | -0.024 | -0.049 | **-0.229 *** |
| LF/HF | -0.056 | -0.027 | 0.016 | **0.342 ** ** | 0.130 |

*TUG* Time-up-and-go, *HGS* Hand Grip Strength, *PASE* Physical Activity Scale for the Elderly, *LAWTON* Lawton Instrumental Activities of Daily Living Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SDNN* standard deviation of NN interval, *CV* coefficient variation, *ARV* average real variability, *RMSRV* root mean square of real variability, *LF-nu* low-frequency normalized unit, *HF-nu* high-frequency normalized unit, *TP* total power, *LF/HF* ratio of LF and HF

* Pearson's correlation significant at *p*-value < 0.05

** Pearson's correlation significant at *p*-value <0.001

## 4.4 Independent Predictors Model of Autonomic Nervous System (ANS)

Predictors of autonomic nervous system (ANS) were tested using history of falls, psychological disorder (DASS-21 Depression, DASS-21 Anxiety, FES-1) and physical performance (PASE, TUG and Lawton IADL). SBPV-CV and DBPV-CV were used as a time-domain BPV representative for autonomic function during supine and standing. Table 4.7 shows that stress score ($r^2 = 0.063$, $p = 0.017$) and LAWTON IADL ($r^2 = 0.049$, $p = 0.035$) were predictors of SBPV-CV in supine, but not history of falls, DASS-21 depression and DASS-21 anxiety scores, PASE, as well as TUG. On the other hand, only PASE ($r^2 = 0.022$, $p = 0.045$) and LAWTON IADL ($r^2 = 0.049$, $p = 0.037$) were found to be predictors of DBPV-CV during standing.

HRV-SDNN was chosen as the time-domain HRV representative for autonomic function during supine and standing. Table 4.8 shows that LAWTON IADL ($r^2 = 0.045$, $p = 0.042$) was the only variables that found to be predictors of HRV-SDNN during supine. On the contrary, during standing, only history of falls ($r^2 = 0.051$, $p = 0.032$), DASS-21 depression ($r^2 = 0.063$, $p = 0.018$) and LAWTON IADL ($r^2 = 0.086$, $p = 0.005$) were found to be predictors to HRV-SDNN.

Ratio of LF and HF (LF/HF) of SBPV and DBPV was chosen as the frequency-domain BPV representative for autonomic function in the independent predictors model during supine and standing. Table 4.9 shows that PASE score ($r^2 = 0.120$, $p = 0.001$) and LAWTON IADL ($r^2 = 0.042$, $p = 0.050$) were found to be predictors for SBPV-LF/HF, whilst only PASE score ($r^2 = 0.104$, $p = 0.002$) was found to be predictor for DBPV-LF/HF in supine. During standing, only PASE score ($r^2 = 0.117$, $p = 0.001$) was the independent predictor for DBPV-LF/HF. None of the variables were associated with SBPV-LF/HF during standing. Lastly, for frequency-domain HRV index, Table 4.10

shows that only TUG was the independent predictor for HRV-LFnu ($r^2 = 0.061$, $p = 0.018$) and HRV-HFnu ($r^2 = 0.061$, $p = 0.018$) during supine.

**Table 4.7: Independent Predictors of Autonomic Function (Time Domain BPV)**

| Variables | Mean difference (95% Confidence Interval) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Supine Rest | | | | Standing Position | | | |
| | CV-SBPV | $R^2$ | CV-DBPV | $R^2$ | CV-SBPV | $R^2$ | CV-DBPV | $R^2$ |
| History of Falls | -0.010 (-0.024 to 0.003) | 0.025 | -0.008 (-0.021 to 0.004) | 0.021 | -0.007 (-0.020 to 0.006) | 0.014 | -0.009 (-0.021 to 0.003) | 0.023 |
| Depression score | 0.000 (-0.001 to 0.002) | 0.004 | 0.000 (-0.001 to 0.001) | 0.002 | 0.000 (-0.001 to 0.001) | 0.002 | 0.000 (-0.001 to 0.002) | 0.004 |
| Anxiety score | 0.000 (-0.002 to 0.001) | 0.001 | 0.000 (-0.002 to 0.001) | 0.005 | 0.000 (-0.001 to 0.002) | 0.003 | 0.000 (-0.001 to 0.002) | 0.002 |
| **Stress Score** | 0.001 (0.000 to 0.002) | **0.063** | 0.001 (0.000 to 0.002) | 0.031 | 0.001 (0.000 to 0.002) | 0.015 | 0.001 (0.000 to 0.002) | 0.022 |
| PASE | 0.000 (0.000 to 0.000) | 0.026 | 0.000 (0.000 to 0.000) | 0.021 | 0.000 (0.000 to 0.000) | 0.035 | 0.000 (0.000 to 0.000) | **0.045** |
| TUG | 0.000 (0.000 to 0.001) | 0.023 | 0.000 (0.000 to 0.001) | 0.015 | 0.000 (0.000 to 0.001) | 0.001 | 0.000 (0.000 to 0.001) | 0.002 |
| **Lawton IADL** | -0.003 (-0.006 to 0.000) | **0.049** | -0.003 (-0.005 to 0.000) | 0.041 | -0.003 (-0.005 to 0.000) | 0.040 | -0.003 (-0.005 to 0.000) | **0.049** |
| **Adjusted $R^2$** | 0.071 | | 0.019 | | -0.021 | | -0.001 | |

*SBPV* systolic blood pressure variability, *DBPV* diastolic blood pressure variability, *CV* coefficient variation, *CI* confidence interval, $R^2$ R squared, *PASE* Physical Activity Scale for the Elderly, *TUG* Time-up-and-go, *Lawton IADL* Lawton Instrumental Activities of Daily Living Scale

Bolded font indicates *p*-value <0.05

**Table 4.8: Independent Predictors of Autonomic Function (Time Domain HRV)**

| **Variables** | **Mean difference (95% Confidence Interval)** | | | |
|---|---|---|---|---|
| | Supine Rest | | Standing Position | |
| | SDNN-HRV | $R^2$ | SDNN-HRV | $R^2$ |
| History of Falls | 5.669 (-1.080 to 12.418) | 0.030 | 8.506 (0.767 to 16.246) | **0.051** |
| Depression score | -0.419 (-1.064 to 0.227) | 0.018 | -0.887 (-1.615 to 0.158) | **0.063** |
| Anxiety score | -0.075 (-0.819 to 0.669) | 0.000 | -0.594 (-1.444 to 0.256) | 0.022 |
| Stress Score | 0.183 (-0.347 to 0.713) | 0.005 | 0.254 (-0.421 to 0.930) | 0.006 |
| PASE | 0.054 (-0.003 to 0.112) | 0.038 | 0.048 (-0.018 to 0.115) | 0.023 |
| TUG | -0.003 (-0.236 to 0.230) | 0.000 | -0.212 (-0.489 to 0.065) | 0.026 |
| Lawton IADL | 1.481 (0.005 to 2.907) | **0.045** | 2.367 (0.727 to 4.006) | **0.086** |
| **Adjusted $R^2$** | 0.045 | | 0.133 | |

*HRV* Heart rate variability, *SDNN* standard deviation of NN interval, *CI* confidence interval, $R^2$ R squared, *PASE* Physical Activity Scale for the Elderly, *TUG* Time-up-and-go, *Lawton IADL* Lawton Instrumental Activities of Daily Living Scale

Bolded font indicates *p*-value <0.05

**Table 4.9: Independent Predictors of Autonomic Function (Frequency Domain BPV)**

| **Variables** | **Mean difference (95% Confidence Interval)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Supine Rest | | | | Standing Position | | | |
| | LF/HF-SBPV | $R^2$ | LF/HF-DBPV | $R^2$ | LF/HF-SBPV | $R^2$ | LF/HF-DBPV | $R^2$ |
| History of Falls | 0.859 (-0.659 to 2.377) | 0.014 | 0.330 (-0.976 to 1.636) | 0.003 | 1.710 (-0.429 to 3.850) | 0.028 | 1.351 (-1.094 to 3.795) | 0.014 |
| Depression score | -0.083 (-0.228 to 0.061) | 0.014 | -0.050 (-0.174 to 0.075) | 0.007 | -0.114 (-0.318 to 0.090) | 0.014 | -0.092 (-0.324 to 0.140) | 0.007 |
| Anxiety score | 0.092 (-0.074 to 0.257) | 0.013 | 0.080 (-0.061 to 0.221) | 0.014 | 0.101 (-0.132 to 0.334) | 0.008 | 0.088 (-0.177 to 0.354) | 0.005 |
| Stress Score | 0.003 (-0.116 to 0.122) | 0.000 | 0.023 (-0.078 to 0.125) | 0.002 | -0.019 (-0.204 to 0.165) | 0.000 | -0.075 (-0.284 to 0.134) | 0.006 |
| PASE | 0.021 (0.009 to 0.034) | **0.120** | 0.017 (0.007 to 0.028) | **0.104** | 0.006 (-0.012 to 0.024) | 0.005 | 0.034 (0.014 to 0.053) | **0.117** |
| TUG | -0.025 (-0.076 to 0.027) | 0.010 | -0.029 (-0.073 to 0.015) | 0.019 | -0.005 (-0.081 to 0.072) | 0.000 | -0.023 (-0.109 to 0.064) | 0.003 |
| Lawton IADL | 0.319 (0.00 to 0.637) | **0.042** | 0.260 (-0.013 to 0.533) | 0.038 | 0.102 (-0.365 to 0.570) | 0.002 | 0.325 (-0.202 to 0.852) | 0.017 |
| **Adjusted $R^2$** | 0.088 | | 0.073 | | -0.013 | | 0.073 | |

*LF/HF* Ratio of Low-Frequency and High-Frequency, *SBPV* systolic blood pressure variability, *DBPV* diastolic blood pressure variability, *CI* confidence interval, $R^2$ R squared, *PASE* Physical Activity Scale for the Elderly, *TUG* Time-up-and-go, *Lawton IADL* Lawton Instrumental Activities of Daily Living Scale

Bolded font indicates *p*-value <0.05

**Table 4.10: Independent Predictors of Autonomic Function (Frequency Domain HRV)**

| Variables | Mean difference (95% Confidence Interval) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Supine Rest | | | | Standing Position | | | |
| | LF-nu HRV | $R^2$ | HF-nu HRV | $R^2$ | LF-nu HRV | $R^2$ | HF-nu HRV | $R^2$ |
| History of Falls | -1.865 (-9.777 to 6.046) | 0.002 | 1.865 (-6.046 to 9.777) | 0.002 | 1.741 (-6.625 to 10.106) | 0.002 | -1.741 (-10.106 to 6.625) | 0.002 |
| Depression score | 0.420 (-0.329 to 1.169) | 0.014 | -0.420 (-1.169 to 0.329) | 0.014 | 0.175 (-0.618 to 0.968) | 0.002 | -0.175 (-0.968 to 0.618) | 0.002 |
| Anxiety score | 0.312 (-0.548 to 1.171) | 0.006 | -0.312 (-1.171 to 0.548) | 0.006 | 0.039 (-0.867 to 0.946) | 0.000 | -0.039 (-0.946 to 0.867) | 0.000 |
| Stress Score | 0.084 (-0.531 to 0.699) | 0.001 | -0.084 (-0.699 to 0.531) | 0.001 | -0.254 (-0.966 to 0.459) | 0.006 | 0.254 (-0.459 to 0.966) | 0.006 |
| PASE | -0.023 (-0.090 to 0.044) | 0.005 | 0.023 (-0.044 to 0.090) | 0.005 | 0.056 (-0.013 to 0.126) | 0.028 | -0.056 (-0.126 to 0.013) | 0.028 |
| TUG | 0.307 (0.054 to 0.560) | **0.061** | -0.307 (-0.560 to -0.054) | **0.061** | -0.023 (-0.315 to 0.270) | 0.000 | 0.023 (-0.270 to 0.315) | 0.000 |
| Lawton IADL | -0.257 (-1.943 to 1.429) | 0.001 | 0.257 (-1.429 to 1.943) | 0.001 | 1.552 (-0.225 to 3.328) | 0.033 | -1.552 (-3.328 to 0.225) | 0.033 |
| **Adjusted $R^2$** | -0.004 | | -0.004 | | -0.001 | | -0.001 | |

*LFnu* Low-Frequency normalized unit, *HFnu* High-Frequency normalized unit, *HRV* Heart rate variability, $R^2$ R squared, *PASE* Physical Activity Scale for the Elderly, *TUG* Time-up-and-go, *Lawton IADL* Lawton Instrumental Activities of Daily Living Scale

Bolded font indicates *p*-value <0.05

# CHAPTER 5: DISCUSSION

## 5.1 Baseline Demographic and Study population

Within our cohort study which included community-dwelling older adults aged 60 years and above, 49% of older individuals experienced at least one fall in the past two months. While most previously published studies recruited fallers who had at least an incidence of falls within the past 12 months (Stevens et al., 2008; Stevens et al., 2006; Kenny et al., 2017), this study only include those who fell in the past two months.

Our finding showed poorer physical performance in fallers as compared to non-fallers, as reflected by their poorer TUG level, weaker hand-grip strength and lower physical activity level (Salzman, 2011; Pijnappels et al., 2008). Fallers may develop fear of recurrent falls, that further impede their physical activity, reduce mobility level (Vellas et al., 1997; Akosile et al., 2014; Duray & Genç, 2017; Bell, 2008), muscular strength, flexibility, gait and fitness, ultimately worsen their physical performance and increased risk of future falls (Furtado et al., 2015; Gouveia et al., 2013). Furthermore, fall-related injuries resulted in an inability to socialize, cognitive impairment, and increased dependency towards family members to maintain mobility. This led to worsen emotional and psychological well-being among fallers, indirectly reducing their quality of life (Salkeld et al., 2000; Cumming et al., 2000; Li & Harmer, 2020). Other falls characteristics, including physical performance, psychological status and cognitive performance, were shown to be poorer among fallers as compared to non-fallers. This is consistent with findings reported by other studies (Ambrose et al., 2013; Kenny et al., 2017; Salzman, 2011; Pijnappels et al., 2008; Hellström et al., 2009).

## 5.2 Autonomic Nervous System Indices Between Fallers and Non-Fallers

Studies on heart rate variability (HRV) and blood pressure variability (BPV) have primarily used time domain and frequency domain analysis methods to determine very short-term HRV and BPV, as shown in Tables 4.2 and Table 4.3. While previous studies have only adopted several time domain indices to represent autonomic nervous system (ANS) (e.g., the average real variability (ARV), root mean square of real variability (RMSRV) or standard deviation (SD)) (Mena et al., 2005; Goh et al., 2017), the current study has presented both time-domain and frequency-domain indices for the analysis of ANS.

Generally, in the supine position, time domain indices (ARV and RMSRV), as well as frequency domain (TP) SBPV, which represent the overall ANS function, were consistently higher among older fallers as compared to non-fallers. These findings were consistent with observations reported by other studies, which demonstrated that RMSRV discriminated fallers and non-fallers better than other time domain indices (Goh et al., 2017). In addition, the ARV index has been shown to be a reliable indicator for BPV (Mena et al., 2005). Elevated RMSRV/ARV values reflected functional impairment in the sympathetic and parasympathetic branches (sympathovagal balance) as well as blunted baroreflex sensitivity (Pertiwi et al., 2018; Zhang et al., 2012; Isik et al., 2012) among fallers.

On the other hand, during upright posture, significant differences in the sympathetic and parasympathetic pathways were revealed. This was shown by a difference in the changes of the low frequency (LF) and high frequency (HF) HRV/BPV magnitude in both fallers and non-fallers from supine to standing. As compared to non-fallers, fallers demonstrated lower HRV-SDNN and low-frequency normalised unit (LFnu) SBPV, but higher high frequency normalised unit (HFnu) in both SBPV and

DBPV, during upright posture. While LF-power is influenced by sympathetic control, a reaction occurring during a fight-or flight situation, HF-power involves vagal or parasympathetic reaction, mainly occurring during calm and relaxed situation (Andriessen et al., 2004). As a result, LF/HF ratio reflects sympathetic predominance (Martinez et al., 2010; Goh et al., 2017).

Our findings on the reduction of SBPV-LFnu and HRV-SDNN during standing in fallers were opposite to that observed in the healthy population (Goh et al., 2017). In an upright posture, sympathetic activity was assumed to increase, which in turn increases the peripheral vascular tone (increase blood vessel contraction, increase vasoconstriction, increase blood pressure) to prevent the reduction of blood pressure that occurred due to gravitational effects. This helped to reduce the risk of orthostatic hypotension (OH) symptoms (Finucane et al., 2017) upon standing. The observed differences in SBPV and HRV responses among fallers may suggest a reduction in their BP control reactivity during standing (Goh et al., 2017), which may be associated with age-related conditions such as arterial stiffness or autonomic dysfunction (McLaren et al., 2005). Similar findings have also been observed in a previous study (Goh et al., 2017). A reduction in BP control during standing could possibly explain the susceptibility to falls among the fallers group, as fall events are usually associated with a reduced ability to maintain the centre of gravity. On the other hand, the higher HF-SBPV and DBPV observed in this study among fallers during standing reflects a higher parasympathetic reaction as compared to non-fallers. This may be interpreted as fallers are prone to be more cautious when changing position due to fear of recurrent fall. Therefore, they are more prepared to changes in posture during standing, which may lead to increased vagal reaction.

## 5.3 Physical Performance

Numerous studies have been performed to investigate the bidirectional relationship between physical performance and cardiac autonomic modulation (Espinoza-salinas et al., c2021; Nascimento et al., 2019; Tebar et al., 2020). Results from this study showed that physical performance was closely correlated with autonomic function. Previous studies have also suggested that regular physical activity could contribute to the enhancement of the overall ANS activity in both lean and obese children (Nagai & Moritani, 2004). An increase in HRV has also been reported among adolescent men with an active lifestyle (Tornberg et al., 2019).

Although an increase in the physical activity level have been shown to be advantageous to cardiac autonomic control, no study has investigated on the types of physical activity measures that best predict autonomic response. According to the percentage of R squared between two variables, multivariate analysis performed in this study showed that Lawton Instrumental Activities of Daily Living (IADL) Scale, a self-reported questionnaire which measures functional independence in the basic activities of daily living, was the best predictor for time domain autonomic function indices, while Physical Activity Scale for the Elderly (PASE), an instrument that measures the level of physical activity in elderly (focusing on occupational, household and leisure), was the best predictor for frequency domain autonomic function indices. While self-reported Lawton IADL and PASE look at physical independency and daily lifestyle of an individual, other physical performance tests, such as time-up-and-go, hand-grip strength and functional reach, only look at the functional ability of certain body parts, such as muscle strength, walking speed and dynamic balance, at a particular moment, and therefore are not reliable predictors for an individual overall well-being. To summarize, a higher $R^2$ value indicates a stronger predictive value between two variables. Generally, the adjusted $R^2$ values were relatively small indicating a large proportion of the variance remain unexplained although significant associations were observed between Lawton IADL, PASE and autonomic function indices. This can be due to the smaller sample size between fallers and non-fallers.

Lawton IADL, which reflects an individual's physical independence, was found to be associated with the coefficient variation index of the HRV and BPV. Coefficient variation is a time domain index which measures the dispersion of average values over a given time; i.e., during 10 minutes lying rest and 3 minutes standing. PASE questionnaires, on the other hand, focused on an individual's daily lifestyle (Li-Fan, 2017). Study on the influence of lifestyle factors on cardiac autonomic function showed that regular exercise routine would modify the activities of the sympathetic and parasympathetic of autonomic function over time (Hu et al., 2017). PASE was shown to be significantly associated with frequency domain index, specifically the LF/HF index. An increase in the LF/HF index reflects a shift to sympathetic predominance, while a decrease in the index corresponds to parasympathetic dominance (Malik et al., 1996).

With regards to physical performance tests, only time-up-and-go (TUG) was predominantly associated with frequency domain HRV indices (LF-nu and HF-nu) during supine. American Heart Association (AHA) have revised the guideline for exercise and training, where they divided muscular contraction into two types; isotonic (dynamic/locomotory) and isometric (static) (Fletcher et al., 2001). TUG can be categorized as isotonic muscle contraction as it was the only physical assessment test in this study that involves movement (capability of an individual to stand and walk), whereas hand-grip strength and functional reach were categorized as isometric muscular contraction, as they only involve activation of the muscle's tendon without movement.

The precise mechanism underlying the positive association between TUG and frequency domain HRV indices is still unclear, but changes of cardiac modulation function involving sympathetic and parasympathetic activity may provide some clues as to the mechanism involved. Generally, TUG represents the capability of an individual to perform physical activities. Active lifestyle among adults is associated with a consistent increase in the cardiorespiratory physical fitness level, lowering of heart rate and resting heart rate, as well as an increase in the stroke volume, which are strongly associated with an increase in the parasympathetic action of the heart at rest (Tebar et al., 2020; Tornberg et al., 2019). As opposed to an active lifestyle, sedentary lifestyle would result in lesser stimulation of the baroreflex mechanisms, leading to sympathetic predominance and a reduction in the vagal activity at rest (Espinoza-salinas et al., 2021).

### 5.4 Psychological Status

The current study also demonstrated a significant association between psychological status and autonomic nervous system, as represented by time domain indices of BPV and HRV. This is in agreement with other similar studies (Jung et al., 2019; Carr et al., 2018; Yang et al., 2010; Perna et al., 2020; Martinez et al., 2010; Yeragani et al., 2004; Piccirillo et al., 1997; Virtanen et al., 2003). Among indices presented in this study, the coefficient variation (CV) index for SBPV has the best correlation with psychological disorder during supine, while the standard deviation of NN interval (SDNN) index for HRV has the best correlation with psychological disorder during standing. CV has been suggested to be superior due to its ability to minimize baseline blood pressure shift from supine to standing posture (Murata et al., 2012). According to Malik et al. (1996), standard deviation (SDNN) is mathematically equivalent to the total power (TP) of spectral analysis and can help in estimating the overall HRV in an individual.

To date, we are not aware of any study which investigated the correlation between psychological disorder and autonomic nervous system among elderly adults under different postures. Our results indicated a significantly negative correlation between stress score and SBPV-CV in supine as well as depression and HRV-SDNN in standing. This correlation is further strengthened by findings on multivariate analysis, where stress and depression existed as independent predictors for ANS.

During supine, the relationship between stress and autonomic function may be explained by a consistent hyperactivation of the hypothalamic pituitary-adrenal (HPA) axis, a central stress response system, in adults with high stress level. Stress would lead to hyperactivity of the ANS, as reflected by high sympathetic activity at rest and during standing (Teixeira et al., 2015). This psychological situation may affect cognitive performance and further deteriorate the ANS function. However, the correlation between stress and ANS was only predominant in SBPV but not DBPV. SBPV has been previously shown to be more significantly related to mental health as compared to DBPV (Wright et al., 2014; García-Vera et al., 2004). Increased SBPV was observed to be significantly associated with perceived mental health among young undergraduate students (Wright et al., 2014), and a reduction in the day-to-day SBPV was reported among non-hypertensive subjects who underwent stress management training (García-Vera et al., 2004). A meta-analysis on stress and cardiovascular diseases showed that individuals with heightened stress reactivity or slow post-stress recovery may experience disturbed haemodynamic reaction (i.e., repeated heightening of blood pressure), which was later found to be associated with poorer cardiovascular events in longitudinal studies (Chida & Steptoe, 2010). The outcome from this meta-analysis showed that an increase in the systolic blood pressure (SBP) reactivity towards stress is the best predictor for future morbidity related to cardiovascular diseases (Chida & Steptoe, 2010; Phillips et al., 2009; de Rooij & Roseboom, 2010).

During standing, a more severe depression is associated with a lower HRV, which may indicate impaired autonomic function. Sudden change to the upright posture after lying down triggers an interaction between the destabilising forces, such as gravity or the external environment, towards the body, which prepares the postural control system to react, in order to prevent any loss of balance (Levitan et al., 2012). Impairment in the autonomic function causes low balance efficacy during upright posture, and may mediate orthostatic hypotension (OH) symptoms: a decrease in blood pressure after standing which leads to dizziness, nausea, fainting, falls or syncope in an individual (Lanier et al., 2011). OH is closely related with cardiac autonomic modulation; sympathetic and parasympathetic activity of the heart (Moraes-Silva et al., 2013; Tebar et al., 2020; Nascimento et al., 2019). An increase in the sympathetic activation upon standing among healthy individuals provides evidence for greater adaptation to postural challenge (Martinez et al., 2010). An impairment in the autonomic function has been reported among depressed elderly adults in several published studies related to OH. A study comprising of a group of older people aged 60 years and above found that a higher proportion of older adults with OH existed among the depressed group, who showed a greater drop in systolic blood pressure upon standing (Richardson et al., 2009). Another study has also shown that symptomatic orthostatic hypotension (SOH) was associated with depression in older adults (O Regan et al., 2013).

# CHAPTER 6: CONCLUSION

In conclusion, this study included a total number of 45 fallers and 47 non-fallers aged 60 years and above. Comprehensive data including beat-to-beat measurements of heart rate and blood pressure were collected, which enabled detailed analysis on the relationship between falls and autonomic nervous function in older individuals. Differences between fallers and non-fallers, with regards to their heart rate and blood pressure variability, physical activity and physical performance, as well as psychological status, were analysed using statistical methods and biomedical engineering knowledge.

Generally, the results showed that community dwelling older adults who experienced a fall in the past two months had poorer ANS function, as indicated by several HRV/BPV indices presented in this study. Total power (TP) of SBPV were found to be higher among older fallers as compared to non-fallers, suggesting an impairment in their overall autonomic nervous system function (sympathetic and parasympathetic). During standing, lower sympathetic reaction was observed in fallers, suggesting a reduction in their overall blood pressure reactivity towards gravitational forces and blunted baroreflex response.

Specifically, Lawton Instrumental Activities of Daily Living (IADL) Scale and Physical Activity Scale for the Elderly (PASE) that look at physical dependency and daily lifestyle of an individual were found to be the best independent predictors for autonomic function as measured by the HRV and BPV indices. On the other hand, the stress and depression scores in the DASS-21 questionnaire best predict autonomic function (as measured by the HRV and BPV indices) during supine and standing, respectively. By knowing the association between these modifiable risk factors and autonomic function, early identification of patients at risk of recurrent falls and cardiovascular diseases can be performed to allow timely intervention.

## 6.1 Clinical Implications of the Study

The ageing population is growing, and the potential problems associated with ageing include cardiovascular diseases and injuries caused by falls. As these complications are closely related to autonomic function, clinicians have frequently adopted the tilt-table test (i.e., an autonomic function test) to detect any abnormality in the autonomic function by observing blood pressure and heart rate changes in the patients during the test. However, this requires the use of non-invasive, beat-to-beat hemodynamic monitoring technologies, which are not widely available in all clinical centres. In addition, it requires the patients to travel to the designated clinical centres, which may cause weariness and stress among the elderly adults and their caregivers. In the tilt table/sit-to-stand assessment, the patients are required to stand upright after lying down for several minutes, which may be challenging for elderly frail adults.

A pre-screening assessment which could help identify patients with an increased risk of autonomic dysfunction is therefore useful for early intervention. Our findings suggest that validated questionnaires such as DASS-21, LAWTON and PASE could serve as pre-screening tools to identify patients with autonomic dysfunction. As these questionnaires are freely available online, virtual communication between physicians and patients can be conducted, thus reducing the time taken for travel to clinical centres for autonomic function tests. This could aid in the diagnosis of autonomic dysfunction severity and reduce the risk of future falls and cardiovascular diseases.

## 6.2 Limitations of the Study

This study has several limitations that should be highlighted. Firstly, data on medical illness, psychological condition, and daily physical activity level of the participants were obtained from self-report of physician-diagnosed conditions. To reduce the possibility of error, the research assistant responsible of each interview would crosscheck the collected data with family members whenever possible. Second, as available data only studied the cross-sectional relationship between autonomic function and psychological and functional status, we are unable to establish causation or define any temporal relationship. However, the relationship between psychological, functional status and autonomic function was addressed among elderly fallers cohort. Third, the reliability of the blood pressure and heart rate (ECG) signals can be questioned. However, after the assessments were conducted, continuous blood pressure and ECG signals were directly exported, and the signals were processed and double-checked to ensure that the clean and acceptable signals were used for the computation of blood pressure and heart rate variability. Lastly, several factors which may influence the variability in postural changes in blood pressure and heart rate remains uncounted for as potential factors (e.g. medication) had not been considered in this study.

### 6.3 Recommendations for Future Research

While DASS-21, LAWTON, PASE and TUG were shown to be predictive of autonomic dysfunction, the small adjusted $R^2$ values suggested that the haemodynamic parameters evaluated only accounted for a small amount of the variability in the above outcomes. However, using the rule of thumb of multivariate regression, with an absolute minimum of 10 participants per predictor variables, the current study had sufficient sample for the number of parameters input into the multivariate regression. The autonomic parameters have the potential to detect autonomic function problem in the older population, which currently remains underdiagnosed. Future studies should involve larger sample size to ascertain the usefulness of these parameters. Furthermore, future work should also investigate the relevance of very short-term HRV and BPV indices as indicators of autonomic function in fallers, and their associated risk factors, using larger sample size. As HRV and BPV are potentially modifiable risk factors for falls in older adults, future studies should identify factors that could alter these indices, which also serve as important biomarkers for the autonomic nervous system function.

In addition, although this study successfully strengthened the relationship between autonomic function and physical activity/performance, as well as psychological status and, the usage of self-reported questionnaires may lead to some bias, especially when participants failed to recall their activity and mental states retrospectively. Hence, future studies are needed to further explore the usage of objective measurement tools, such as walking treadmill, aerobic exercise or 24-hour physical activity measurement using accelerometer or pedometers in accessing physical activities of the participants.

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## LIST OF PUBLICATIONS AND PAPERS PRESENTED

<u>Publication</u>

a) Shahimi, N.H., Lim, R., Mat, S. et al. (2022). Association between mental illness and blood pressure variability: a systematic review. *BioMedical Engineering OnLine, 21*(19), 1-22. https://doi.org/10.1186/s12938-022-00985-w.

b) Shahimi, N.H., Goh, C.-H., Mat, S. et al. (2022). Psychological status and physical performance are independently associated with autonomic function. *BioMedical Engineering OnLine, 21*(29), 1-19. https://doi.org/10.1186/s12938-022-00996-7.

<u>Paper Presented (Conference)</u>

a) Nur Husna Shahimi, Choon-Hian Goh, Maw Pin Tan & Einly Lim. (2021. November 9-10). *Association between physical performance and autonomic nervous system in elderly fallers* [Paper Presentation]. 1st National Biomedical Engineering Conference (NBEC) 2021: Kuala Lumpur, Malaysia.

b) Nur Husna Shahimi, Choon-Hian Goh, Sumaiyah Mat, Maw Pin Tan & Einly Lim. (2021, December 4-5). *Association between psychological disorder and autonomic nervous system in elderly fallers.* Malaysia Falls Prevention Network (MyFalls) 1st Scientific Hybrid Meeting 2021: Kuala Lumpur, Malaysia.